Cytopenias in people with Advanced HIV Disease

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Talk outline

- Definitions
- Background
- Broad concepts related to cytopenias
- An approach to:
  - Anaemia
  - Neutropenia
  - Thrombocytopenia
  - Bi- and Pancytopenia

What is Advanced HIV Disease (AHD)?

- WHO define AHD as:
  - CD4 count < 200 cells/mm
  - WHO stage 3 or 4 disease

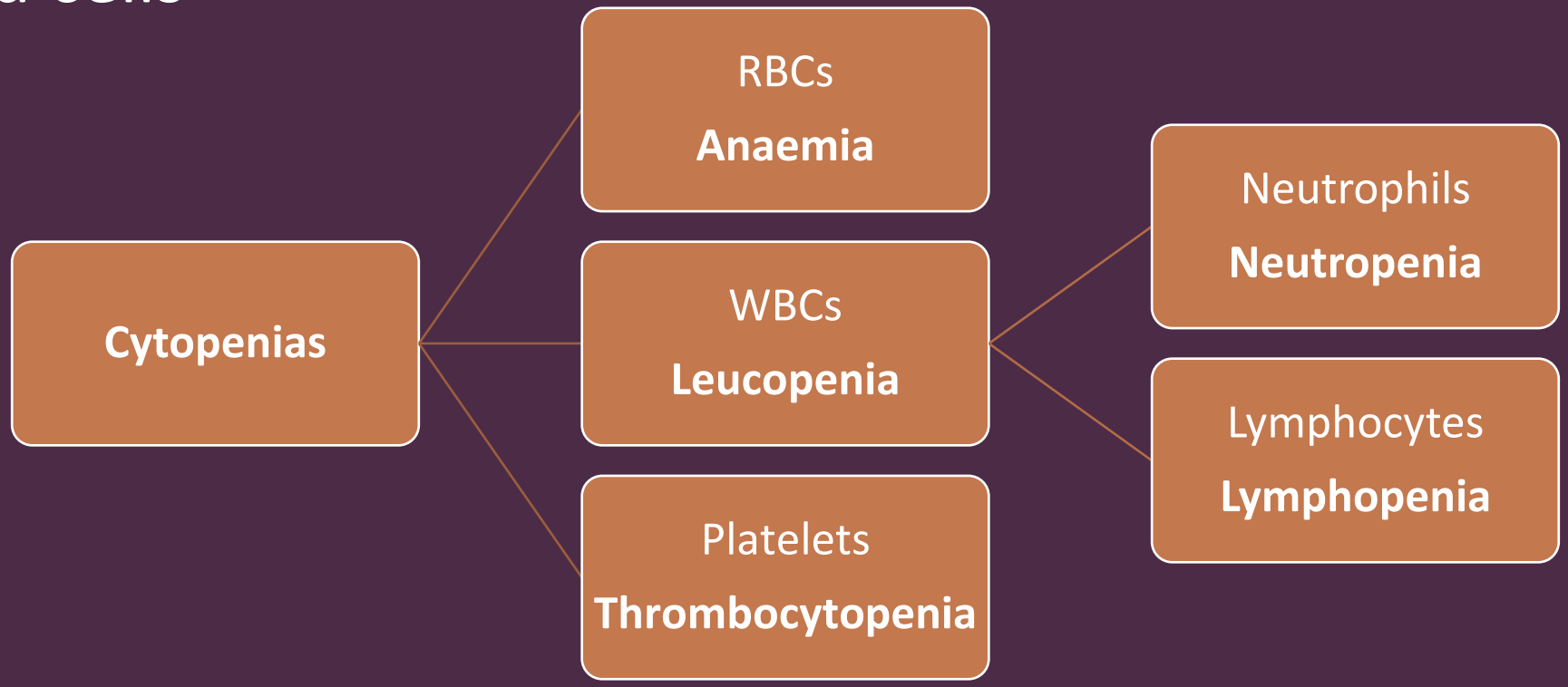
What is a cytopenia?

“cyto-” = cell

“-penia” = “poverty” or an absence, lack or deficiency of some body constituent

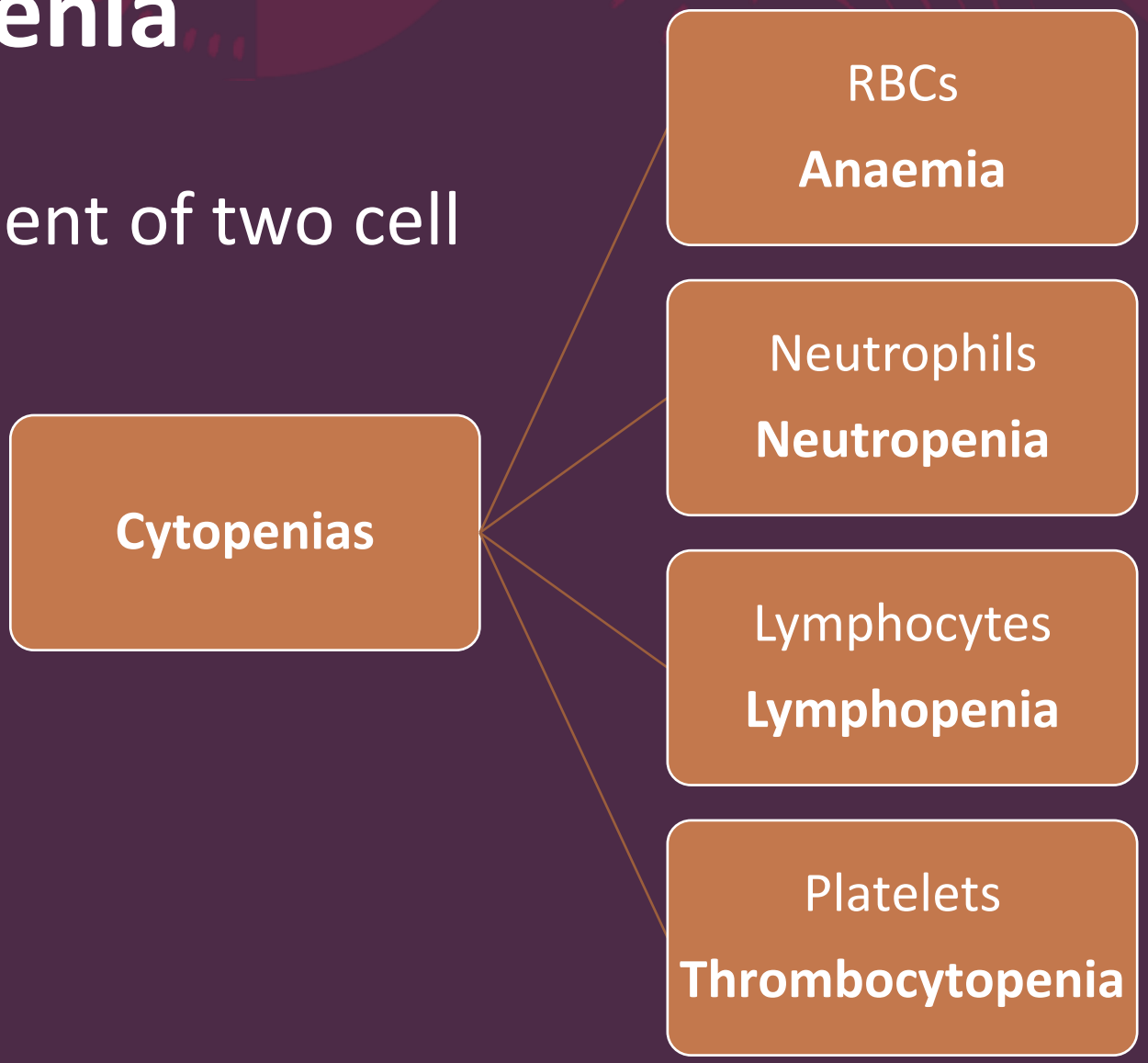
What is a cytopenia?

