HIV and haematopoiesis

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Human immunodeficiency virus (HIV) infection not only leads to a compromised immune system, but also disrupts normal haematopoiesis, resulting in the frequent manifestation of cytopenias (anaemia, thrombocytopenia and neutropenia). Although there is a definite association between the severity of cytopenia and HIV disease stage, this relationship is not always linear. For example, cytopenias such as thrombocytopenia may occur during early stages of infection. The aetiology of these haematological abnormalities is complex and multifactorial, including drug-induced impaired haematopoiesis, bone marrow suppression due to infiltration of infectious agents or malignant cells, HIV-induced impaired haematopoiesis, and several other factors. In this review, we describe the frequencies of anaemia, thrombocytopenia and neutropenia reported for HIV-infected, treatment-naïve cohorts studied in eastern and southern sub-Saharan African countries. We present a rational approach for the use of diagnostic tests during the workup of HIV-infected patients presenting with cytopenia, and discuss how HIV impacts on haematopoietic stem/progenitor cells (HSPCs) resulting in impaired haematopoiesis. Finally, we describe the direct and indirect effects of HIV on HSPCs which result in defective haematopoiesis leading to cytopenias.

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The 2017 World Health Organization report[1] indicates that ~37 million people are infected with human immunodeficiency virus (HIV) in sub-Saharan Africa. Southern and eastern sub-Saharan Africa are most affected by the pandemic, contributing 53% of global HIV-infected cases. With ~7 million persons infected (12.6% of the total population), South Africa (SA) carries the highest HIV-associated disease burden in this region.[1] As its name indicates, HIV targets the immune system, resulting in progressive immune dysfunction. HIV infection leads not only to a weakened immune system, but also impacts negatively on the haematopoietic system of infected individuals. This is not surprising, as a close link exists between the haematopoietic and immune systems.

Haematopoietic stem/progenitor cells

Haematopoietic stem/progenitor cells (HSPCs) constitute a heterogeneous population that resides in the bone marrow (BM) and has the ability to differentiate into all the mature blood cell types (Fig. 1), thereby contributing to continuous maintenance of healthy blood cell production (haematopoiesis).[2]

It is currently not possible to distinguish between true haematopoietic stem cells (HSCs) and early haematopoietic progenitor cells (HPCs). Both true (primitive) stem cells and progenitors reside in the bone marrow and both sub-populations have self-renewal properties, in addition to their differentiation capabilities.[3] In this review

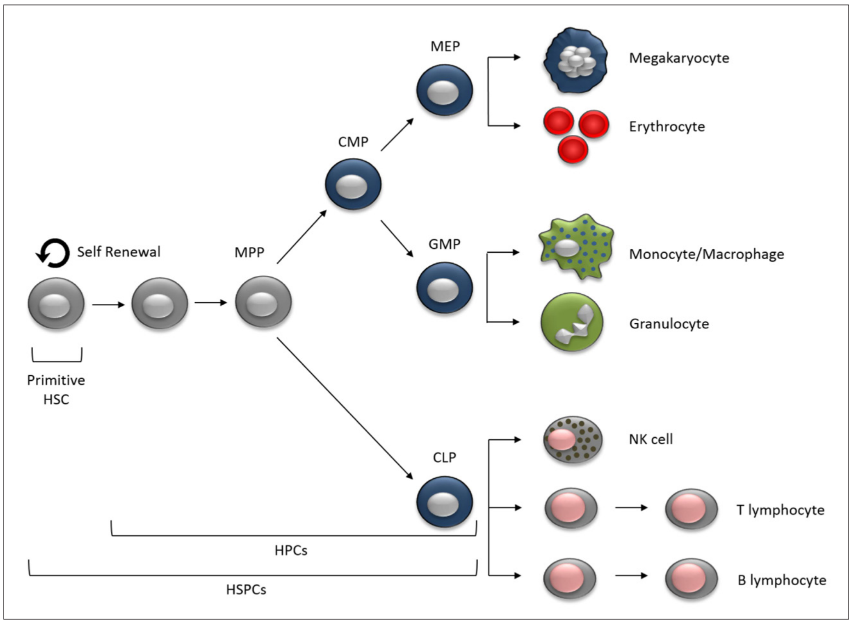

Fig. 1. Schematic illustration of the differentiation of haematopoietic stem/progenitor cells (HSPCs) into mature blood cell types. (MPP = multipotent progenitor; CMP = common myeloid progenitor; CLP = common lymphoid progenitor; MEP = megakaryocyte-erythroid progenitor; GMP = granulocyte-macrophage progenitor; NK = natural killer cell.)

