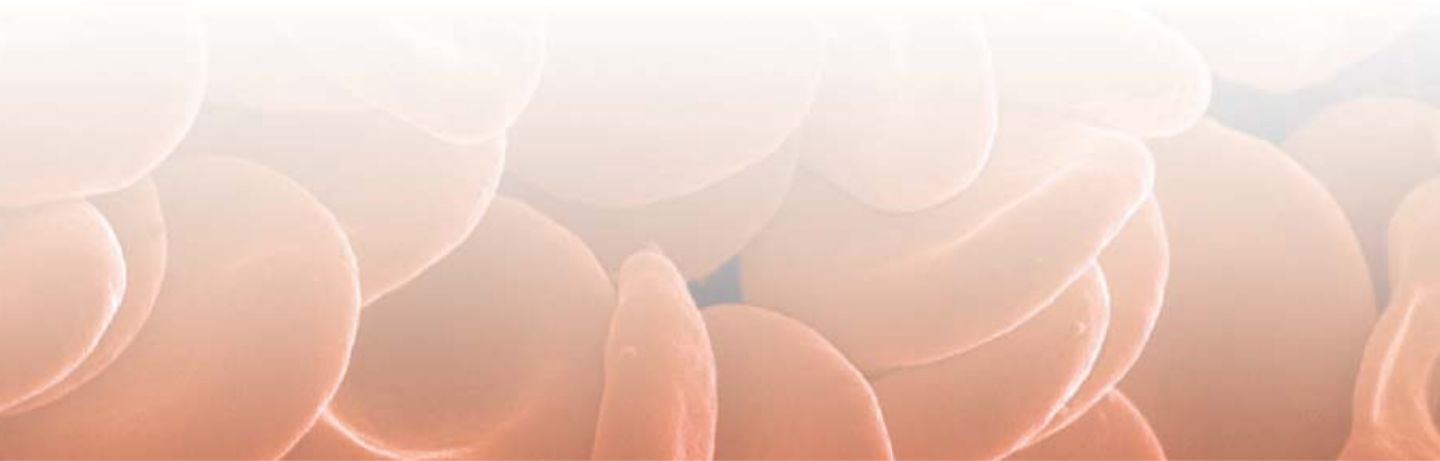
"Anemia has been associated with progression to AIDS and shorter survival times for HIV$^+$ patients."

VI *Anemia &* HIV/AIDS

Key Points

- Multiple factors, both disease-related and treatment-related, can cause anemia during HIV infection.
- Although some HIV drugs may increase the risk of anemia, HAART may prevent or ameliorate anemia in HIV$^+$ patients.
- The prevalence of anemia is higher in HIV$^+$ patients with more severe disease.
- Anemia has been associated with shorter survival times and diminished quality of life in HIV$^+$ patients.
- Management of anemia has been shown to improve survival and quality of life in HIV$^+$ patients.



Multiple Factors Contribute to Anemia

Multiple factors, both disease-related and treatment-related, can cause anemia during HIV infection. HIV plasma viral load appears to correlate inversely with all hematologic values, suggesting a causative role of HIV in hematologic disorders.[1] The disease can cause anemia by influencing cytokine production and suppressing hematopoiesis; decreasing erythropoietin concentrations; and increasing the risk of opportunistic infection with agents, such as *Mycobacterium avium* complex and parvovirus B-19.[2]

HIV infection also causes immunosuppression. In a recent longitudinal study of 797 HIV-infected patients, Semba and colleagues demonstrated that a $CD4^+$ T-lymphocyte count <200 cells/µL is independently associated with the development of anemia. In the period prior to the widespread use of highly active antiretroviral therapy (HAART), 1993 to 1996, patients with $CD4^+$ counts <200 cells/µL had an 86% increased risk of developing anemia (OR, 1.86; 95% CI, 1.51-2.30). Moreover, this study noted that this relationship was maintained in the first years of the HAART era, 1996 to 2000 (OR, 1.62; 95% CI, 1.35-1.94).[3]

Less common mechanisms for HIV-associated anemia include vitamin B_{12} deficiency and the autoimmune destruction of red blood cells.[2,4] According to findings of a cohort study of about 200 consecutive HIV^+ patients, circulating autoantibodies to endogenous erythropoietin were present in about a quarter of the patients, and this subgroup was at a 5- to 10-fold increased risk of anemia compared to HIV^+ patients without autoantibodies.[4]