"cytopenia" = reduction or deficiency in number of mature blood cells

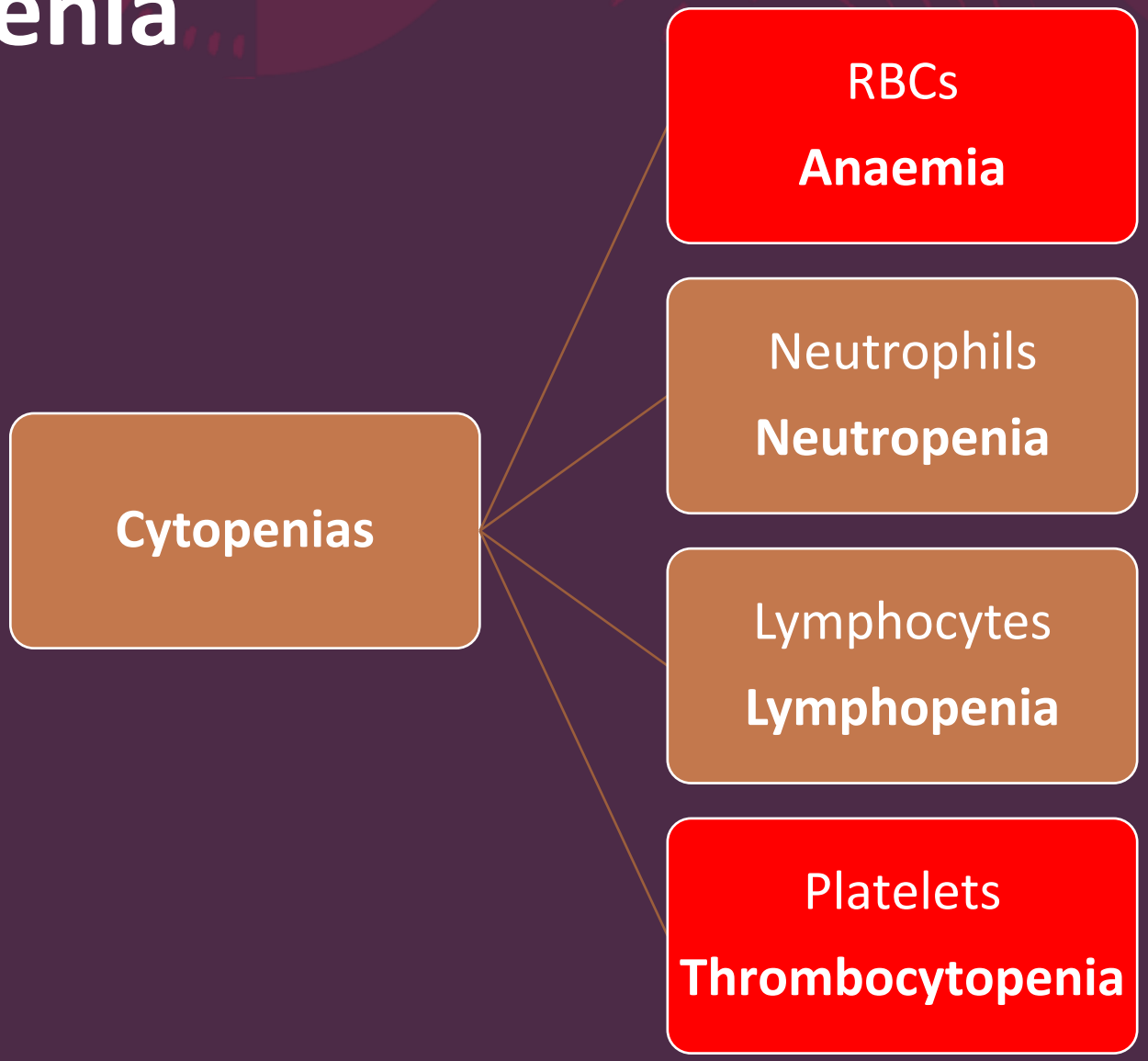


Bicytopenia

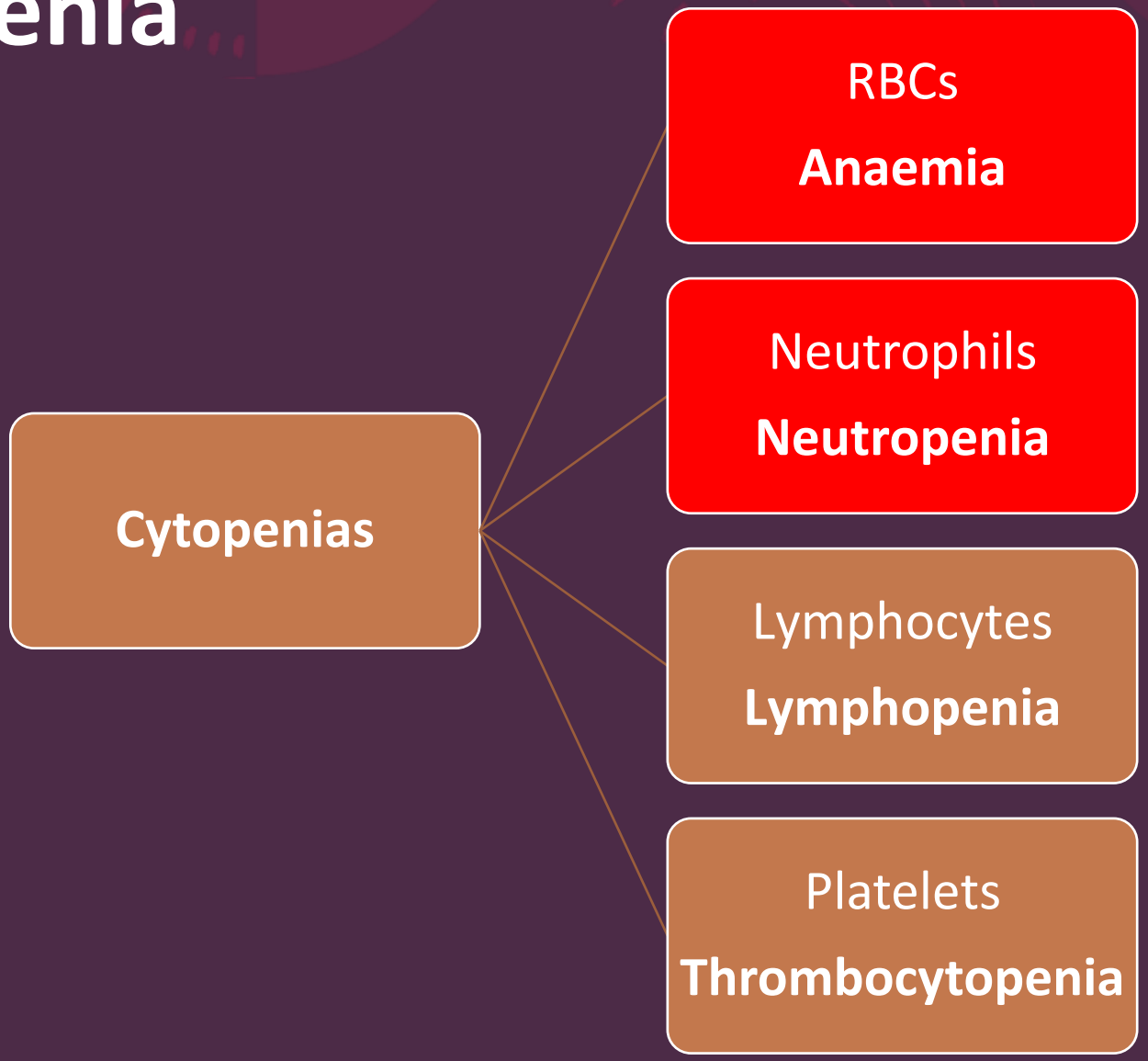
= Involvement of two cell lines



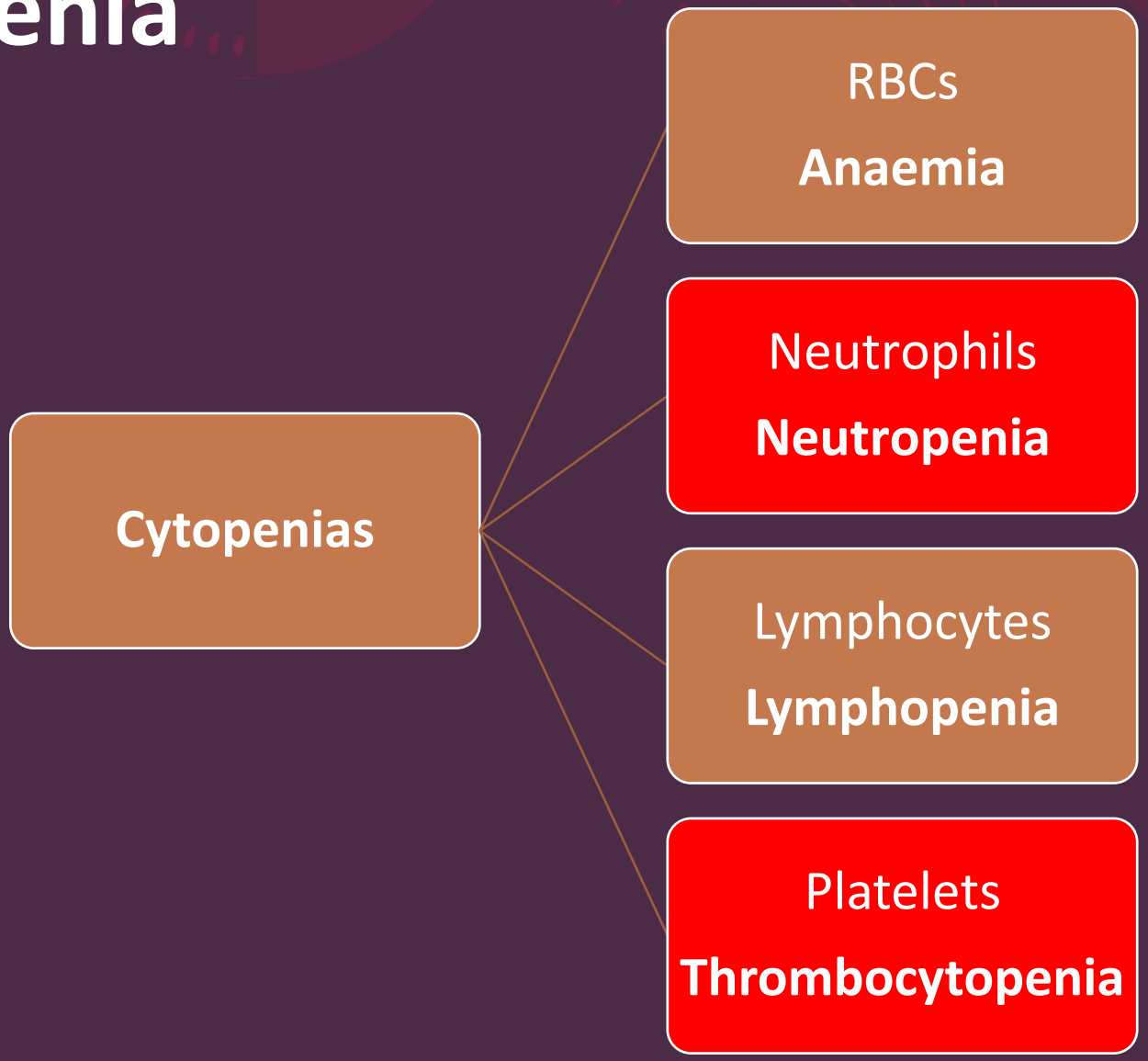
