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Prevalence, Risk Factors, Clinical Significance and Management of Anaemia among People Living with HIV/AIDS: A Review

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Abstract

Anaemia is a common haematological complication among those who have human immunodeficiency virus (HIV) and is linked to a reduced quality of life, faster disease progression and higher mortality rates. This review looks at the extent of the problem, the mechanisms involved, the risk factors, the significance and the management of anaemia in people with HIV/AIDS, using evidence from sub-Saharan African areas, including Nigeria. Anaemia in HIV patients is due to a number of factors and can be caused by chronic immune activation and inflammation, by altered iron regulation via the interleukin-6-hepcidin pathway, by bone-marrow dysfunction, by decreased erythropoiesis, by a shorter red-cell survival time, by nutritional deficiencies, by opportunistic infections, by blood loss, by renal disease and by medication-related toxicity. The occurrence of anaemia depends on age, sex, nutritional status, CD4 cell count, viral

load, the stage of the disease and the use of antiretroviral therapy (ART). Even though antiretroviral therapy can help to reduce HIV-related anaemia by suppressing viral replication and decreasing inflammation, some of the drugs, especially zidovudine, may lead to bone-marrow suppression. Anaemia is still common among those who are on treatment, particularly in settings with limited resources, and more severe anaemia is connected with worse outcomes and a higher risk of death. Effective management therefore involves identifying and treating the underlying causes, monitoring haemoglobin and other haematological indices, dealing with nutritional deficiencies and co-infections, and reviewing any medicines that could have a myelosuppressive effect. The review stresses the importance of assessing anaemia as part of HIV care in areas where the burden of the disease is high.

Keywords: Anaemia, HIV/AIDS, Antiretroviral Therapy, Risk Factors, Haematological Abnormalities, Sub-Saharan Africa, Bone-marrow Dysfunction

Introduction

Anaemia is one of the most frequently met haematological problems in clinical practice and is usually seen as a sign of either poor nutrition or poor general health^[1]. By definition, anaemia is the condition in which the haemoglobin concentration falls below the recommended lower limits set for age, sex and physiological status, the limits most often being those established by the World Health Organization^[2]. Haemoglobin is the pigment in the red blood cell that is responsible for carrying oxygen, and when its concentration is less than the amount required by the body, the blood's ability to carry oxygen is reduced, leading to the clinical symptoms of fatigue, weakness, paleness, shortness of breath when exerting oneself and a decreased capacity for work^[3]. Anaemia is rarely a disease on its own; instead it is a sign of an underlying disorder and in clinical practice it is often due to more than one factor^[4]. The main cause of anaemia globally is dietary iron deficiency, which is responsible for about half of all cases, then come other nutritional deficiencies, chronic diseases, parasitic infections such as malaria, haemoglobinopathies and blood loss^[5]. In an individual patient, more than one of these mechanisms may be at work, and the difference between "health" and "disease" is made more difficult by the fact that haemoglobin levels in healthy populations are lower and more spread out in tropical areas than in temperate ones^[4].

The classification and grading of anaemia

To enable standardised diagnosis and facilitate international comparisons, the World Health Organisation sets criteria for anaemia based on haemoglobin levels in people living at sea level: 130 g/L for men aged 15 years and over, 120 g/L for non-pregnant women, 110 g/L for pregnant women, and 110, 115 and 120 g/L for children aged 6 months to under 5 years, 5 to

under 12 years and 12 to under 15 years respectively [2]. Since haemoglobin concentration is affected by iron and other nutrient deficiencies, inflammation, kidney disease and genetic disorders, these thresholds represent the 5th centile of the haemoglobin distribution in apparently healthy populations, a standard which the WHO is at present reviewing in view of new reference data [6]. Recent statistical studies covering the whole life cycle have generally supported the current WHO cut-off values, even though the estimates for adult men (5th centile of 135.1 g/L) and for children aged 6 to 23 months (104.5 g/L) indicate that adjustments to some of the thresholds might be necessary [7, 6]. After anaemia has been diagnosed, it is classified according to how severe it is. The WHO classification system states that anaemia in non-pregnant adult women is considered mild if the level is between 11.0 and 11.9 g/dL, moderate if it is between 8.0 and 10.9 g/dL and severe when it is below 8 g/dL; the corresponding ranges for adult men are 11.0 to 12.9 g/dL (mild), 8.0 to 10.9 g/dL (moderate) and below 8 g/dL (severe) (Table 1) [8].

Table 1: WHO classification of anaemia according to haemoglobin concentration

Population group	No anaemia (g/dL)	Mild anaemia (g/dL)	Moderate anaemia (g/dL)	Severe anaemia (g/dL)
Children 6–23 months	≥10.5	9.5–10.4	7.0–9.4	<7.0
Children 24–59 months	≥11.0	10.0–10.9	7.0–9.9	<7.0
Children 5–11 years	≥11.5	11.0–11.4	8.0–10.9	<8.0
Adolescents 12–14 years – girls	≥12.0	11.0–11.9	8.0–10.9	<8.0
Adolescents 12–14 years – boys	≥12.0	11.0–11.9	8.0–10.9	<8.0
Young/non-pregnant women 15–65 years	≥12.0	11.0–11.9	8.0–10.9	<8.0
Young men 15–65 years	≥13.0	11.0–12.9	8.0–10.9	<8.0

Source: Adapted from [8]

Global Burden of Anaemia

Anaemia is a significant global public health issue and is believed to be affecting nearly two billion people, which is about 25% of the world's population, the vast majority of them living in poor-resource countries [5]. The Global Burden of Disease Study 2019 found that the global prevalence of anaemia in all age groups was 22.8% in 2019, a drop from 27.0% in 1990; yet, due to population growth, the total number of cases increased from 1.42 billion in 1990 to 1.74 billion in 2019 [9]. In 2019 the global age-standardised prevalence rate was 23,176.2 per 100,000 people, reflecting a 13.4% reduction between 1990 and 2019 [10]. The condition affects approximately 40% of children and 30% of women of reproductive age [10] with estimates from 2019 showing 39.7% in children less than five years of age and 30.1% in women of reproductive age worldwide [9, 11]. By 2021 the global prevalence of anaemia in all age groups had reached 24.3%, an improvement on the 28.2% recorded in 1990, and anaemia was responsible for an estimated 52.0 million years lived with disability [12]. The greatest burden of the disease is found in Western sub-Saharan Africa, South Asia and Central sub-Saharan Africa [9] and the burden is inversely related to the socio-demographic index; the World Health Organization estimates that 66% of pregnant women in Africa have anaemia [12]. Dietary iron deficiency, haemoglobinopathies, haemolytic anaemia and neglected tropical diseases are the

main underlying causes, accounting for 84.7% of anaemia-related disability [12]. These figures are the reason why reducing anaemia among women of reproductive age by 50% is a formal WHO Global Nutrition Target [11].

Concept of HIV/AIDS

Human immunodeficiency virus is a retrovirus which infects and gradually destroys the CD4-positive T-lymphocytes, the cells that play a central role in coordinating the immune response. The immunodeficiency that results makes the host vulnerable to a variety of opportunistic infections and cancers that are characteristic of acquired immunodeficiency syndrome, the most advanced phase of HIV infection. HIV can be passed on through unprotected sexual intercourse, via the transfusion of blood or blood products that are contaminated, by sharing contaminated needles and other equipment used for injection, and from mother to child during pregnancy, at childbirth or through breastfeeding. Since the first cases were identified in the early 1980s, HIV infection has changed from being a rapidly lethal disease to a chronic and manageable one in situations where antiretroviral therapy is available, even though the infection still cannot be cured and demands lifelong treatment [13]. Particularly relevant to this study, HIV infection is linked to a broad range of haematological abnormalities, anaemia being the most common, this reflecting both the direct and indirect effects of the virus on the bone marrow and on erythropoiesis [14].

