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South African National Blood Service
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HIV & Blood Transfusion:

A review of the use of blood and blood products in HIV-infected patients

SANBS
South African National Blood Service

Dr Karin van den Berg
o.b.o. The HIV & Blood Transfusion Collaborative Group
SA HIV Clinicians Society Conference
26 November 2012

**“Blood transfusion is like marriage:
it should not be entered upon lightly,
unadvisedly or wantonly,
or more often than is absolutely necessary”**

R.W Beal, New Zealand Journal of Surgery, 1976

Items for Discussion

- Why look at Blood Transfusion & HIV?
- Anaemia in HIV
- HIV associated TTP
- Legal and Human Rights Considerations

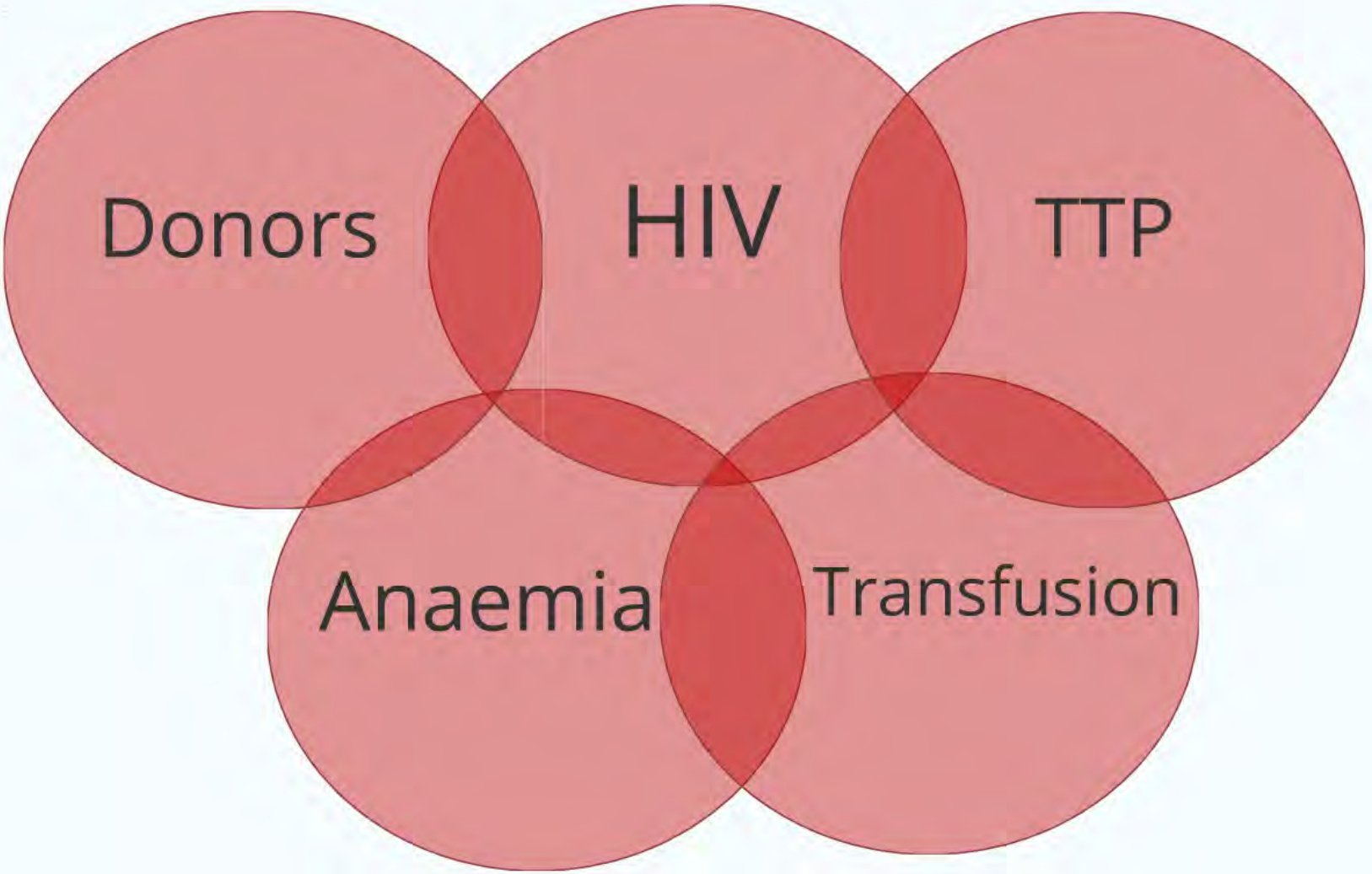
Why Look at Blood Transfusion & HIV?

No other disease has impacted Blood Transfusion the way HIV has!

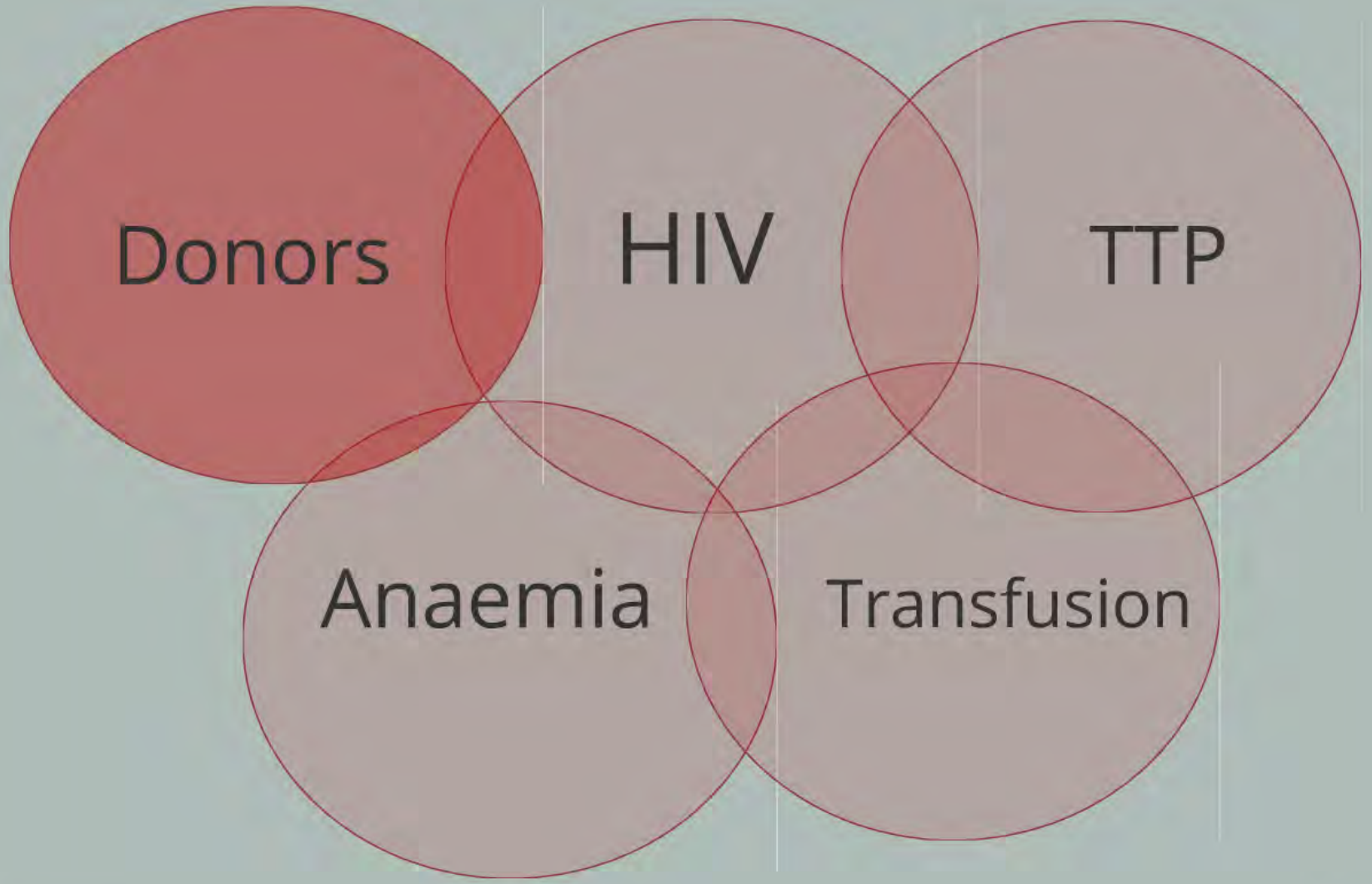
Transfusion Transmitted HIV during the '80's and '90's impacted national and international healthcare policy [1-3]

1. Derrick JB. Canadian Anaesthetists' Society 1986; 33:117-22
2. Barnes DM. Science 1986; 233:514-5
3. Aymard JP et al. Bulletin De La Société Nationale De Transfusion Sanguine 1989;32:421-9

HIV & Blood Transfusion



HIV & Blood Transfusion

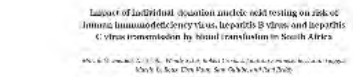


HIV & Blood Donors

- HIV resculptured the face of blood collection
    - Donor education
    - Donor selection
        - Donor questionnaire
        - One-on-one assessment
    - Donation testing
    - Blood issuing policies
- Detracts attention:
    - HIV not biggest risk to recipients
    - Only thing pts and drs worry about

HIV & Donation Testing

- **NAT:**
  - *HIV, HBV & HCV*
- **Serology**
  - *HIV, HBV, HCV & Syphilis*
  - *ABO, Rh & DAT*



HIV Transmission Risk*:
- **HIV Window Period: 4.6 days**
- **Calculated residual risk: 1: 208,338**
- **Confirmed transmissions (post Oct 2006): 0**
- **Confirmed transmissions pre-Oct 2006: ~2-4 per annum**

* Vermeulen M et al. Transfusion 2009; 49:1115-1125

- Cost: R240-00 per unit
  - ~ 2 500 unit /day; 7 days a week
  - = R600 000 per day
  - = R4,2mil per week
  - = R16,8mil per month
  - = R201,6mil per year

Impact of individual-donation nucleic acid testing on risk of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission by blood transfusion in South Africa

Marion Vermeulen, Nico Lelie, Wendy Sykes, Robert Crookes, Johanna Swanevelder, Lilian Gaggia, Martin Le Roux, Eben Kuun, Sam Gulube, and Ravi Reddy

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*** Vermuelen M et al. Transfusion 2009; 49:1115-1125**