we have therefore opted to collectively refer to these cells as HSPCs, which encompasses both HSCs and HPCs. Progressive depletion of HSPCs or suppression of HSPC function both result in defective haematopoiesis which manifests clinically as cytopenias.

Cytopenias are indeed common in HIV-infected individuals and are briefly summarised later in the review. The pathophysiology of the haematological abnormalities have not been fully elucidated, but has been suggested to be complex and multifactorial.[4] The pathophysiology of cytopenias can broadly be divided into two groups: factors (*i*) directly associated with the impact of HIV on HSPC function, and (*ii*) not directly associated with HSPC function. The suggested mechanisms directly resulting from HIV are briefly discussed in this review, while factors not directly associated with HSPC function are summarised in Fig. 2.

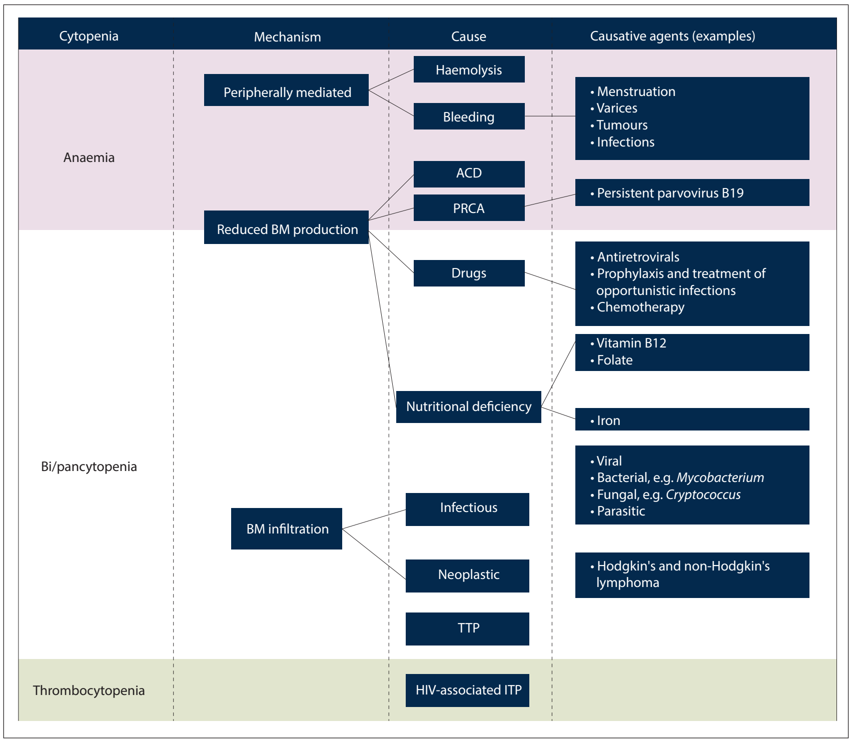

Fig. 2. A schematic breakdown of the most relevant non HSPC-associated causes that contribute to the development of cytopenias in infected individuals. The pink block (top) summarises causes that result in the presentation of isolated anaemia. The white area summarises causes that may lead to multiple cytopenias simultaneously (bi- or pancytopenias). HIV-associated ITP (green block, bottom) leads to the presentation of isolated thrombocytopenia. (BM = bone marrow; ACD = anaemia of chronic disease; PRCA = pure red cell aplasia; TP = thrombotic thrombocytopenic purpura; ITP = immune thrombocytopenic purpura.)

