

# Thrombocytopenia in HIV

## Thrombocytopenia in HIV is challenging and difficult to treat.

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Thrombocytopenia in HIV can at times be a very challenging illness to treat, mainly because of its multifactorial aetiology. The astute practitioner should be aware of all these possibilities so that the necessary tests are done initially and the correct treatment started. Knowledge of megakaryocyte physiology helps to understand the condition.

### Thrombopoiesis

The exact mechanisms of thrombopoiesis are still not fully understood. We know that between 1 000 – 3 000 platelets are derived from a megakaryocyte, and that 30 000 - 45 000 platelets/ $\mu$ l/day are produced in the normal bone marrow. We also know that there is a physiological reserve that allows our marrow to increase production 6-fold. It has become apparent that megakaryocyte morphology plays an important role in thrombopoiesis and that large megakaryocytes produce more platelets than smaller ones. The higher the ploidy (nuclear lobulation), the higher the platelet production (preferably a ploidy > 8). Fig. 1 depicts a normal megakaryocyte.

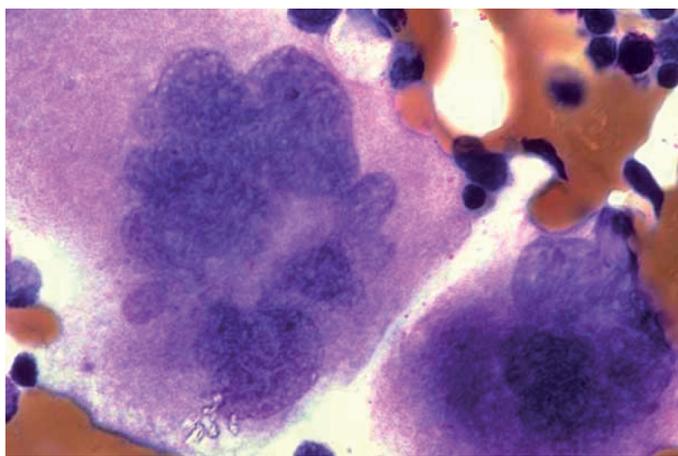


Fig. 1. A normal megakaryocyte.

The mechanisms that control platelet size are poorly understood but it seems that the body tries to maintain the total platelet mass and not the total platelet count. The total platelet mass is the **constant** derived when multiplying the total platelet count by the mean platelet volume. When the platelet count decreases, the mean platelet volume increases. When megathrombocytes (giant platelets) are seen on the peripheral smear it usually indicates peripheral consumption of platelets. There is evidence that large platelets can be produced by large and small megakaryocytes and that these large platelets may be more active than smaller ones.

### Thrombopoietin

Thrombopoietin is a molecule that is produced in the liver at a constant steady state. Its ligand, C-Mpl, is found on platelets, megakaryocytes, stem cells and other immature cells in the bone marrow. Thrombopoietin stimulates stem cells to differentiate into megakaryocytes, prevents apoptosis in megakaryocytes and stimulates megakaryocytes to proliferate in number, size and ploidy. It will also stimulate peripheral platelets and makes them sticky.

Once thrombopoietin binds with its ligand it is internalised and will then through secondary messenger systems, JCK and STAT, cause its effects. If there is a normal or increased peripheral platelet count, most of the thrombopoietin will bind to the peripheral platelets, leaving little to bind with cells in the marrow. However if the peripheral platelet count is low, more thrombopoietin will enter the marrow and bind with marrow cells, thereby stimulating the marrow to increase its output. As mentioned earlier, this output can be increased to a maximum of 6-fold. The incidence of diseases such as hepatitis B and C is increasing within the HIV-infected community and can severely hamper thrombopoietin production, due to liver damage.

### HIV and platelets

Thrombocytopenia in HIV was first described in 1982. The prevalence is more or less 40%, depending on which literature is quoted. Thrombocytopenia is associated with increased morbidity and mortality, accelerated deterioration in CD4 counts and accelerated progression to full-blown AIDS.<sup>1</sup> In a meta-analysis of 5 trials involving > 3 000 patients, both treatment-naïve and treatment-experienced patients, thrombocytopenia was found to be one of 8 factors that correlated with a poorer prognosis and more rapid progression to full-blown AIDS in spite of antiretroviral treatment.<sup>1</sup>

A recent study showed that platelets have the ability to 'engulf' the HI virus and *Staphylococcus aureus* – perhaps another reason why thrombocytopenia is prone to a more rapid acceleration of disease. Severe thrombocytopenia also limits one's treatment options, as many drugs cause bone marrow suppression and peripheral platelet consumption.