The global and regional epidemiology of HIV/AIDS

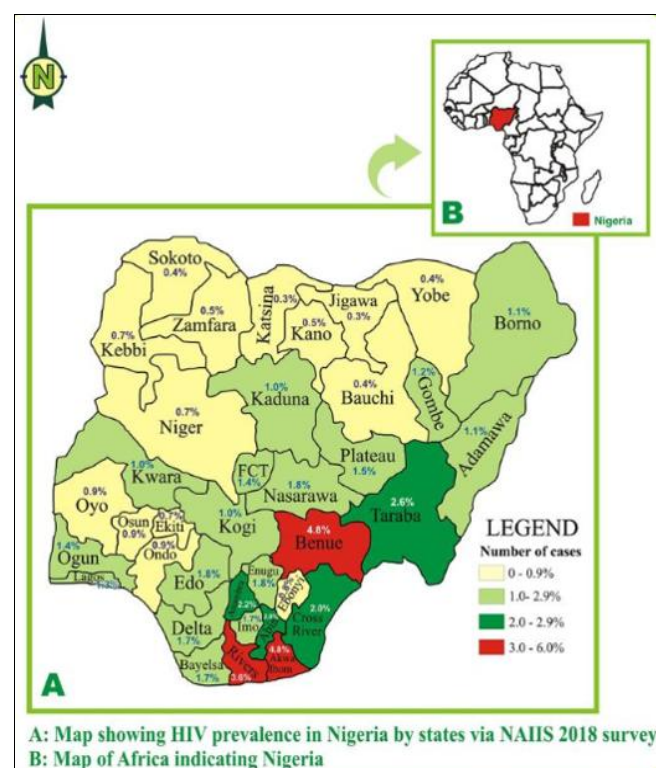
HIV/AIDS is still one of the most significant infectious disease challenges of the modern age. By the end of 2024, it was estimated that 40.8 million (95% range 37.0–45.6 million) people worldwide were living with HIV, 77% of them being on antiretroviral therapy and 73% having suppressed viral loads [13]. Some 1.3 million people acquired HIV in 2024 that is 40% less than in 2010 and 630,000 people died from AIDS-related causes, representing a 54% decrease since 2010 [13]. While progress towards the 95–95–95 targets for testing and treatment has been considerable it has been uneven: In 2024, about 87% of people living with HIV knew their status, 89% of those who knew their status were on antiretroviral therapy (ART), and 94% of those on treatment had suppressed viral loads [13]. Sub-Saharan Africa carries the highest burden, hosting more than 60% of all people living with HIV and accounting for half of all new infections globally; the region saw a 56% reduction in new infections between 2010 and 2024, which helped lead to a rise in life expectancy from 56.5 years in 2010 to 62.3 years in 2024 [13]. The Global Burden of Disease Study 2019 estimated that in 2019 there were 36.8 million people living with HIV worldwide, with the reductions in new cases and deaths mainly attributable to sub-Saharan Africa [15]. Nevertheless, more than 0.5% of the world's population is still infected, approximately 5,000 new infections occur every day, and incidence is once again increasing in certain areas of North America, Europe, Latin America and eastern Europe and central Asia [16].

HIV/AIDS in Nigeria

Nigeria has one of the biggest HIV epidemics in the world. Although the national rate is relatively low (1.4% among adults 15–49 years of age as of the end of 2020 and estimated at 1.36% among adults 15–64 years of age in the

2018 Nigeria HIV/AIDS Indicator and Impact Survey), the country's large population makes it second in the world for the total number of people affected by HIV and fourth in the HIV burden overall, with about 1.8 million people living with HIV as of 2019 [17, 18, 19]. Okoroiwu *et al.*, (2022) [19] (Fig 1) reported a national HIV prevalence of about 1.4% with higher prevalence in Akwa Ibom (5.6%), Benue (4.9%), Rivers (3.8%), Taraba (2.7%) and Anambra (2.7%). However, Jigawa and Katsina recorded the lowest prevalence at about 0.3%. The uneven distribution of the geographic burden shows that HIV infection is not evenly distributed in Nigeria and some states may be carrying a disproportionately higher burden than others.

A recent analysis of data from national surveys reported an HIV prevalence of 1.58% (95% CI 1.52–1.64) in Nigeria [20]. The impact is highly concentrated and the distribution is uneven: Benue State (5.37%) and Akwa Ibom State (5.07%) have the highest rates, while Yobe (0.30%), Katsina (0.32%) and Jigawa (0.37%) have the lowest [20]; the South-South region has the highest prevalence at the zonal level of 2.84% [20], and six states account for 41% of all people living with HIV [17]. In the past, national prevalence increased from 1.8% in the first sentinel survey carried out in 1991 to a peak of 5.8% in 2001 before dropping steadily to 3.4% by 2013 [19]. In 2018 the national coverage of antiretroviral therapy was estimated at 45.3% (95% UI 42.8–48.0) [18], and it was estimated that about half of the Nigerians living with HIV did not know their status [17] a situation which highlights the continued need for studies conducted in health facilities regarding the clinical complications of HIV, such as anaemia.



Source: Adopted from [19]

Fig 1: HIV prevalence in Nigeria by states

Pathophysiological Mechanisms of HIV-Associated Anaemia

The pathophysiology of anaemia in infection with HIV

Anaemia is the most common haematological complication associated with HIV infection and acts both as an indicator of the progression of the disease and as an independent factor affecting health outcomes [21]. In terms of red cell kinetics, the pathophysiology of anaemia can be divided into three basic mechanisms: Increased destruction of red blood cells, decreased production of red blood cells, and ineffective production of red blood cells [22]. The bone marrow, the primary site of hematopoiesis, undergoes considerable changes during HIV infection (Table 2) [23], thus greatly affecting erythropoiesis through direct viral effects, inflammatory processes and dysregulation of the cytokine network [21].

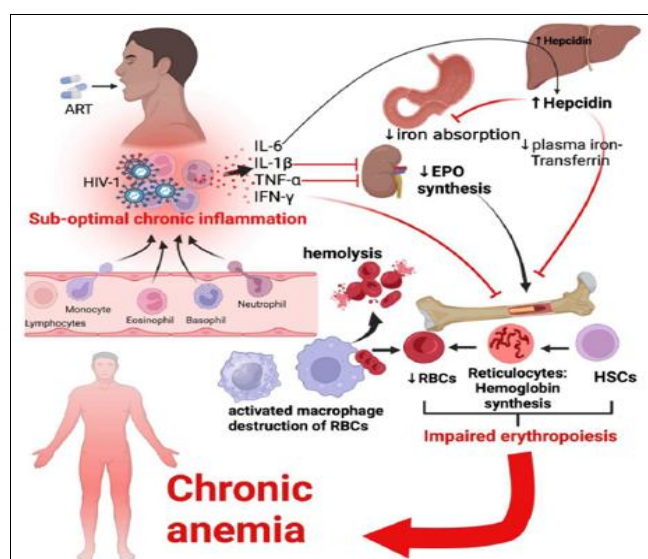
Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV) and is characterised by the development of opportunistic infections and tumours [24], as well as a progressive and fatal weakening of the immune system (WHO, 2026). HIV infection is characterised by immune system dysfunction and a reduction in CD4+ T cell count and activity [25]. Additionally, it is crucial to keep in mind that HIV may impact various cell types. The majority of AIDS patients and some HIV-positive naive individuals develop peripheral blood cytopenias, such as anaemia, neutropenia, and thrombocytopenia, in the early stages of the disease's progression, particularly when high plasma levels of HIV RNA are detectable in relation to the progressive depletion of CD4+ T lymphocytes [24]. Anaemia is often diagnosed with a laboratory test based on a reduction in haemoglobin (Hb) value and erythrocyte count. The symptoms of anaemia in HIV-positive people are identical to those in HIV-negative patients [24].