Bicytopenia



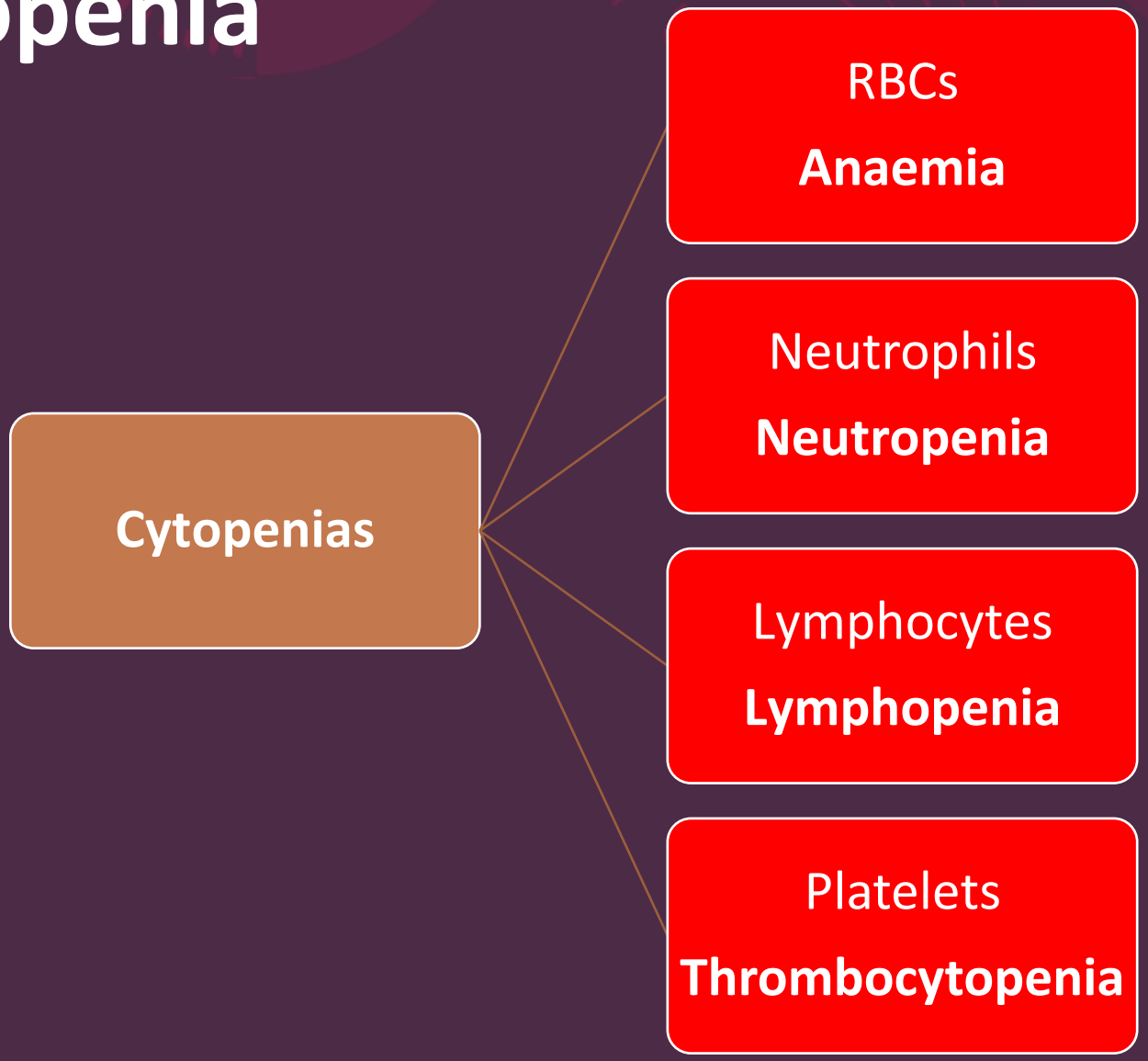
Bicytopenia



Bicytopenia



Pancytopenia

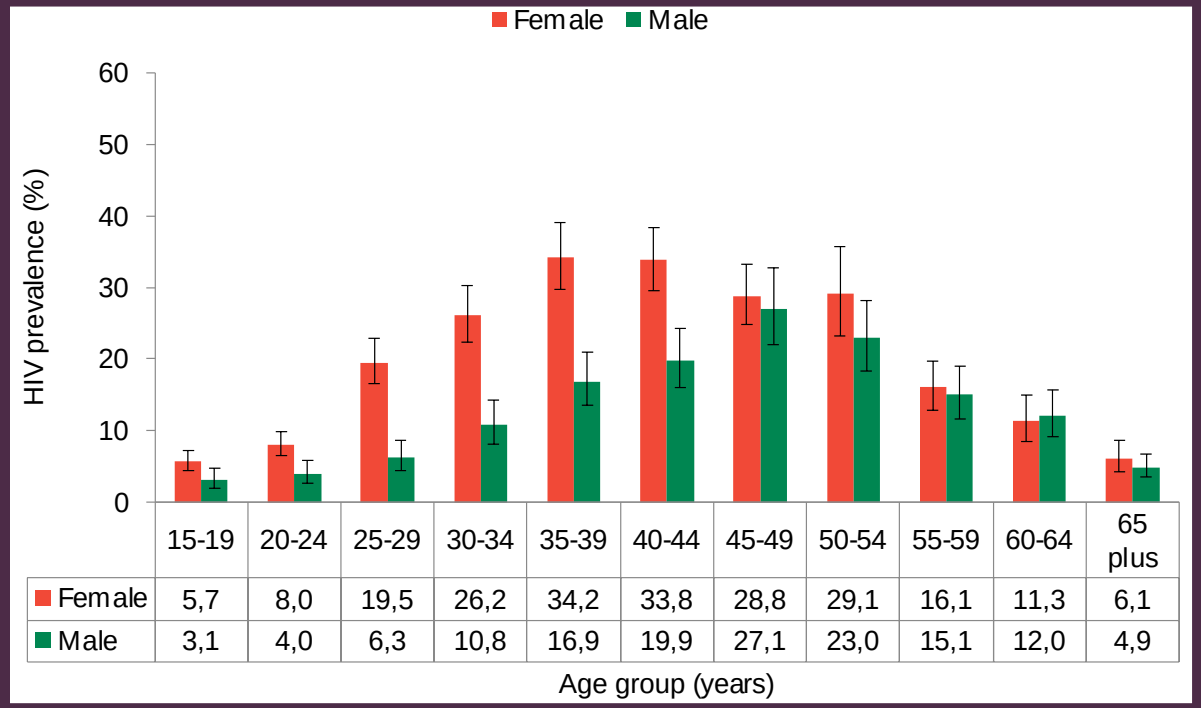


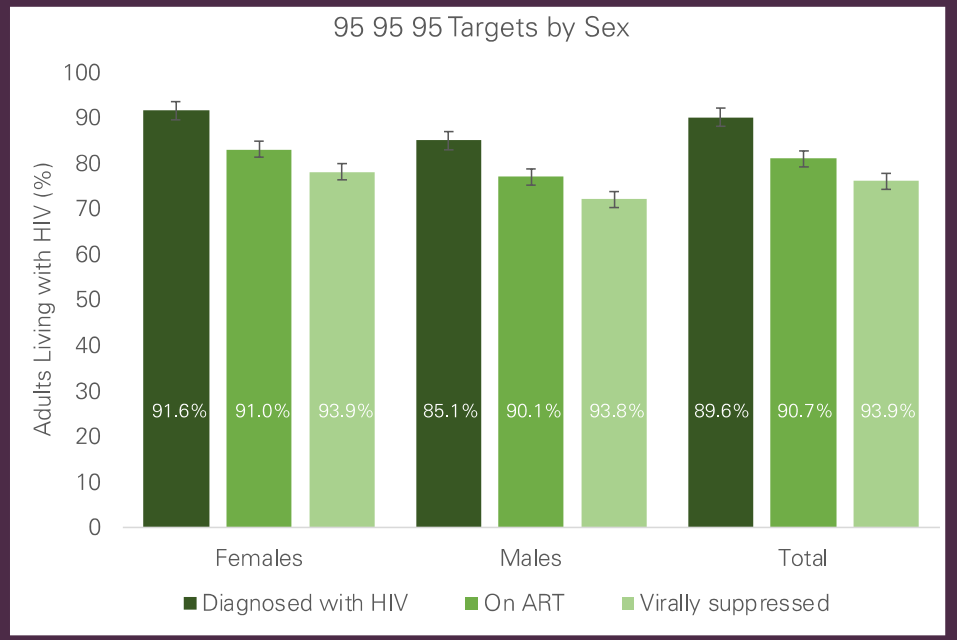
What is a cytopenia?

