Thank You!!

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HIV & Blood Transfusion:
A review of the use of blood and blood products in HIV-infected patients

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 '80s and '90s impacted national and international healthcare policy

1. Derrick JB. Canadian Anaesthetists' Society 1986; 33:117-22
HIV & Blood Transfusion

- Donors
- HIV
- TTP
- Anaemia
- 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

- 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
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

* Vermuelen M et al. Transfusion 2009; 49:1115-1125
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  • ~ 2 500 unit /day; 7 days a week
  • = R600 000 per day
  • = R4,2mil per week
  • = R16,8mil per month
  • = R201,6mil per year
## HIV & Blood Issuing Policies

<table>
<thead>
<tr>
<th>Risk Categories: Level</th>
<th>Cohort</th>
<th>Residual Risk (Bush Model)</th>
</tr>
</thead>
</table>
| Risk Category C       | Active or rejoined donors: 4 or more donations in previous 24 month period | FY 08/09 = 1/116 897  
FY 09/10 = 1/116 113  
FY 10/11 = 1/116 113  
Target: < 1/100 000 |
| All componented products to be made from this category | FY 09/10 = 1/80 188 |
| Risk Category R       | 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 |
| Not for paediatric and neonatal RCC. | FY 09/10 = 1/80 188 |
| Risk Category P       | 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 |
| Only issue the Donor Retested Plasma and limited release of RCC | FY 09/10 = 1/80 188 |

SANBS 2011; HIV residual risk based hierarchical blood issuing procedure
HIV & Blood Transfusion

Donors

HIV

Anaemia

TTP

Transfusion
HIV Epidemiology

Change in the South African HIV epidemic, 2002 to 2010

HIV Epidemiology

- SA has largest epidemic in the world
  - 17% of all HIV cases (0.7% world population)\(^1\)\(^-\)\(^2\)
  - \(\approx\) 5.6 million cases (> all of Asia combined)\(^3\)

- Continued incidence of \(\approx\) 1.5%\(^3\)

- No of people living with HIV expected \(\uparrow\)
  - 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
HIV & Transfusion

HIV & Blood Issues

- Red Cell Products Issues
- No of people on ART in 100 000's
- AIDS-related deaths in 100 000's

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

Donors

HIV

TTP

Anaemia

Transfusion
Epidemiology

- Occurs commonly¹
  - 63-95% of infected persons
  - Incidence↑ with disease progression

- Independent predictor of mortality²
  - Correction of anaemia decreases morbidity and mortality

- Associated with QOL↓³

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, occurring 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
- Neoplasms
- Bone marrow infiltrative disorders
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
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
## Aetiology

### Table 1. Anaemia and HIV-infection

<table>
<thead>
<tr>
<th>Decreased production</th>
<th>Increased loss and/or destruction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deficiencies</strong></td>
<td><strong>Haemolysis</strong></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Autoimmune haemolytic anaemia</td>
</tr>
<tr>
<td>Iron</td>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
</tr>
<tr>
<td>Folate</td>
<td>Disseminated intravascular coagulation (DIC)</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td></td>
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<tr>
<td>Drugs</td>
<td></td>
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<tr>
<td>Zidovudine</td>
<td></td>
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<tr>
<td>Co-trimoxazole</td>
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<tr>
<td>Anti-mycobacterial therapy</td>
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<tr>
<td>Amphotericin B</td>
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<tr>
<td>Ganciclovir</td>
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<tr>
<td>Dapsone</td>
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<tr>
<td>Chemotherapy</td>
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<tr>
<td>Infections</td>
<td></td>
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<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td></td>
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<tr>
<td>Epstein-Barr Virus (EBV)</td>
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<tr>
<td>Parovovirus B19</td>
<td></td>
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<tr>
<td>Mycobacterium tuberculosis (MTB)</td>
<td></td>
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<tr>
<td>Mycobacterium avium complex (MAC)</td>
<td></td>
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<tr>
<td>Histoplasma capsulatum</td>
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<tr>
<td>Neoplasia</td>
<td></td>
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<tr>
<td>Hodgkin's disease</td>
<td></td>
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<tr>
<td>Non-Hodgkin's lymphoma</td>
<td></td>
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<tr>
<td>Kaposi's sarcoma</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Anaemia of chronic disease</td>
<td></td>
</tr>
<tr>
<td>Pure red cell aplasia (PRCA)</td>
<td></td>
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<tr>
<td>Hypoplastic/aplastic anaemia</td>
<td></td>
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<tr>
<td>Haemophagocytic syndrome</td>
<td></td>
</tr>
<tr>
<td>Secondary myelodysplastic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

**Most Common Causes:**
- ACD
- Infections (Incl HIV)
- Nutritional deficiencies
- Drugs

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
Hb < 12.4 (Males)*
Hb < 10.0 (Females)*

Check
- B12
- Folate
- Ferritin

Reticulocyte Production Index

< 1
- MCV Low
  - Iron deficiency
  - Anaemia of chronic disease
  - Chronic blood loss
  - Thalassaemia

- MCV Normal
- MCV High
  - HIV Dyserythropoiesis
  - Vit B12 and/or Folate deficiency, e.g., chemotherapy, PCP prophylaxis (co-trimoxazole)
  - Hypothyroidism
  - Alcohol abuse
  - Liver disease
  - Myelodysplasia
  - Thalassaemia

- 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

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- 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
- Ethnicity

Stronger predictors of anaemia than AZT

**Co-trimoxazole:**

Similarly, extended CTX is associated with anaemia.

Secondary analysis of HIV Prevention Trials Network data of HIV-1 Infants (Placebo arm stopped early):

- All received CTX from 6 weeks
- 96% developed anaemia
- 50% had severe anaemia
- But improved over time

Ahire, et al. AHD 2010;26:325-323
Zidovudine:

Several studies confirmed potential for bone marrow suppression, however:

CD4 count
Gender
Ethnicity

Stronger predictors of anaemia than AZT

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


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But improved over time

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

However:

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

However:

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

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)

- Transfusion
Establish the cause!

Establish the cause!!

Establish the cause!!!
Treat the cause

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value Range</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>&gt;8 g/dl</td>
<td>Monitor</td>
</tr>
<tr>
<td></td>
<td>7.0 - 7.9</td>
<td>Repeat 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce AZT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg bd or consider switching AZT</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1 - 1.5x10⁹/l</td>
<td>0.75 - 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat 2 weeks</td>
</tr>
<tr>
<td></td>
<td>0.50 - 0.75</td>
<td>Repeat 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider switching AZT</td>
</tr>
<tr>
<td></td>
<td>&lt;0.5</td>
<td>Switch AZT</td>
</tr>
</tbody>
</table>

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 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

TTP: Defining Clinical Features

- Thrombocytopenia
- Microangiopathic haemolytic anaemia
  - Low Hb
  - Red cell fragments
  - Reticulocytosis
  - Raised LDH
  - Raised indirect bilirubin

- Renal dysfunction
- Neurological Sx & Tx
- Fever
Microangiopathic

- Low Hb
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TTP: Defining Clinical Features

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  - Raised indirect bilirubin
- 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).


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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

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.
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.
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 (thrombocytopenia). 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.
TMA Associated Factors

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
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!!

Your **DONation** can make all the difference

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