A key theoretical aspect of HIV related anemia is that it is similar to the 'anaemia of chronic disease' as it is characterized by an impaired erythropoietin response to anemia and the inability to mobilize iron from hepatic stores (Fig 2) [26]. Erythropoietin (EPO) synthesis is inhibited and hepcidin synthesis is increased in the liver by inflammatory cytokines generated by activated and HIV-1-infected cells. This leads to a decrease in erythropoiesis, which eventually results in anaemia. RBCs are destroyed by activated macrophages. HSCs, haematopoietic stem cells; RBCs, red blood cells; EPO, erythropoietin; TNF- α , tumour necrosis factor alpha; ART, antiretroviral therapy [26]. HIV directly and indirectly affects hematopoietic stem and progenitor cells that affect the balance in the bone marrow and prevent proliferation and differentiation in all lineages. High levels of plasma HIV-1 RNA and low CD4 count (<200 cells/ μ l) are both associated with increased risk of anemia [27]. It is important, however, that the CD34+ bone marrow progenitors from HIV-infected patients are generally free of proviral DNA, showing that HIV interferes with haematopoiesis mainly indirectly rather than by productively infecting the progenitor cells themselves [28]. The difference between direct and indirect mechanisms is the one that guides the subsections that follow.

Table 2: Pathophysiology of HIV-Induced Anemia

Mechanism	Description	Clinical Implications
Direct HIV Bone Marrow Suppression	HIV infects stromal and progenitor cells, impairing erythropoiesis and marrow cellularity	Normocytic anemia; associated with low reticulocyte count and pancytopenia in advanced cases.
Chronic Inflammation & Cytokine Release	Elevated TNF- α , IL-1, and IFN- γ suppress erythropoietin response and iron utilization.	Anemia of chronic disease with normocytic, normochromic features; low serum iron but normal/high ferritin.
Opportunistic Infections	Infections such as parvovirus B19, CMV, TB, and fungal pathogens infiltrate or suppress marrow.	Severe or aplastic anemia; may be reversible with infection control.
Nutritional Deficiencies	Common deficiencies include iron, folate, and vitamin B12 due to malabsorption or poor intake.	Microcytic (iron deficiency) or macrocytic (B12/folate deficiency) anemia.
ART-Related Myelotoxicity	Drugs like zidovudine (AZT) inhibit DNA synthesis in erythroid precursors.	Macrocytic anemia; dose-dependent; may resolve with drug substitution.
Autoimmune Hemolysis	HIV-related immune dysregulation may trigger hemolytic anemia or pure red cell aplasia.	Elevated LDH, indirect bilirubin; low haptoglobin; positive Coombs test.
Renal Insufficiency	HIV-associated nephropathy reduces erythropoietin production.	Normocytic anemia with low reticulocyte count; often requires ESA therapy.

Source: Adopted from [23]



Source: Adopted from [26]

Fig 2: Chronic Anemia in treated HIV infection

Immune activation and chronic inflammation

The main inflammatory mechanism by which HIV leads to anaemia is mediated by hepcidin and involves the sequestration of iron. Anemia that occurs during infection is caused by several factors including inflammatory cytokines such as IL-6 that induce hypoferremia through hepcidin production. IL-6 is the main regulator of hepcidin production in the liver and disruption of iron homeostasis is a common feature of chronic inflammatory and infectious diseases [29]. Importantly, this state of inflammation continues even when the virus is suppressed: Individuals living with HIV have a remaining chronic immune activation and inflammation, which are now known to be major causes of haematological problems such as anaemia [30]. High levels of IL-6 lead to an excessive production of hepcidin, which then binds to the iron transporter ferroportin and causes iron to be retained in storage cells, resulting in a functional iron deficiency in which iron is present in the stores but cannot be used for erythropoiesis [30]. In groups of children receiving ART, this mechanism is evident in the way the anaemia is presented, since 72.2% of them have normocytic anaemia this being the typical form of anaemia caused by hepcidin-mediated iron sequestration [30]. Data from prospective studies show that hepcidin induction is part of the pathogenically significant systemic

inflammatory response that occurs during HIV-1 infection: When acute viraemia is detected, hepcidin levels rise and plasma iron levels fall, and hepcidin stays high both in cases of untreated chronic infection and in people receiving antiretroviral therapy [31]. In addition to hepcidin, inflammatory cytokines have a direct inhibitory effect on erythroid progenitor cells in the bone marrow and can reduce the erythropoietin response, thus further disrupting erythropoiesis [30]. Persistent immune activation and chronic inflammation are now accepted as key features of HIV infection and make a significant contribution to the pathogenesis of the disease and to its complications [21]. The causes of this include microbial translocation from a damaged gastrointestinal tract, low-level viraemia and co-infections such as cytomegalovirus and hepatitis C virus [32]. These inflammatory biomarkers remain elevated even while on antiretroviral therapy and are associated with an increased risk of morbidity and mortality [33].

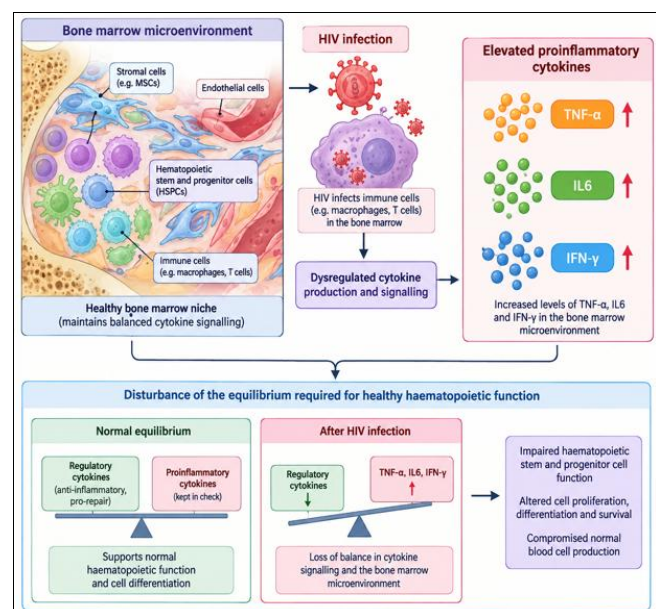
You can see how important this pathway is in the case of people living with HIV who achieve viral suppression. In a cohort of 155 persons with HIV and viral suppression, anemia was present in 28.4% and was significantly more common in women 40.9% versus 15.6%. Interferon-gamma was the only cytokine found to be significantly increased in those with anemia [34]. Elevated levels of IL-6, CRP, and D-dimer have also been linked to persistent mild chronic anaemia even when treatment is suppressive, as have measures of monocyte activation [29]. At a molecular level, the HIV Nef protein might lead to excessive iron accumulation in macrophages by interacting with the human homeostatic iron regulator and reducing its expression on the cell surface [35], while in HIV patients higher immune activation is associated with lower haemoglobin levels and the reduction in immune activation seen with ART helps to prevent the drop in haemoglobin [36].

