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Impact of Antiretroviral Therapy on Sickle Cell Disease Progression: A Narrative Review

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Abstract
The co-occurrence of HIV and sickle cell disease (SCD) poses significant clinical challenges, with both conditions contributing to immune dysfunction and systemic inflammation. Antiretroviral therapy (ART), which has revolutionized the treatment of HIV, may influence the progression of SCD, although its impact remains underexplored. This review aims to examine the potential effects of ART on the progression of SCD, focusing on immune modulation, inflammation, hematologic changes, and clinical outcomes in individuals with both conditions. ART's ability to suppress HIV replication and enhance immune function may provide indirect benefits to individuals with SCD by reducing opportunistic infections and inflammation that could exacerbate sickle cell crises. ART's anti-inflammatory effects could reduce some of the chronic inflammation seen in SCD, potentially alleviating vascular dysfunction and organ damage. However, certain ART regimens, especially those containing drugs like zidovudine, may contribute to hematologic side effects, including bone marrow suppression, which could worsen anemia in SCD patients. Additionally, potential drug-drug interactions between ART and sickle cell medications, such as hydroxyurea, highlight the importance of careful management to avoid adverse effects. Furthermore, ART's role in improving overall health and quality of life for individuals with both HIV and SCD underscores the need for a comprehensive, patient-centered approach.
Keywords*: Antiretroviral therapy, Sickle cell disease, Hemolysis, Vaso-occlusive crises, HIV-SCD co-infection*

Introduction

The co-infection of HIV and sickle cell disease (SCD) presents a unique clinical challenge that requires a comprehensive and integrated approach to treatment. Sickle cell disease, a hereditary hemoglobinopathy, leads to abnormal red blood cell shapes, resulting in vaso-occlusive crises, chronic pain, organ damage, and progressive disability. In parallel, HIV, a viral infection that targets and weakens the immune system, leads to immune suppression and increased susceptibility to opportunistic infections. When both diseases are present in an individual, the combined burden on the immune system, hematopoietic function, and organ systems creates a complex therapeutic dilemma. Despite significant advancements in the management of both conditions, particularly with the introduction of antiretroviral therapy (ART) for HIV, the effects of ART on SCD progression remain poorly understood.[1-2] Antiretroviral therapy has been transformative in the treatment of HIV, improving patient outcomes and life expectancy significantly. ART works by suppressing HIV replication, thus reducing viral load and improving immune function. ART regimens typically include a combination of drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INIs), which work at different stages of the HIV life cycle. ART has been pivotal in preventing the progression of HIV to acquired immunodeficiency syndrome (AIDS), reducing the incidence of opportunistic infections, and enhancing the quality of life for individuals living with HIV. However, the effects of ART in patients with co-existing SCD remain an area of significant interest, as both diseases have distinct path physiologies that may interact in complex ways.[3-4] Sickle cell disease itself is a result of a genetic mutation that causes hemoglobin molecules to form abnormally, leading to rigid and sickle-shaped red blood cells that cause blockages in blood vessels. This vaso-occlusion leads to episodes of acute pain, organ damage, and a reduced life expectancy. SCD also involves chronic inflammation, endothelial dysfunction, and an increased risk of infections. These systemic issues complicate the management of co-infected individuals, as HIV's immune suppression can exacerbate the inflammatory responses seen in SCD. Additionally, the immune system's compromised state in individuals with HIV may leave them more susceptible to infections that can trigger sickle cell crises. Given the complexities of both conditions, understanding the potential impacts of ART on SCD progression is critical for improving treatment outcomes.[5-6]

One potential benefit of ART in individuals with both HIV and SCD is its effect on immune function. By suppressing HIV replication, ART can help restore immune function, which may, in turn, reduce the frequency and severity of infections in patients with SCD. Infections are a major trigger for sickle cell crises, and the ability to prevent or mitigate these infections through ART may offer a protective effect. Additionally, ART's role in reducing HIV-related inflammation could have secondary benefits for SCD patients by mitigating the chronic inflammation that exacerbates the pathophysiology of the disease. However, while ART's immune-boosting effects are well-established in HIV treatment, its precise role in modulating the immune dysfunction associated with SCD remains an area of ongoing research.[7-8] Another potential benefit of ART is its

effect on the inflammatory processes seen in both diseases. Sickle cell disease is characterized by systemic inflammation, which contributes to endothelial damage, vaso-occlusion, and organ dysfunction. ART has been shown to possess anti-inflammatory properties, which could theoretically reduce the level of inflammation in co-infected individuals. This reduction in inflammation may help alleviate some of the vascular and tissue damage associated with SCD, particularly in organs such as the spleen, kidneys, and lungs. However, this potential benefit must be weighed against the possible side effects of ART, particularly those that may exacerbate hematologic complications in SCD, such as bone marrow suppression.[9-10]