Haematological abnormalities

Cytopenias are the most common haematological abnormality associated with HIV infection and may affect any of the major blood lineages leading to anaemia, thrombocytopenia and/or neutropenia.[4,5] The prevalence of cytopenias in treatment-naïve HIV-infected adult cohorts, reported between 2010 and 2018, in English-speaking eastern and southern sub-Saharan African countries, is summarised in Fig. 3. There are no published reports available from French-speaking countries in the eastern and southern sub-Saharan African region. These countries include: Ethiopia (10 reports);[6-15] Malawi (1 report);[16] SA (6 reports);[17-21] Rwanda (1 report);[22] Tanzania (1 report);[23] Uganda (4 reports);[24-27] and Zimbabwe (1 report).[19] The size of the cohorts ranged from 30 - 15 030 patients.

The severity and prevalence of cytopenias are associated with disease stage and generally improve with combination antiretroviral therapy (cART). Severe cytopenias, especially anaemia and thrombocytopenia, are associated with increased morbidity and poorer quality of life.[7,10,17] HIV-associated haematological abnormalities should be managed appropriately by healthcare providers.[4,5] The diagnosis and treatment of haematological abnormalities in HIV-infected individuals have been comprehensively reviewed elsewhere.[4,5]

Criteria used to define cytopenias

The criteria used by the respective studies represented in Fig. 3 to define anaemia, thrombocytopenia and neutropenia are listed in Table 1.

The most common cytopenias observed in HIV-infected individuals in the English-speaking eastern and southern sub-Saharan region are briefly discussed below. The frequencies of anaemia, thrombocytopenia, neutropenia represent the percentage of individuals, within the respective study populations (Fig. 3), who presented with the specific cytopenia, irrespective of it being observed in the presence of other cytopenias (bi- and pancytopenia). The reported percentages are thus not necessarily representative of isolated cytopenias.

Anaemia

Anaemia is the most common cytopenia observed in HIV-infected individuals and is often associated with other cytopenias (Fig. 2). The reported prevalence of anaemia ranges from 8.4% to 70% (median 29.9; interquartile range (IQR) 21.2 - 52.6) (Fig. 3) in the treatment-naïve cohorts studied.[6-10,13-25,27-30] The severity of anaemia is often used as an indicator of a poor prognosis in resource-poor settings, independent of the CD4 count. This practice should be discouraged as some causes of anaemia, such as nutritional deficiencies, are unrelated to HIV infection and disease stage (Fig. 2).[7] Factors causing anaemia in HIV-infected individuals can broadly be divided into three main categories: (*i*) decreased red blood cell (RBC) production in the BM; (*ii*) increased RBC destruction; and (*iii*) ineffective RBC production due to nutritional deficiencies[31] (Fig. 2). It is therefore not surprising that, despite the wide use of cART, HIV-related anaemia remains a significant problem.[4] However, recent reports indicate that HIV-infected patients generally recover from anaemia when receiving cART regimens.[7,10]

Thrombocytopenia

The reported prevalence of thrombocytopenia ranges from 4.1% to 26.7% (median 16.2; IQR 12.0 - 25.1) (Fig. 3) in the treatment-naïve cohorts studied.[7,8,11,12,21-26] Although the prevalence and severity of thrombocytopenia is associated with disease stage, the relationship is not always linear as newly infected patients with HIV may also present with thrombocytopenia.[4] Thrombocytopenia is also more frequently