Effects of HIV on Bone marrow

HIV infection is known to cause haematopoiesis, a range of changes in the bone marrow. The bone marrow microenvironment is greatly impacted by these alterations, upsetting the delicate balance required for effective haematopoietic activity [21]. HIV has a preference for bone marrow stromal elements and haematopoietic progenitor cells. These cells become dysfunctional due to direct infection, which impairs their capacity to sustain regular haematopoiesis. The virus prevents haematopoietic stem

cells from differentiating and proliferating, which hinders their ability to produce adult blood cells [21]. In the bone marrow microenvironment, HIV infection causes dysregulated cytokine production and signalling. The equilibrium required for healthy haematopoietic function is disturbed by elevated levels of proinflammatory cytokines including TNF- α , IL6, and IFN- γ . Impaired haematopoiesis, including erythropoiesis, is a result of this dysregulation (Fig 3) [37]. The bone marrow is significantly impacted by chronic inflammation brought on by HIV infection. The activity and development of haematopoietic stem cells are negatively impacted by persistent immunological activation and inflammation, which changes the bone marrow's cellular makeup and impairs its capacity to promote erythropoiesis [37]. The bone marrow can be directly impacted by opportunistic infections, which are frequently linked to HIV. These infections, including Cytomegalovirus (CMV) and Mycobacterium avium complex, might inhibit bone marrow, aggravating the already impaired haematopoietic function associated with HIV [21]. Certain antiretroviral medications have been linked to haematologic adverse effects, despite the fact that ART is crucial for limiting viral replication and lessening the systemic symptoms of HIV. Haematopoiesis may change as a result of some drugs' direct or indirect effects on bone marrow function [38].

A weakened haematopoietic microenvironment is the overall outcome of these changes in the bone marrow during HIV infection. Anaemia and other haematologic issues that are frequently seen in people with HIV are caused by these alterations, which interfere with the regular processes of erythropoiesis and other blood cell synthesis. Developing tailored therapy approaches to lessen their effects on haematopoiesis and enhance the general health outcomes of HIV-positive people requires an understanding of these bone marrow changes.



Source: Adapted from [37]

Fig 3: HIV-Induced Dysregulation of Cytokine Signalling in the Bone Marrow Microenvironment

The direct viral effects on erythropoiesis

Ineffective erythropoiesis was the result of HIV-induced changes in the bone marrow microenvironment. A reduced ability to produce red blood cells efficiently is caused by

disruption of haematopoietic stem cell activity, poor differentiation, and decreased formation of erythroid progenitor cells [21]. Red blood cells can have a shorter lifespan due to increased destruction caused by HIV infection, chronic inflammation, and immunological activation. Chronic anaemia is a result of this increased turnover.

HIV does not productively infect CD34+ progenitors, various viral proteins have measurable suppressive effects on erythroid development. *In vitro*, HIV-1 Nef inhibited the ability of CD34+ haematopoietic stem and progenitor cells to form colonies in both myeloid and erythroid lineages, as shown by a decrease in the number of CFU-GM, BFU-E, and CFU-GEMM colonies [39]. Further experimental studies have involved several viral components: heat-inactivated HIV-1 and cross-linked envelope glycoprotein gp120 both reduced the clonogenic capacity and induced apoptosis via a Fas-dependent mechanism, the Gag protein suppressed colony formation from haematopoietic progenitor cells, and Tat has been associated with myelosuppression [40]. A specific mechanism by which Tat exerts its suppressive effect is that it stimulates bone marrow macrophages to produce transforming growth factor- β 1; since TGF- β 1 is one of the most powerful negative regulators of haematopoiesis, its levels were increased by Tat and almost complete reversal of the suppressive effect of the supernatants from bone marrow macrophages on CD34+ cells was achieved upon neutralisation of TGF- β 1 [41].

More recently, it has been demonstrated that both HIV and simian immunodeficiency virus cause a deregulation of early haematopoiesis in macaques via a Nef/PPAR γ /STAT5 signalling pathway, immunological viruses modifying the haematopoietic microenvironment and influencing the progenitors by means of gp120, Gag p24, and Nef [42]. The net effect of these virus- and cytokine-induced processes is a reduced ability to produce new red blood cells and ineffective erythropoiesis, which in the clinic manifests as a reduced response to erythropoietin and a reduced red blood cell lifespan [21]. Together, this evidence supports an indirect mechanism in which the viral proteins act on the bone marrow microenvironment and on accessory cells rather than directly on the erythroid progenitors.

Erythropoiesis is impacted by dietary inadequacies and concomitant diseases that are frequently brought on by HIV infection and its related consequences (Table 3). By limiting the availability of vital nutrients needed for the synthesis of red blood cells, malnutrition, gastrointestinal issues, and persistent infections can make anaemia worse. Bone marrow suppression can be brought on by some drugs used in HIV treatment, especially chemotherapy for related infections or cancers. Erythropoiesis is directly impacted by this suppression, which lowers the synthesis of red blood cells and exacerbates anaemia. People with HIV frequently experience chronic anaemia as a result of these factors' combined effects on erythropoiesis. Fatigue, weakness, and a lower quality of life are all consequences of anaemia, which is defined by low haemoglobin and red blood cell counts. For the purpose of creating focused therapies meant to reduce anaemia and enhance general health outcomes in HIV-positive people, it is essential to comprehend the complex interactions between HIV-induced bone marrow changes and their effects on erythropoiesis. The comprehensive therapy of anaemia in the setting of HIV requires strategies that minimise medication-induced bone

marrow suppression, optimise erythropoietin responses, address nutritional inadequacies, and manage bone marrow dysfunction^[21].

Table 3: The Interconnected Drivers of Impaired Erythropoiesis

Contributing Factor	Primary Mechanism of Action	Impact on Erythropoiesis
Chronic Inflammation	HIV-induced immune activation increases pro-inflammatory cytokines (such as IL-6 and TNF-alpha).	Elevates hepcidin , causing iron trapping in macrophages, restricted iron delivery to the bone marrow (anemia of chronic disease), and blunted erythropoietin (EPO) responsiveness.
Dietary Inadequacies & Malabsorption	Anorexia, altered metabolism, and HIV-related gastrointestinal mucosal damage limit nutrient uptake.	Induces critical micronutrient deficiencies (iron, vitamin B12, and folate) required as structural building blocks for red blood cell maturation.
Opportunistic Infections	Concomitant diseases like <i>Mycobacterium avium</i> complex (MAC), cytomegalovirus (CMV), or parvovirus B19 infiltrate or stress the body.	Causes direct bone marrow suppression, destroys erythroid progenitor cells, or accelerates peripheral red blood cell destruction.
Medication Side Effects	Certain older antiretroviral therapies (such as Zidovudine/AZT) or antimicrobials used to treat opportunistic infections.	Induces direct myelosuppression and drug-induced toxicity within the bone marrow niche.

