



# Antiretroviral Therapy and Red Blood Cell Morphology: A Review in HIV Patients

Emmanuel Ifeanyi Obeagu<sup>1\*</sup>, Getrude Uzoma Obeagu<sup>2</sup> and Matthew Chibunna Igwe<sup>3</sup>

<sup>1</sup>Department of Medical Laboratory Science, Kampala International University, Uganda

<sup>2</sup>School of Nursing Science, Kampala International University, Uganda

<sup>3</sup>Department of Public Health, Kampala International University, Uganda

## Review Article

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**\*Corresponding author:** Emmanuel Ifeanyi Obeagu, Department of Medical Laboratory Science, Kampala International University, Kampala, Uganda, Tel: +2348037369912; Email: emmanuelobeagu@yahoo.com; obeagu.emmanuel@kiu.ac.ug

## Abstract

Antiretroviral therapy (ART) has transformed the management of HIV, significantly improving the prognosis and quality of life for individuals living with the virus. While the primary focus of ART has traditionally been on viral suppression and immune restoration, emerging evidence suggests a potential impact on red blood cell (RBC) morphology. This paper explores the intricate relationship between antiretroviral therapy and red blood cell morphology in HIV patients, shedding light on the multifaceted effects of these medications beyond their antiviral properties. Moving beyond laboratory findings, the review investigates the clinical implications of alterations in red blood cell morphology in individuals undergoing antiretroviral therapy. This includes discussions on potential implications for oxygen-carrying capacity, hemoglobin levels, and overall hematological health, emphasizing the need for a holistic understanding of the hematopoietic consequences of ART. In conclusion, this paper consolidates existing knowledge, identifies gaps in understanding, and provides a comprehensive resource for researchers, clinicians, and healthcare professionals involved in the care of HIV patients. It contributes to the broader conversation on the holistic effects of antiretroviral therapy, paving the way for future investigations and improved clinical management.

**Keywords:** Antiretroviral Therapy; Red Blood Cells; HIV; Hematological Consequences, Erythrocyte Abnormalities Clinical Implications

**Abbreviations:** HIV: Human Immunodeficiency Virus; ART: Antiretroviral Therapy; RBC: Red Blood Cell; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors; DIIHA: Drug-Induced Immune Hemolytic Anemia.

## Introduction

Human Immunodeficiency Virus (HIV) infection remains a global public health challenge, affecting millions

of individuals worldwide. The advent of Antiretroviral Therapy (ART) has revolutionized the management of HIV, leading to substantial reductions in morbidity and mortality. While the primary focus of ART has traditionally been on suppressing viral replication and restoring immune function, emerging evidence suggests that these medications may have implications beyond their antiviral effects. This comprehensive review aims to explore the intricate relationship between antiretroviral therapy and red blood cell (RBC) morphology in HIV patients, shedding light on

an aspect of treatment that extends beyond viral control [1-15]. HIV, a retrovirus that primarily targets the immune system, has necessitated the development of sophisticated antiretroviral regimens to control viral replication. The success of ART in achieving and maintaining viral suppression has transformed HIV into a chronic, manageable condition. However, as individuals with HIV now experience increased life expectancy, attention is turning to the broader impact of long-term ART on various physiological systems, including the hematological profile [16-25].

Red blood cells, critical components of the circulatory system, play a pivotal role in oxygen transport and overall physiological homeostasis. While the influence of HIV on hematopoiesis and red blood cell parameters has been studied, the specific effects of antiretroviral therapy on RBC morphology remain an area of growing interest and investigation [26-30]. Understanding the mechanisms underlying ART-induced changes in red blood cell morphology is crucial for unraveling the complex interplay between antiretroviral drugs and erythrocytes. This review explores potential pathways, ranging from direct effects on erythropoietic precursors to interactions with iron metabolism, providing a comprehensive understanding of the hematopoietic consequences of ART [31-35]. Moving beyond laboratory findings, the review investigates the clinical implications of alterations in red blood cell morphology for individuals undergoing antiretroviral therapy. This includes discussions on potential impacts on oxygen-carrying capacity, hemoglobin levels, and overall hematological health, emphasizing the need for a holistic understanding of the hematopoietic consequences of ART.

