

# TLALELETSO

## HIV & Anemia

In this issue we review anemia and HIV. Medical professionals across all disciplines need to be alert to the hematological complications of HIV infection.

### INTRODUCTION

Anemia is the most common complication of HIV, occurring in the vast majority of HIV patients during the course of the disease. Other forms of cytopoenia (thrombocytopenia and leucopenia) are also incredibly common. In this issue of Tlaleletso we review the common causes of anemia and the diagnostic steps that can be taken to determine the cause and initiate the right treatment.

### INCIDENCE & SIGNIFICANCE

Anemia is the most common hematologic abnormality associated with HIV, affecting 60 to 80 percent of patients in late stage disease. The clinical manifestations of anemia in HIV-infected individuals are similar to those in uninfected individuals and are outlined in

The earliest symptoms of anemia affect functional status, manifesting as fatigue, weakness, exertional dyspnea, and slowed cognition. These symptoms will occur in some individuals when hemoglobin levels decrease to 10-12 g/dL.

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### Notes from the Editor.....

Tlaleletso is a monthly publication produced by the Botswana UPenn Partnership, in response to your expressed need for accessible, digestible clinical information.

In this edition we review anemia, diagnosis and treatment in HIV infected adults.

#### DID YOU KNOW?

Pagophagia – the disorder of compulsive consumption of ice or iced drinks is associated with iron deficiency and is known to respond to iron supplementation.

## SIGNS & SYMPTOMS

Later symptoms include rapid heart rate, bounding pulse, dyspnea at rest, severe fatigue, confusion, angina, and congestive heart failure. These manifestations of anemia may occur with hemoglobin levels  $\leq 8$ -9 g/dL. While anemia may manifest as a mere laboratory abnormality in some individuals, others may experience typical symptoms — fatigue, dyspnea, reduced exercise tolerance, and diminished functional capacity — that are directly related to a reduction in hematocrit.

## AETIOLOGY

Correct treatment of anemia must first involve accurate diagnosis. (Please refer to page 8 for a simplified approach to determining the cause). Causes of anemia in HIV-infected adults include:

**ANEMIA OF CHRONIC DISEASE:** The major cause of anemia in HIV-infected patients is impaired erythropoiesis (Table 2), probably as a result of release of inflammatory cytokines and decreased production of hematopoietic growth factors and upregulation of hepcidin synthesis with resultant reduction in intestinal absorption and recycling of iron.

### Causes of Anemia in HIV Infection

#### Decreased Red Blood Cell Production

- HIV induced (similar to anemia of chronic disease)
- Iron deficiency (blood loss, commonly gastrointestinal; consider heavy menses in women)
- Neoplasm infiltrating bone marrow (lymphoma, Kaposi's sarcoma, other)
- Infection in marrow (*Mycobacterium avium* complex, *Mycobacterium tuberculosis*, parvovirus B19, cytomegalovirus, fungal)
- Drugs: zidovudine, pyrimethamine, amphotericin B, phenytoin, valganciclovir

#### Ineffective Red Blood Cell Production

- Folic acid deficiency
- Vitamin B12 deficiency

#### Red Blood Cell Destruction (Hemolysis)

- Coombs-positive hemolytic anemia
- Thrombotic thrombocytopenic purpura
- Disseminated intravascular coagulation
- Drugs: sulfonamides, drugs such as dapsone, primaquine with G6PD deficiency



## AETIOLOGY

The anemia observed during HIV infection has features of anemia associated with chronic disease and is usually normochromic and normocytic. Similar to other chronic inflammatory diseases, erythropoietin production is decreased in patients with HIV-associated anemia. Of note, the strain of HIV seen most commonly in Botswana – HIV-1C – is often associated with anemia. The ability of the HIV-1C strain to infect hematopoietic progenitor cells is greater than that of HIV-1B.

Typically, patients with ACD have a low serum iron level and iron-binding capacity but a normal to elevated ferritin level and adequate iron stores in the bone marrow. The reticulocyte count is inappropriately low.