Source: Adapted from^[26]

Nutritional Deficiencies and Blood Loss

Nutritional deficiencies and blood loss are an important and in part modifiable cause of anaemia associated with HIV. The deficiencies most often involved are iron, folic acid and vitamin B12; in patients with HIV, folic acid deficiency is usually due to inadequate dietary intake or to a disorder of the jejunum, while vitamin B12 deficiency can be the result of malabsorption in the ileum or of gastric pathology involving the gastric mucosa^[43]. Deficiencies of nutrients are frequent in immunosuppressed patients, caused by anorexia, gastrointestinal disturbances associated with medication, wasting and malabsorption; in some instances the iron deficiency anaemia associated with HIV is due to blood loss from the gastrointestinal tract and folate deficiency occurs because of both reduced dietary intake and impaired intestinal absorption this helps to account for the occurrence of both microcytic and macrocytic anaemia^[44].

In parts of sub-Saharan Africa, common causes add to the effects of HIV. These consist of chronic malnutrition (Table 3); deficiencies in nutrients such as iron, vitamin B12, and folate; and infections and parasitic infestations including malaria, schistosomiasis and hookworms, as well as pregnancy and haemoglobin disorders such as thalassaemia^[45]. There is a strong connection between intestinal parasite infection and malnutrition people who had one or more intestinal parasites were 2.85 times more likely to be malnourished because of the increased nutrient demand by

the parasites, diarrhoea, reduced appetite and impaired absorption; hookworm leads to iron deficiency anaemia through blood loss, and Trichuris is likewise thought to cause anaemia by means of iron deficiency^[46]. Geohelminths, such as hookworms which suck blood, make anaemia worse in people living with HIV and are linked to faster disease progression^[47], and severe cases such as lower gastrointestinal haemorrhage due to a heavy hookworm infection^[48] and gastrointestinal bleeding in cases of Strongyloides stercoralis hyperinfection^[49] have been recorded in HIV patients. The individual's nutritional status itself is a predictor of anaemia^[50]. For the framework, this means that the type of anaemia changes as a result of treatment: In a longitudinal cohort, anaemia of chronic disease and microcytic anaemia decreased considerably while macrocytic anaemia increased over the 18-month period on HAART, showing a shift in the main cause over time^[51].

The effect of antiretroviral therapy on haematopoiesis

Within this framework, ART holds a dual role since it cures HIV-associated anaemia in most patients, although some of the drugs have a direct myelosuppressive effect. Zidovudine, which is a pyrimidine analogue, is the classic example of a myelosuppressive agent; its main adverse effect after long-term use is myelosuppression neutropenia and anaemia^[52]. The effect is toxic in that zidovudine leads to a deficiency of thymidine triphosphate, which prevents the maturation of erythroid stem cells and can result in red blood cell aplasia, this being marked by low levels of reticulocytes and haemoglobin without haemolysis or significant blood loss^[53]. According to comparative data, patients on regimens based on zidovudine had haemoglobin decreases as high as 82.7% compared with 50.9% in those on the tenofovir regimen^[53]. Both zidovudine and stavudine cause macrocytosis, but zidovudine has more extensive myelosuppressive effects both *in vitro* and *in vivo*^[54].

Many other agents have an effect on haematopoiesis: When lamivudine is used in combination with zidovudine, it leads to neutropenia, anaemia and thrombocytopenia; nevirapine has been linked to eosinophilia and granulopenia; and stavudine has been reported to cause anaemia, neutropenia and thrombocytopenia^[55, 56]. Pure red cell aplasia is rarely connected with lamivudine and in such cases there is severe anaemia together with a low reticulocyte index^[57]. Programmes have provided evidence of the clinical importance of these effects: A first-line treatment regimen which included zidovudine was an independent predictor of persistent anaemia^[58], and the use of a treatment regimen containing zidovudine was strongly linked to anaemia^[59]. There are, however, some regimens that provide protection: The occurrence of macrocytic anaemia was inversely related to the use of efavirenz in HAART and in adults who received HAART containing nevirapine the incidence of anemia of chronic disease was reduced by 90%^[51]. It has been found that long-term use of highly active antiretroviral therapy can correct certain cytopenias, but blood cell counts and CD4+ levels still have to be checked regularly in order to evaluate the effectiveness of the treatment^[56].

Anaemia in HIV/AIDS

Prevalence of Anaemia in HIV-Positive Patients

Anaemia is one of the most common haematological complications affecting people who have human

immunodeficiency virus (HIV). The rate at which it occurs differs greatly depending on geographical area, age, the severity of the disease, whether or not the individual is receiving antiretroviral therapy and the criteria applied to define anaemia. Anemia is a major public health issue affecting some 1.8 billion people worldwide. In 2021 the prevalence of anemia was 24.3% among all age groups, which amounts to 1.92 billion cases [27]. Anemia is most common in Sub-Saharan Africa, since 52% of pregnant women and 60% of children under the age of five years there are affected with anemia as compared to the global rates of 30% and 40% respectively [60]. A systematic review and meta-analysis of 63 observational studies involving 110,113 people living with HIV found that the pooled prevalence of anaemia was 39.7% in children under 15 years of age, 46.6% in adults aged 15 years and over, and 48.6% in pregnant women living with HIV. For adults, the pooled prevalences of mild, moderate and severe anaemia were 21.6%, 22.6% and 6.2% respectively [61]. The reasons for this are mainly iron, folic acid and vitamin B12 deficiencies, infections such as helminthiasis and malaria, and inadequate access to healthcare [60].

Anaemia is far more prevalent than the base figures among individuals living with HIV. A meta-analysis which was published in 2022 shows that anaemia affects 30 to 40% of the people living with HIV and who are receiving antiretroviral therapy around the world, the figure in sub-Saharan Africa going as high as 50 to 70% [60]. Evidence from Nigeria also shows that a high burden of anemia is found among people infected with HIV. A study on the prevalence of anemia among HIV infected patients in Benin City, Nigeria revealed that the overall prevalence of anemia was 60.61%. The prevalence was greater among patients who had not started highly active antiretroviral therapy (69.17%) than in those who were receiving HAART (51.15%), indicating that treatment status may affect the occurrence of anaemia in people living with HIV [62]. At the higher end of the range, 84% of the participants in a cross-sectional study of 250 HIV patients on HAART for at least six months in Jamshoro, Pakistan, developed anaemia, as compared with 16% of those using standard measurements [63].

Global data covering a long period show that in some communities the level of the problem is gradually decreasing. The proportion of adolescents and young adults (aged 10 to 24) affected by anaemia among those with HIV/AIDS dropped from 70.6% in 1990 to 34.7% in 2019; this was mostly cases of mild to moderate anaemia and was far more common in girls than in boys. The largest decreases were observed in Central Sub-Saharan Africa, High-income North America, and Eastern Sub-Saharan Africa (EAPC -2.8, -2.34, and -2.17 respectively) [64]. Yet anaemia impairment is still strongly associated with levels of the sociodemographic index, a considerable amount of the impairment taking place in areas that have a low SDI [64]. Variations in the reported prevalence rates could be attributed to differences in the study population, geographical area, stage of HIV disease, nutritional status, presence of other infections, exposure to antiretroviral therapy (ART) and the hemoglobin cut-offs used to define anemia. It follows that local studies are still important when it comes to assessing the extent of anaemia among HIV-positive patients in particular healthcare settings.