- AB

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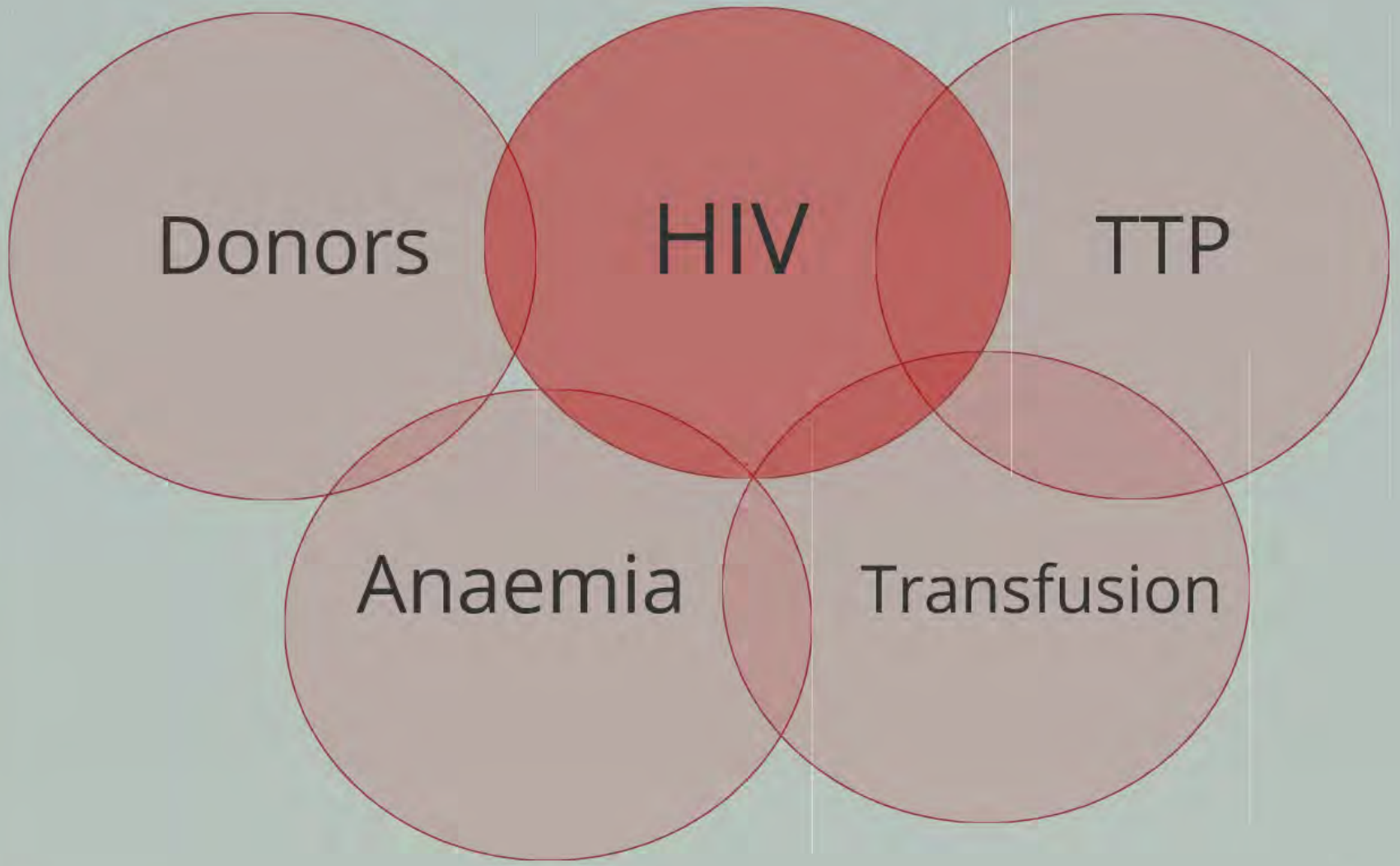
HIV & Blood Issuing Policies

Risk Categories: Level	Cohort	Residual Risk (Bush Model)
Risk Category C All componented products to be made from this category	Active or rejoined donors: 4 or more donations in previous 24 month period	FY 08/09 = 1/116 897 FY 09/10 = 1/ 80 188 FY 10/11 = 1/116 113 Target: < 1/100 000
Risk Category R Not for paediatric and neonatal RCC.	Active or rejoined donors: 2 – 3 donations in previous 24 month period	FY 08/09 = 1/53 156 FY 09/10 = 1/54 687 FY 10/11 = 1/30 638 Target: < 1/40 000
Risk Category P Only issue the Donor Retested Plasma and limited release of RCC	First time donors or one donation from rejoined donors in past 24 month period	FY 08/09 = 1/25 283 FY 09/10 = 1/28 585 FY 10/11 = 1/29 633 Target: < 1/25 000

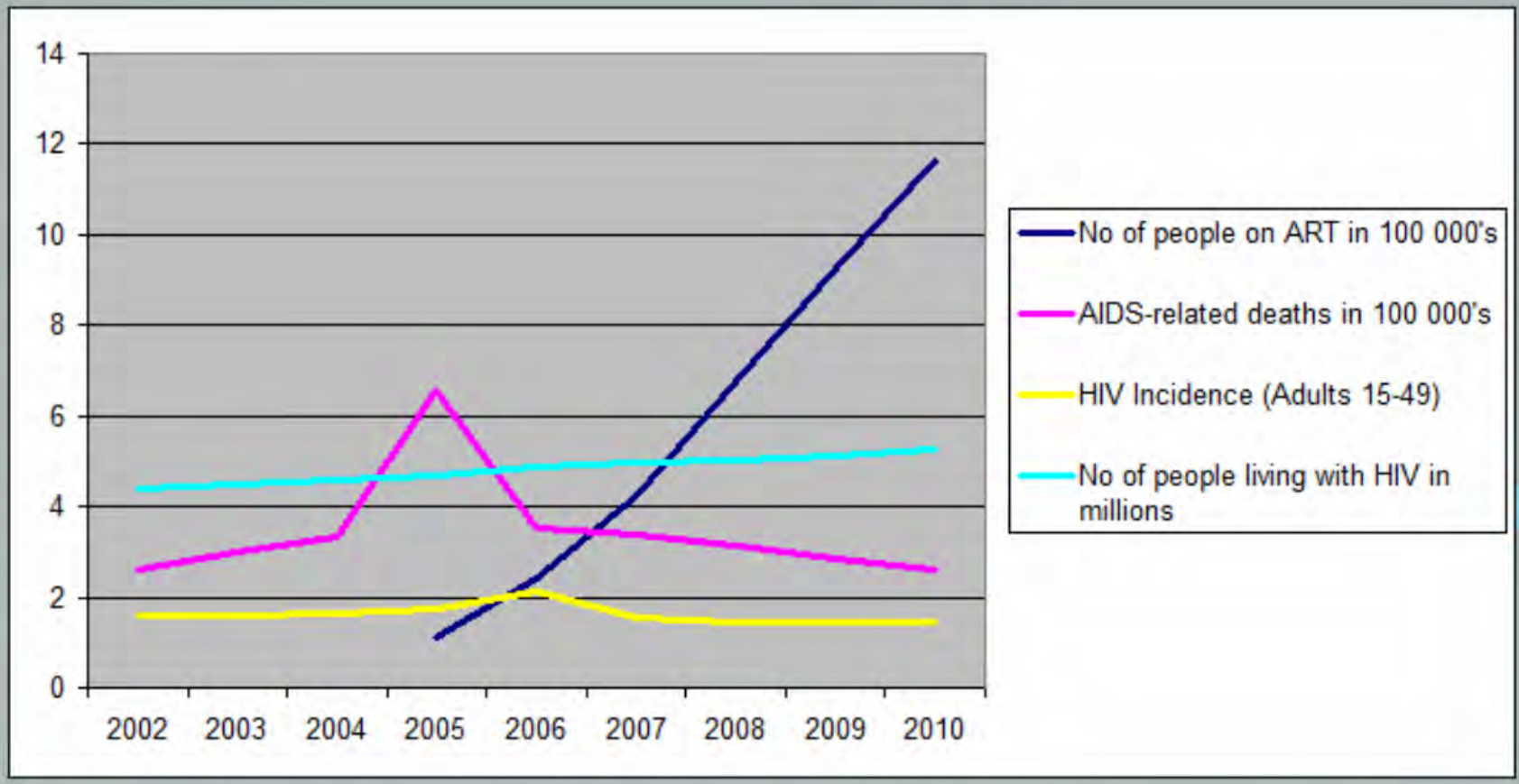
SANBS 2011; HIV residual risk based hierarchical blood issuing procedure

HIV & Blood Transfusion



HIV Epidemiology

Change in the South African HIV epidemic, 2002 to 2010



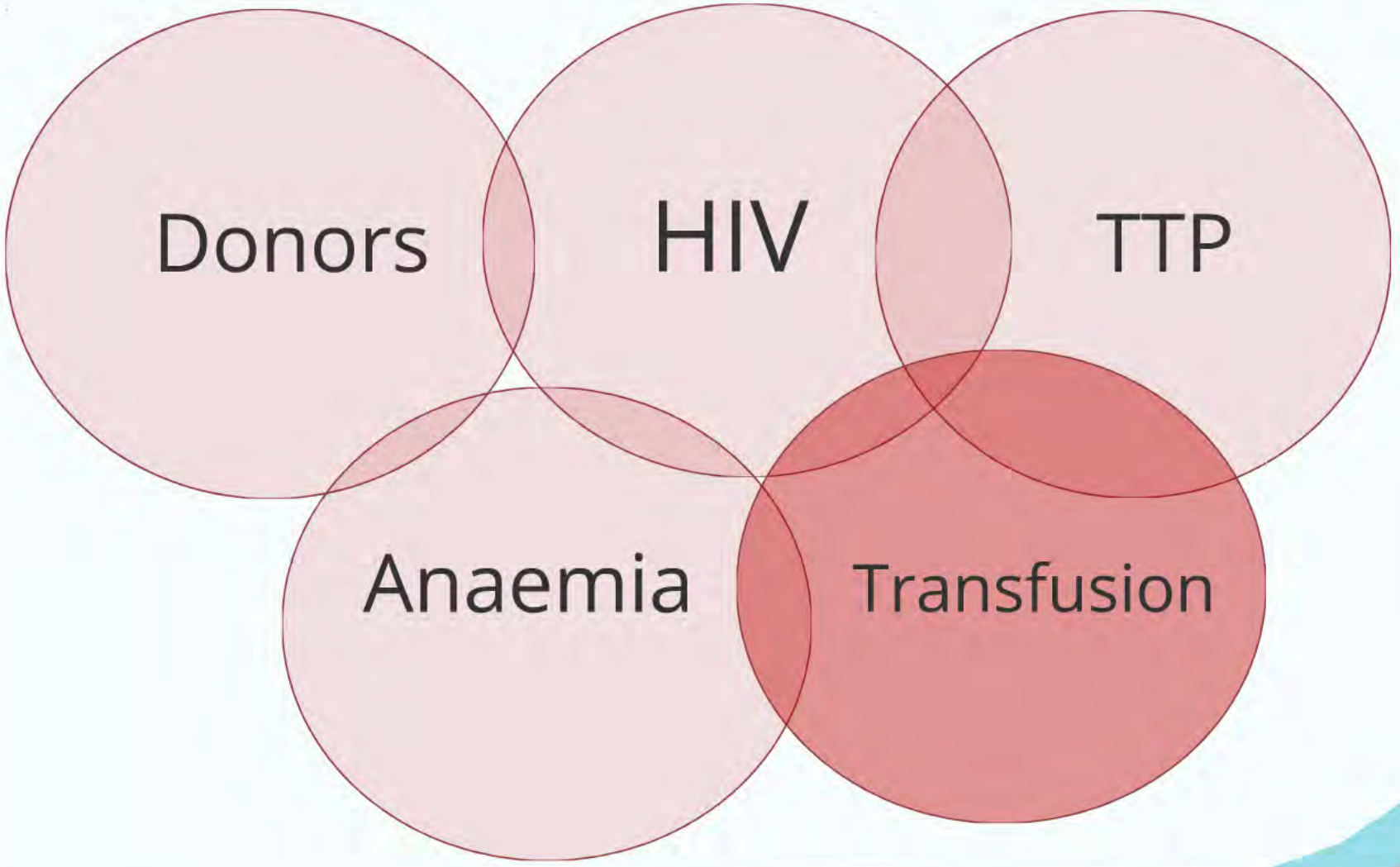
Adapted from Global HIV/AIDS response: Epidemic update and health sector progress towards Universal Access. Progress Report 20112