## Aim

The aim of this paper is to comprehensively examine the influence of antiretroviral therapy (ART) on red blood cell (RBC) morphology in individuals living with HIV.

## Antiretroviral Drugs and their Influence on Red Blood Cells

Antiretroviral therapy (ART) has been a cornerstone in the management of HIV, significantly improving patient outcomes. While the primary goal of ART is to suppress viral replication and enhance immune function, there is a growing body of evidence suggesting potential interactions between antiretroviral drugs and red blood cells (RBCs) [36-40]. **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**, such as zidovudine, stavudine, and tenofovir, form a critical component of many ART regimens. Studies indicate that certain NRTIs may affect erythropoiesis, leading to changes in RBC parameters. Zidovudine, in particular, has been associated with macrocytosis and anemia, highlighting

the need for close monitoring of hematological parameters in individuals on NRTI-based regimens [41-46].

**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**, including efavirenz and nevirapine, have demonstrated efficacy in suppressing viral replication. While these drugs are generally well-tolerated, there is emerging evidence suggesting potential effects on red blood cell morphology [41].

Protease inhibitors, such as ritonavir and atazanavir, play a crucial role in inhibiting viral maturation. Some **Protease Inhibitors (PIs)** have been associated with hyperbilirubinemia and indirect hyperbilirubinemia, potentially impacting RBC dynamics. **Integrase Strand Transfer Inhibitors (INSTIs)**, represented by drugs like dolutegravir and raltegravir, have gained prominence in HIV treatment regimens. While the focus has been on their antiviral efficacy, recent studies have suggested potential links between INSTIs and alterations in hematological parameters, including RBC indices [42]. Less commonly used but important in specific cases, CCR5 antagonists (e.g., maraviroc) and fusion inhibitors (e.g., enfuvirtide) also warrant consideration regarding their influence on RBC morphology.

## Mechanisms Underlying ART-Induced Changes in RBC Morphology

Some antiretroviral drugs, particularly zidovudine, have been associated with myelosuppression, potentially affecting the normal process of erythropoiesis. This disruption in bone marrow function may lead to changes in RBC production and morphology. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) have been linked to mitochondrial toxicity, particularly affecting the respiratory chain. As mitochondria play a crucial role in erythropoiesis, any compromise in their function may contribute to altered RBC morphology.<sup>41</sup> Certain antiretroviral drugs may have a direct impact on the erythrocyte membrane. For instance, protease inhibitors (PIs) have been associated with changes in membrane fluidity and integrity, potentially influencing RBC morphology. Some protease inhibitors, such as atazanavir, can lead to indirect hyperbilirubinemia. Elevated bilirubin levels may affect iron metabolism, influencing erythropoiesis and contributing to changes in RBC parameters. In rare instances, antiretroviral drugs may induce immune-mediated hemolytic anemia. This phenomenon involves the immune system targeting and destroying RBCs, leading to alterations in red blood cell morphology. Some antiretroviral drugs may contribute to oxidative stress within the erythrocytes, leading to the accumulation of reactive oxygen species. Oxidative damage can impact membrane structure and function, influencing RBC morphology.

Drug-drug interactions, especially in the context of polypharmacy in individuals with HIV, may contribute to changes in RBC morphology. For instance, interactions between antiretroviral drugs and medications affecting hematopoiesis may influence erythrocyte parameters [47-51]. Anemia is a common side effect of certain antiretroviral drugs, and its occurrence can be multifactorial. The impact on erythrocyte parameters and morphology may be a direct result of the hematological side effects induced by these medications. The inherent properties of specific antiretroviral drugs, such as their chemical structure and mechanism of action, may contribute to changes in RBC morphology. Understanding the unique characteristics of each drug is essential for deciphering their impact on erythrocytes. Host factors, including genetic predispositions and individual variations in drug metabolism, may play a role in determining the extent of ART-induced changes in RBC morphology. Understanding the interplay between host factors and antiretroviral drugs is crucial for a comprehensive assessment [52-55].