Risk Factors Associated with Anaemia in HIV/AIDS Patients

Anaemia in individuals living with HIV/AIDS is a complication with multiple causes that arise from the interaction of mechanisms associated with HIV, the progression of the disease, nutritional deficiencies, opportunistic infections, other existing conditions, and factors related to treatment. HIV infection can hinder erythropoiesis by causing chronic immune activation and inflammation, and infections together with nutritional deficiencies can either decrease the production of red blood cells or increase their destruction and cause blood loss. Moreover, the risk of developing anaemia is affected by the level of immune suppression and by how well the HIV disease is controlled. Therefore, the evaluation of anemia in people living with HIV/AIDS must take into account socio-demographic characteristics, clinical signs, hematological and nutritional status and co-infections [65].

Socio-Demographic Factors

Factors in the social and demographic field such as age, sex, socioeconomic status, educational level and access to nutrition may affect the occurrence of anaemia among people living with HIV/AIDS. Although these factors do not cause anaemia directly they can affect exposure to nutritional deficiencies, chronic infections, access to healthcare and other underlying reasons for a reduced concentration of haemoglobin.

It is an important factor since women of reproductive age have, alongside menstruation and pregnancy, other causes of blood loss and greater iron needs. Recent systematic review and meta-analysis of people living with HIV demonstrated significant association between female sex and anemia but the size of the association varied between the different populations [66]. In various sub-Saharan African nations, the incidence of anaemia among women living with HIV varies, with rates as high as 48.6% for pregnant women and 45.1% for general populations [67]. The prevalence of anaemia among Ethiopian women living with HIV varies from 22.2 to 59%, indicating notable geographic and demographic differences that call for additional research [68]. In a study carried out in India, it was reported that the prevalence of anemia in female (84.15%) was higher as compared to males (70.70%) amongst the people living with HIV/AIDS [69].

Another factor that may affect the risk of anemia is age. Children are more vulnerable to anemia as they grow fast and have more nutritional needs [70]. Older individuals may have a greater prevalence of chronic diseases, nutritional deficiencies and inflammatory conditions. In a similar way, people who come from households with a low socioeconomic status may have inadequate dietary intake, face food insecurity and delay in accessing healthcare, thus increasing their exposure to both nutritional and infectious causes of anaemia [71].

Socioeconomic and educational factors may therefore have an indirect effect by influencing dietary quality, access to treatment and the timely management of HIV and the conditions associated with it. Education proves to be a consistent predictor; in Meru County, Kenya, the level of education was the only sociodemographic factor found to be significantly associated with anaemia status [72]. Data from Ethiopia also indicate that the group consisting of people

who have not had formal education should be the one that receives special attention when ART is started^[73]. It follows that when anaemia is assessed in people living with HIV these features should be taken into account together with biological and clinical factors rather than considering anaemia merely as a result of HIV infection.

Clinical factors (CD4 count, WHO clinical stage and viral load)

The CD4 cell count, WHO clinical stage, and viral load are important markers of how HIV is progressing and the state of the immune system. People with advanced HIV disease are especially at risk for anaemia because they have more inflammation, more opportunistic infections, nutritional problems, and other issues caused by a weak immune system. WHO now defines advanced HIV disease in adults and adolescents as a CD4 cell count below 200 cells per mm³ or WHO clinical stage 3 or 4 disease^[74, 75].

It is commonly observed that a low CD4 count is linked to a greater incidence of anaemia in people who have HIV. Since there is severe immune suppression, individuals become more susceptible to opportunistic infections and other AIDS-related illnesses, and anaemia can result from these as a result of chronic inflammation, bone-marrow suppression, nutritional depletion and blood loss. The World Health Organization also points out that the risk of poor outcomes in advanced HIV disease goes up as the CD4 cell count decreases^[76].

The clinical stage according to the WHO offers yet another indication of the severity of the disease. In cases of advanced clinical-stage disease, patients might be at a higher risk of developing anaemia since they are more prone to having chronic infections, malignancies, wasting, nutritional deficiencies and other complications which disrupt normal erythropoiesis. Nevertheless, the link between clinical stage and anaemia is not always consistent among different populations. For instance, a recent systematic review showed that the connection between an advanced HIV clinical stage and anaemia was not statistically significant in the small number of studies that were available for that particular analysis, thereby underscoring the need to take into account differences between populations and study settings^[66].

Viral load is also a significant clinical factor since ongoing viral replication can lead to immune activation and chronic inflammation, and this may affect normal red-cell production. In particular, inflammatory cytokines such as interleukin-6 (IL-6) cause the liver to produce hepcidin. When hepcidin levels rise, ferroportin is degraded, which in turn reduces the release of stored iron from macrophages and decreases the absorption of iron in the intestine. As a result, iron becomes less available to the erythroid cells even though iron stores are present, and this results in anaemia of inflammation^[77].

A recent systematic review and meta-analysis also showed a link between viral load and anaemia, the strength of the association however varying from study to study^[66].

Blood and nutritional factors

Abnormalities in the blood and nutrition play an important role in the development of anaemia in individuals living with HIV/AIDS. Anaemia associated with HIV can be caused by a failure of erythropoiesis, chronic inflammation, reduced erythropoietin activity, a shorter lifespan of red

blood cells, problems in the bone marrow and nutritional deficiencies. Deficiencies in iron, folic acid and vitamin B12 can each on their own interfere with the production of red blood cells and may occur together with HIV-related anaemia^[14].

Iron deficiency can result from insufficient intake of food, from chronic blood loss, from gastrointestinal disorders or from poor absorption. However, when assessing iron status in people who have HIV the situation can be made more difficult by chronic inflammation since ferritin is an acute-phase protein and can remain normal or even be increased even though iron is not readily available for erythropoiesis. Because of inflammatory activation hepcidin increases, which in turn limits iron absorption and causes iron to be trapped in the macrophages. As a result, there is functional iron restriction, meaning that iron stores may be present but still there is not enough iron to reach the developing erythroid cells^[77]. Folate and vitamin B12 deficiency can likewise lead to anaemia by disrupting DNA synthesis and causing ineffective erythropoiesis. The risk of such deficiencies may be greater among people living with HIV because of poor dietary intake, malabsorption and chronic illness. Moreover, HIV-associated gastrointestinal disease may interfere with nutrient absorption and thus further deteriorate nutritional status^[78].

Body weight and nutritional status are also relevant, with a recent systematic review and meta-analysis finding a strong association between anaemia and underweight among people living with HIV, thus supporting the notion that poor nutritional status is an important risk factor^[66]. Haematological indices may offer further information regarding the possible cause of anaemia; microcytosis and hypochromia could point to iron deficiency or haemoglobinopathies, whereas macrocytosis is seen in cases of folate or vitamin B12 deficiency and may also be linked to some antiretroviral drugs^[79]. In instances where anaemia is accompanied by leukopenia or thrombocytopenia there might be a sign of more widespread bone-marrow involvement, advanced disease, an opportunistic infection or medication-induced marrow suppression.

Co-infections and opportunistic infections

Infections that occur together with HIV/AIDS and those that take advantage of a weakened immune system are important risk factors for anaemia in people living with the virus, especially in cases of advanced immunosuppression. The immune dysfunction caused by HIV makes individuals more susceptible to infections such as tuberculosis, malaria, bacterial infections, fungal infections and viral hepatitis^[23]. Such infections can lead to anaemia as a result of chronic inflammation, nutritional depletion, haemolysis, blood loss and the suppression of bone-marrow activity. The World Health Organization lists tuberculosis, cryptococcal meningitis and severe bacterial infections as the main causes of illness and death linked to advanced HIV disease^[74].