In addition to anemia caused by disease, therapies used to treat HIV have been implicated as a cause of anemia. Sullivan and colleagues found in their study of nearly 33,000 HIV^+ patients that 22% of those diagnosed with anemia were identified by physicians as having treatment-related anemia.[2] Many HIV therapies have significant myelotoxic side effects, with the nucleoside reverse transcriptase inhibitor zidovudine (AZT) generally considered to be more myelotoxic compared with other drugs in its class and the protease inhibitors.[5] In the pre-HAART era, AZT at a dose of 600 mg/day was associated with transfusion-dependent anemia in approximately 30% of patients with AIDS and 1% of patients with asymptomatic HIV disease.[6] In the study by Semba and colleagues, patients taking AZT in the pre-HAART era had a 28% greater chance of developing anemia than those not taking the drug (OR, 1.28; 95% CI, 1.05-1.56). This association, however, did not hold true in the HAART era (OR, 1.02; 95% CI, 0.87-1.22).[3]

Didanosine (ddI) and stavudine (d4T) have been associated with anemia as well, but less frequently and less strongly than AZT.[2,7] Lamivudine (3TC) has also been associated with anemia, although primarily in conjunction with AZT.[8,9] Interestingly, however, a case report has suggested that 3TC without AZT can cause anemia.[10]

Several reports indicate that HAART prevents or ameliorates anemia in some HIV^+ patients.[1,11,12] Servais and colleagues have shown that HIV-associated hematologic disorders improve with HAART regimens containing at least one protease inhibitor.[1] Another report notes that prior to the introduction of HAART, anemia developed in close to 90% of HIV^+

patients, but that the prevalence of anemia in the HAART era has decreased to about 46%.[11] However, according to a longitudinal study of 2,078 HIV^+ women, improvements in anemia are negated when AZT is included in the HAART regimen.[12]

numerous factors related to genetics, disease progression, and treatment may contribute to the anemia associated with HIV/AIDS.

Table 6-1 **Risk Factors In HIV^+ Patients**

$CD4^+$ counts <200 cells/μL	History of clinical AIDS
MCV <80 fL	History of pneumonia
African American race	History of fever
Increased age	Zidovudine use
Lower body mass index	Increased HIV RNA in plasma
Oral candidiasis	

3, 13

While not proving cause and effect, some studies have shown that HIV/AIDS patients with anemia are more likely to demonstrate certain characteristics than those without anemia. One longitudinal study of over 1,100 HIV^+ and HIV^- women, who were enrolled between 1993 and 1995 and followed for at least 2 years, noted that factors associated with an increased risk of anemia were African American race, increased age, lower body mass index, history of pneumonia, oral candidiasis, $CD4^+$ count <200 cells/μL, history of fever, and zidovudine use.[3] Similarly, findings of another study of more than 2,500 HIV^+ and HIV^- women, enrolled between 1994 and 1995, indicated that factors predicting anemia in HIV^+ women included African American race, mean corpuscular volume <80 fL, $CD4^+$ count <200 cells/μL, increased HIV RNA in plasma, current use of zidovudine, and history of clinical AIDS.[13] HIV^- women who were African American and/or had low MCV values were also at increased risk for anemia. Thus,

Anemia Prevalence Increases with Disease Progression

In general, patients who are in the beginning stages of HIV infection have a lower prevalence of anemia than those with more advanced stages of the disease. For example, the Multistate Adult and Adolescent Spectrum of HIV Disease Project, which evaluated nearly 33,000 patients between 1990 and 1996, identified anemia in 28% of men with HIV infection, in 55% of men with AIDS due to a $CD4^+$ count <200 cells/μL, and in 87% of men with AIDS due to the presence of opportunistic infections.[2] A similar trend of increasing prevalence of anemia with progression of HIV disease was also observed in women.[2] Findings of a study of nearly 800 HIV^+ women found that the prevalence of anemia at enrollment (between 1993 and 1995) was 28.1%. The cumulative incidence of anemia in this study over a 5.4-year follow-up was more than 60%, with higher rates of anemia seen in patients with lower $CD4^+$ counts (P <0.0001).[3] The EuroSIDA study, a European prospective observational study of 6,725 patients enrolled during the HAART era, showed

that 59.6% of HIV$^+$ patients evaluated were anemic and that Hb levels correlated with CD4$^+$ counts (P <0.0001).[14]

Anemia Associated with Increased Morbidity and Mortality

Anemia has been associated with progression to AIDS and shorter survival times for HIV$^+$ patients.[15] In the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project, lower Hb levels were associated with decreased survival at all levels of CD4$^+$ counts.[2] In HIV$^+$ patients with a CD4$^+$ count of ≥200 cells/µL at the beginning of the survival analysis, the risk of death for those with anemia was 48% greater than for those without anemia (OR, 1.48; 99% CI, 114%-188%). For patients whose CD4$^+$ count was <200 cells/µL, the risk of death for those who developed anemia was 56% greater than for those without anemia (OR; 1.56, 99% CI, 43%-71%). Additionally, for patients who did not recover from anemia, the risk of death was 70% greater than for those who did recover (OR; 1.70, 99% CI, 132%-203%).