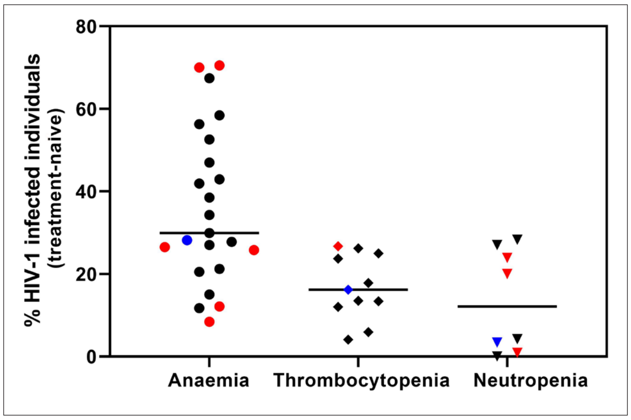

Fig. 3. Prevalence of cytopenias reported in HIV-infected, treatment-naive cohorts. Scatter dot plot is used to illustrate the percentage ranges reported in 22 (anaemia),[6-10,13-25,27-30] *8 (thrombocytopenia)*[7,8,11,12,21-26] *and 6 (neutropenia)*[7,8,19,21,22,25,30] *studies (black symbols). Median percentages are indicated by a solid black horizontal line within each group (cytopenia). Red symbols indicate frequencies reported in South African studies. Blue symbols represent data obtained from an HIV-infected, treatment-naive cohort at Eersterust Community Health Clinic, Pretoria, South Africa, between February and July 2016 (n=117; unpublished data).*

Table 1. Criteria used to define cytopenias

Cytopenia	Criteria	References*
Anaemia (Hb; g/dL)	<9.5	16, 20
	<10	6, 11, 12, 15, 17, 22
	<10.5	9
	<13 (males) <12 (females)	7, 8, 10, 13, 21, 24-26
	<14 (males) <12 (females)	14, 19
	<12 (males) <10 (females)	18, 27
Thrombocytopenia (platelet count; 10^3/μL)	<125	18, 19, 24, 26, 28
	<150	7, 29
	<125 (females) <156 (males)	27
	<750	11, 20
Neutropenia (Neutrophil count; cells/μL)	<1 000	7
	<1 000 WBC <2 000	18
	<2 000	19

WBC = white blood cells.
*Some studies did not mention the criteria that were used and were therefore excluded from the table.

seen in patients with viral hepatitis co-infection. The main causes of thrombocytopenia are inadequate platelet production and/or auto-immune-mediated platelet destruction.[24]

Immune thrombocytopenic purpura (ITP) is the most common cause of thrombocytopenia in HIV-infected individuals, and often occurs at the initial stages of infection.[4,5] The pathogenesis of ITP is still not clear, but both antibody-mediated and/or T cell-mediated processes seem to be involved in ITP-associated platelet destruction.[32] However, it is not clear if both these processes are also involved in HIV-associated ITP. The manifestation of ITP appears to be primarily in response to an auto-immune reaction in which HIV envelope glycoprotein 160/120 antigens are recognised by the immune system to be similar to the immunodominant GPIIIa49-66 epitope of platelet glycoprotein IIIa (GPIIIa) integrin through a process called molecular mimicry. This gives rise to cross-reactive anti-platelet auto-antibodies and ultimately auto-immune mediated platelet destruction.[32] Although ITP occurs more frequently during the initial stages of HIV infection, it may manifest at any stage of the disease.[5]

In addition, HIV-infected individuals, particularly those with advanced disease, have elevated serum markers of systemic immune activation including C-reactive protein (CRP).[33] CRP enhances IgG-mediated platelet destruction by binding to phagocytes where it enhances phagocytosis of opsonised platelets.[34] This role of CRP provides important insight into the onset and exacerbations of ITP in the broad setting of systemic immune activation secondary to chronic infection.

The more severe and potentially lethal thrombotic thrombocytopenic purpura (TTP) manifests less frequently than ITP. HIV is the most common virus precipitating TTP[5] and the most common cause of TTP in SA. In general, women are more affected by idiopathic TTP than men.[5,35] Furthermore, treatment-naïve African females with advanced HIV are at a significantly higher risk of presenting with TTP, suggesting a potential underlying genetic pre-disposition in the African female population.[35] Acquired TTP is an auto-immune disease caused by circulating auto-antibodies to the metabolically active A Disintegrin And Metalloproteinase with Thrombospondin type 1 Motif 13 (ADAMTS13) enzyme.[35] Ineffective cleavage by ADAMTS13 leads to ultra-large, uncleaved von Willebrand factor (VWF) strings, which bind to platelets to form microthrombi causing intravascular haemolysis and organ ischaemia.[5] The exact role of HIV in the pathophysiology of TTP is, however, still not clear. Because of the severity of TTP, it is important to rule it out in HIV-infected individuals, especially African women, presenting with severe thrombocytopenia.[4] As most automatic haematology analysers are unable to reliably detect and report erythrocyte fragments, it is important to request a blood smear investigation when TTP is suspected.