HIV Epidemiology

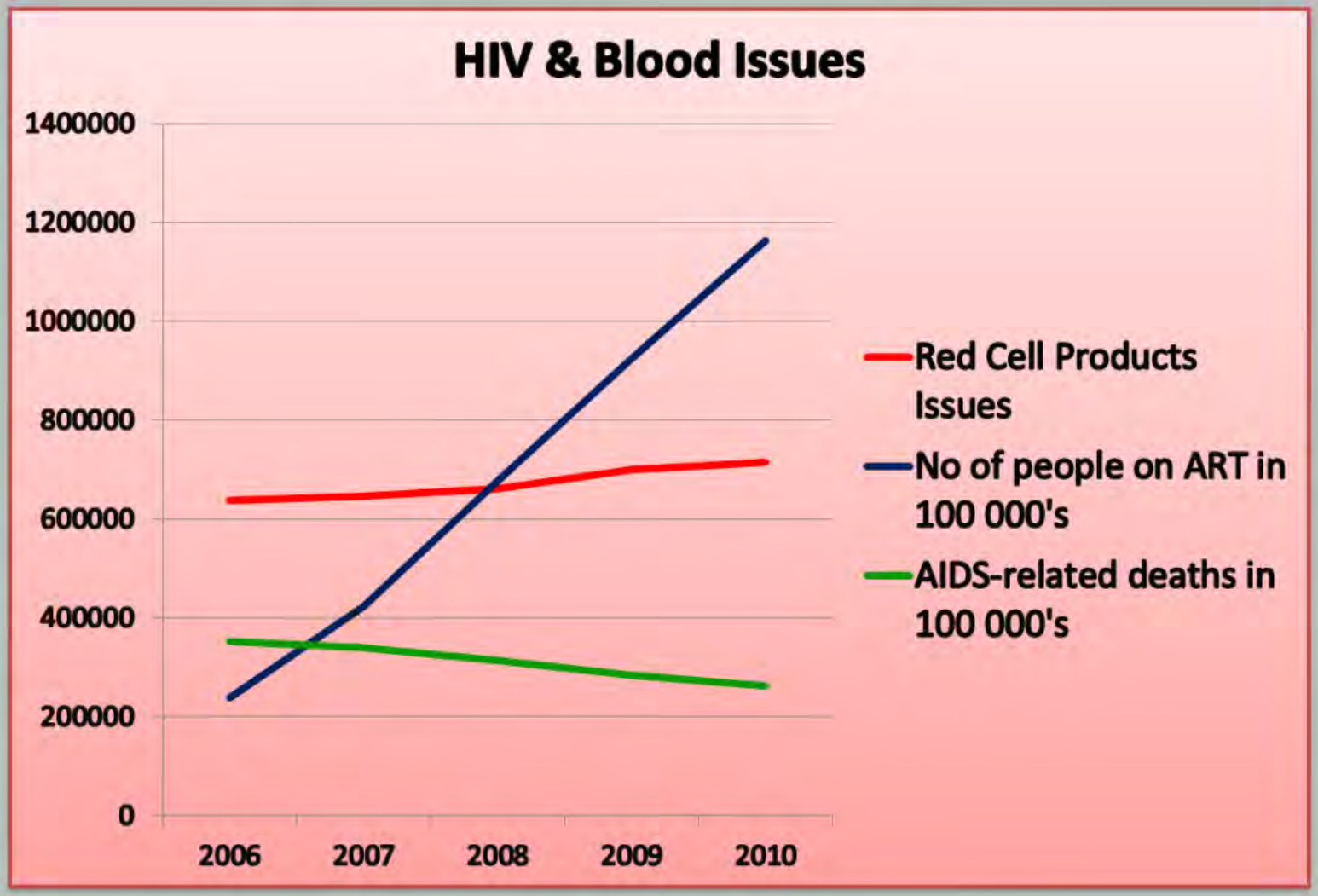
- SA has largest epidemic in the world
  - 17% of all HIV cases (0.7% world population) [1-2]
  - ~5.6 million cases (> all of Asia combined)[3]
- Continued incidence of ~1.5%[3]
- No of people living with HIV expected ↑
  - Rapid uptake of ART [4]
  - Increase in life expectancy [5]

1. UNAIDS. AIDS epidemic update. 2007
2. SA DoH. National HIV & syphilis prevalence survey. 2007
3. UNAIDS.Global HIV/AIDS reponse. 2011
4. Johnson LF.SA J HIV Med 2012;13:22-7
5. ART Cohort Collaboration. Lancet 2008; 372:293-9

HIV & Blood Transfusion



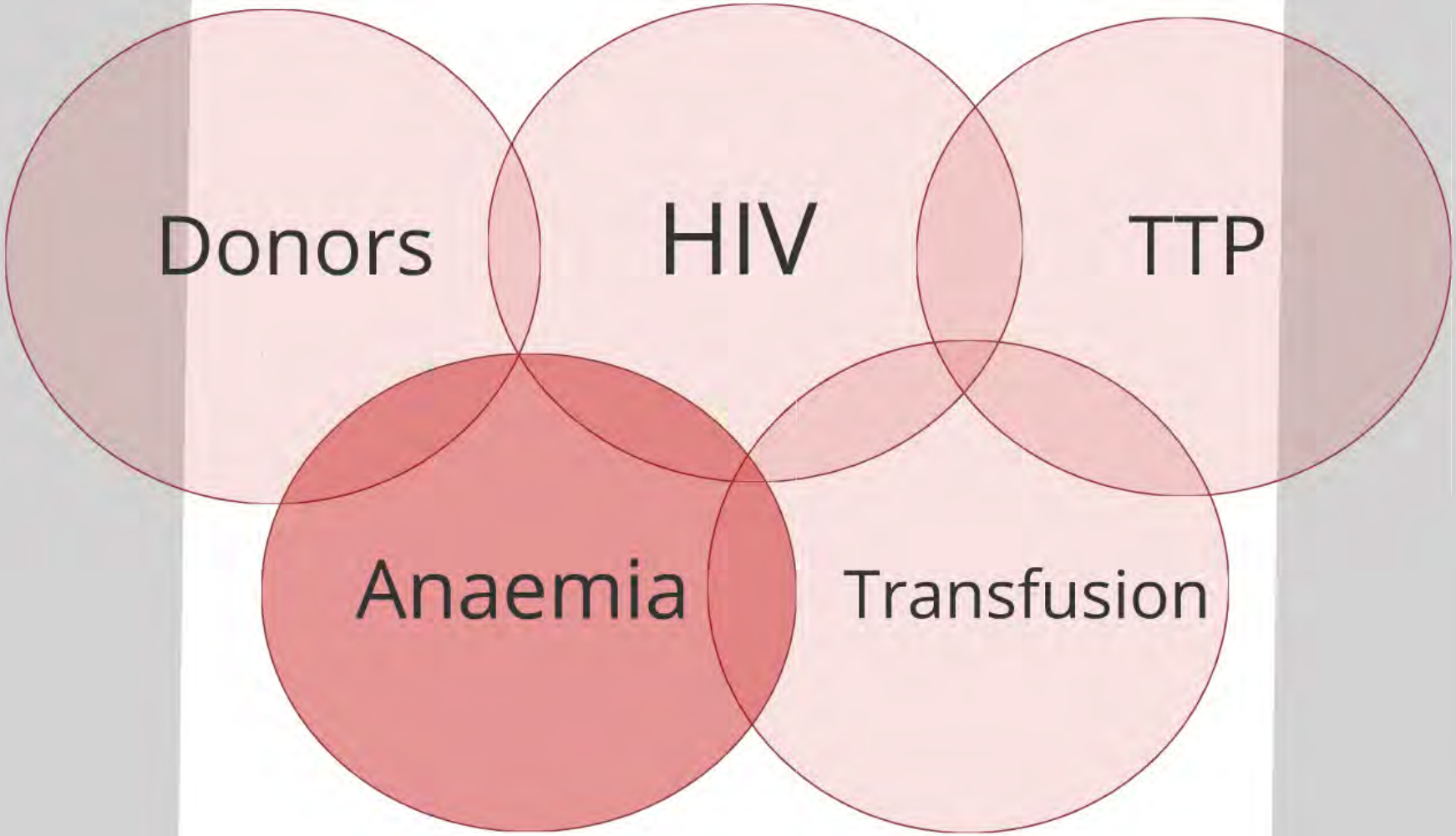
HIV & Transfusion



SANBS. Haemovigilance Report 2007.

However, there are two conditions associated with HIV which has greatly impacted on blood transfusion ...

HIV & Blood Transfusion



Epidemiology

- Occurs commonly [1]
  - 63-95% of infected persons
    - Incidence ↑ with disease progression
- Independent predictor of mortality [2]
  - Correction of anaemia decreases morbidity and mortality
- Associated with QOL ↓ [3]

1. Sullivan PS et al. Blood 1998;91:301-8
2. Moore RD et al. J AIDS & HRV 1998;19:29-33
3. Volberding P. J of Inf Diseases 2002;185 Suppl 2:S110-S4

Risk Factors

- High Viral load
- Women
- CD4 count <200
- Black race
- Increasing age
- Lower body mass index
- Oral candidiasis
- AZT
- History of clinical AIDS
- History of bacterial pneumonia
- History of fever

Sullivan P. J of Inf Diseases 2002;185 Suppl 2:S138-S42

Aetiology of Anaemia in HIV

- Multifactorial, often overlapping, ocuring simultaneously in one patient

Direct effects:

- Infect red cell precursors and bone marrow stromal cells
- Release of cytokines
- Contributes to ACD

Indirect effects

- Nutritional deficiencies
- Opportunistic infections
- Immune mediated destruction
- Neoplasmas
- Bone marrow infiltrative disorders

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Aetiology of Anaemia in HIV

- Conditions on previous slide mostly affects production
- Can also cause ↓ RBC survival & ↑ destruction
    - ~ 30% of HIV+ pts may have +DAT
    - Yet clinically significant AIHA uncommon
    - BUT risk of under-diagnosed & under-reported
    - Dx requires: +DAT, Anaemia, Reticulocytosis, etc
    - +DAT & Anaemia is common, but reticulocytosis not
    - BUT...
- HIV suppresses reticulocytosis, complicating the diagnoses of the condition

Coyle TE. The Medical Clinics of North America 1997;99:1-8
Telen MJ et al. Journal of AIDS 1990;3:933-7
Olayemi E et al. Annals of African Medicine 2008;7:72-6