The hematologic effects of ART, particularly in relation to anemia and blood cell production, are another important consideration in the management of co-infected individuals. Sickle cell disease is characterized by chronic hemolysis and anemia due to the destruction of sickle-shaped red blood cells. Some ART drugs, such as zidovudine (AZT), have been associated with bone marrow suppression, which could potentially exacerbate the anemia seen in SCD patients. Other ART medications may have neutral or even beneficial effects on hematologic parameters, but further research is needed to understand how ART influences blood cell production and how these effects might differ in individuals with SCD. This area of research is critical to optimizing ART regimens for individuals with both HIV and SCD, as some ART drugs may require adjustments or substitutions to avoid complications.[11-12] Finally, the potential for drug-drug interactions between ART and medications used to manage SCD presents another layer of complexity. Many individuals with SCD are treated with hydroxyurea, a drug that helps reduce the frequency of sickle cell crises and improve overall blood counts. However, hydroxyurea may interact with certain ART drugs, potentially leading to either reduced efficacy or increased toxicity. It is crucial for clinicians to carefully monitor drug interactions and adjust treatment plans accordingly to prevent adverse effects. Furthermore, the interaction between ART and other supportive therapies, such as blood transfusions or pain management, requires ongoing evaluation to ensure optimal patient care.[13-14]

ART and Hemolysis in Sickle Cell Disease

The impact of antiretroviral therapy (ART) on hemolysis in sickle cell disease (SCD) is an underexplored area of research, but it holds significant implications for the management of patients co-infected with HIV and SCD. Sickle cell disease is characterized by the chronic breakdown of red blood cells, leading to hemolysis, anemia, and a range of associated complications, including vaso-occlusion, pain crises, and organ damage. ART, which has revolutionized HIV management by suppressing viral replication and improving immune function, may have unintended effects on the hematologic processes in SCD patients, particularly in relation to hemolysis and red blood cell turnover. Understanding the potential effects of ART on hemolysis is critical for optimizing treatment and improving outcomes in this complex patient population.[15-16] In SCD, the hemolytic process is primarily driven by the abnormal sickling of red blood cells, which leads to their premature destruction in the bloodstream and in the spleen. This chronic hemolysis contributes to anemia, low hemoglobin levels, and the release of hemoglobin into the bloodstream, potentially leading to complications such as pulmonary hypertension, iron overload, and organ damage. ART, which can include drugs like nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INIs), has been shown to impact hematologic function in various ways. Some ART drugs, such as zidovudine (AZT), are known to cause bone marrow suppression, which could potentially exacerbate anemia in SCD patients by inhibiting erythropoiesis, thereby complicating the already existing hemolytic anemia.[17-18]

In addition to the direct effects of ART on hematopoiesis, ART may also influence the inflammatory and oxidative stress pathways that contribute to hemolysis in SCD. Chronic inflammation is a hallmark of SCD, and it contributes to endothelial dysfunction, vascular occlusion, and increased red blood cell destruction. ART's anti-inflammatory effects may theoretically reduce some of the inflammatory processes that drive hemolysis in SCD, potentially slowing the rate of red blood cell destruction. However, this is not a uniform effect, as certain ART drugs may have pro-inflammatory properties, and the complex interactions between ART and the immune system in SCD are not fully understood. Therefore, it is important to monitor patients closely for any changes in their hemolytic status, especially when introducing or changing ART regimens.[19-20]Furthermore, the role of ART in modulating oxidative stress in SCD remains a subject of interest. Oxidative stress, resulting from an imbalance between the production of reactive oxygen species and the body's ability to neutralize them, plays a crucial role in the path physiology of SCD and contributes to the early destruction of sickled red blood cells. ART's potential antioxidant effects could theoretically help mitigate oxidative damage to red blood cells, thus reducing hemolysis. On the other hand, some ART drugs might exacerbate oxidative stress, further contributing to hemolysis in SCD patients. The precise mechanisms through which ART influences oxidative stress in this population are not well defined, and further research is needed to explore whether ART has a protective or harmful effect on red blood cell survival.[21-22]

