Priority uses of Plasma derived Medicinal products for patients living with HIV/AIDS in endemic low resource settings

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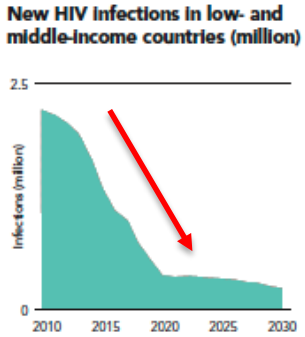
Overview

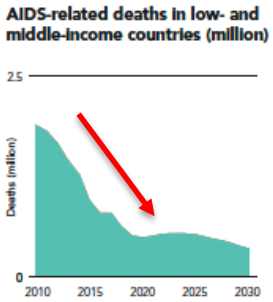


- Where are we in the HIV epidemic?
- The immunodeficiency of HIV
- PDMPs use in HIV-related conditions
- Antibody replacement
- Immunomodulation in autoimmunity
  - Neurology
  - Haematology
  - Other
- Hyperimmune globulin and immunoglobulins for TB
- TTP and FFP

HIV/AIDS by numbers

The GOOD







There were an estimated **34% fewer** AIDS-related deaths in sub-Saharan Africa in 2014 than in 2000.

2000 1.2 million [1 million–1.5 million]
2014 790 000 [670 000–990 000]

The BAD

36.9

million people living with HIV globally in 2014

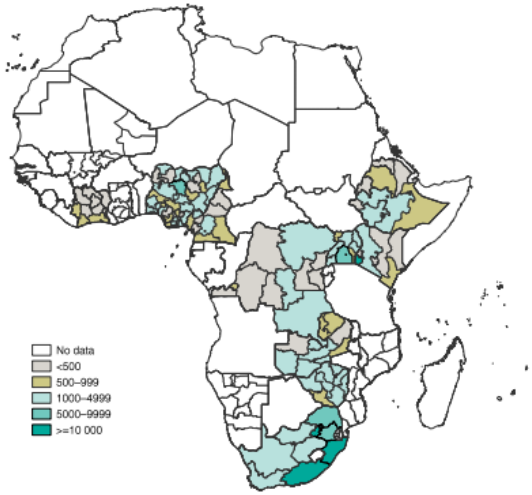
22

million people who need to be reached with antiretroviral therapy

17.1

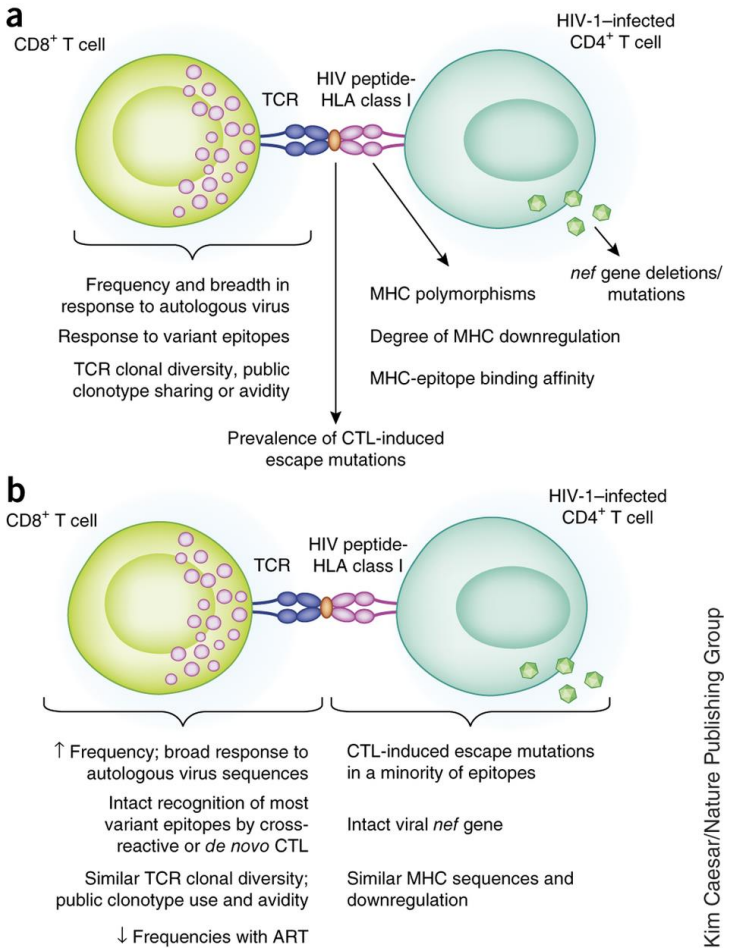
million people living with HIV do not know they have the virus