**INFECTIONS:** Opportunistic infections, such as *M. tuberculosis*, *M. avium* complex (MAC) and *Cryptococcus neoformans* can lead to anemia through infiltration of the bone marrow and causing reactive granuloma formation. In most instances bone marrow infection will lead to pancytopenia rather than anemia alone. A bone marrow biopsy can provide a diagnosis within a few days. Mycolytic cultures of the blood and bone marrow are important adjunct tests if TB infiltration is suspected.

Viral infections may be associated with suppression of normal bone marrow function. Mild-to-moderate anemia is a common finding in patients with acute cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection.

Immunosuppressed HIV patients are also predisposed to parvovirus B19 infection which should be suspected in all cases of isolated severe anemia, usually with preserved platelet and white cell counts. Morphologic features on the bone marrow biopsy are seen with B19. However, the diagnosis can be confirmed by a PCR blood test.

**MALIGNANCY:** Infiltration of the bone marrow by malignant cells is a potential cause of anemia and other cytopenias. The small noncleaved cell type of **non-Hodgkin lymphoma** is the most common offender, followed by other malignant lymphomas and, rarely, **Kaposi's sarcoma**.

**NUTRITIONAL DEFICIENCIES:** These are common in patients with advanced immunosuppression, stemming from the combined impact of anorexia, medication-associated gastrointestinal disturbances, wasting, and malabsorption.

Nutritional deficiencies in patients with HIV infection may also include disorders of iron metabolism or iron deficiency from chronic blood loss (e.g, menses, Kaposi's sarcoma or lymphoma of the gastrointestinal tract, alcohol abuse and hemorrhagic gastritis, or various infectious enterocolitides.)

Vitamin B12 deficiency occurs in up to 30% of HIV-infected patients. Low vitamin B12 levels may result from abnormalities in vitamin B12-binding proteins and decreased serum transport of vitamin B12, and abnormal absorption of vitamin B12 may also occur in patients with advanced HIV infection. By contrast to vitamin B12 deficiency, folate deficiency is not prevalent in this patient population, and would most likely occur in advanced HIV infection associated with poor food intake.

**HYPOGONADISM:** Hypogonadism is frequently reported among patients with advanced HIV infection. Anemia is associated with low testosterone levels.

## AETIOLOGY (cont.d)

**ABNORMAL IRON METABOLISM**— Iron deficiency anemia in HIV infected adults is typically related to blood loss through the gastrointestinal tract. Potential causes include intestinal Kaposi's sarcoma, gastrointestinal ulceration, gastritis and intestinal infections with various viral (especially CMV), bacterial, and parasitic agents.

**HEMOLYSIS:** Hemolysis may play a role in HIV-associated anemia. A variety of mechanisms may be involved including antibody-mediated hemolysis, drug-induced disease in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and microangiopathic hemolysis.

**ANTIBODY-MEDIATED:** The presence of antibodies directed against red cell antigens is more common than overt hemolysis. In one study, a positive direct antiglobulin test (Coombs' test) was encountered in 18 percent of patients with AIDS, compared with less than 1 percent of non-infected blood donors. Despite this finding, clinically evident hemolysis was not noted in any of the 55 HIV-infected patients.

**DRUG-INDUCED:** Dapsone may cause mild reductions in hemoglobin values. Severe, life-threatening hemolysis occurs in HIV-infected patients with G6PD deficiency who are exposed to these or other medications with oxidant potential.

**MICROANGIOPATHY:** Microangiopathic hemolysis is a hallmark of disseminated intravascular coagulation (DIC) secondary to bacterial sepsis and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). The presence of schistocytes on the peripheral blood smear is a hallmark of this disorder.

**BONE MARROW SUPPRESSION:** Multiple therapies used in the management of HIV infection and its related conditions can depress erythropoiesis. Bone marrow suppression is the most common toxicity observed in patients treated with zidovudine (AZT). Experience has demonstrated a reduced frequency of anemia with lower daily doses of AZT. Patients with advanced immunosuppression are more prone to inhibition of normal erythropoiesis by AZT.

Bone marrow suppression can also be induced by many other drugs used for the prophylaxis or therapy of opportunistic processes including ganciclovir, valganciclovir, hydroxyurea, Amphotericin B, and cotrimoxazole. Thus, specific attention to a patient's current medications is a necessity in the assessment of anemia.

## WHEN TO DO A BONE MARROW ASPIRATE...

Bone marrow aspiration is often performed during the evaluation of anemia and other cytopenias in patients with HIV infection.