Importantly, hemolysis in SCD is not solely influenced by ART itself but also by the overall clinical management of the patient, including concomitant therapies such as hydroxyurea, blood transfusions, and pain management. Hydroxyurea, commonly used to reduce the frequency of sickle cell crises, may interact with ART drugs, potentially altering their efficacy or toxicity. For example, certain ART regimens may influence the metabolism of hydroxyurea, potentially modifying its therapeutic effects on hemolysis. Additionally, regular blood transfusions, a common practice in managing severe SCD, may interact with ART by influencing iron metabolism and potentially altering the pharmacokinetics of ART drugs. These interactions underscore the complexity of managing co-infected individuals, highlighting the need for individualized treatment strategies and careful monitoring of hematologic

parameters.[23-24] The potential for ART to influence hemolysis in SCD raises important questions about the optimization of therapy for patients with both HIV and SCD. While ART has proven to be life-saving for individuals with HIV, its effects on hemolytic processes in SCD patients are less clear and require further investigation. Clinicians managing these patients must consider the potential effects of ART on hemolysis, anemia, and red blood cell turnover, especially in the context of existing therapies for SCD. Close monitoring of hemoglobin levels, red blood cell indices, and signs of iron overload is crucial to ensure that ART does not exacerbate the already significant hematologic challenges faced by individuals with SCD.[25]

Vaso-Occlusive Crises and ART-Related Inflammation

Vaso-occlusive crises (VOC) are one of the hallmark complications of sickle cell disease (SCD), characterized by episodes of severe pain and tissue ischemia caused by the blockage of blood flow due to sickled red blood cells. These crises contribute significantly to the morbidity and reduced quality of life in individuals with SCD. Inflammation plays a crucial role in the pathophysiology of VOC, as the sickled cells trigger inflammatory responses that exacerbate endothelial dysfunction, increase leukocyte adhesion, and promote vasoconstriction. However, antiretroviral therapy (ART), which is primarily used to manage HIV infection, may influence these inflammatory pathways in individuals with both HIV and SCD. The interaction between ART-related inflammation and VOC is an area of increasing interest, as ART's effects on immune function and inflammation could have both beneficial and detrimental outcomes for patients with SCD.[26-27] ART is known to modulate immune responses in individuals living with HIV, reducing viral load and improving immune cell function. One of the primary mechanisms by which ART improves outcomes in HIV is through its anti-inflammatory effects. HIV infection induces chronic inflammation, which can aggravate various conditions, including SCD. By suppressing HIV replication and reducing immune activation, ART may help decrease overall systemic inflammation. This reduction in inflammation could potentially alleviate the severity of VOC in individuals with both HIV and SCD by reducing the inflammatory triggers that exacerbate vaso-occlusion. However, while ART may reduce HIV-related inflammation, the impact on the systemic inflammation associated with SCD itself is less well-understood.[28-29]

On the other hand, certain ART regimens may induce or exacerbate inflammation, particularly through immune reconstitution inflammatory syndrome (IRIS), a phenomenon where the immune system mounts an exaggerated inflammatory response as it recovers from HIV suppression. This reactivation of the immune system may increase the inflammatory burden in individuals with both HIV and SCD, potentially triggering or exacerbating vaso-occlusive crises. Additionally, ART-induced inflammation could contribute to endothelial dysfunction, which is a critical component in the development of VOC. The precise relationship between ART - related inflammation and VOC remains complex and may depend on the specific ART regimen used, the stage of HIV infection, and the individual patient's inflammatory profile.[30] Furthermore, the effects of ART on the endothelial cells and the vasculature in SCD are important to consider in the context of VOC. Endothelial dysfunction is a key feature of both SCD and HIV infection, and inflammation plays a major role in its development. ART's role in modulating endothelial function is still being explored. While some ART drugs have anti-inflammatory properties, others may exacerbate endothelial injury, leading to increased risk of vaso-occlusion. Additionally, the use of ART in co-infected individuals may also affect the levels of pro-inflammatory cytokines, such as TNF-α and IL-6, which are implicated in the pathophysiology of both HIV and SCD. A more detailed understanding of how ART modulates these cytokines and their contribution to VOC could provide insights into improving management strategies for co-infected individuals.[31-32]