HIV-associated neutropenia

Neutropenia has been reported in 0% to 28.3% (median 12.1%; IQR 1.5 - 26.2%) (Fig. 3) of treatment-naïve patients studied.[7,8,19-22,25,30] The wide range of frequencies reported for HIV-associated neutropenia is likely to be associated with the severity of HIV disease and the use of prophylactic drugs, such as cotrimoxazole, which is known to cause bone marrow suppression through the inhibition of folic acid metabolism. A low CD4 T cell count and high HIV plasma viral load are risk factors for developing neutropenia. Thus, neutropenia is especially prevalent in persons with advanced disease and is usually associated with other cytopenias, i.e. bicytopenia and pancytopenia (Fig. 2).[13,23,25] In addition, neutropenia severity is related to risk of opportunistic co-infection, with a count below 1 ×10^9 neutrophils/L indicating a significantly increased risk.[4] Benign, ethnic neutropenia has a high prevalence in individuals of African descent.[36,37] Therefore, ethnic neutropenia should be considered and ruled out in individuals who present with low neutrophil counts (<2 500 cells/μL).[38]

Direct effect of HIV on haematopoiesis: Suggested mechanisms

Morphological changes of secondary dysplasia are often observed in the bone marrow of HIV-infected individuals. HIV itself may be responsible for impaired haematopoiesis, either through (*i*) direct infection of HSPCs, (*ii*) HIV-induced apoptosis of HSPCs, (*iii*) disruption of the optimal functioning of the stromal cell network within the bone marrow, (*iv*) HIV-associated auto-immune reactions; and/or (*v*) through HIV-induced changes in cell signalling events regulating proliferation and differentiation of HSPCs. These mechanisms ultimately lead to the depletion of HSPCs and/or an altered proliferation and differentiation capacity of their progeny. These five mechanisms are briefly discussed below.

Direct infection of HSPCs

C-C motif chemokine receptor type 5 (CCR5) and C-X-C motif chemokine receptor type 4 (CXCR4) are co-receptors which, together with CD4, enable receptor-mediated entry of HIV into host cells, such as CD4$^+$ T cells.[39] As HSPCs express low levels of CD4[40,41] and variable levels of CCR5 and CXCR4,[42] they are potentially susceptible to HIV infection. Primitive HSCs (Fig. 1) tend to express CXCR4, but not CCR5, suggesting that primitive HSCs are more susceptible to CXCR4-tropic virus.[43,44] This observation may explain the rapid disease progression upon viral transition from CCR5 to the more virulent CXCR4 tropism.[45] However, the jury is still out as to whether HIV is able to directly infect HSPCs. Carter *et al.*[42] and Nixon *et al.*, [43] among others, propose that HIV is able to infect HSPCs and thereby contribute to a latent reservoir pool. Other authors[46,47] oppose this view as they could find no evidence of HIV infection in HSPCs. Despite uncertainty about direct infection, *in vitro* and *ex vivo* studies have shown that HIV decreases the ability of HSPCs to optimally proliferate and differentiate into mature blood cell lineages.[5,40]

The majority of studies that have investigated the ability of HIV to infect HSPCs are laboratory-based.[40-42,47,48] Due to ethical and logistical challenges related to obtaining sufficient volumes of bone marrow aspirate from HIV-infected individuals, patient (*ex vivo*)-based studies are scarce. In an isolated study, Redd *et al.*[40] reported that HIV-1 subtype C (HIV-1C), but not HIV-1 subtype B (HIV-1B), has the potential to infect HSCs. Several studies have suggested that the pathogenicity of HIV-1C may differ significantly from HIV-1B.[51,52] HIV-1C is reported to be less cytopathic than other subtypes, which may result in a greater ability to persist in a latent form for long periods of time in infected host cells.[52] This may have important implications for sub-Saharan African populations, which have the world's largest proportion of HIV-1C infections.