A broad spectrum of biopsy findings can be seen but no histologic abnormality can be considered pathognomonic. Normocellular marrows are the most common, occurring in over 70 percent of patients (according to one series).

Bone marrow aspirates and biopsies may reveal the etiology of anemia by demonstrating infiltrative malignancies, infiltrative infections caused by mycobacteria or fungi, or the characteristic giant pronormoblasts encountered in parvovirus B19 disease.

(continued)

## BONE MARROW EVALUATION (cont.d)

Existing data do not support the use of bone marrow sampling as a routine diagnostic test in HIV-infected patients with anemia.

However, the one advantage of marrow sampling is the rapidity with which a histologic diagnosis may be made. Thus, in patients with a rapidly changing clinical picture, the speed of processing justifies marrow sampling.

Bone marrow biopsies are also performed in the setting of cytopenia with unexplained constitutional symptoms (fever, weight loss, anorexia), when atypical cells are noted in the peripheral blood, or as staging for a diagnosed lymphoma.

## TREATMENT

Treatment of anemia in HIV-infected patients should begin with therapy of HIV and correction of reversible causes of anemia.

**EFFECT OF HAART:** A number of studies have shown that initiation of HAART reduces both the incidence and degree of anemia in all groups of HIV-infected patients (ie, men, women).

According to an American study, the WIHS (Women's Interagency HIV Study), HIV-infected women were significantly less likely to have resolution of their anemia during the follow-up period if they had any of four factors associated with an increased risk of developing anemia:

- Mean corpuscular volume (MCV) <80 fL.
- CD4 count <200/microL.
- HIV-1 viral load >50,000/mL.
- Use of AZT in the past six months.

**TREATING THE CAUSE:** In addition to primary treatment of the underlying HIV infection, therapy of the anemia should also focus on correcting potentially reversible causes: Infectious etiologies warrant aggressive treatment.

Intravenous immune globulin is the therapy of choice for patients with pure red cell aplasia and documented parvovirus B19 infection.

Supplementation of the diet with vitamin B12, folate, and iron is indicated when these deficiencies are detected. When clinically feasible, attempts at dose reduction or discontinuation of implicated medications should be considered. When discontinuation of medications is not possible or when secondary causes are not identified, alternative strategies for augmenting red blood cell reserves are indicated (see below).

**TRANSFUSION:** Transfusion remains the mainstay of therapy for acute, life-endangering blood loss or symptomatic chronic anemia. While the administration of packed red blood cells offers rapid correction of anemia and reversal of symptoms, there are several inherent risks, such as transfusion reaction, transmissible infection (eg, viral hepatitis, HTLV-I, CMV), development of alloantibodies and, when repeated transfusion is expected, iron overload and its associated complications.

**RECOMBINANT ERYTHROPOIETIN—** Recombinant human erythropoietin (rEPO) can raise the hematocrit and reduce the transfusion requirements in patients with HIV infection, although no studies have evaluated the effect of EPO on survival of these patients.

## SUMMARY

Anemia is extremely common in HIV-infected patients, but not all anemia may be explained by HIV by itself

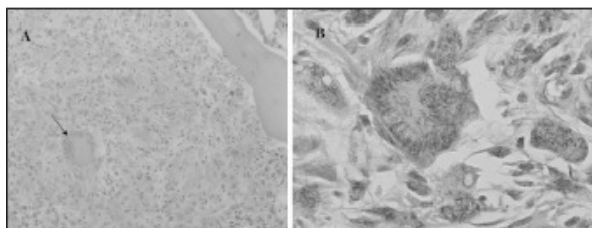
### Diagnosis

- Medication history
- Physical exam (looking for signs of malignancy, rectal/vaginal exams for bleeding sources)
- FBC with MCV and RDW
- Evaluation of peripheral smear
- Reticulocyte count (to evaluate whether bone marrow is functioning or suppressed)
- Iron studies (Iron and ferritin) if low MCV or high RDW
- LDH and bilirubin if hemolysis is suspected
- Bone marrow biopsy useful if:
  - Peripheral smear shows atypical cells
  - Malignancy or infiltrative infective process (fungi, TB) is suspected

### Treatment

- Transfusion for symptomatic chronic anemia or extremely low Hb (<5-6)
- Empiric iron therapy for low MCV (after studies sent) and high suspicion for iron deficiency.
- If ferritin is normal or high, must investigate other causes and stop iron therapy (can cause hemochromatosis). In patients with anemia of chronic disease, there is very limited role for iron supplementation.