Organ Damage and ART-Related Toxicities

Organ damage in sickle cell disease (SCD) is a well-documented consequence of the chronic vaso-occlusion, hemolysis, and inflammation associated with the disorder. Commonly affected organs include the spleen, kidneys, lungs, heart, and brain, with damage often occurring as a result of sustained ischemia, infarction, and inflammatory processes. When combined with HIV, which also contributes to immune suppression and chronic inflammation, the burden of organ damage is further compounded. Antiretroviral therapy (ART) has been a cornerstone in the treatment of HIV, improving viral suppression and immune function. However, ART-related toxicities, particularly those that affect organ systems, pose additional challenges in the management of co-infected individuals. These toxicities may interact with the pathophysiology of SCD, potentially accelerating organ damage or leading to new complications.[33-34] The kidneys are one of the most vulnerable organs in both HIV and SCD, with both conditions contributing to renal dysfunction. In SCD, kidney damage arises from microvascular occlusion, hemolysis, and proteinuria, which can eventually lead to chronic kidney disease. In HIV-infected individuals, nephropathy is a common complication, often exacerbated by the direct effects of the virus and certain ART drugs. ART-related nephrotoxicity, particularly from older drugs like tenofovir and protease inhibitors, has been well-documented. These medications can cause tubular dysfunction, renal fibrosis, and a decline in glomerular filtration rate. In co-infected individuals, the dual impact of SCD-related kidney damage and ART-related nephrotoxicity increases the risk of renal failure, complicating treatment strategies and requiring close monitoring of kidney function.[35-36]

Similarly, the cardiovascular system is affected by both SCD and HIV, and ART-related toxicities can exacerbate these effects. Sickle cell disease often leads to chronic anemia and increased blood viscosity, which can result in cardiac complications such as heart failure, arrhythmias, and pulmonary hypertension. ART, particularly with certain protease inhibitors (PIs), has been associated with dyslipidemia, insulin resistance, and atherosclerosis, which may increase the risk of cardiovascular events in co-infected

individuals. Additionally, ART-related cardio toxicity, especially with long-term use, may accelerate cardiovascular decline in patients with SCD who are already at risk for heart failure and other cardiac complications. The interaction between HIV-related immune dysfunction, SCD-associated cardiovascular stress, and ART-induced metabolic changes requires careful management to minimize further cardiovascular damage.[37-38] The liver is another organ that is susceptible to damage from both HIV and ART. Chronic HIV infection can cause liver inflammation, fibrosis, and cirrhosis, particularly when co-infected with hepatitis B or C. ART, while necessary to control HIV, may contribute to hepatic toxicity. Certain ART drugs, such as those in the nucleoside reverse transcriptase inhibitor (NRTI) class, can lead to mitochondrial toxicity and liver enzyme abnormalities. This toxicity may be compounded in individuals with SCD, where chronic hemolysis and the resulting increased bilirubin load can already strain liver function. In co-infected individuals, liver function must be carefully monitored, as ART-related liver toxicity can exacerbate the existing liver damage caused by SCD-related hemolysis, potentially leading to further complications such as cholestasis, hepatic steatosis, or liver failure.[39-40]

The central nervous system (CNS) is particularly vulnerable in both SCD and HIV-infected individuals. Sickle cell disease frequently causes cerebrovascular events, including strokes, which are common in pediatric patients with the condition. Chronic ischemia and microinfarcts in the brain lead to cognitive decline, developmental delays, and long-term neurological deficits. HIV-related neurocognitive disorders, which range from mild cognitive impairment to full-blown AIDS-related dementia, also contribute to CNS dysfunction. Certain ART drugs, particularly those in the nucleoside reverse transcriptase inhibitor (NRTI) class, have been associated with neurotoxicity, leading to peripheral neuropathy and other CNS complications. In co-infected individuals, the combined effects of SCD-related cerebrovascular disease, HIV-related neurocognitive decline, and ART-induced neurotoxicity may significantly increase the burden of neurological impairment.[41-42]

Pulmonary complications are another area of concern for individuals with both HIV and SCD. Sickle cell disease can cause acute chest syndrome (ACS), which is a leading cause of morbidity and mortality in these patients. The damage to lung tissue from vaso-occlusion, infection, and infarction leads to impaired gas exchange, reduced lung function, and respiratory failure. In HIV-infected individuals, lung damage may be exacerbated by opportunistic infections, such as pneumonia and tuberculosis, as well as ART-related pulmonary toxicity. Protease inhibitors and some NRTIs are known to have adverse effects on lung tissue, potentially leading to interstitial lung disease or pulmonary hypertension. In co-infected individuals, the combined impact of SCD-related pulmonary damage and ART-related lung toxicity heightens the risk of respiratory failure, making pulmonary function monitoring essential in managing this patient population.[43]