Other authors have maintained that there is a causal relationship between *Haemophilus pylori* infection and thrombocytopenia in HIV and insist on eradication therapy as part of their treatment strategy. This association has however not been reproducible in other centres.

HIV enters the megakaryocytes and platelets via the CXCR4 receptors. Once the virus is in the megakaryocyte it starts to cause havoc, as shown by the change in megakaryocyte morphology. The following are common signs of HIV in the bone marrow:

- dysplasia in the bone marrow
- naked nuclei or bare nuclei – apoptotic megakaryocytes
- hypolobation of the nuclei
- tendency to form discrete separate nuclear lobules
- clustering of the megakaryocytes.

Fig. 2 depicts a dysplastic megakaryocyte.

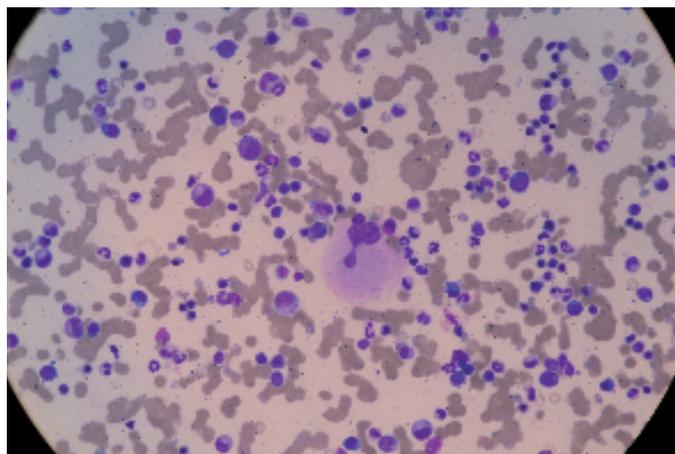


Fig. 2. A dysplastic megakaryocyte.

Platelets have the tendency to shed their epitopes and can 'donate' their CXCR4 receptors to CD4null and CXCR4null cells, e.g. cardiac muscle and astrocytes in the brain, thereby allowing these cells to be infected.

The gp120 Ab directed towards HIV can and does cross-react with the GP111A receptor on the platelet, as does the P24 Ab. The Ab can be found coated to HIV-infected individuals with normal platelet counts. Platelet life span is decreased in HIV-induced idiopathic thrombocytopenic purpura (ITP) and in HIV patients without ITP.

It seems as if HIV stimulates CD5+ cells to produce IgM rheumatoid antibodies directed against the Fc portion of IgG antibodies as well as Ab directed to the F(Ab)2 portion of the anti GP111A Ab, thereby protecting the platelet. Thrombocytopenia early on in HIV is mainly due to peripheral destruction, while later on in the advanced stage (AIDS) it is more likely to be due to decreased production. In fact, CD4 counts above 200 are associated with increased peripheral destruction while thrombocytopenia in CD4 counts of < 200 is associated with decreased platelet production.

In one study the authors found a 3-fold increase in megakaryocytes in patients with HIV. However, there was no increase in the mean platelet mass, suggesting the presence of dysmegakaryopoiesis. This suggests that thrombocytopenia in HIV is multifactorial because of:

- direct HIV infection of the megakaryocyte, causing apoptosis
- dysmegakaryopoiesis, abnormal and dysfunctional production of megakaryocytes and platelets
- peripheral destruction of platelets due to cross-reactivity of HIV Abs.

### Who to treat

This is probably one of the most difficult questions to answer along with 'how to treat'. There are no standardised guidelines in the treatment of HIV-induced thrombocytopenia and there is a paucity of forthcoming trials on this topic since antiretrovirals have become commonly used. Most trials available are small,

uni-centre, non-RCT, and do not include triple therapy, only AZT monotherapy.