The UGLY



- 80% women 15-24 with HIV are in SSA
- 5000 young women acquire HIV every week, vast majority in SSA
- Inequalities and domestic violence, poverty, lack of access to education

HIV immunodeficiency



- CD4 lymphopaenia and APCs loss (DCs)
- Inability to trap Ag and support T/B cell interactions
- Impaired production of specific antibody (CSR and SHM problems)
- B-cell hyperreactivity and polyclonal expansion (autoantibodies and malignant transformation)
- Chronic immune activation

Milgueles S and Connors M *Nature immunology* 2015

PDMPs used in HIV

- Immunoglobulins
  - Replacement and immunomodulation
- Fresh frozen plasma (FFP)
- Albumin/Stabilised human serum
- Anti-D immunoglobulin
- Hyperimmuneglobulin preparations for passive infectious disease immunity e.g. heptatitis B

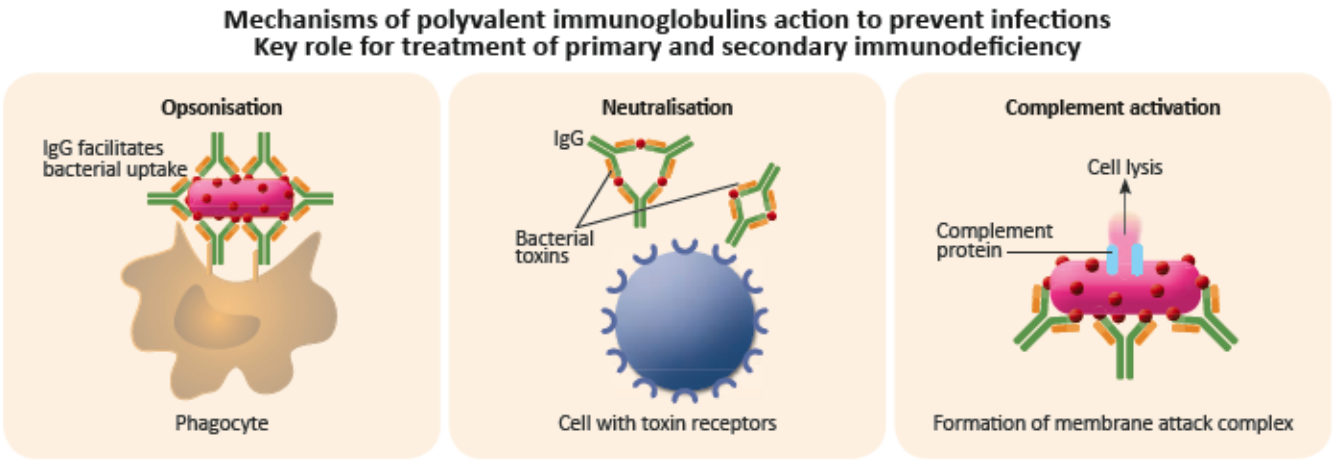






Antibody replacement in HIV/AIDS

- B-cell defects more notable in children than adults with HIV-1
- Defective in vivo primary and secondary antibody responses to T-cell dependent antigens e.g. tetanus and B-cell dependent pneumococcal polysaccharide antigens
- Benefits on immune parameters e.g. decreased B2-microglobulin, TNF-a, neopterin and immune complexes, and reduced infections (early studies)



Was it necessary in post-ART era? Huge cost implications?

Deever A et al *Immunol Allergy Clin N Am* 2008
Peter J et al *SAMJ* 2015

Patient important impacts

Children

- DBRCT pre-ART did not show robust clinical benefits for IRT (400mg/kg/28days)
- ART treatment does not completely correct B-cell immunity

However, clinically:

- RCT of IVI withdrawal in ART-treated HIV patients showed no impact on infections
- Intermittent use of IVIg in hospital setting with severe infections no benefit (retrospective)