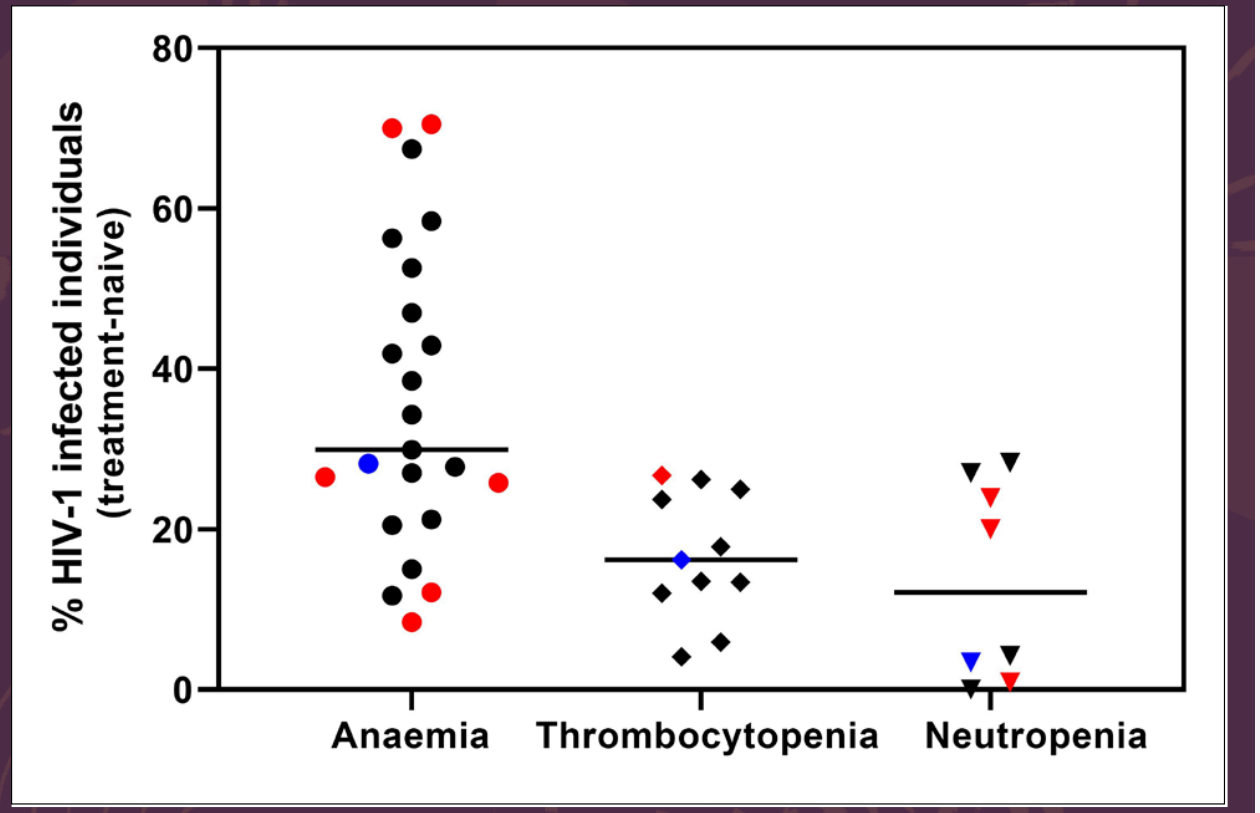
	Normal range (NHLS)		Cytopenia definition (WHO)
Haemoglobin	Men: 13.4 – 17.5 g/dL	**Anaemia**	< 13.0 g/dL
	Women: 11.6 – 16.4 g/dL		< 12.0 g/dL
Leucocytes	3.92 – 10.40 $x10^9$/L	**Leucopenia**	<4.0 $x10^9$/L
Neutrophils	1.60 – 6.98 $x10^9$/L	**Neutropenia**	< 1.50 $x10^9$/L
Lymphocytes	1.40 – 4.20 $x10^9$/L	**Lymphopenia**	< 1.0 $x10^9$/L
Platelets	171 – 388 $x10^9$/L	**Thrombocytopenia**	< 150 $x10^9$/L

Why worry about cytopenias in AHD?

- 2022 - 12.7% SA national HIV prevalence ~ 7.8 million people





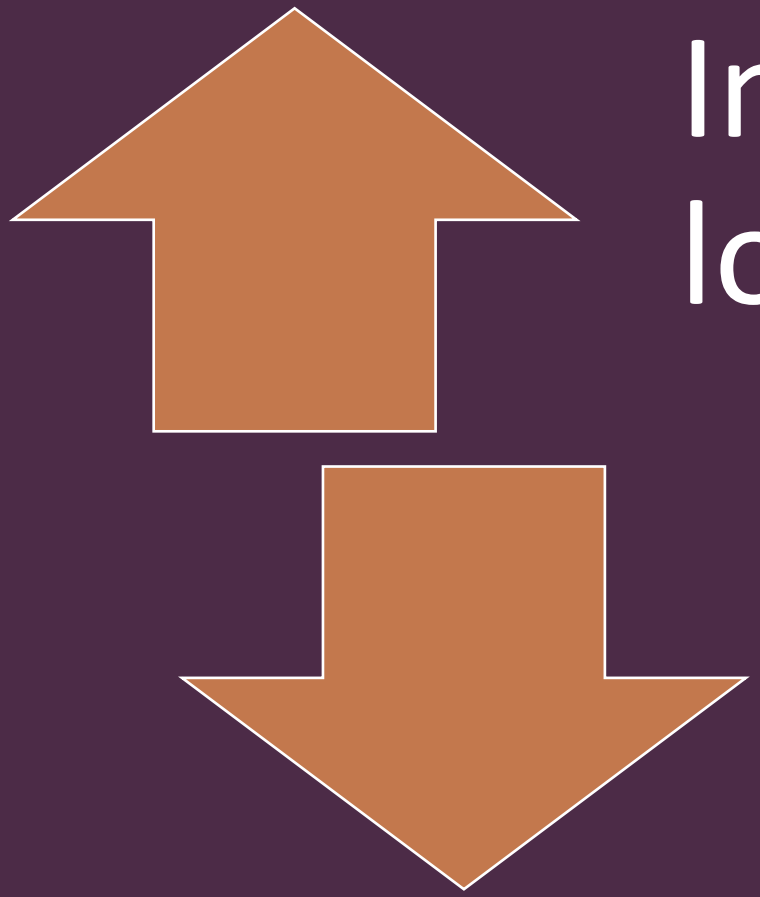


Durandt et al., SAMJ, 2022

Why worry about cytopenias in AHD?

- Cytopenias are the most common haematological abnormality associated with HIV
- Severity and prevalence of cytopenias are associated with HIV disease stage and generally improve on ART
- Severe cytopenias are associated with increased morbidity and mortality, as well as decreased quality of life
- Cytopenias may indicate the presence of important, life-threating co-existing conditions