HIV-induced apoptosis of HSPCs

In vitro studies have shown that antibody/viral protein complexes such as anti-gp120/gp120 complexes are able to bind with high affinity to CD4 molecules expressed on the surface of HSPCs and in so doing induce apoptosis via a Fas-dependent mechanism. This mechanism is independent of direct HIV infection of HSPCs. Viral proteins such as gp120 and Tat not only seem to play a role in HIV-mediated apoptosis of HSPCs, but also impair proliferation of HSPCs by increasing the production of transforming growth factor β1 (TGFβ1), a negative regulator of haematopoiesis, by HSPCs.[53,54]

Impaired stromal cell network in the bone marrow niche

The bone marrow stroma refers to the cellular fraction of the bone marrow, excluding HSPCs. Bone marrow stroma consists of a heterogeneous pool of cells, including macrophages, endothelial cells, mesenchymal stromal cells and Schwann cells.[55] An optimal bone marrow stroma micro-environment is essential for the maintenance, regulation and support of HSC proliferation and differentiation. HIV infection results in changes in the bone marrow stromal structure. For example, increased numbers of fibroblasts and macrophage-like cells are observed in the bone marrow of HIV-infected individuals. In addition, bone marrow-associated macrophages are susceptible to both the CCR5- and CXCR4-tropic HIV-1 strains.[56] HIV infections also result in changes in the multipotent clonogenic potential of bone marrow-associated mesenchymal stromal cells. Both *in vitro* and *ex vivo* studies suggest that bone marrow-derived mesenchymal and endothelial cells can be directly infected with HIV, resulting in altered cytokine signalling and consequently HSPC death.[57,58] These HIV-associated alterations in bone marrow stroma composition and the cell signalling milieu result in a supporting micro-environment that is sub-optimal for HSPCs. Defective haematopoiesis therefore ensues.[54,59]

HIV-associated auto-immune reactions

The main cause of HIV-associated ITP is immune-mediated destruction of platelets due to an auto-immune reaction resulting in antibodies against HIV envelope proteins cross reacting with the GPIIIa49-66 epitope present on the surface of platelets.[60] It is also suggested that a cross reaction between anti-erythropoietin (anti-EP1) antibodies and the viral Gag fragment results in impaired erythropoiesis and the consequent manifestation of anaemia.[53]

Auto-antibody-mediated destruction of erythrocytes results in the presentation of autoimmune haemolytic anaemia (AIHA).[61] Although rare, there are reports of HIV-infected individuals that present with AIHA.[62,63] The pathophysiology of HIV-associated AIHA is not fully elucidated and several potential mechanisms have been proposed. Suggested mechanisms include abnormal B cell regulation by HIV-infected T cells, direct HIV-induced B cell activation and B-cell responses to CMV or Epstein-Barr virus.[61] It is proposed that these mechanisms lead to HIV-associated dysregulation of antibody production.[61]

HIV-mediated disruption of the cell signalling network

HIV alters the cytokine milieu within the bone marrow stroma.[54] HIV-mediated cytokine signalling disruption involves various cytokines and haematopoietic factors, such as interleukin (IL)-1, IL-6, IL-18 and granulocyte colony-stimulating factor (G-CSF) among others. These cytokines play a critical role in regulating and maintaining normal haematopoiesis and any imbalance may negatively impact on haematopoiesis. Several studies have shown that the plasma cytokine profiles of HIV-infected individuals differ from the profiles of uninfected individuals.[64,65] Higher levels of IL-1, IL-6, IL-7, G-CSF and tumour necrosis factor α (TNFα) were detected in the plasma of HIV-infected patients. Pro-inflammatory cytokines TNFα, IL-1 and IL-6 and chemokines macrophage inflammatory protein (MIP)-1α, MIP-1β and RANTES were also found to be up-regulated in the bone marrow of HIV-infected individuals.[54] This chronic dysregulation of cell signalling pathways has a negative impact on HSPC proliferation and differentiation. HIV infection also causes a decrease in endogenous G-CSF,[4,13] which in turn results in impaired proliferation and differentiation of GMPs, the progenitors that give rise to neutrophils, monocytes and macrophages (Fig. 1). It has been found that G-CSF treatment results in increased neutrophil counts and restores neutrophil function in HIV-infected individuals, reducing the risk of co-infection in neutropenic patients.[4]