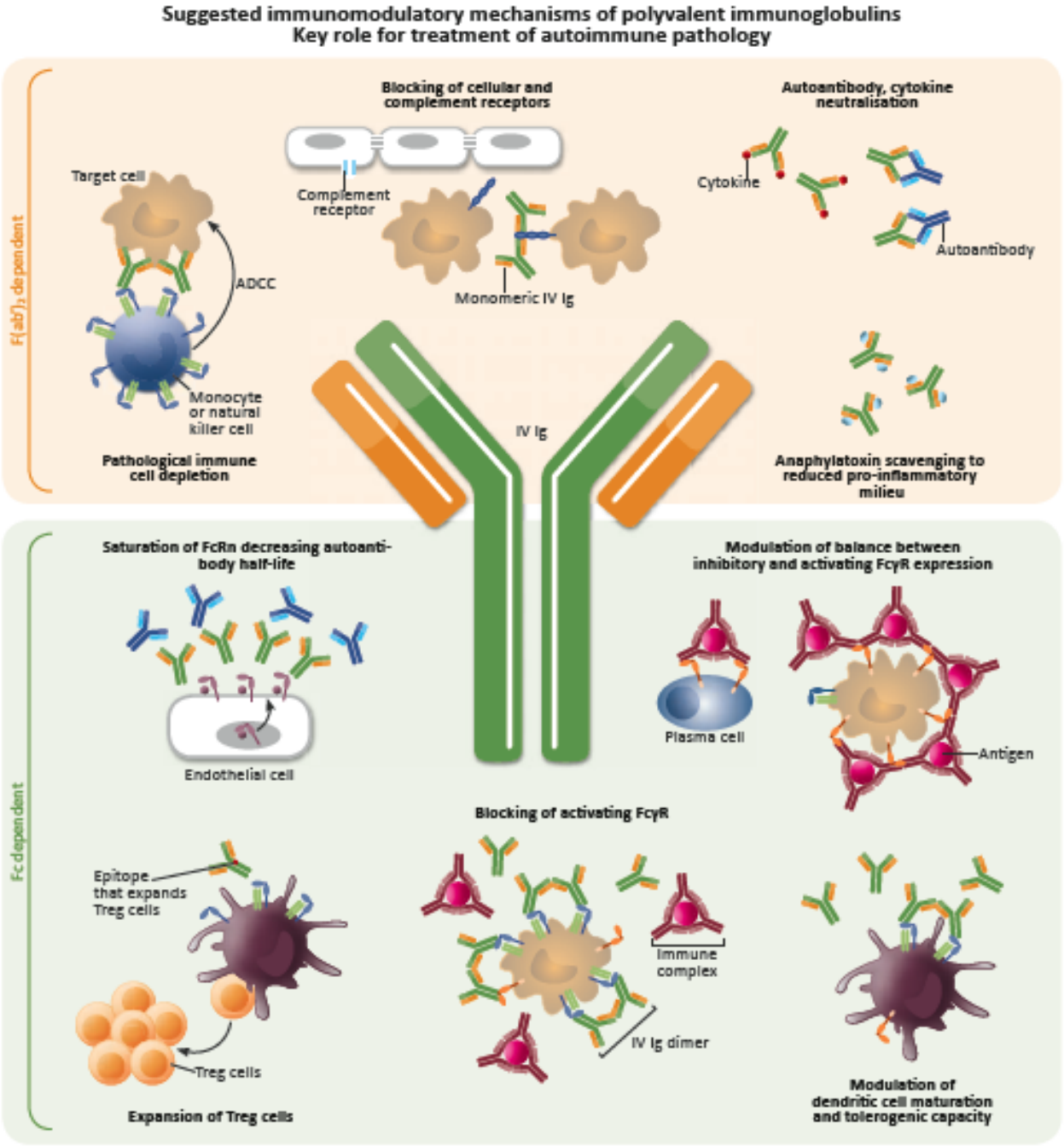
The NCHD intravenous immunoglobulin study group *NEJM* 1991
Huany LC et al *BMC infectious diseases 2008*

Adults

- Several uncontrolled studies showed no conclusive benefits to routine IVIg prophylaxis
- Vaccine strategies e.g. serial pneumoccocal vaccination currently the most promising and cost-appropriate action

Imagine the implications if it had really worked!

Deever A et al *Immunol Allergy Clin N Am* 2008



Peter J et al *SAMJ* 2015

High dose IVIg for HIV-related autoimmunity

Neurology	*Haematology*	*Other*
Guillain-Barre syndrome (Acute inflammatory demylinating polyneuropathy)	HIV-related immune thrombocytopenic purpura	Kawasaki disease
Chronic inflammatory demyelinating polyradiculoneuropathy	Parvovirus B19 associated aplasia	
	Autoimmune haemolytic anaemia and neutropaenia	

AIDP (GBS)

- Clinical and electrophysiological picture similar irrespective of HIV status
- Occurs more commonly with higher CD4 cell counts, or as an HIV seroconversion illness, also as IRIS
- Treatment does not differ based on HIV status and has similar efficacy
- Non-HIV related GBS, IVIg (0.4g/kg for 5 days) or plasma exchange improves recovery
- No benefit of giving IVIg after plasma exchange

Centner CM *Lancet Neurology* 2013
Lindholm et al *J AIDS clin Res* 2013

CIDP

- More common in HIV than AIDP
- Occurs in moderately advanced disease
- Clinical, electrophysiology and CSF findings similar to non-HIV infected patients
- Corticosteroids or IVIg (one course 2g/kg) considered first-line usually with excellent responses
- ART an important additional component of treatment even if CD4 count well preserved