Tuberculosis is especially significant in areas where both HIV and TB are common. Since the infection is chronic, it leads to ongoing inflammatory activation and this in turn raises the levels of IL-6 and hepcidin^[80]. The higher hepcidin levels decrease the amount of iron available in the blood for erythropoiesis and thus play a role in causing anaemia as a result of inflammation. The poor appetite, weight loss and nutritional deficiencies that occur as a result of chronic tuberculosis can also worsen the anaemia.

Management of advanced HIV disease therefore involves giving particular attention to tuberculosis and other major opportunistic infections^[81].

Malaria is also a major factor in the development of anaemia among people living with HIV in malaria-prone areas such as sub-Saharan Africa. It leads to anaemia by destroying both parasitised and unparasitised red blood cells, through the spleen's removal of red blood cells and by inhibiting erythropoiesis^[82]. As a result, the presence of both HIV and malaria together may raise the total risk and the severity of anaemia. Anaemia can also result from other opportunistic infections through the action of chronic inflammation, due to either direct or indirect suppression of the bone marrow, from blood loss in the gastrointestinal tract, or as a result of nutritional depletion. Moreover, some of the medications employed in the treatment of HIV and opportunistic infections may lead to haematological abnormalities in individuals who are susceptible. A recent systematic review and meta-analysis has provided evidence showing how important opportunistic infections are, finding a significant association between them and anaemia in people living with HIV^[66].

HIV/AIDS patients suffer from anaemia as a result of a combination of various factors rather than one single cause. Advanced immunosuppression, high levels of viral replication, chronic inflammation, poor nutritional condition, opportunistic infections and other existing illnesses can either act on their own or together to lower the concentration of haemoglobin. The IL-6-hepcidin-ferroportin pathway offers a key mechanistic connection between chronic inflammation and the reduced availability of iron in anaemia associated with HIV^[77].

Clinical and Prognostic Significance of Anaemia in HIV

Anaemia is one of the most common haematological complications seen in people living with human immunodeficiency virus (HIV). Its clinical importance goes beyond a lowered haemoglobin level since anaemia can indicate underlying HIV disease activity, chronic inflammation, nutritional deficiencies, opportunistic infections, renal dysfunction, malignancy or side effects from medications. Anaemia remains highly prevalent in the ART era, particularly among those with advanced disease and other clinical risk factors, a systematic review and meta-analysis of over 110,000 people living with HIV has found^[61].

The connection between HIV and anaemia is complex and two-way. The immune activation and chronic inflammation associated with HIV can have a detrimental effect on erythropoiesis, change iron metabolism and decrease the amount of iron available to erythroid cells^[65]. Moreover, HIV can influence the function of haematopoietic stem cells and their response to erythropoietin. Other infections, especially tuberculosis and other opportunistic infections, nutritional deficiencies and renal disease may also lead to worsening anaemia^[26].

As a result, the presence and seriousness of anaemia can offer useful clinical information regarding the health of a person who has HIV. It has recently been shown that anaemia is linked to an increased risk of death even in those who are on ART, which underlines its value as a prognostic indicator. Moreover, chronic anaemia may lead to fatigue, a reduction in physical functioning and a deterioration in quality of life. It follows that anaemia should be identified

and the cause of it investigated as part of full HIV care.

Anaemia as a Predictor of Progression of Disease and of Mortality

Anaemia has always been linked to worse clinical outcomes in people living with HIV; the more severe the anaemia, the more important it is since falling haemoglobin levels can be a sign of more advanced HIV disease, chronic inflammation, opportunistic infections, nutritional problems or other systemic complications. Earlier studies based on cohort data showed a dose-response relationship between the severity of anaemia and death after the start of ART. In a joint analysis of 10 prospective cohorts which included 12,100 previously untreated HIV-positive individuals, baseline anaemia was found to be independently associated with mortality even after having taken into account the CD4 count and other factors; the adjusted hazard ratios rose from 1.42 in the case of mild anaemia to 2.56 for moderate anaemia and 5.26 for severe anaemia^[83].

More recent evidence has shown that this relationship is still relevant in the current ART era. An analysis of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which included people with HIV who started ART between 2007 and 2016, found that those participants who had anaemia had a considerably greater mortality risk than those who did not have anaemia. Moreover, the mortality risk increased as the severity of anaemia increased, with mild, moderate and severe anaemia showing ever higher associations with mortality. The study also observed that haemoglobin levels were falling particularly in the years leading up to death, suggesting that changes in haemoglobin may provide useful prognostic information for clinical practice^[84].

Evidence from sub-Saharan Africa also shows the prognostic value of anaemia. A systematic review and meta-analysis, published in 2024 and based on 27 studies involving 61,796 children who were receiving antiretroviral therapy in that region, found that anaemia was associated with a higher rate of HIV-related deaths, the estimated hazard ratio being 2.58. This association was especially strong in children under five years of age, which suggests anaemia could be an important marker of vulnerability in pediatric HIV infection^[85].

There are a number of mechanisms through which anaemia is associated with mortality. Anaemia reduces oxygen carrying capacity of the blood and increases tissue hypoxia and stress on the cardiovascular system. Anaemia may also be a marker of underlying pathological conditions, including chronic inflammation, opportunistic infections, nutritional deficiencies, renal dysfunction, and advanced HIV disease^[65]. Chronic inflammation can lead to functional iron restriction by means of hepcidin-mediated hormonal regulation, which suppresses erythropoiesis and iron utilization^[26].

Anaemia should not be regarded as a mere laboratory abnormality. When it is found in someone who has HIV, it may lead to a more detailed examination of their HIV disease stage, their adherence to treatment and their response to antiretroviral therapy (ART), their nutritional status, any opportunistic infections, their renal function, possible medication-related toxicity and other potential causes. The World Health Organization's 2025 guidelines on advanced HIV disease stress the importance of early identification and the comprehensive management of people

who are at higher risk of HIV-related morbidity and mortality^[81].

Effect on the quality of life and on treatment outcomes

Anaemia can have a major effect on the physical and psychosocial well-being of people who have HIV^[65]. When the concentration of haemoglobin falls, the amount of oxygen delivered to the tissues decreases and this can cause fatigue, weakness, a reduced tolerance for exercise, dizziness, shortness of breath and a lower physical capacity^[86]. Such symptoms can interfere with a person's ability to work, with their duties at home, with participation in social activities and with sticking to their regular healthcare. The effects are likely to be especially significant in cases of moderate or severe anaemia or in those individuals who have other illnesses associated with HIV^[59].

The way in which anaemia affects quality of life is also determined by the underlying causes of anaemia; chronic HIV-related inflammation, frequent infections, nutritional deficiencies and other comorbid conditions can each on their own lead to fatigue and a decreased ability to carry out daily activities^[65]. Consequently, anaemia not only reflects but also exacerbates the total burden of disease felt by people living with HIV. Reviews of anaemia associated with HIV have pointed out that chronic inflammation, impaired erythropoiesis, altered iron metabolism and comorbid disease constitute interconnected pathways that contribute to the ongoing anaemia and its clinical effects^[26]. Further evidence from Nigeria shows that health-related quality of life is still a significant aspect of HIV care. In 2024, a study was conducted among people living with HIV/AIDS in Lagos to assess the health-related quality of life and to identify the clinical and psychosocial factors associated with the quality-of-life outcomes^[87]. PubMed Central However, even though these studies do not necessarily prove that anaemia alone led to a lower quality of life, they do highlight the need to take into account functional and patient-reported outcomes together with virological and immunological measures when assessing HIV treatment.