Diagnostic usefulness of bone marrow examination to determine the cause of cytopenias

While it is appreciated that the causes of cytopenias in HIV are multifactorial, bone marrow aspirates and trephine biopsies may demonstrate marrow involvement by a malignant process or bone marrow infiltrating opportunistic infections, such as *Mycobacterium* *tuberculosis*.[66,67] Routine bone marrow sampling to elucidate the cause of a single cytopenia may be less valuable.[4,67] Bone marrow sampling should only be considered in the presence of multiple cytopenias, as well as constitutional symptoms such as fever.[68] A distinct advantage of marrow sampling over other diagnostic tests such as blood cultures, is the rapidity with which a diagnosis can be made and acted upon.[66,67]

Future treatment strategies involving restoration of an immune/haematopoietic system resistant to HIV-infection

In 2007, Timothy Brown, also known as the 'Berlin patient', was cured of HIV after receiving a haematopoietic stem cell transplant for acute myeloid leukaemia from a CCR5-null stem cell donor.[69] A germline mutation in the CCR5 gene (delta-32 deletion) was identified in the donor cells; all transplanted cells and their progeny were resistant to CCR5-tropic (R5) HIV-1 infection.[69] This observation has focused attention on the interactions between HIV and HSPCs and has sparked interest in using genetically modified HSPCs as a treatment strategy to eliminate HIV in infected individuals. Findings thus far are encouraging, and importantly such approaches have been shown to be safe in humans. In addition to HSPC-based CCR5-targeted gene therapy, there is increasing evidence that CCR5 gene-modified T cells may be a useful cell therapy strategy for achieving a potential HIV cure and may therefore be an attractive alternative to genetically modified HSPCs in the future.[70]

Conclusion

The severity of cytopenias (except thrombocytopenia) presented by patients infected with HIV is usually associated with advancing disease stage. Thus, clinicians should have a high index of suspicion of possible HIV infection in any patient presenting with a cytopenia. The cause of cytopenias in the context of HIV infection is usually multifactorial. In patients who are afebrile and asymptomatic, HIV itself may be the cause. Suggested mechanisms of HIV impairment of haematopoiesis include those unrelated to HIV/HSPCs interactions (e.g. drug and/or coinfection induced), indirect influence of HIV on HSPCs (e.g. HIV-induced changes in the cytokine signalling milieu) and mechanisms in which HIV directly impacts on the functioning and survival of HSPC (e.g. direct infection of HSPCs by HIV). Diagnostic workups of cytopenias should be rational, carefully employing history and clinical examination together with a logical step-wise use of laboratory tests before bone marrow sampling is considered. Lastly, further research is necessary to elucidate the interactions between HIV and HSPCs. A better understanding of these interactions may contribute to unlocking the potential contained in genetically modified cell therapies as a treatment modality for patients infected with HIV.

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Author contributions. CD: co-conceptualisation, designing, collating contributions from co-authors, drafting of manuscript. Also performed data analysis and prepared Fig. 3. JCP: assisted with drafting of manuscript and prepared Fig. 2. RK: assisted with drafting of manuscript. JGN: editing of manuscript. CLH: assisted with drafting of manuscript. Assisted JM in creating Fig. 1. JM: assisted with drafting of manuscript; created Fig. 1. TR: provided samples for pilot study (used to generate Fig. 1); assisted with editing of manuscript. MSP: initial conceptualisation and planning, as well as editing of manuscript.

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Conflicts of interest. None.

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