Aetiology

Table 1. Anaemia and HIV-infection

Decreased production	Increased loss and/or destruction
Deficiencies	Haemolysis
Erythropoietin	Autoimmune haemolytic anaemia
Iron	Thrombotic thrombocytopaenic purpura (TTP)
Folate	Disseminated intravascular coagulation (DIC)
Vitamin B_{12}	Infections: Malaria
Drugs	Pre-existing conditions
Zidovudine	Glucose-6-phosphate dehydrogenase deficiency
Co-trimoxazole	Sickle cell disease
Anti-mycobacterial therapy	Thalassaemia
Amphotericin B	Gastrointestinal bleeding
Ganciclovir	Infections (CMV, Candida, parasites)
Dapsone	Kaposi's sarcoma
Chemotherapy	GIT lymphoma
Infections	Hypersplenism
HIV	Infection
Cytomegalovirus (CMV)	Haemophagocytosis
Epstein-Barr Virus (EBV)	Lymphoma
Parvovirus B19	Idiopathic
Mycobacterium tuberculosis (MTB)	
Mycobacterium avium complex (MAC)	
Histoplasma capsulatum	
Neoplasia	
Hodgkin's disease	
Non-Hodgkin's lymphoma	
Kaposi's sarcoma	
Miscellaneous	
Anaemia of chronic disease	
Pure red cell aplasia (PRCA)	
Hypoplastic/aplastic anaemia	
Haemophagocytic syndrome	
Secondary myelodysplastic syndrome	

Most Common Causes:

- *ACD*
- *Infections (Incl HIV)*
- *Nutritional deficiencies*
- *Drugs*

Van den Berg K et al. S Afr J HIV Med 2012;13(2):87-103

Investigation

Why is the aetiology important ?

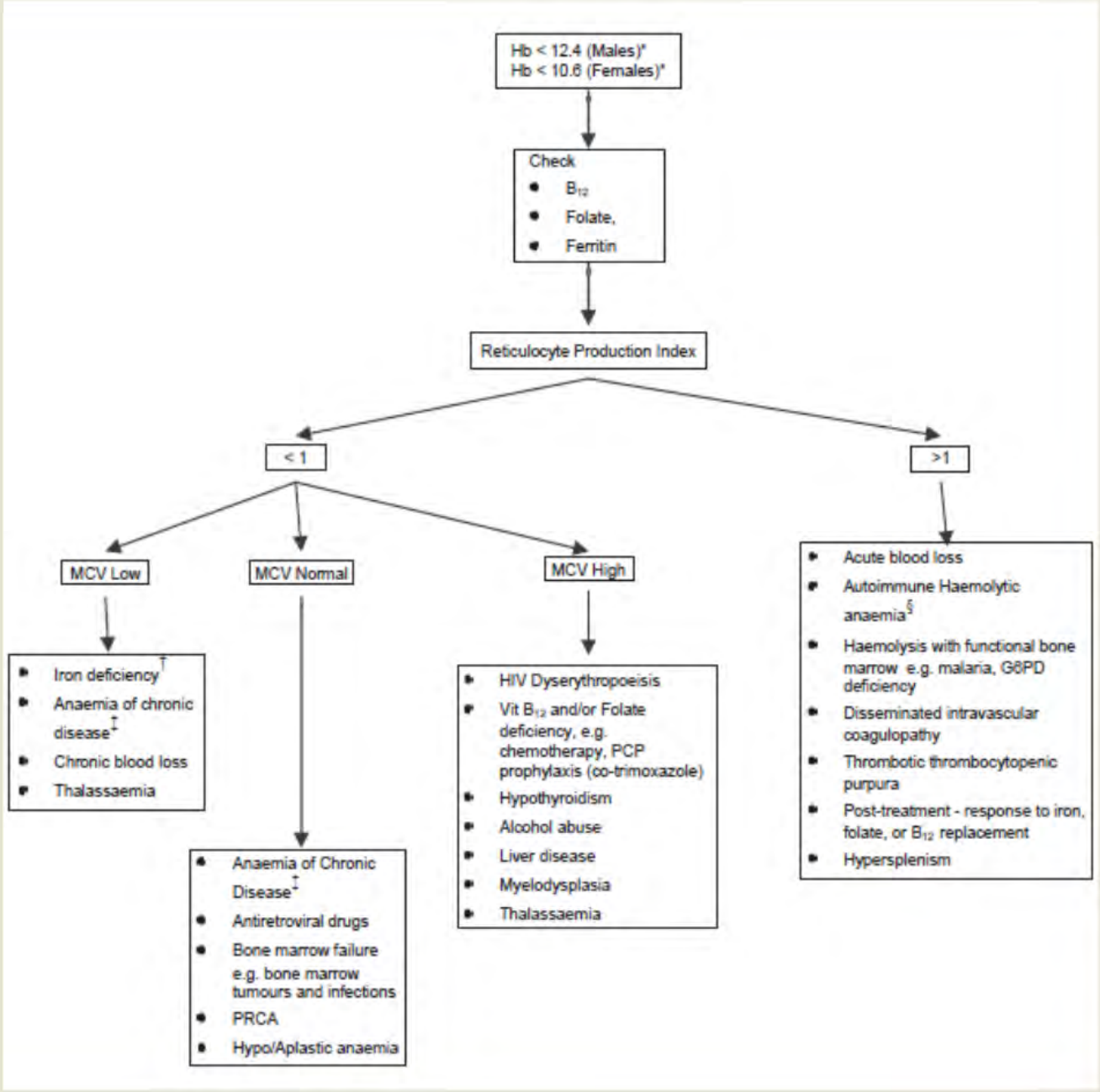
- Guides investigation & dictates management

- Must recognise it when you see it
- Need to look for it to be able to find it

Investigation:

Step-wise investigation:

- Exclude nutritional deficiencies
- Confirm bone marrow functioning
- Evaluate Red Cell Morphology
- Exclude drugs
- Exclude infections