Causes of cytopenias in AHD



Increased cell loss

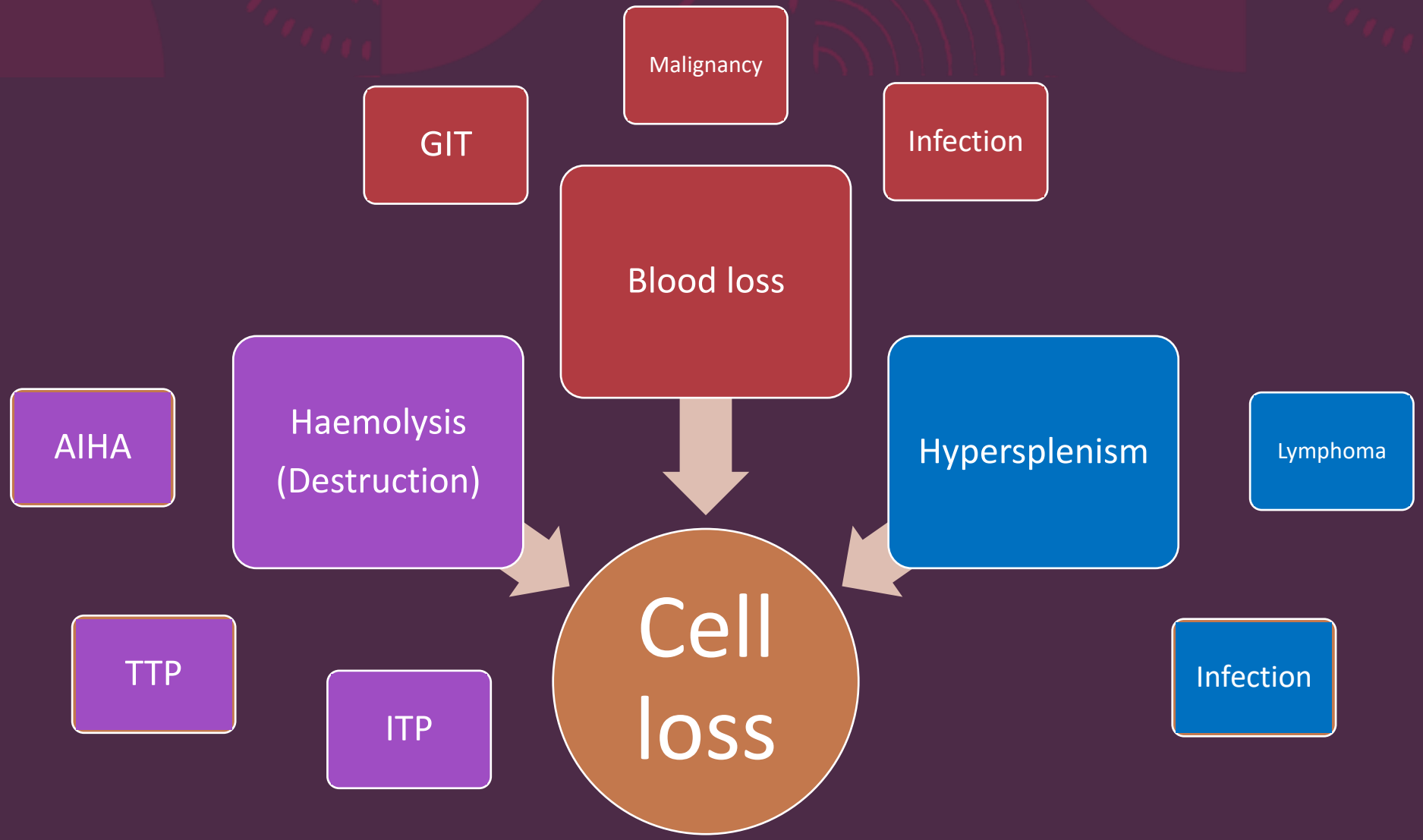
Decreased cell production

Causes of cytopenias in AHD

HIV-RELATED

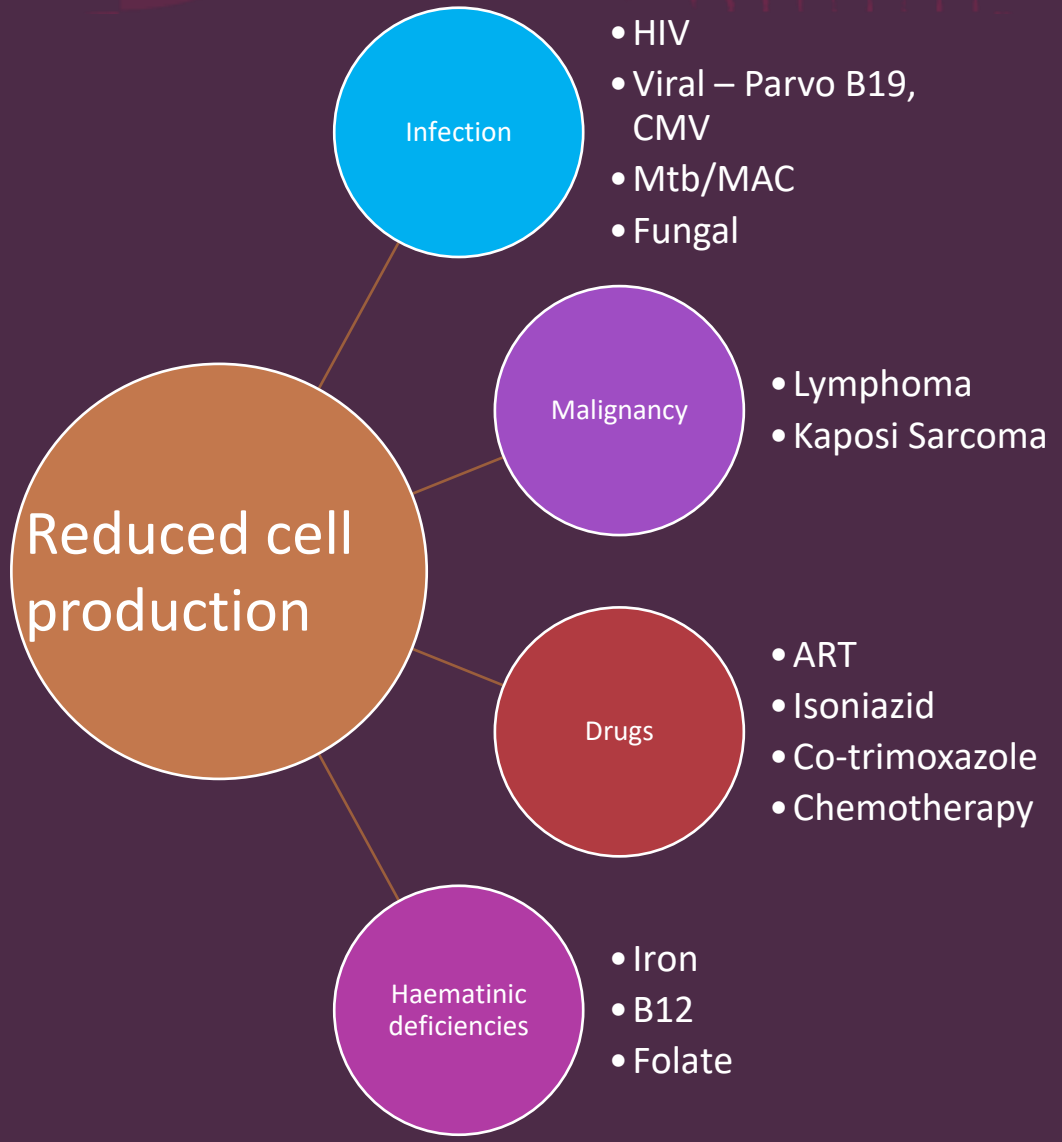
NON-HIV RELATED

Causes of cytopenias in AHD



Durandt et al., SAMJ, 2019
Opie, SAMJ, 2012

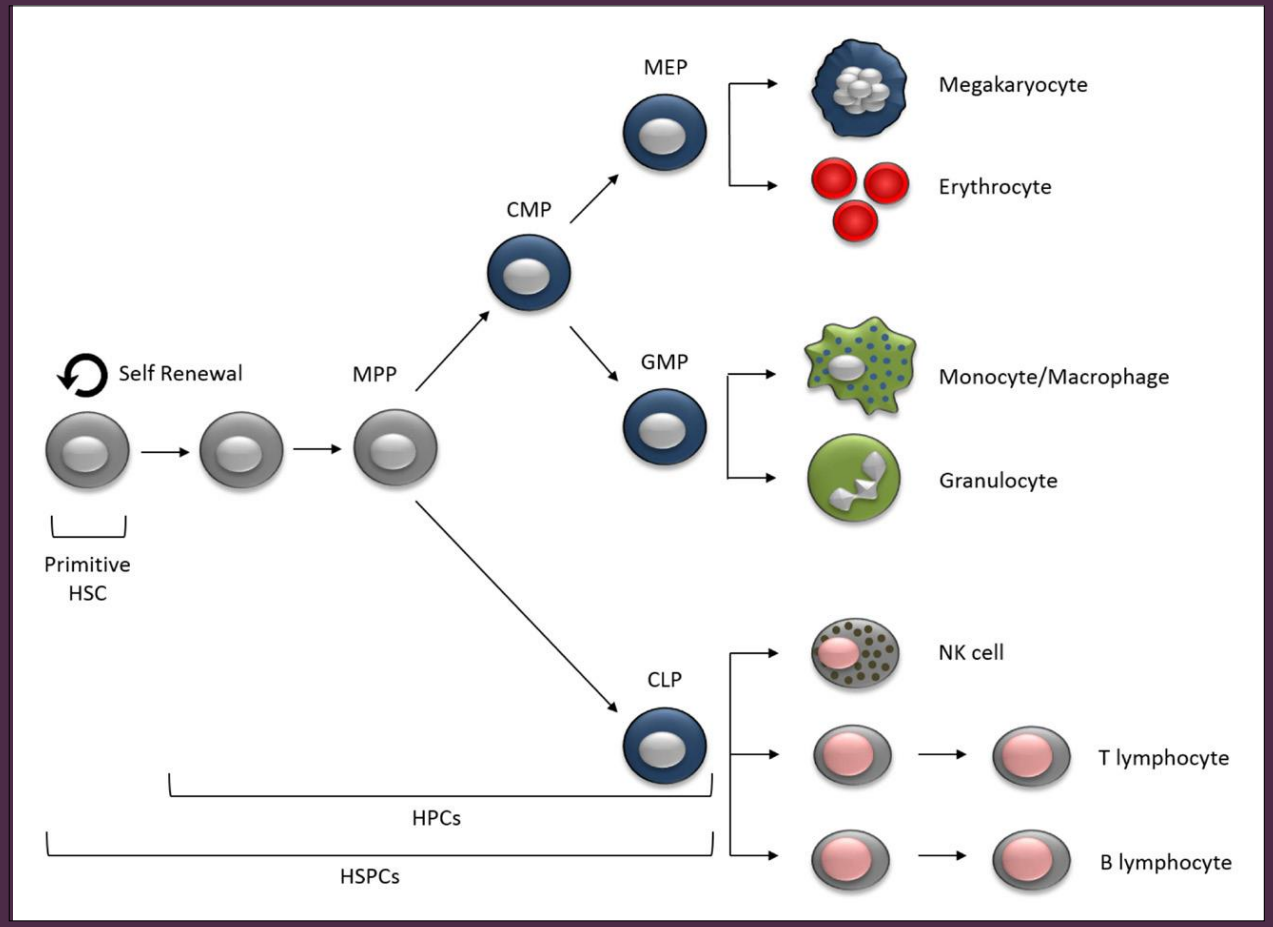
Causes of cytopenias in AHD



Durandt et al., SAMJ, 2019
Opie, SAMJ, 2012

Impact of HIV itself

- HIV itself may be responsible for impaired haematopoiesis through different mechanisms:
  - Direct impact on HSCs
  - HIV proteins contribute to immune activation and inflammation resulting in cytokine production and impact on BM
  - HIV infection affects lymphocytes, monocytes/MPs and neutrophils with decreased G-CSF



Durandt et al., SAMJ, 2019
Vishnu & Aboulafia, BJ Haem, 2015

Drug-induced cytopenias

Table I. Commonly prescribed drugs associated with cytopenias with HIV infection.