**Special thanks to Matt Dasco for providing much of the content for this month's Tlaleletso**



## Upcoming Lectures

### August

Anemia & Anemia

### September

Nutrition & HIV

### October

Hepatitis & HIV

### November

Neuropathy & HIV

Got a clinical question about a complicated medical patient or a patient with HIV?

**Mike Reid**

267 724 78 777

**OR**

**Miriam Haverkamp**

267 76516520



Bone Marrow findings consistent with Mycobacterium Avium Complex infection; image courtesy of samj, 2012

## DIAGNOSING ANEMIA

| Diagnosis   | Laboratory  | Treatment   |
|---|---|---|
| <b>Iron deficiency</b>                              | <ul style="list-style-type: none"> <li>• Fe &lt; 60 µg/dL</li> <li>Transferrin &lt; 300 µg/dL</li> <li>Ferritin &lt; 80 ng/mL</li> <li>MCV &lt; 80 fL</li> <li>• Reticulocytes &lt; 2.0%</li> </ul>   | Ferrous sulfate 300 mg 3 times daily; oral iron may not correct the deficit in setting of erythropoietin use and frequent phlebotomy; consider intravenous iron |
| <b>Folate deficiency</b>                            | <ul style="list-style-type: none"> <li>• Serum folate &lt; 2-4 ng/mL</li> <li>• MCV &gt; 100 fL</li> <li>• Reticulocytes &lt; 2.0%</li> </ul>   | Folic acid 1-5 mg/day for 1-4 mos   |
| <b>Vitamin B12 deficiency</b>                       | <ul style="list-style-type: none"> <li>• Serum B12 (cyanocobalamin) &lt; 125-200 pg/mL</li> <li>MCV &gt; 100 fL</li> <li>• Reticulocytes &lt; 2.0%</li> </ul>   | Vitamin B12 1 mg/day intramuscular injection for 7 days, then once wkly x 4, then monthly until malabsorption resolved  |
| <b>Parvovirus B19</b>                               | <ul style="list-style-type: none"> <li>• Severe anemia (hemoglobin &lt; 10 g/dL, hematocrit &lt; 24%), typically with normal neutrophils and platelets</li> <li>• PCR or DNA dot-blot hybridization for parvovirus B19</li> </ul>   | HIV suppressive antiretroviral therapy may be effective   |
| <b>HIV</b>  | <ul style="list-style-type: none"> <li>• MCV low/normal</li> <li>• Normal bone marrow iron</li> <li>• Low erythropoietin level, but laboratory appearance of iron deficiency anemia with Fe &lt; 60 µg/dL, transferrin &lt; 300 µg/dL, ferritin &gt; 100 ng/mL</li> </ul> | Antiretroviral therapy, hematopoietic growth factors  |
| <b>Marrow infiltration by tumor or infection</b>    | <ul style="list-style-type: none"> <li>• MCV 80-100 fL</li> <li>• Reticulocytes &lt; 2.0%</li> <li>• Possible pancytopenia</li> <li>• Bone marrow biopsy abnormal</li> </ul>  | Treat the specific cause  |
| <b>Drug-induced anemia</b>                          | <ul style="list-style-type: none"> <li>• MCV &gt; 100 fL with zidovudine (and stavudine)</li> </ul>   | Discontinue drug or use hematopoietic growth factors with antiretroviral cause  |
| <b>G6PD deficiency, and other hemolytic anemias</b> | <ul style="list-style-type: none"> <li>• MCV 80-100 fL</li> <li>Reticulocytes &gt; 2.0%</li> <li>• Indirect bilirubin &gt; 1.2 mg/dL LDH &gt; 220 IU/L</li> <li>• Haptoglobin &lt; 25 mg/dL</li> </ul>  | Severe methemoglobinemia (in patients without G6PD deficiency) can be treated with intravenous methylene blue 1 mg/kg   |