The generally accepted guideline is to treat when there are < 30 000 platelets or < 50 000 if the patient is on warfarin or a haemophiliac.<sup>6</sup> One must still remember that thrombocytopenia correlates with a poorer outcome and accelerated HIV course and at least a 2-fold increase in mortality. In opposition to this, treatment of thrombocytopenia is immunosuppressive in its nature and therefore should be given in conjunction with antiretrovirals. If this is early on in the disease, it may cause problems with long-term compliance or with the local centres providing antiretrovirals, because they are subjected to dogmatic criteria from the DOH. A platelet count of 50 post-treatment is quite acceptable for protection against bleeding, but still does predict a poorer outcome with regards to mortality and morbidity.

Therefore thrombocytopenia occurs as a result of:

- increased peripheral destruction or
- increased peripheral sequestration or
- decreased production or
- a combination of the above.

### Table I. Drugs that directly affect thrombopoiesis

- Co-trimoxazole
- Pentamidine
- Pyrimethamine
- Ganciclovir
- Fluconazole
- Rifabutin
- Alpha-interferon
- Clarithromycin
- Didanosine
- Amphotericin B
- Indinavir
- Ritonavir

Table I lists drugs that directly affect thrombopoiesis. The causes of thrombocytopenia are listed in Table II.

### Approach to management

As with any other patient, start with a good history. Try to ascertain how long the problem has been going on and the clinical severity. It is also of value to find out about recent infections, any recent medications taken and any traditional medicines. A full blood count is recommended with a peripheral smear, as well as antinuclear factor, syphilis serology and if the diagnosis of HIV has just been made, then viral load and CD4 counts. The policy in my department and of most other centres is to do a bone marrow biopsy, to assess megakaryocyte numbers and morphology. One can then easily exclude granulomas, Kaposi's sarcoma and lymphoma or even fibrosis in the marrow. It is policy in my department to do a TB culture with every marrow done on an HIV-positive individual.

Once the decision is made to treat, then the difficulty is deciding how to treat.

### Steroids

A dose of 1 mg/kg/day prednisone should be started as a first-line therapy. Monitor the platelet counts regularly and be alert for opportunistic infections. If no response is seen within a 2-week period, one can try a higher dosage of 2 mg/kg/day. This is the dosage used in the HIV-negative cohort. These patients should be monitored carefully and be on antiretrovirals. Patients

**Table II. Causes of thrombocytopenia**

**Decreased production**

- Haematinic deficiencies, e.g. folate vit B12
- Dysmegakaryopoiesis (direct HIV infection, drugs, cytokines from other infections or malignancies, etc.)
- Direct infections of the bone marrow
- Malignancies infiltrating the bone marrow
- Amegakaryopoiesis, hereditary causes (May-Hegglin, etc.)
- Drugs: delavirdine and nelfinavir (see Table I)

**Peripheral consumption**

- Idiopathic thrombocytopenic purpura
- Diffuse intravascular coagulopathy
- Thrombotic thrombocytopenic purpura

**Peripheral sequestration/hypersplenism**

- Infections
- Haemophagocytosis
- Cirrhosis

should not stay on high-dosage therapy for more than a month. If no response or a nominal response is seen, it should be considered as treatment failure and alternative treatment given. I find it most risky to keep patients on low-dose steroids for protracted periods of time, due to the side-effects and the immunosuppression.

Prednisone does not stimulate viral replication but does however accelerate the course of Kaposi's sarcoma.<sup>2</sup>

*Intravenous immunoglobulin*

Intravenous immunoglobulin (IVIg) is effective in raising a patient's platelet counts. However, it is not cheap and results can be timeous and short lasting. It is not a cost-effective way of maintaining a platelet count and should only be used in chronic cases as a last resort. In the acute setting it is good for raising counts prior to a splenectomy or if patients have severe or uncontrollable haemorrhage. This would then be used in conjunction with platelet transfusions. The exact mechanisms of action are not entirely understood – suffice to say that excessive immunoglobulin (Ig) overwhelms the immune system and stimulates the suppressor B cells to suppress endogenous Ig production. The IVIg also blocks the Fc receptors in the spleen and macrophages, thereby limiting their platelet-destroying function. The dosage of the IVIg can differ from 0.5 g/kg to 2 g/kg either as a bolus but mostly given over 2 - 5 days. The cost and availability of IVIg are the most limiting factors.