Anaemia	Neutropenia	Thrombocytopenia
Amphotericin B	Amphotericin B	Cancer chemotherapy
Cancer chemotherapy	Cancer chemotherapy	Flucytosine
Ganciclovir	Flucytosine	Ganciclovir
Interferon α	Foscarnet	Heparin
Phenytoin	Ganciclovir	Quinidine/quinine
Primaquine	Interferon α	Sulphonamides
Pyrimethamine	Pentamidine	Thiazides
Ribavirin	Pyrimethamine	Valganciclovir
Sulphonamides	Sulphonamides	
Valganciclovir	Valganciclovir	
Zidovudine	Zidovudine	
Amprenavir*		
Fosamprenavir*		
Tipranavir*		
Darunavir*		

*Protease inhibitors containing sulfa moieties.Adapted from www.in-practice.com/textbooks/HIV

Vishnu & Aboulafia, BJ Haem, 2015

Signs and Symptoms associated with cytopenias

	Anaemia	Lymphopenia	Neutropenia	Thrombocytopenia
Signs	Pallor (Jaundice–haemolysis) Tachycardia AV systolic flow murmur	Frequent opportunistic infections	Frequent bacterial infections	Petechiae Purpura Bleeding
Symptoms	Fatigue Weakness Dyspnoea Dizziness Palpitations	Related to above	Fever Skin erythema, ulcerations and fissures Gingivitis	Bleeding gums (or GIT) Easy bruising Confusion

An approach to specific cytopenias

Anaemia

- Anaemia is the most common haematological abnormality in PLWH, particularly in AHD (worse with lower CD4 and AIDS-defining illnesses)
- It remains a common problem in PLWH on ART (~35%)
- Risk factors – low CD4, low BMI, female, IVDU, co-infections (TB, Hepatitis B+C, Malaria)
- In patients initiating ART Hb may increase 2-3 g/dL

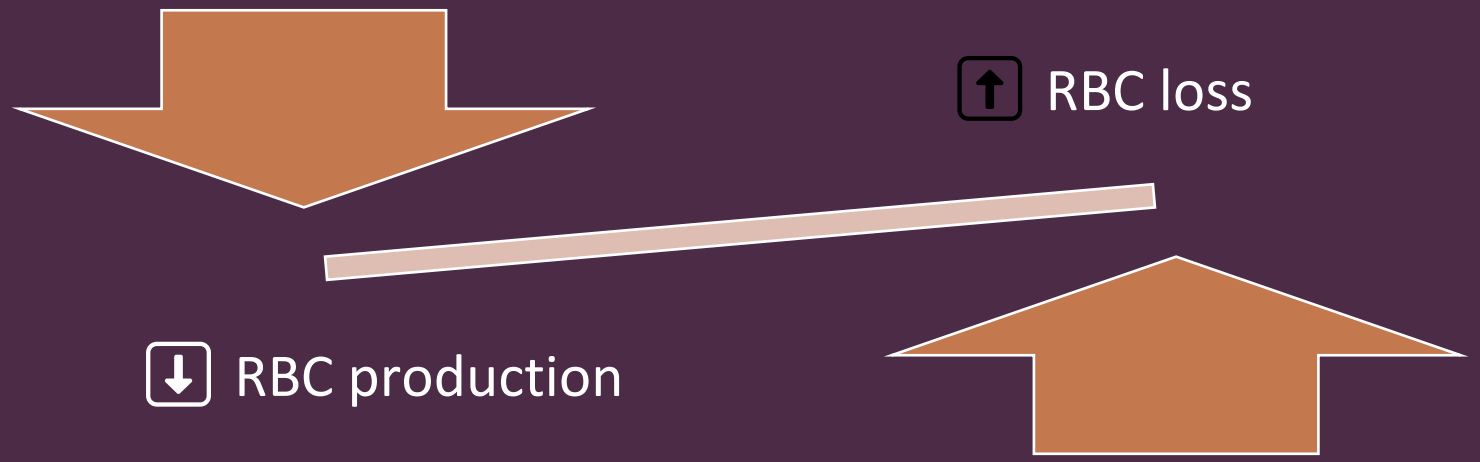
Vishnu & Aboulafia, BJ Haem, 2015

Causes of anaemia

Anaemia of Chronic Disease

BM failure
- Drugs
- Infection
  - Infiltration
  - Parvo B19
- Malignancy

Haematinic deficiencies
- Iron, B12 and Folate



Haemolysis
- AIHA
- TTP

Bleeding

Hypersplenism

Anaemia of chronic disease

- Due to HIV itself, or associated co-infections
- Diagnosis of exclusion
- MCV commonly NORMAL but may be low
- Normal to elevated ferritin and adequate bone marrow iron stores
- Reticulocyte count is LOW

Drug-induced anaemia

ART	TB therapy	Other

• **Zidovudine (AZT)**
  • Macrocytosis (MCV >100)
  • May involve neutropenia
  • Peripheral neuropathy
• **Lamivudine**
  • Pure red cell aplasia (Rare)
• **Stavudine**
  • Megaloblastic changes, neutropenia, thrombosytopenia
	• **Linezolid**
	  • Anaemia, neutropenia, thrombocytopenia
	  • Optic neuritis
	  • Peripheral neuropathy
	• **Isoniazid**
	  • PRCA
	  • Haemolysis
	  • Sideroblastic anaemia
	• **Rifampicin**
	  • Haemolytic anaemia (immune)
		• **Co-trimoxazole**
		  • Megaloblastic anaemia, neutropenia, thrombocytopenia
		• **Amphotericin B**
		  • Anaemia, neutropenia, thrombocytopenia
		• **Ganciclovir**
		  • Anaemia, neutropenia, thrombocytopenia

Durandt et al., SAMJ, 2019
Vishnu & Aboulafia, BJ Haem, 2015
Opie et al., SAMJ, 2012

Parvovirus B19

- Parvovirus B19 is a DNA virus, usually acquired through the respiratory tract
- Infects RBC precursors in the bone marrow, lysing RBCs when replicating
- Results in marked reduction in erythroid activity
- “Pure red cell aplasia” - PRCA

When to suspect?

- Isolated SEVERE anaemia with a PRESERVED WBC and platelet count
- Low to absent reticulocytes

Diagnosis

- Parvovirus B19 PCR on peripheral blood or bone marrow aspirate

Treatment

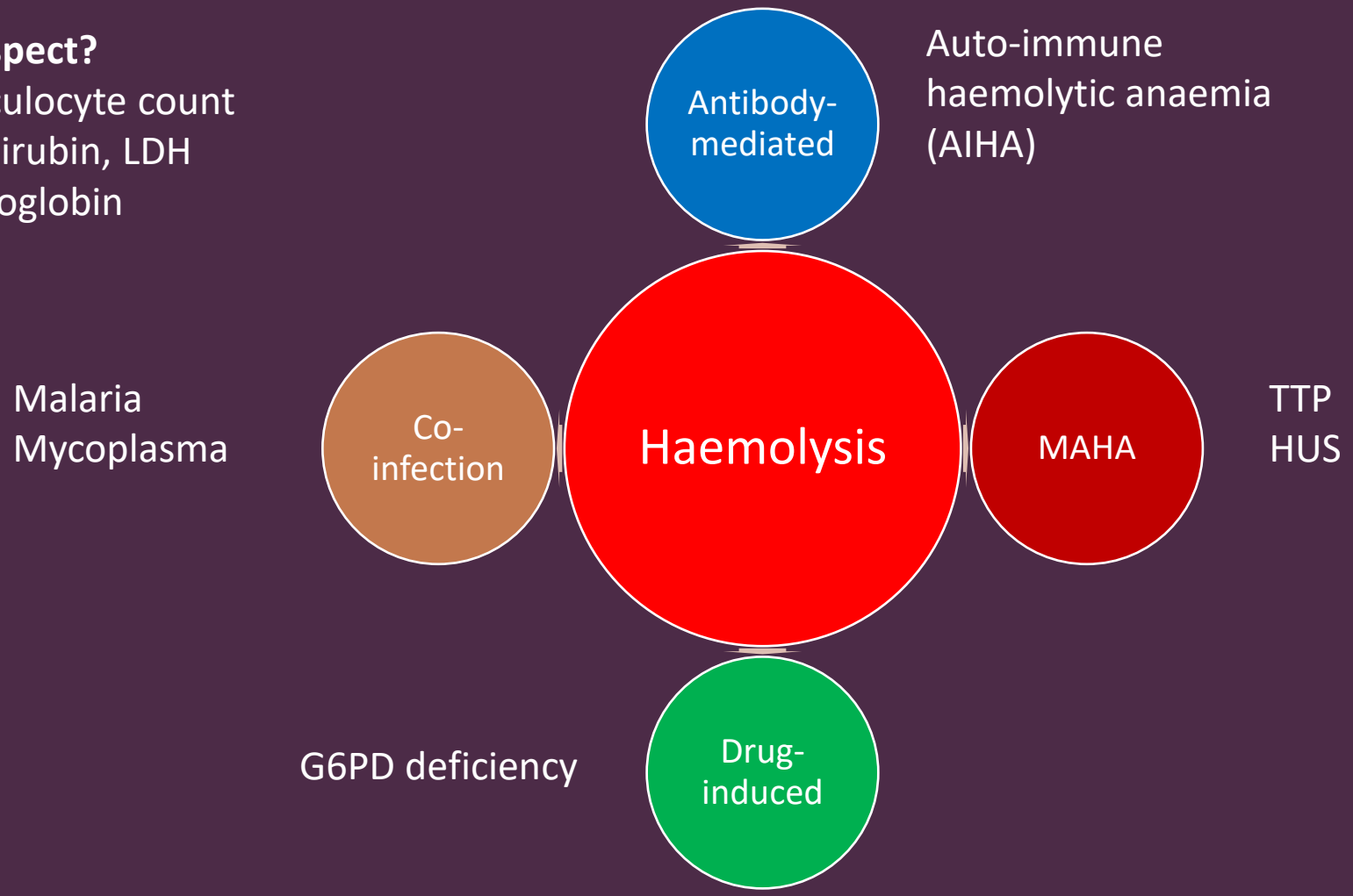
- Refer to specialist centre
- RBC transfusions
- Initiate ART
- IVIG