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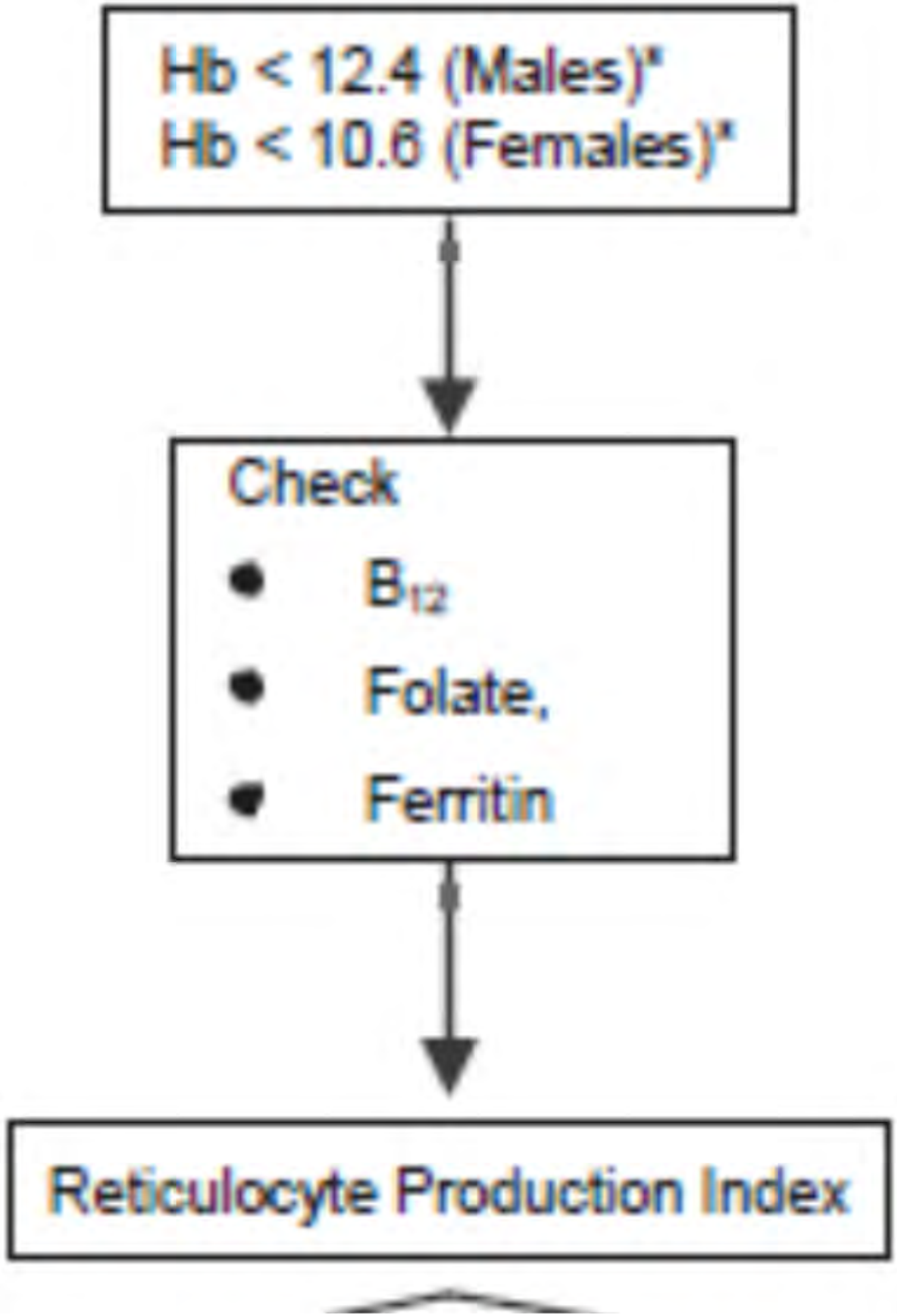
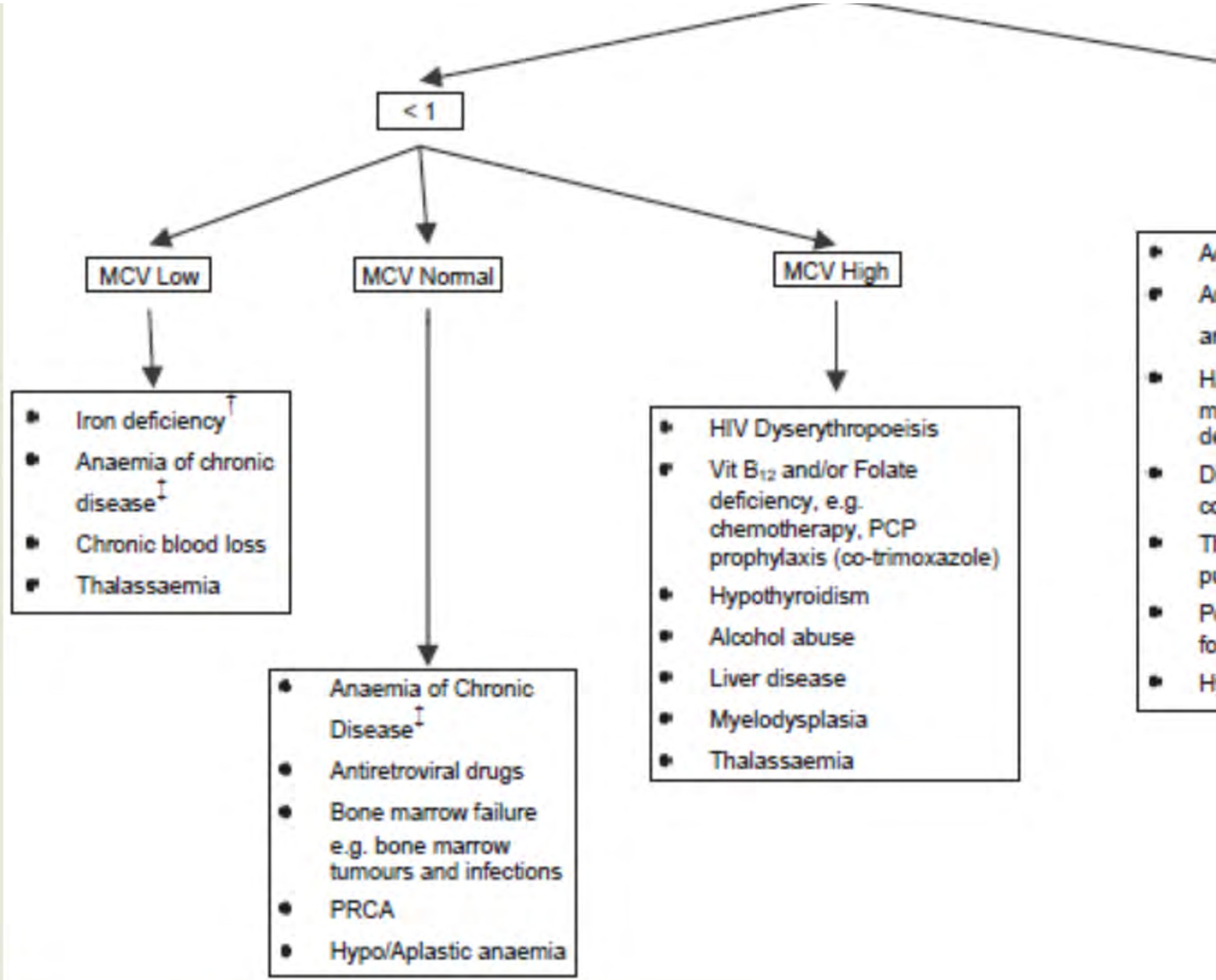
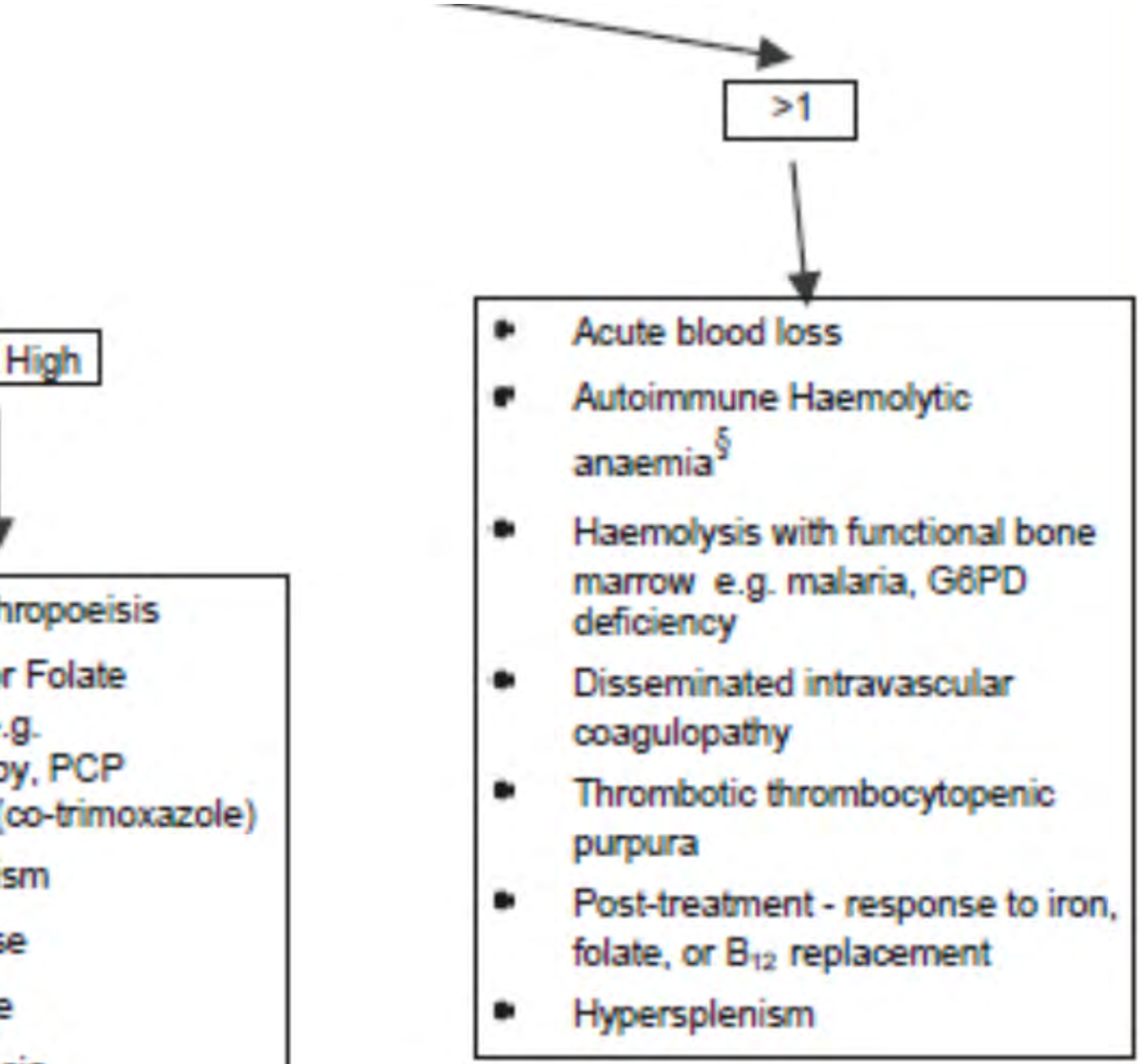

Hb < 12.4 (Males)*
Hb < 10.6 (Females)*
Check
B12
Folate,
Ferritin
Reticulocyte Production Index


< 1
MCV Low
MCV Normal
MCV High
Iron deficiency
Anaemia of chronic disease
Chronic blood loss
Thalassaemia
Anaemia of Chronic Disease
Antiretroviral drugs
Bone marrow failure e.g. bone marrow tumours and infections
PRCA
Hypo/Aplastic anaemia
HIV Dyserythropoeisis
Vit B_{12} and/or Folate deficiency, e.g. chemotherapy, PCP prophylaxis (co-trimoxazole)
Hypothyroidism
Alcohol abuse
Liver disease
Myelodysplasia
Thalassaemia


>1
High
hropoeisis
r Folate
.g.
oy, PCP
(co-trimoxazole)
sm
se
e
sia
ia
Acute blood loss
Autoimmune Haemolytic anaemia§
Haemolysis with functional bone marrow e.g. malaria, G6PD deficiency
Disseminated intravascular coagulopathy
Thrombotic thrombocytopenic purpura
Post-treatment - response to iron, folate, or B12 replacement
Hypersplenism

HIV Drugs & Anaemia

Drugs associated with anaemia in HIV:

Most common
Zidovudine
Co-trimoxazole

Others:
3TC (pure red cell aplasia)
Anti-mycobacterial therapy
Amphotericin B
Ganciclovir
Dapsone
Chemotherapy

Zidovudine:

Several studies confirmed potential for bone marrow suppression, however:

CD4 count
Gender
Ethinicity

Stronger predictors of anaemia than AZT

Mildvan D, et al. Cur Med Research and Opinions 2007;23(2):343-355

Co-trimoxazole:

Similarly, extended CTX is associated with anaemia.

Secondary analysis of HIV Prevention Trials Network data of HIV-EU infancts (Placebo arm stopped early):

All received CTX from 6 weeks

96% developed anaemia
50% had severe anaemia
But improved over time

Aizire, et al. AIDS 2012;26:325-333

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In addition:

If anaemic and on HAART, more likely to RESOLVE anaemia than if not on HAART

AND

If not anaemic and on HAART less likely to DEVELOP anaemia than if not on HAART

Even if on AZT-containing regime

Berhane K, et al. J Acquir Immune Defic Syndr 2004; 37(2):1245-1253

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Secondary analysis of CHAP trial involving HIV-infected treatment naive children in Zambia randomized to receive CTX or placebo:

Those on CTX had significantly:
- slower decreases in weight-for-age
- slower decreases in height-for-age
- greater INCREASE in Hb levels

Prendergast A, et al. Clinical Infectious Diseases 2011;52(7):953-956

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So what??

Why is this any different to any other anaemia??

It's not!!

But it's often treated differently:
Neglected or over-transfused

Management

Does not differ from any other anaemia!

Treat the cause

- Initiate ART if appropriate
- Supportive treatment
  - Haematinics (Do not over treat with iron)
  - Erythropoietin (If poor response)

Establish the cause!

Establish the cause!!

Establish the cause!!!


Guidelines for antiretroviral therapy in adults

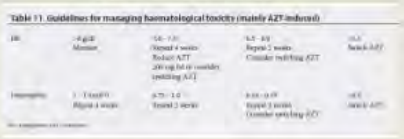
Table 11. Guidelines for managing haematological toxicity (mainly AZT-induced)

- Transfusion

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Establish the cause!!!