The EuroSIDA study also evaluated Hb level and its association with mortality in more than 6,700 HIV-infected patients.[16] At 12 months after recruitment, the proportion of patients estimated to have died was 3.1% for patients without anemia, 15.9% for patients with mild anemia, and 40.8% for patients with severe anemia. Although severe anemia was present in only 1.4% of the patients at the time of recruitment, it was associated with a much faster rate of disease progression. Among patients with similar viral load and CD4$^+$ counts, Hb value was a strong independent predictor of death.[16] Furthermore, the Multicenter AIDS Cohort Study, a prospective pre-HAART study of more than 700 AIDS-free patients initiating AZT therapy, identified baseline levels of CD4$^+$ lymphocytes, platelets, and Hb as significant predictors of AIDS and death.[17]

In addition to influencing disease progression and mortality, HIV-related anemia dramatically influences quality of life (QOL), especially because of its contribution to fatigue,[18,19] and it also appears to increase the requirement for transfusions.[20,21]

Beneficial Effects of Anemia Management

The effects of anemia on morbidity and mortality suggest that anemia management may dramatically benefit HIV$^+$ patients and that treatment of anemia improves survival rates in patients with HIV disease.[21,22]

An important step in the treatment of anemia in HIV$^+$ patients is to address and correct the underlying cause of the anemia (eg, infection, tumor, hemolysis, drugs).[23,24] However, if immediate treatment is warranted or anemia persists, then several non-mutually exclusive options should be considered.

Transfusions may be indicated in the setting of acute hemorrhage; however, this approach is not without potential risks.[25] A retrospective study of 2,348 HIV$^+$ patients has demonstrated that blood transfusions are independently associated with an increased risk of death.[22] Other study findings have shown that blood transfusions may transiently increase HIV RNA levels,[26] increase the risk of opportunistic infec-

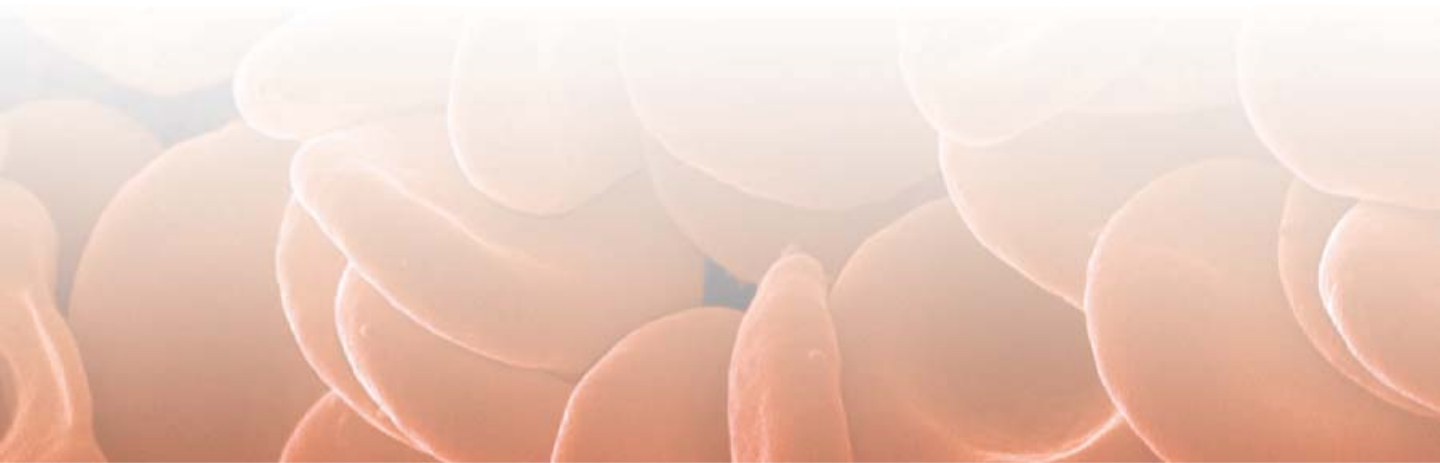
tions,[27] transmit blood borne infections, result in adverse reactions secondary to blood borne product incompatibilities, and cause iron overload.[25]