UpToDate.com
Opie et al., SAMJ, 2012

Haemolytic anaemia

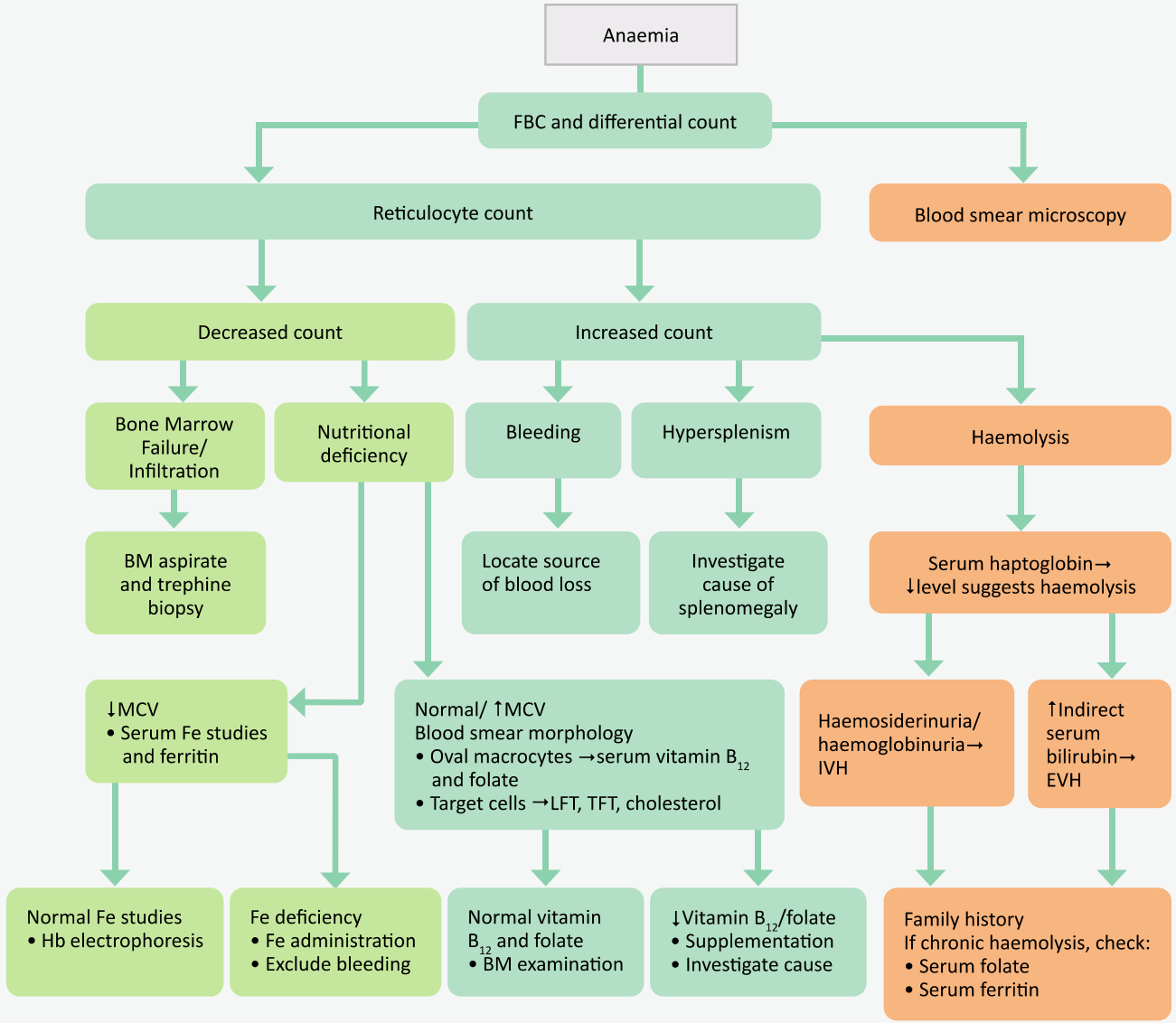
When to suspect?

- High reticulocyte count
- Raised bilirubin, LDH
- Low haptoglobin



An approach to anaemia

- FBC and differential count with blood smear microscopy
  - Anaemia alone or other cell lines
  - MCV
- Reticulocyte count or reticulocyte production index (RPI)
- Haematinics – Iron, B12 and folate
- LDH, bilirubin and haptoglobin
- Bone marrow aspirate and trephine



Management of anaemia

- Removal of causal agent / correction of underlying cause
  - Replacement of Fe, B12 or folate
  - Stopping offending drugs etc
- Early initiation of ART, if treatment naïve
- Blood transfusion if symptomatic or particularly severe
- EPO is not given routinely and should only be considered under the guidance of a Specialist Haematologist

When to refer - Anaemia

- Pure red cell anaemia
- Haemolytic anaemia
- Severe symptomatic anaemia

Neutropenia

- Reported in up to 28.3% of ART-naïve PLWH
- Usually associated with other cytopenias (bi- or pancytopenia)
- Increased with more advanced HIV disease – low CD4 and high HIVVL are risk factors
- Less common in individuals on ART
- Neutropenia severity is related to risk for infection (< 1.0 x 10^9/L)
- Generally the risk for infection is less than for chemo-induced neutropenia
- Benign ethnic neutropenia has a high prevalence in individuals of African descent

Causes of neutropenia

- Advanced HIV disease
- Drugs
  - Zidovudine (AZT)
  - Co-trimoxazole, ganciclovir, INH
- Bone marrow infiltration
  - Infections
  - Malignancy
- Hypersplenism
- Benign, ethnic neutropenia (diagnosis of exclusion)

Management of neutropenia

- Correction of reversible causes
- Early initiation of ART
- G-CSF – “Neupogen” – severe neutropenia <0.5 x 10^9/L in whom there is concern for possible infection (under specialist guidance)
  - Fever
  - Localising symptoms

When to refer - Neutropenia

- Severe neutropenia <0.5x 10^9/L
- Neutropenic sepsis

Thrombocytopenia

- May occur at anytime during course of HIV infection
- Although the prevalence increases with AHD, relationship is not always linear
- Risk factors: low CD4, high HIVVL, age >50 yrs, IVDU, anaemia and hepatitis co-infection

When to suspect?

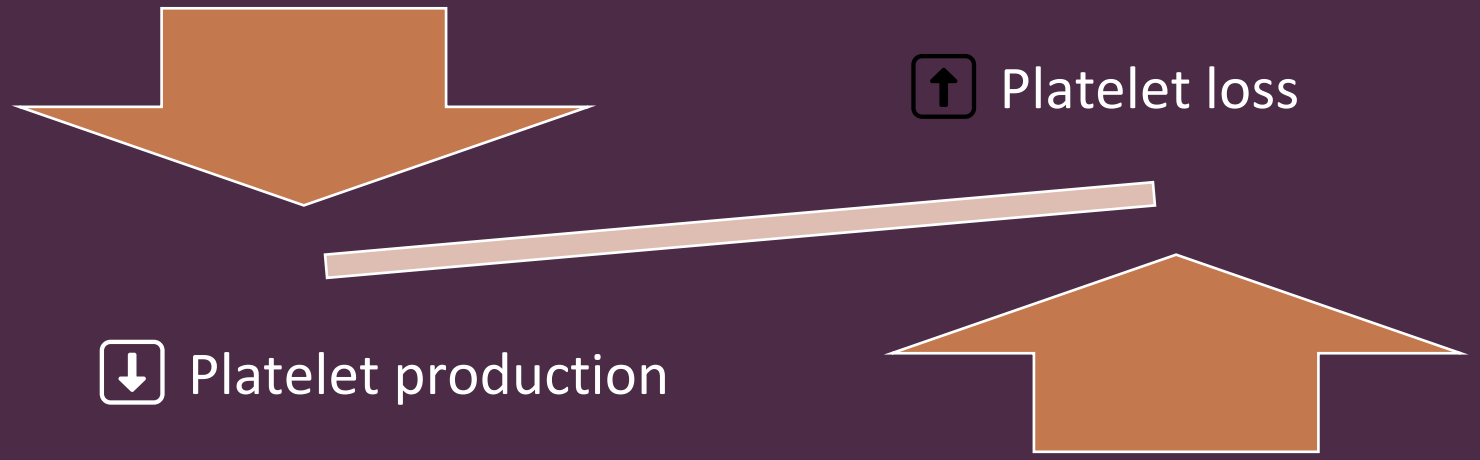
- Bleeding – cutaneous, mucous membranes, menorrhagia, epistaxis
- Petechiae
- Ecchymoses

Causes of thrombocytopenia

Pseudothrombocytopenia
"Platelet clumping"

BM failure
- Drugs
- Infection
  - Infiltration
- Malignancy

Haematinic deficiencies
- B12 and Folate



ITP

TTP

Hypersplenism

Immune thrombocytopenia (ITP)

- ITP is the most common cause of thrombocytopenia in PLWH (up to 30%)
- Often occurs at initial stages of infection (but can occur anytime)
- Both antibody- and T cell-mediated processes involved – AI mediated platelet destruction
- May be severe and life-threatening
- Usually responds to ART

When to suspect?