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Guidelines for antiretroviral therapy in adults

by the Southern African HIV Clinicians Society

Graeme Meintjes, Gary Maartens (Chairpersons of the Adult Guidelines Committee), **Andrew Boulle, Francesca Conradie, Eric Goemaere, Eric Hefer, Dave Johnson, Moeketsi Mathe, Yunus Moosa, Regina Osih, Theresa Rossouw, Gilles van Cutsem, Ebrahim Variava, Francois Venter** (Expert Panel Members), **Dave Spencer** (Reviewer), **on behalf of the Southern African HIV Clinicians Society**

Table 11. Guidelines for managing haematological toxicity (mainly AZT-induced)

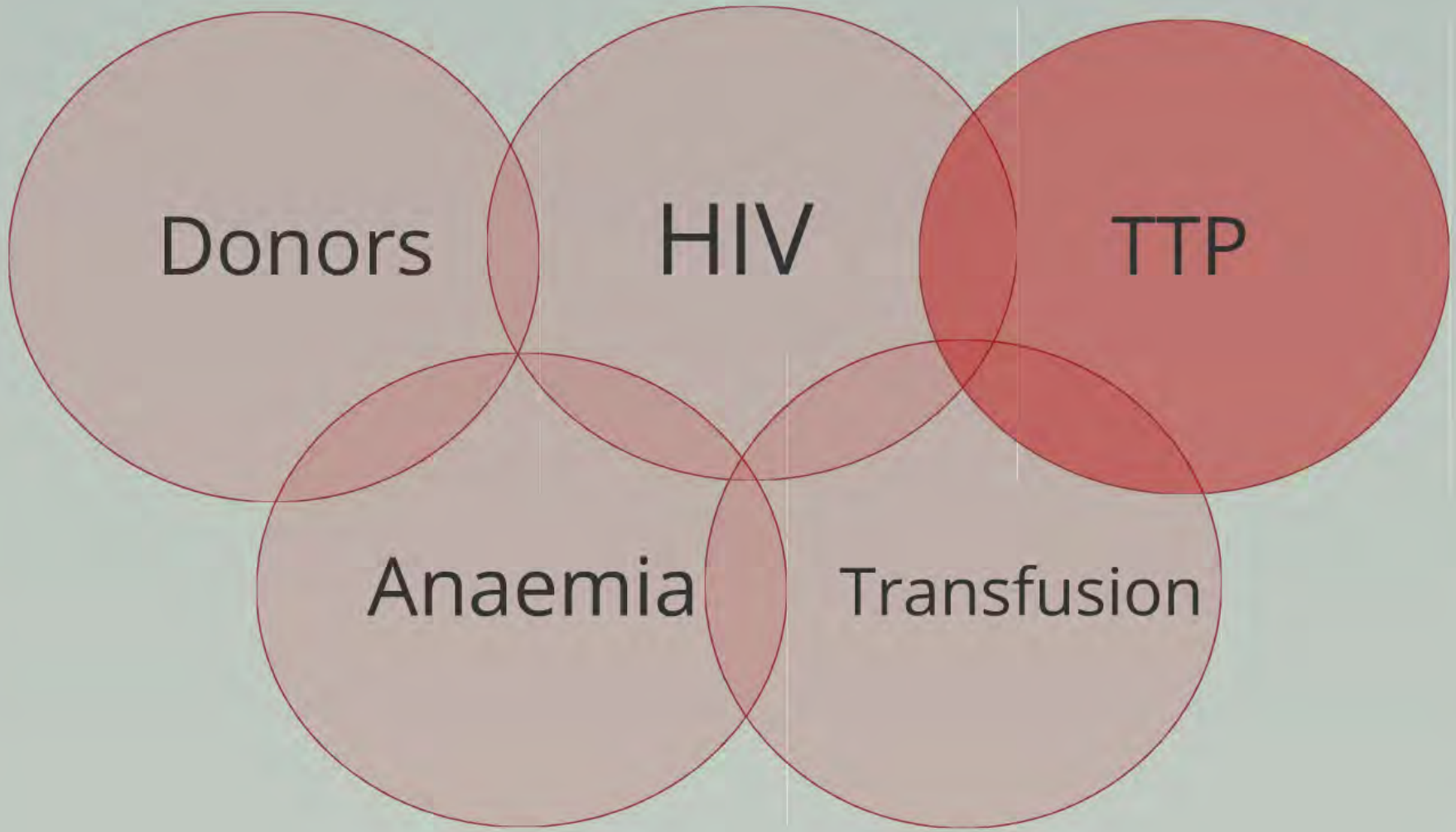
Hb	>8 g/dl Monitor	7.0 - 7.9 Repeat 4 weeks Reduce AZT 200 mg bd or consider switching AZT	6.5 - 6.9 Repeat 2 weeks Consider switching AZT	<6.5 Switch AZT
Neutrophils	1 - 1.5x10^9/l Repeat 4 weeks	0.75 - 1.0 Repeat 2 weeks	0.50 - 0.75 Repeat 2 weeks Consider switching AZT	<0.5 Switch AZT

Hb = haemoglobin; AZT = zidovudine.

Management: Transfusion

- Indications do not differ from those for HIV-negative patients
- Based on:
  - Individual patient's needs
  - Best practice guidelines
  - Only when clinically indicated & benefits outweighs risks
- TREAT THE UNDERLYING CAUSE
- Transfuse MINIMUM effective volume
  - No routine leukodepletion
  - No routine irradiation
  - "CMV" negative blood not available in SA - use leukodepleted products

HIV & Blood Transfusion



HIV Associated TTP

Globally: 14-40% higher incidence in HIV

In RSA:

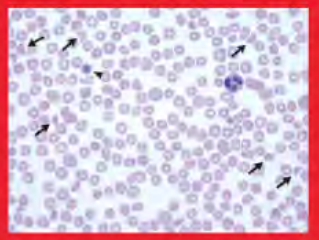
- **HIV TTP >80% of all TTP cases**
- **Associated with advanced HIV**
  - **Low CD4 counts**
  - **High viral load**
  - **More common in females**
- **Incidence decreases with ART**

Can be first manifestation of AIDS

Gunther K, et al. ISBT Science Series 2006;1:246-50
Novitzky N, et al. BJ Haematology 2005;128:373-9
Thompson CE, et al. Blood 1992;80:1890-5

TTP: Defining Clinical Features

- Thrombocytopaenia
- Microangiopathic haemolytic anaemia
  - Low Hb
  - Red cell fragments
  - Reticulocytosis
  - Raised LDH
  - Raised indirect billirubin



- Renal dysfunction
- Neurological Sx & Tx
- Fever

Microangiopathic H

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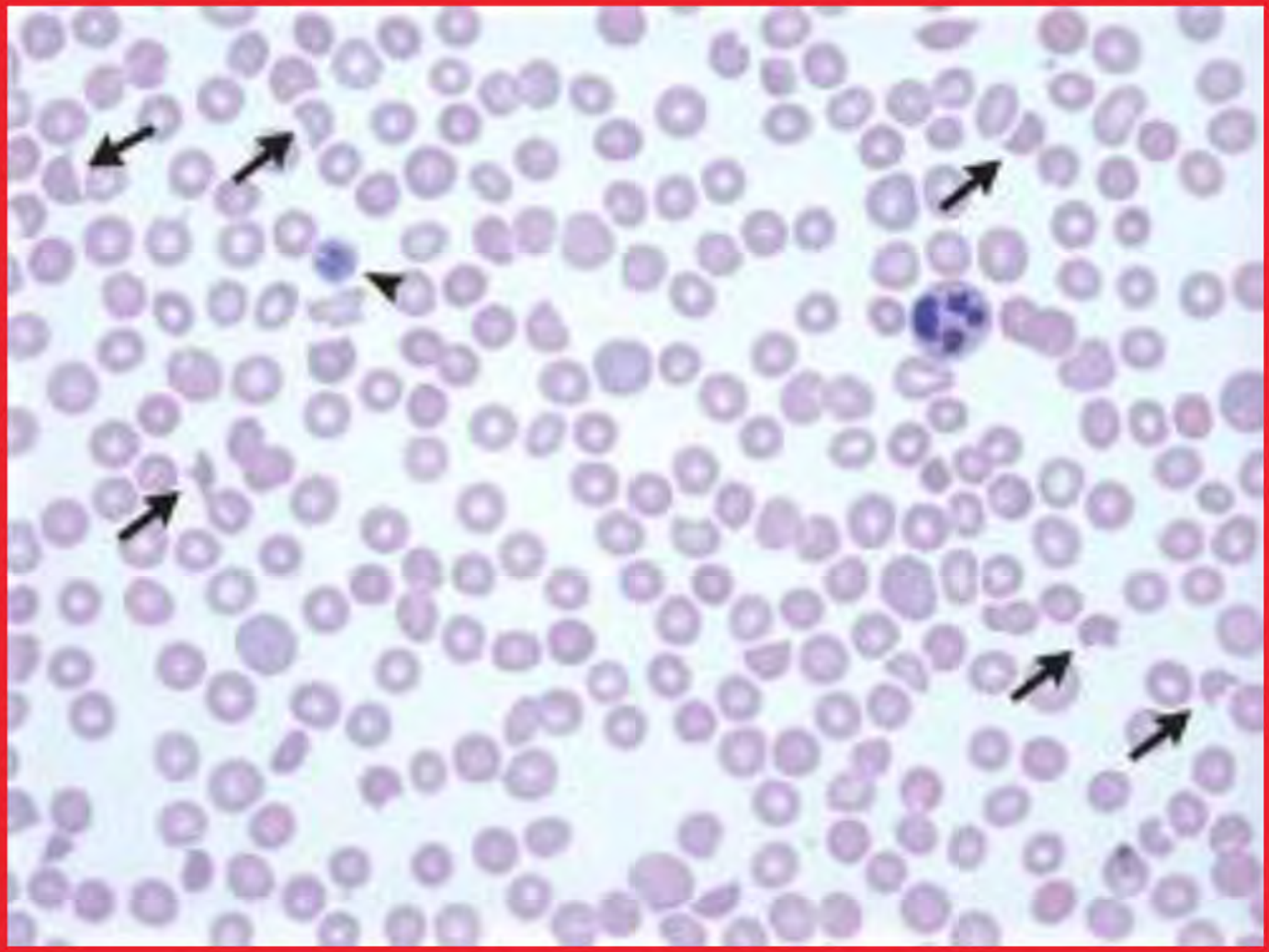

http://blogs.nejm.org/now/index.php/thrombotic-thrombocytopenic-purpura/2010/12/10/

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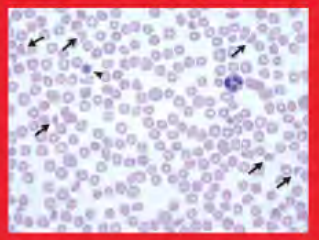
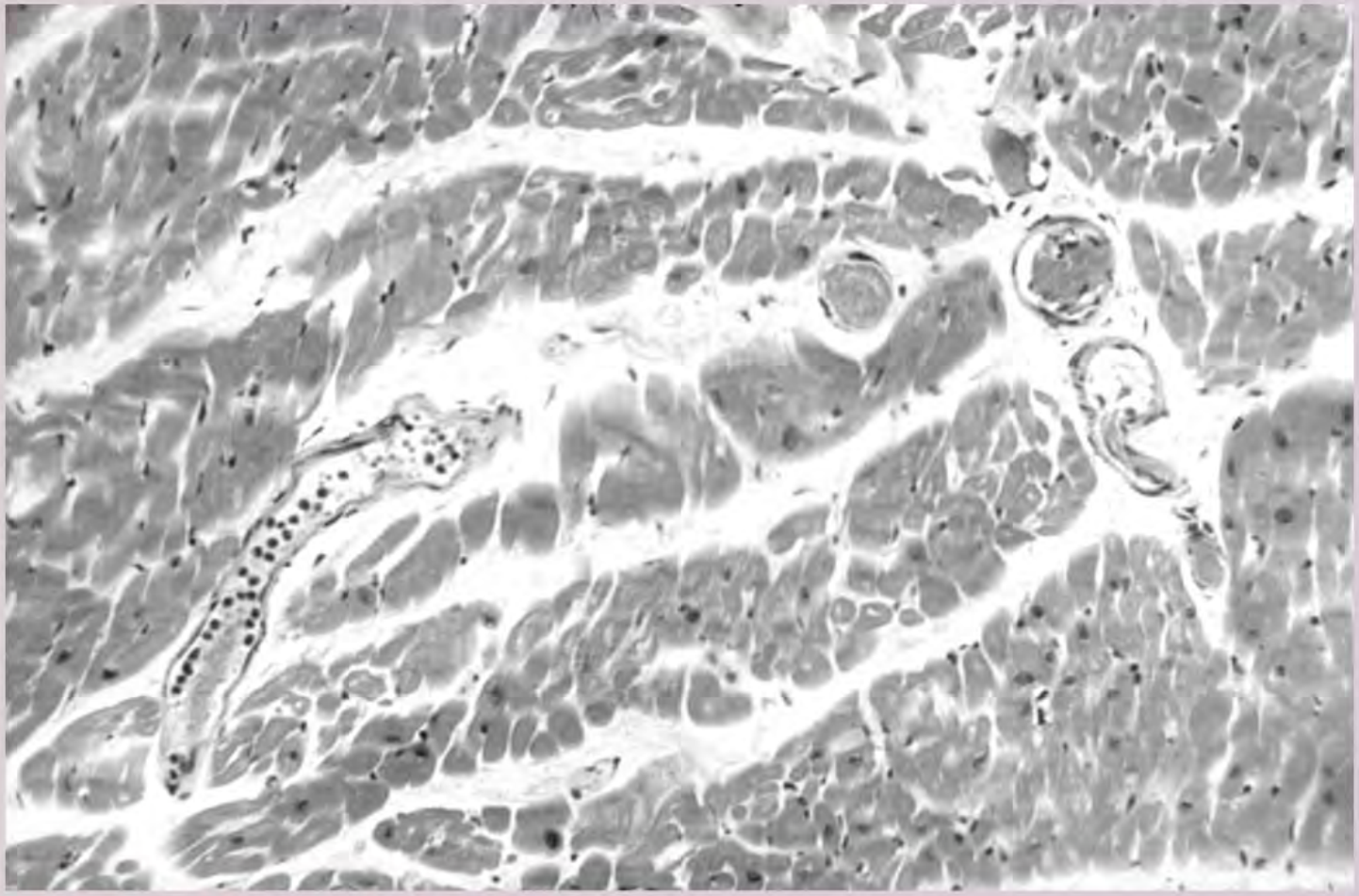