Impact of ART on Immune Function in SCD Patients

The immune system plays a critical role in the pathogenesis of both sickle cell disease (SCD) and HIV, with chronic inflammation and immune dysregulation being common features of both conditions. In individuals with SCD, immune function is often compromised due to ongoing inflammation, hemolysis, and the release of pro-inflammatory cytokines. HIV infection further exacerbates immune dysfunction by directly targeting and depleting CD4+ T-cells, leading to an impaired immune response. Antiretroviral therapy (ART), the cornerstone of HIV treatment, aims to restore immune function by suppressing viral replication, reducing inflammation, and promoting immune reconstitution. However, the impact of ART on immune function in patients with both HIV and SCD remains complex and requires careful consideration of the interplay between these two diseases.[44] ART plays a crucial role in improving immune function in HIV-infected individuals by decreasing the viral load and allowing the immune system, particularly CD4+ T-cells, to recover. In the context of SCD, where immune dysregulation is already present due to the chronic inflammatory state, ART may help to mitigate some of the immune abnormalities associated with both conditions. For instance, ART has been shown to reduce the systemic inflammation that characterizes HIV infection, which may indirectly improve immune function in SCD patients by reducing the levels of inflammatory cytokines such as IL-6, TNF-α, and CRP. These cytokines are known to play a role in the pathogenesis of vaso-occlusive crises (VOC), a hallmark complication of SCD, by promoting endothelial dysfunction and leukocyte adhesion. By reducing the inflammatory burden, ART may contribute to a reduction in the frequency and severity of VOC in co-infected individuals.[45]

However, while ART can improve immune function in HIV, it may not fully restore immune homeostasis in patients with SCD. Sickle cell disease itself is associated with chronic immune activation, characterized by an overactive innate immune response, altered T-cell function, and an increased susceptibility to infections. ART may not completely reverse these immune abnormalities in SCD patients, particularly the altered function of monocytes, neutrophils, and other innate immune cells that are involved in the inflammatory processes of SCD. Moreover, certain ART regimens, especially those that include protease inhibitors (PIs) or nucleoside reverse transcriptase inhibitors (NRTIs), may induce immune activation or contribute to immune reconstitution inflammatory syndrome (IRIS). IRIS is a phenomenon in which the recovery of immune function triggers an exaggerated inflammatory response, potentially worsening immune dysregulation and exacerbating complications such as VOC and other SCD-related symptoms.[46] In addition to immune reconstitution, ART has been shown to influence the function of regulatory T-cells (Tregs), which play a critical role in maintaining immune tolerance and controlling excessive inflammation. In individuals with HIV and SCD, ART may help restore the balance between pro-inflammatory and anti-inflammatory immune responses by promoting Treg function and suppressing the activation of auto reactive T-cells. However, the effect of ART on Treg function in SCD patients remains unclear, and more research is needed to determine whether ART can effectively regulate the immune system to prevent

excessive inflammation and tissue damage in SCD.[47] The interplay between ART and immune function in individuals with both HIV and SCD is further complicated by the potential for ART-related toxicities. For example, certain ART drugs can have direct toxic effects on immune cells or disrupt the function of the bone marrow, where hematopoiesis occurs. This can lead to cytopenias, including neutropenia, anemia, or thrombocytopenia, which may exacerbate the already existing hematologic abnormalities in SCD patients. ART-induced immune suppression or bone marrow toxicity may increase the risk of infections, a concern in SCD patients who are already at higher risk for infections due to splenic dysfunction and compromised immune responses. The potential for ART-related bone marrow toxicity in SCD patients requires careful monitoring and adjustment of treatment regimens to prevent adverse outcomes.[48]

Conclusion

The management of individuals with both HIV and sickle cell disease (SCD) presents a unique set of challenges, particularly when considering the impact of antiretroviral therapy (ART) on immune function. ART plays a vital role in improving immune function and reducing HIV-related inflammation, which may help mitigate some of the immune abnormalities in co-infected patients. However, its effect on SCD-related immune dysfunction remains complex, as ART may not fully restore immune balance, especially given the chronic inflammatory state and immune dysregulation inherent in SCD. Furthermore, ART-related toxicities, including potential impacts on immune cells, bone marrow function, and organ systems, can complicate treatment, requiring careful monitoring and adjustments to minimize adverse outcomes. The interplay between HIV, SCD, and ART highlights the need for a personalized, multidisciplinary approach to care. Clinicians must carefully consider ART regimens, monitor for immune reconstitution inflammatory syndrome (IRIS), and address potential ART-induced toxicities that could worsen the clinical course of both HIV and SCD. Additionally, ongoing research into the long-term effects of ART in co-infected patients is essential to further understand its impact on immune function and to develop strategies that minimize complications while maximizing therapeutic benefits. Ultimately, achieving optimal outcomes for patients with both HIV and SCD requires a nuanced understanding of the complex interactions between these diseases and the treatments used to manage them.

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