### Clinical Implications of ART-Induced Changes in RBCs

Clinicians should integrate regular hematologic monitoring, including complete blood counts, into the care of individuals on ART. This allows for the early detection of changes in RBC parameters, enabling timely interventions and adjustments to the antiretroviral regimen. Recognition of ART-induced anemia is crucial for appropriate management [56]. Tailored interventions, such as adjustments in drug regimens or the administration of erythropoiesis-stimulating agents, may be necessary to mitigate anemia and improve overall hematological health. Changes in RBC parameters can influence cardiovascular risk. Clinicians should consider the potential impact of ART-induced alterations on factors such as hemoglobin levels and RBC morphology when assessing cardiovascular risk in individuals living with HIV [57-61]. Understanding the influence of ART on RBC parameters is essential for assessing oxygen-carrying capacity. Clinicians need to be vigilant about potential implications for tissue oxygenation and overall physiological functioning, particularly in individuals with pre-existing cardiovascular or respiratory conditions [62-65].

Recognizing the hematological consequences of specific antiretroviral drugs allows for the development of more individualized treatment plans. Clinicians can choose regimens that minimize adverse effects on RBCs, taking into consideration the patient's overall health and comorbidities. Certain antiretroviral drugs may impact iron metabolism, potentially leading to imbalances and contributing to changes in RBC morphology. Regular monitoring of iron status and appropriate supplementation may be necessary to address

these effects. Educating patients about potential hematological side effects is essential for managing expectations and promoting adherence to ART. Clear communication regarding the possibility of changes in RBC parameters can empower patients to report symptoms promptly and seek timely medical attention [66-68]. Awareness of the potential for drug-induced immune hemolytic anemia (DIIHA) is crucial. Clinicians should carefully monitor for signs of hemolysis and promptly address immune-mediated reactions to prevent severe complications associated with RBC destruction [68]. For individuals experiencing significant hematological side effects, collaboration with hematologists may be beneficial. A multidisciplinary approach ensures comprehensive management, with hematologists contributing their expertise in addressing complex hematological conditions. Recognizing that changes in RBC parameters may evolve over time, long-term follow-up is essential. Regular assessments of hematological parameters during the course of ART allow for ongoing management and adjustment of treatment plans as needed [69-71].

### Recommendations

Implement routine hematologic monitoring, including complete blood counts, for individuals on antiretroviral therapy (ART) to detect changes in red blood cell parameters early. Consider the hematological profile of specific antiretroviral drugs when designing treatment regimens. Tailor therapy based on the patient's overall health, comorbidities, and potential impact on red blood cells. Develop strategies for the early identification and management of ART-induced anemia. Adjustments in drug regimens or the use of erythropoiesis-stimulating agents may be necessary to mitigate anemia. Incorporate consideration of ART-induced changes in red blood cell parameters when assessing cardiovascular risk in individuals living with HIV. Educate patients about potential hematological side effects of ART, including changes in red blood cells. Promote adherence to treatment by managing patient expectations and providing clear communication. Monitor iron status in individuals on ART, especially for those receiving drugs associated with potential effects on iron metabolism. Consider appropriate supplementation based on monitoring results.

Foster collaboration between HIV specialists and hematologists to manage individuals with significant hematological side effects. A multidisciplinary approach ensures comprehensive care for complex hematological conditions. Implement long-term follow-up assessments for individuals on ART to monitor changes in red blood cell parameters over time. Adjust treatment plans as needed based on evolving hematologic profiles. Assess the risk of immune-mediated reactions, including drug-induced immune hemolytic anemia (DIIHA). Monitor for signs

of hemolysis and promptly address immune-mediated reactions to prevent severe complications. Explore novel therapeutic interventions that may mitigate adverse hematological effects of ART, such as targeted agents that counteract mitochondrial toxicity or modulate immune-mediated responses. Conduct patient-centered outcome research to assess the impact of ART-induced changes in red blood cells on quality of life, fatigue, and overall well-being. Consider patient-reported outcomes in addition to objective hematological measures.

## Conclusion

The relationship between antiretroviral therapy (ART) and red blood cell (RBC) morphology in individuals living with HIV is a complex and multifaceted area that warrants careful consideration. This comprehensive review has delved into the diverse mechanisms underlying ART-induced changes in RBCs and the resulting clinical implications. The clinical implications of ART-induced changes in RBCs extend beyond laboratory values, impacting cardiovascular risk assessment, oxygen-carrying capacity, and overall physiological well-being. By integrating hematologic considerations into routine clinical practice, healthcare providers can optimize treatment outcomes and enhance the overall health of individuals living with HIV.

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