- Renal dysfunction
- Neurological Sx & Tx
- Fever

TTP: Defining Pathological Features

- Thrombotic microangiopathy with:
    - Intraluminal platelet-rich thrombi
    - Localized endothelial cell proliferation & detachment
        - In the absence of inflammation
- Thrombi limited to selected organs, e.g.
    - Kidney, heart, brain
    - Lungs are usually spared

Typical histological findings of acute thrombotic thrombocytopenic purpura (TTP) (cardiac muscle).



Allford S L , Machin S J J Clin Pathol 2000;53:497-501

JCP

HIV vs Non-HIV TTP

- Non-HIV TTP – mostly protease (ADAMTS 13) inhibitor mediated
- HIV TTP mostly lacks protease inhibitors
- Probably different pathophysiology; which may include:
  - Direct infection of endothelial cells
  - Endothelial injury
    - Loss of thrombo-resistance
    - Overwhelming release of VWF

Gunther K, et al. ISBT Science Series 2006;1:246-50
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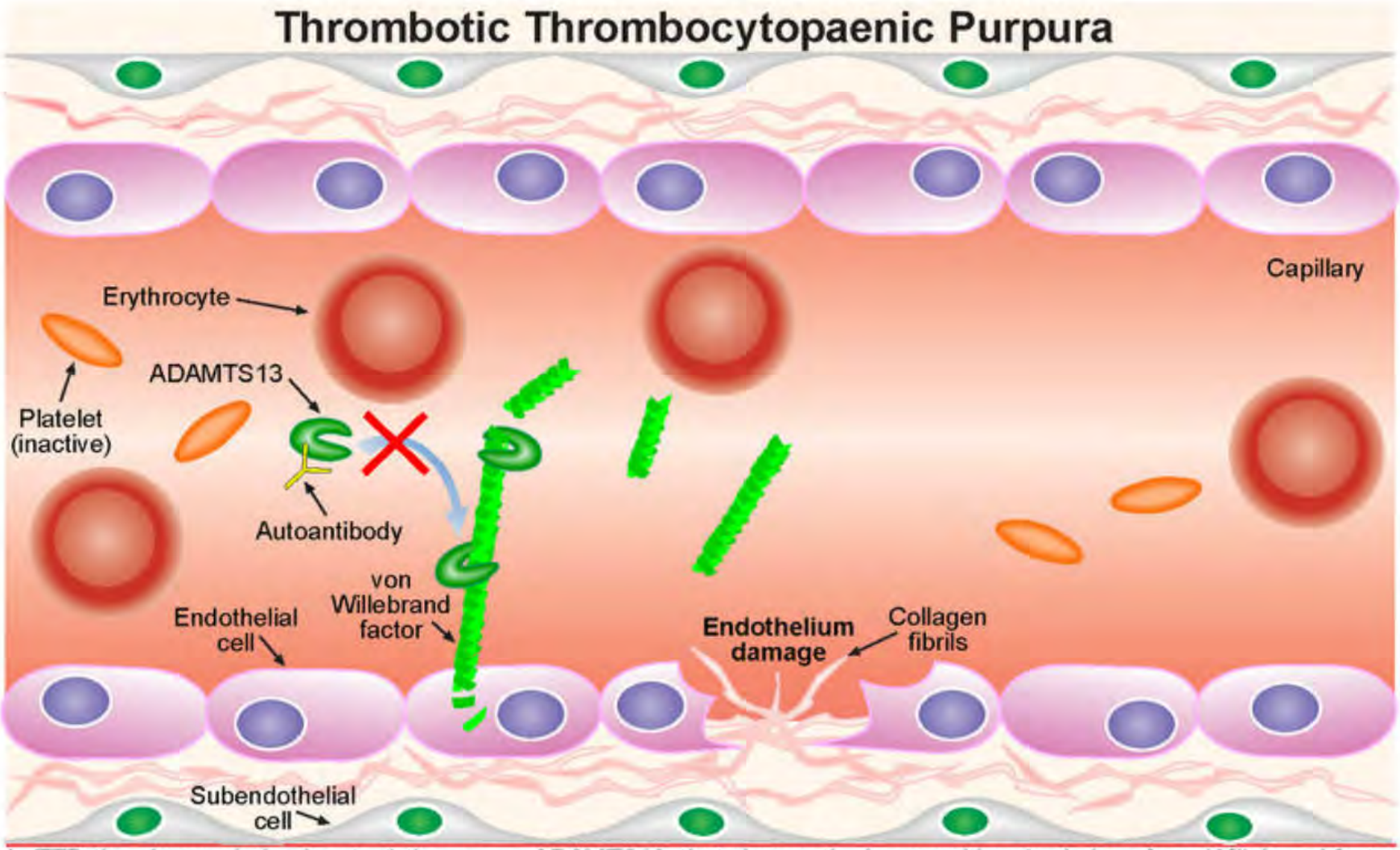
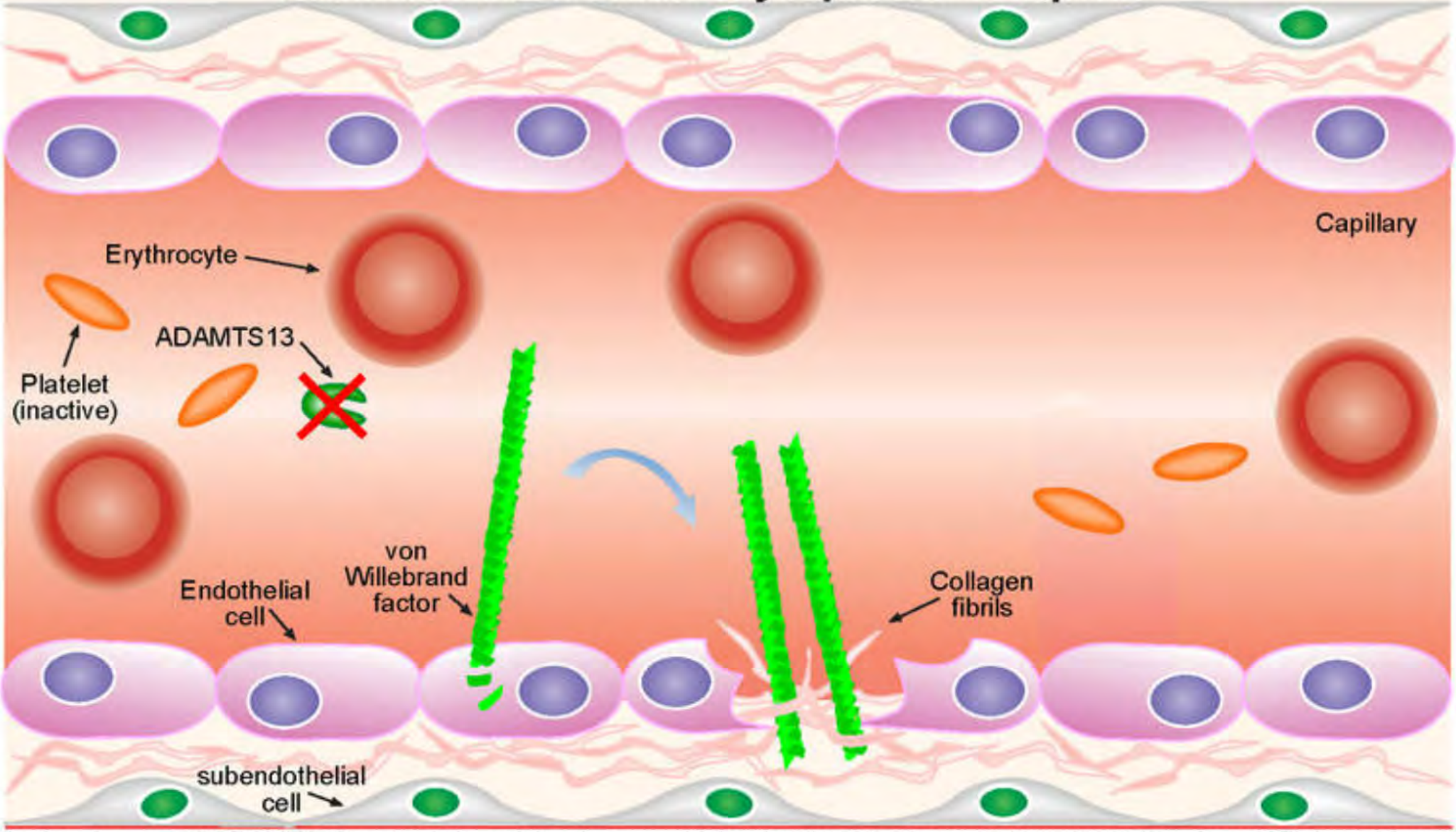
Non-HIV TTP



In TTP, the plasma-derived proteolytic enzyme ADAMTS13, that cleaves the large multimeric chains of von Willebrand factor into smaller fragments, is depleted due to the presence of an inhibitor, commonly an autoantibody. Autoantibodies can be produced through molecular mimicry following a humoral response to an infection or by disruption of tolerance to self-antigens, such as observed in diseases like SLE or HIV infection. TTP can also occur during pregnancy and may be related to the increased risk of developing autoantibodies when immune responses are polarised towards Th2 T cytokine profile, which favours development of humoral immunity.