*Anti-D*

The anti-rhesus globulin can also be used with varying success. This should not be used in patients who are Rh+ as it may cause haemolysis. It can however be used if the patient has a normal haemoglobin. Its effects, if there is going to be a response, are said to be longer lasting than IVIg.

*Splenectomy*

Splenectomy is the usual 2nd-line of therapy with the HIV-negative cohort. There were concerns initially that it would accelerate the course of HIV. This was before antiretroviral therapy was commonly available. At the moment, besides the concerns of infections from capsulated organisms and malaria, splenectomy may be a good alternative.<sup>3</sup> The literature has shown splenectomy to attenuate immune reconstitution syndrome and has shown to produce patients with a higher CD4 and CD8 counts along with a slower progression to AIDS.

Splenic irradiation is of no value in this situation.

*Megestrol acetate*

This drug was initially used to treat cachexia and anorexia in HIV. It is known

to block the Fc receptors in macrophages. Trials have shown that megestrol acetate (MA) increases peripheral platelet counts and improves platelet survival. There were no improvements in body mass index (BMI), peripheral CD4 counts or viral loads.

Danazol is still of value in idiopathic thrombocytopenic purpura, even in HIV-induced ITP.<sup>4</sup>

*Transfusions*

Transfusions have a transient effect, they are expensive and should be limited to emergencies and theatre. Normally they should be given with IVIg to have a longer lasting effect. Transfusions have other side-effects, e.g. transfusion reactions, infections and transfusion-related acute lung injury (TRALI). Multiple transfusions are known to decrease immunity and stimulate HIV-1 expression.

*Novel therapies*

These are still in experimental phases but include entities such as recombinant thrombopoietin, alpha interferon and Il-6, Il-3, and Il-11. Vincristine is very seldom used.

*Thrombotic thrombocytopenic purpura*

This is a severe haemolytic disorder characterised by fragmentation of the red cells, low platelets and purpura. In severe and neglected cases renal impairment and cerebrovascular signs are seen. The basic pathophysiology is due to a deficient or dysfunctional protease ADAMTS-13. This protease cleaves the large von Willebrand molecules into smaller molecules, allowing haemostasis to occur. This disease is seen in the HIV-negative and positive cohorts. It can be seen as part of a sero-conversion disease but is mostly seen in the later stages of HIV with low CD4 counts. This disease is very common in South Africa and unfortunately still has a high mortality and morbidity, probably due to underdiagnosis, misdiagnosis and maltreatment.

There are various treatment options for this condition, ranging from plasma exchange, vincristine and cryoglobulin-poor fresh

**Transfusions have a transient effect, they are expensive and should be limited to emergencies and theatre.**

frozen plasma (FFP) with prednisone 1 mg/kg/day. The effectiveness of using cryo-poor FFP and prednisone is similar to plasma exchange and is a practical and viable alternative treatment option for caregivers in the rural settings.<sup>5</sup> At least treatment can be initiated locally and the patient stabilised before transferring to a main centre.

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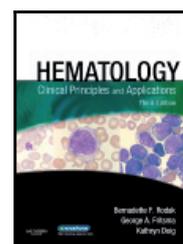
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## In a nutshell

- Thrombocytopenia in HIV is common and multifactorial.
- Normal megakaryocyte morphology is important to maintain normal thrombopoiesis.
- Thrombocytopenia early on in the disease is generally due to peripheral destruction and has large platelets, while in AIDS it is usually associated with decreased production.
- Thrombocytopenia, irrespective of cause and concomitant antiretroviral therapy, is associated with a poorer outcome and accelerated decrease in CD4 counts and AIDS progression.
- An initial bone marrow biopsy is mandatory to assess the thrombopoiesis, among other things, along with CD4 count and viral load.
- Consider starting antiretrovirals when active treatment is decided on, especially when using immunosuppressive agents.
- DO NOT leave patients on steroids for protracted periods without antiretroviral cover and be vigilant for opportunistic infections.
- Always consider thrombotic thrombocytopenic purpura as a cause of thrombocytopenia in HIV.
- If no plasma exchange facility is available or if one chooses not to use it, always use cryo-precipitate-poor FFP, along with steroids and start antiretrovirals.
- When in doubt, refer and leave the decision of splenectomy to specialists.

## Hematology, 3rd edition Clinical Principles and Applications

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