Anaemia can also have an effect on the results of treatment. When effective antiretroviral therapy (ART) is used, it suppresses HIV replication, enhances immune function and decreases the number of various HIV-related complications. Better control of HIV can therefore reduce some of the mechanisms that lead to anaemia. On the other hand, if a person still has anaemia even though they are receiving ART, this could be a sign of ongoing inflammation, a poor nutritional state, an opportunistic infection, renal disease or medication-related toxicity and would then require additional clinical evaluation. A major study carried out in Tanzania which included 70,442 people living with HIV looked at the association between anaemia, iron supplementation, viral load and mortality and thus underlined the continued clinical significance of anaemia even though effective ART is widely available^[88].

The effect of anaemia on treatment outcomes can also be affected by antiretroviral drugs. Certain antiretroviral drugs, especially zidovudine, have in the past been linked to bone-marrow suppression and anaemia. Although current ART regimens have reduced a number of the complications related to the medications, the patient's medication history is still important when looking at cases of unexplained anaemia. Likewise, recent evidence from a systematic review of anaemia associated with HIV found that ART

status and specific antiretroviral exposure were among the factors associated with the prevalence of anaemia^[66]. HIV treatment success should therefore not be judged solely on the basis of viral suppression. It is useful to monitor haemoglobin and other haematological values in order to detect any ongoing or worsening anaemia and to obtain further insight into the patient's overall clinical condition. The World Health Organization's latest HIV clinical-management guidelines stress the importance of optimized ART, the prevention and management of comorbidities, and patient-centred care with the aim of improving health outcomes and quality of life^[89].

Management of Anaemia in People Living with HIV

The management of anaemia in individuals who have HIV should mainly focus on identifying and treating the underlying cause rather than merely treating the reduced haemoglobin level. Since anaemia associated with HIV is multifactorial, the clinical assessment must take into account the patient's HIV disease status, nutritional deficiencies, chronic inflammation, opportunistic infections, medication toxicity, renal disease, blood loss and other haematological disorders. Useful information for directing further investigation can be obtained from the severity and the morphological pattern of the anaemia.

The initial evaluation could involve carrying out a full blood count, measuring haemoglobin concentration, determining the mean corpuscular volume, the mean corpuscular haemoglobin and the red-cell distribution width, and also including a peripheral blood film examination if this is appropriate. In some cases, further tests might be necessary such as testing serum ferritin and other iron studies, assessing vitamin B12 and folate, carrying out renal-function tests, checking the levels of inflammatory markers, screening for tuberculosis or other opportunistic infections, and assessing whether there has been a blood loss (Fig 4). The World Health Organization's 2024 guideline states that accurate measurement of hemoglobin and correct interpretation of hemoglobin concentrations are important in the diagnosis of anemia^[8].

Effective antiretroviral therapy is a key aspect of managing HIV-associated anaemia. By suppressing HIV replication, immune activation and chronic inflammation can be reduced, immune function can be improved and the occurrence of opportunistic infections can be decreased, thus tackling several of the mechanisms that lead to anaemia. The current guidance from the World Health Organization still stresses the importance of quickly starting and optimising ART as a major part of HIV management. The 2025 World Health Organization clinical-management recommendations specifically aim at optimising ART and at improving clinical outcomes and quality of life^[89].

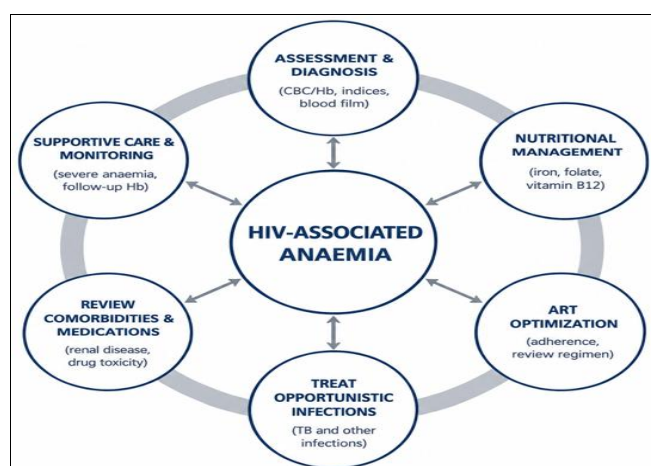
It is important to identify and deal with any nutritional deficiencies; deficiencies in iron, folic acid and vitamin B12 may all play a role in causing anaemia in people living with HIV, especially in cases of poor dietary intake, malabsorption or chronic infection. Nevertheless, iron supplementation should generally be based on an appropriate clinical and laboratory assessment since the anaemia linked to chronic inflammation might be due to a functional iron restriction rather than an actual iron deficiency. The inflammation associated with HIV can lead to increased hepcidin production, which in turn reduces iron absorption in the intestine and causes iron to be trapped in

storage cells, thus limiting the amount of iron available for erythropoiesis^[65].

Opportunistic infections and other comorbidities should also be actively recognised and treated. Tuberculosis, fungal infections, parasitic infections and other chronic infections can lead to anaemia via inflammation, haemolysis, nutritional depletion, blood loss or bone-marrow suppression. Because advanced HIV disease is closely linked with HIV-related morbidity and mortality, the management of it is especially important. The updated WHO 2025 guidelines therefore suggest a comprehensive approach to advanced HIV disease, comprising the identification and management of important comorbidities and the rapid initiation or optimisation of ART^[81].

Anaemia related to medication should be taken into account when this is appropriate. It is important to review the patient's antiretroviral and other medications whenever anaemia develops or continues after treatment has started. In the past, zidovudine has been linked to bone-marrow toxicity and anaemia. If drug-induced anaemia is suspected, the medication in question should be examined by the clinician in charge and an appropriate alternative should be considered in line with the current HIV treatment guidelines. In severe or symptomatic cases of anaemia, further supportive treatment might be necessary. A blood transfusion could be considered depending on the severity of the anaemia, the presence of symptoms, the patient's haemodynamic condition and the underlying clinical illness. Erythropoiesis-stimulating agents have also been looked at as a possible treatment for anaemia associated with HIV; yet reliable evidence to support their routine use is still limited. There was insufficient good quality evidence to show any clear benefits of erythropoietin-based interventions for important outcomes such as mortality and quality of life in people with HIV-associated anemia^[90].

Management should therefore adopt a cause-directed and patient-centred method which includes controlling HIV, investigating and treating nutritional deficiencies, identifying and managing opportunistic infections and any comorbid conditions, reviewing any medications that might have a myelosuppressive effect, and providing appropriate supportive treatment in severe cases. It is important to carry out regular monitoring of haemoglobin and other haematological indices in order to assess the response to treatment and to detect any persistent or recurrent anaemia.



Source: Adapted and synthesized from^[65, 89].

Fig 4: Schematic representation of the management of anaemia in people living with HIV

Conclusion

Anaemia remains a significant complication of HIV/AIDS, contributing to poor quality of life, disease progression and increased mortality. Its development is multifactorial, involving chronic inflammation, bone-marrow suppression, nutritional deficiencies, opportunistic infections and treatment-related effects. Although antiretroviral therapy improves haematological outcomes, regular monitoring remains essential to identify persistent anaemia and medication-related toxicity. Early diagnosis, appropriate treatment of underlying causes, nutritional support and effective management of co-infections are vital for improving patient outcomes. Strengthening routine haematological assessment and integrating anaemia management into comprehensive HIV care, particularly in resource-limited settings, should remain important public health priorities.

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