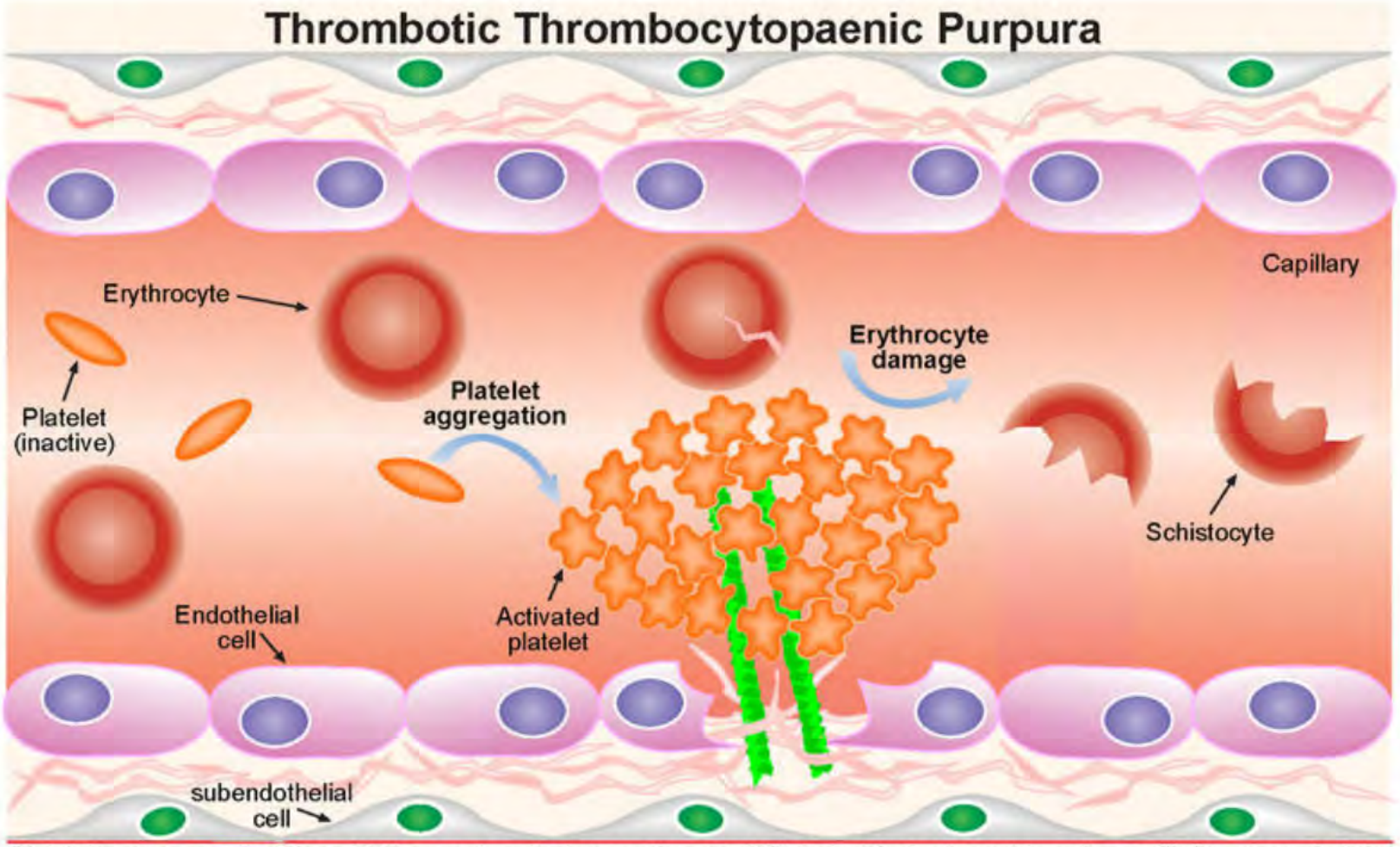
immunopaedia.org

Thrombotic Thrombocytopaenic Purpura



In the absence of ADAMTS13 proteolytic activity, there are higher levels of the large multimeric chains of von Willebrand factor in circulation that are able to bind to exposed subendothelial collagen fibrils and initiate recruitment of large numbers of platelets to sites of endothelium damage.

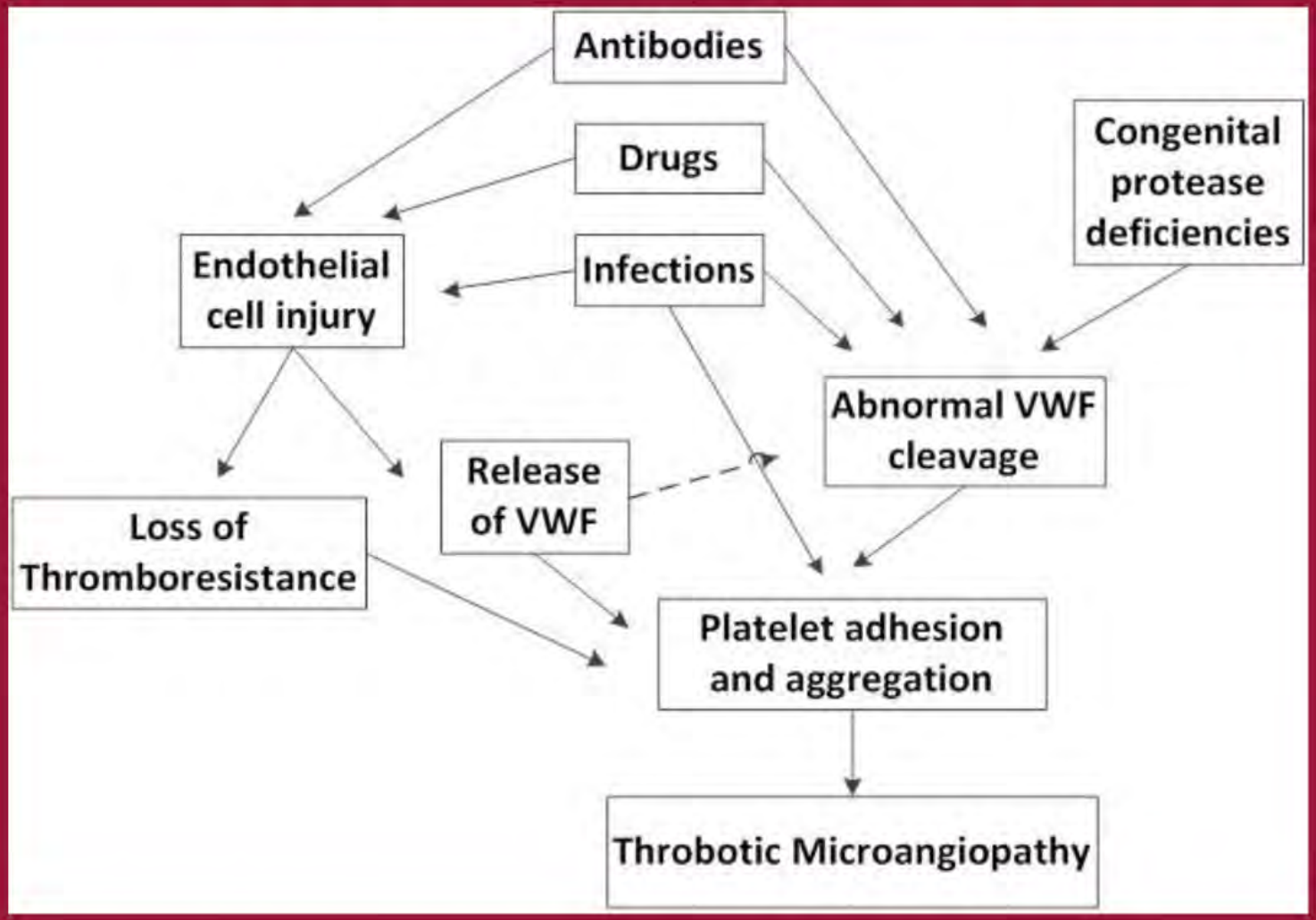
Thrombotic Thrombocytopaenic Purpura



Platelets express cell surface GPIb receptors that recognise von Willebrand factor bound to collagen fibrils exposed at the site of endothelium damage. In TTP, the large multimeric chains of von Willebrand factor recruit and activate excessive numbers of platelets, which in turn leads to platelet depletion (thrombocytopaenia). The large aggregation of platelets also impedes the passage of erythrocytes through small blood vessels and can cause the cells to shear, resulting in anaemia and organ ischaemia. Fragments of erythrocytes are visible in blood smears and are known as schistocytes.

immunopaedia.org

TMA Associated Factors



Gunther K, et al. The pathogenesis of HIV-related thrombotic thrombocytopaemic purpura - is it different? ISBT Science Series 2006;1:246-50

So what??

- HIV TTP usually responds to plasma infusion alone
- Non-HIV TTP does not!
- Why??
- Possibly due to HIV TTP usually not being immune-mediated
- If correct, identifying lack of inhibitors may guide what is very expensive Rx

Legal & Human Rights Considerations

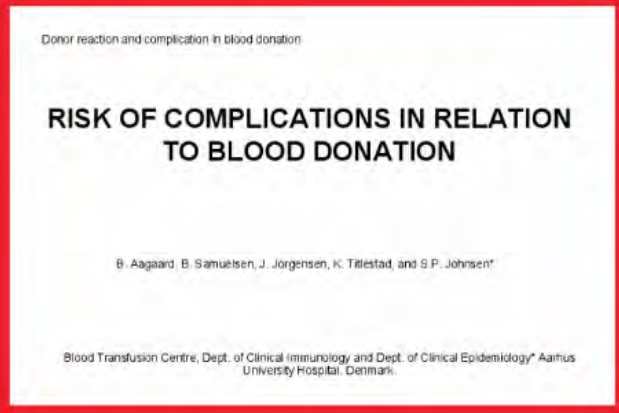
Rights of Donors

- No "right" to donate blood
- BTS constitutionally obliged to ensure safety of the blood supply
- BUT...
- Donors must be treated fairly:
  - No violation of fundamental constitutional rights
  - Any "discrimination" must be reasonable and justifiable

Rights of Donors & Recipients

Informed consent

- Recognised in SA law (National Health Act 61 of 2003)
- Fleshed out by
  - Case law
  - Regulatory council guidelines
  - Patients' Rights Charter
  - Other legislation



Donor reaction and complication in blood donation

RISK OF COMPLICATIONS IN RELATION TO BLOOD DONATION

B. Aagaard, B. Samuelsen, J. Jörgensen, K. Titlestad, and S.P. Johnsen*

Blood Transfusion Centre, Dept. of Clinical Immunology and Dept. of Clinical Epidemiology* Aarhus University Hospital, Denmark.

Rights of Recipients

Right to access

- Guaranteed under Section 27 of the constitution
- May limit access, but must be fair, reasonable and justifiable
- Cannot deny access purely based on HIV Status

Rights of terminally ill patients

- Right to access is not absolute
- Reasonable & fair measures (Soobramoney case)
- Withholding treatment should be decided on by a senior clinician in consultation with the patient / family

Questions??


Thank You!!
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