Initiation or continuation of HAART without AZT or HAART with a lower dose of AZT is another option,[24] as HAART has been shown to ameliorate anemia in many HIV^+ anemic patients.[1,11,12]

Erythropoietin therapy may be appropriate for selected HIV^+ patients, in particular those with baseline endogenous serum erythropoietin levels ≤500 IU/L.[28,29] A review of four 12-week randomized controlled trials noted that administration of epoetin to HIV^+ patients with anemia results in an increase in mean Hct and a decrease in transfusion requirements.[29] Use of epoetin is also associated with a decreased risk of death for HIV^+ patients with anemia. In one retrospective study, 91 HIV^+ patients who received epoetin were found to have a decreased hazard of dying (RH, 0.57; 95% CI, 0.40-0.81).[22]

Anemia management may also improve QOL in HIV^+ patients. By increasing Hb levels, anemia management can decrease fatigue. In one open-label observational study involving 251 anemic AIDS patients receiving epoetin, researchers analyzed 12 QOL indicators, such as energy level, fatigue, and the ability to be cared for at home.[30] After 12 and 24 weeks, patients who responded to epoetin had significantly better scores for several QOL indicators compared to nonresponders. Similarly, in a combined analysis of four randomized, double-blind, controlled clinical trials of AIDS patients receiving AZT, epoetin responders showed significant increases in a number of QOL measures after 12 weeks of treatment.[29] Abrams and colleagues, who conducted a 4-month open-label, nonrandomized trial assessing the effect of epoetin on the QOL of 221 HIV^+ patients, found that transfusion requirements were significantly reduced, from 20% to 5% (P <0.01), and mean total QOL scores improved significantly (P <0.05) after epoetin administration.[20]

As treatment for HIV/AIDS improves and lifespan increases among these patients, the need for awareness of anemia will also increase. Management of anemia has been shown to improve not only survival rates, but also the QOL of HIV/AIDS patients.



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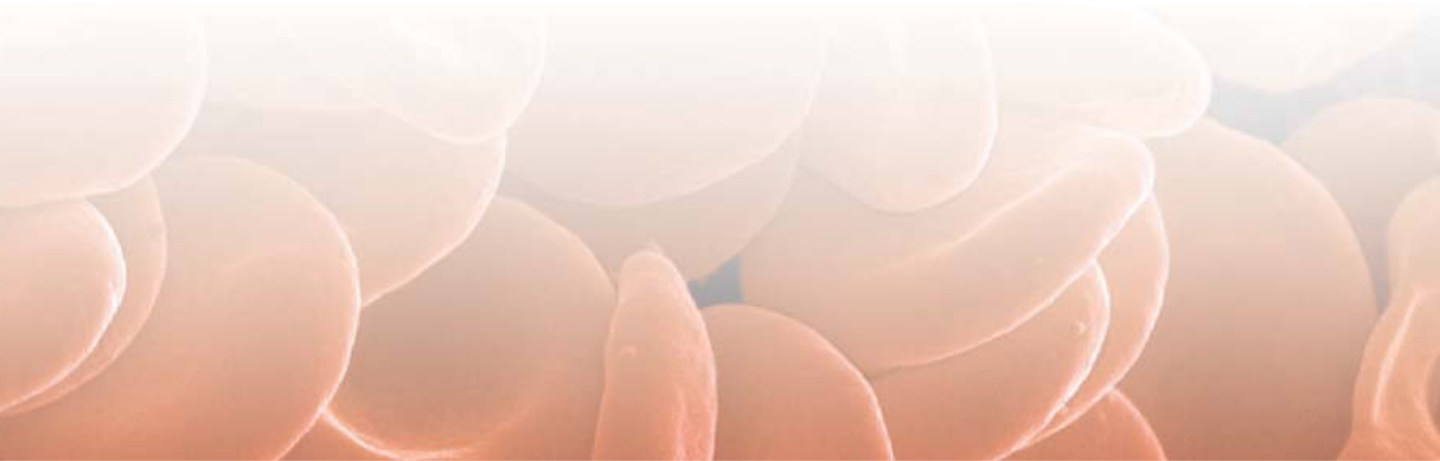

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