- LOW platelets with no other abnormalities on FBC

Diagnosis

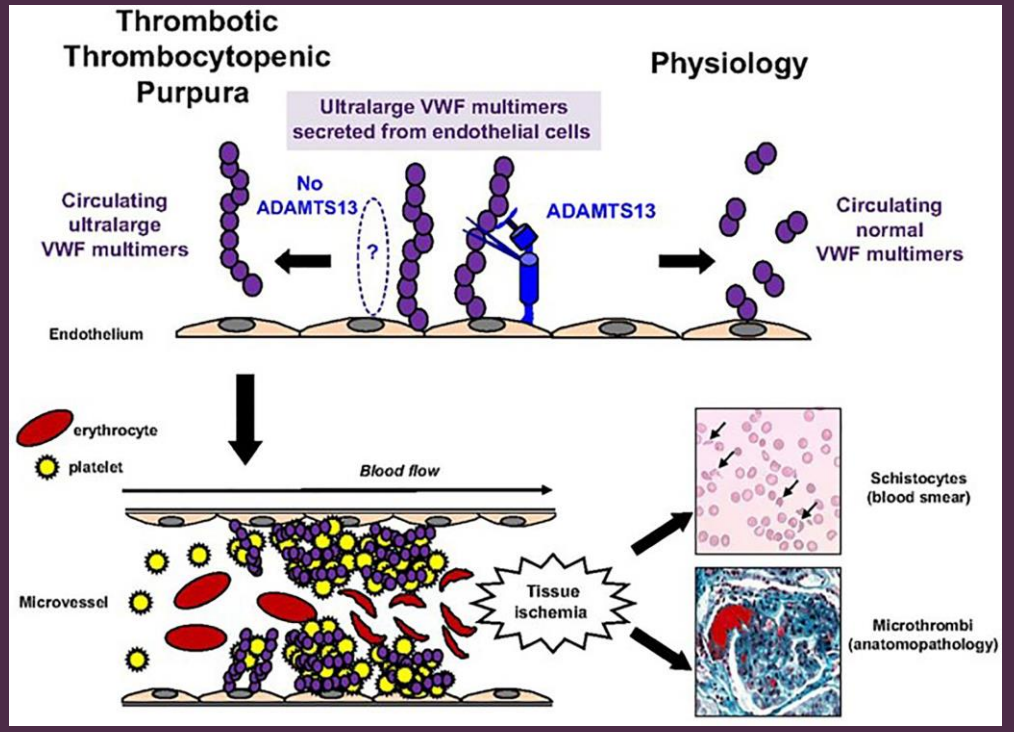
- Diagnosis of exclusion

Treatment

- Refer to specialist centre
- Platelets and RBC transfusion if bleeding
- Initiate ART
- Steroids (Prednisone, dexamethasone, methylprednisolone)
- IVIG
- Rituximab
- Splenectomy

Thrombotic thrombocytopenia purpura (TTP)

- Can be congenital or acquired (more common)
- Most common cause of TTP in SA is HIV
- African HIV+ treatment-naive females at higher risk
- Auto-immune disease caused by circulating antibodies directed at ADAMTS13 enzyme which usually cleaves VWF
  - Results in large VWF multimers that cause platelet microthrombi in blood vessels leading to intravascular haemolysis and organ ischaemia
- Characteristic red-cell fragments or “schistocytes” on blood smear



Karsenty et al., Front Immunol, 2022

Durandt et al., SAMJ, 2019
Opie et al., SAMJ, 2012

Thrombotic thrombocytopenia purpura (TTP)

Characterised by:

I. MAHA (RBC fragments, evidence of haemolysis)
II. Thrombocytopenia
III. Fever
IV. Fluctuating neurological findings
V. Renal dysfunction

PLASMIC SCORE

Parameter	Points[a]
Platelet count $<30 \times 10^9$/L	1
Combined hemolysis parameter Indirect bilirubin >2 mg/dL, OR *34,2umol/L* Reticulocyte count >2.5%, OR Haptoglobin undetectable	1
No active cancer	1
No history of solid-organ or stem cell transplant	1
MCV <90 fL	1
INR <1.5	1
Creatinine <2.0 mg/dL *176umol/L*	1

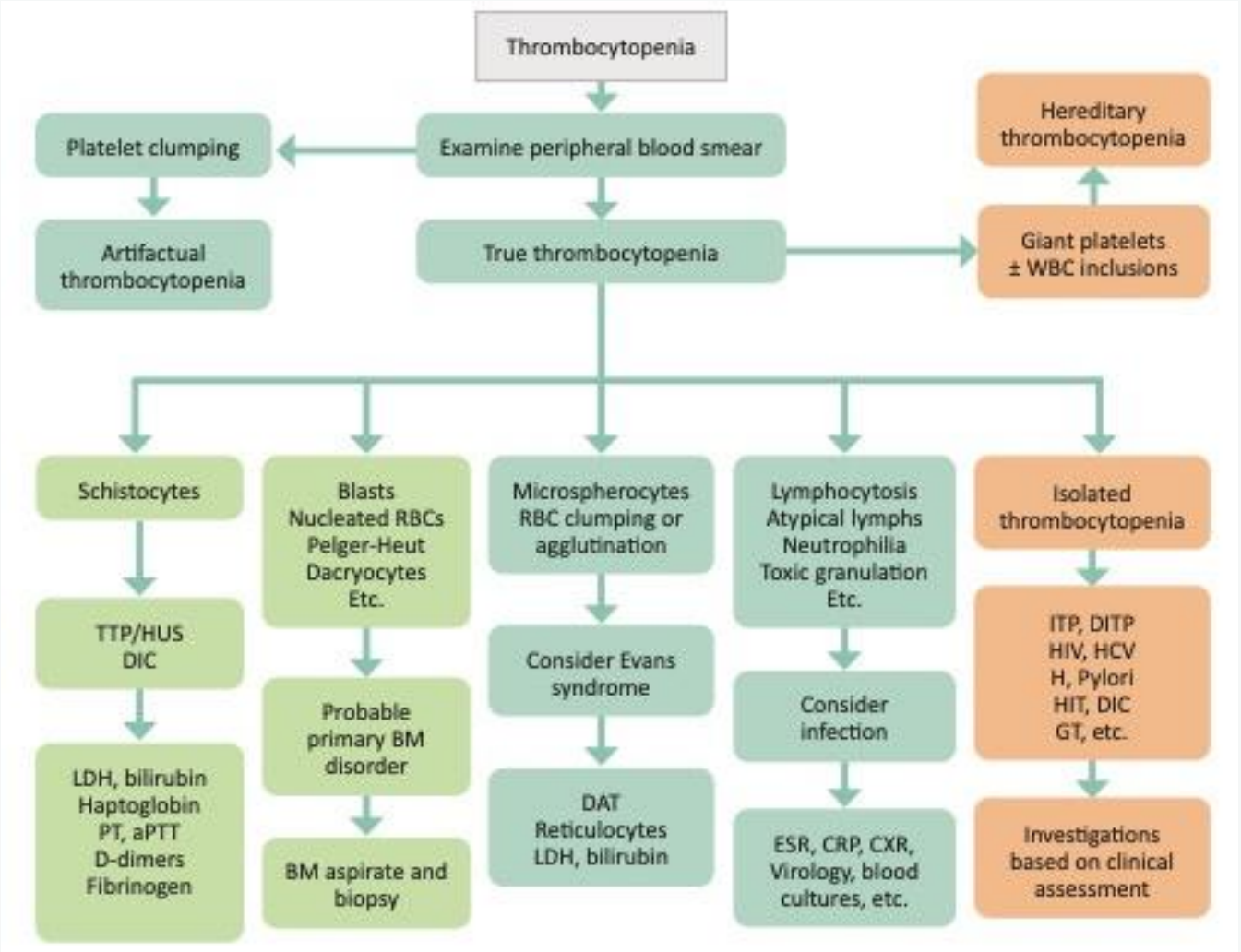
Abbreviations: INR, international normalized ratio; MCV, mean corpuscular volume.
[a]Score <5: low risk for severe ADAMTS13 deficiency, Score 5: intermediate risk, Score >5: high risk.

Treatment of TTP

- Refer to specialized centre
- Therapeutic plasma exchange is mainstay of therapy (SANBS)
- Glucocorticoids
- Rituximab
- Start ART ASAP
- Platelet tranfusions not used unless clinically important bleeding

Approach to thrombocytopenia

- Pseudothrombocytopenia?
  - Clumping
- FBC and differential count with blood smear microscopy
  - **Red cell fragments (MAHA)??**
  - Isolated thrombocytopenia
- Reticulocyte count or reticulocyte production index (RPI)
- ADAMTS13 activity (If available)
- Markers of haemolysis (LDH, Bilirubin, haptoglobin)



When to refer - Thrombocytopenia

- Thrombocytopenia with severe bleeding
- Thrombocytopenia with fever
- Suspected TTP
- Suspected ITP

Bi- or pancytopenia

- Often patients with >1 ***severe cytopenia*** are acutely ill due to a serious infection, malignancy or other condition
- Things to consider
  - Haemophagocytic lymphohistiocytosis (HLH) – cytopenias, fever, high ferritin, triglycerides and LFTs
  - Drugs and haematinics (B12 and folate)
  - Bone marrow infiltration syndromes
    - Infection
      - Mycobacterial – *Mtb, MAC*
      - Fungal – cryptococcosis, histoplasmosis, emergomycosis
      - Viral – CMV, EBV
    - Malignancy
      - Lymphoma
      - Kaposi Sarcoma

When should I do a Bone marrow biopsy (BMAT)?

- More than 1 cytopenia without a clear cause
- To accurately assess BM cellularity and determine central vs peripheral cause
- Concern for a haematological malignancy
- Suspected BM infiltration (infection or malignancy)
- Suspected HLH
- **If unsure, discuss with your referral centre**

Additional resources

- NDOH Advanced Clinical Care Booklet
- NDOH Module 2.8 Management of the HIV-positive person with Haematological abnormalities – KnowledgeHub
- South African HIV Clinicians Society Guidelines for Hospitalised Adults with AHD
- Durandt et al., HIV and Haematopoiesis, SAMJ, 2019
- Vishnu and Aboulafia, Haematological manifestations of HIV, Br J of Haem
- Opie et al., Haematological complications of HIV, SAMJ, 2012

Thank you for listening

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