Centner CM *Lancet Neurology* 2013
Lindholm et al *J AIDS clin Res* 2013

HIV-related thrombocytopenia

- IVIg indicated in HIV-related thrombocytopenia unresponsive to ART (first-line)
- However, treatment of autoimmune thrombocytopenia in the context of HIV still corticosteroids 1st line
- Emergencies – IVIg useful for faster increase in platelets
- Anti-IgD of use in Rh+, nonsplectomised HIV postive patients with thrombocytopenia
- Association of HIV-related thrombocytopenia with non-AIDS defining events e.g. cancer

Peter J et al *SAMJ* 2015
Borges A et al *AIDS* 2014

Pure red cell aplasia (PRCA)

- Pure red cell aplasia has sever anaemia with absent maturing red cell precursors in marrow
- Viral infections, usually parvovirus, are common cause of PRCA in complication of advanced immunosuppression (CD4<50)
- Pre-ART IVIg was gold-standard for refractory PRCA (usual dose of 400mg/kg for 5 days) – excellent responses within 90 days *(impact on requirements for transfusions)*
- ART often adequate and now also part of standard of care

Peter J et al *SAMJ* 2015
Morelli P et al *Eur J Clin Microbiol Infect Dis* 2007

Unusual autoimmune diseases

Kawasaki-like syndrome

- A number of unusual autoimmune diseases described in literature
- Only 10 cases described in literature of Kawasaki syndrome occuring in HIV-infected patients – across spectrum of immunosuppresion
- Rx with ART and IVIg (1-2g/kg) as for HIV uninfected patients

In the majority of these conditions, IVIg can be motivated for as 'rescue therapy' usually in steroid unresponsive disease
e.g. bullous phemphigus

The lack of mortality and only modest benefits in reduced morbidity in the other conditions make it hard to justify cost in resource-limited settings

Peter J et al *SAMJ* 2015
Pastori D et al *Int Reviews of Immunol* 2011

Hepatitis B immune globulin in HIV

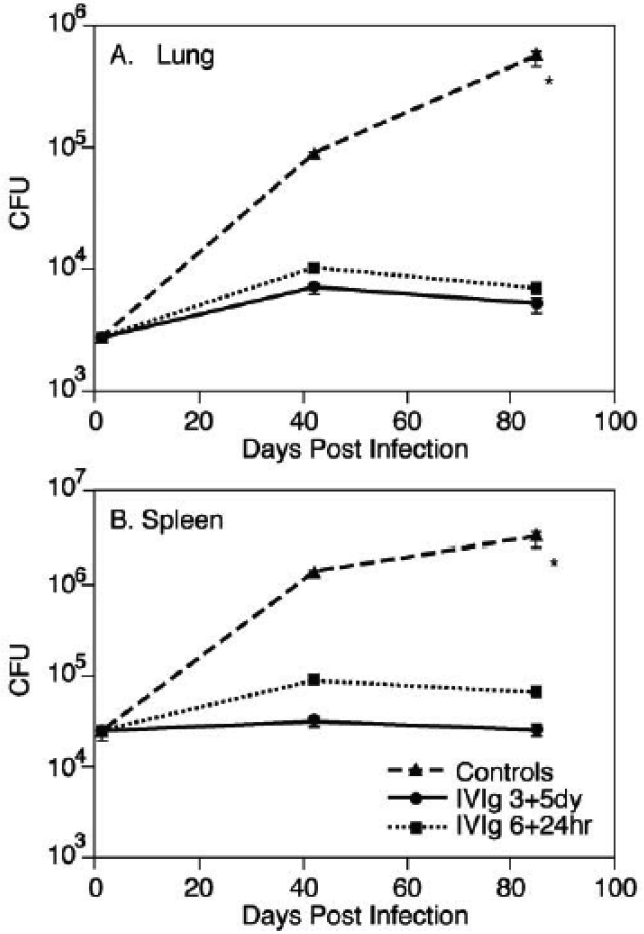
- Hepatitis B co-infection in ~10% (up to 20%) HIV infected patients
- Vaccine responsiveness decreased in HIV depending on immunosuppression
- ART era - longer life-span and increased oncological presentations and requirements for chemotherapy
- HBV exposure and reactivation important considerations

- Passive immunisation with Hepatitis B immune globulin available for:
  - post-exposure prophylaxis
  - Prevent allograft infection in liver transplantation for chronic hep B
- Higher doses needed to prevent allograft infection (protocols vary) but require section 21

Soriano V et al *Curr HIV/AIDS Rep* 2015
Buchner A et al *SAMJ* 2014

IVIg for MDR-TB/XDR-TB Rx

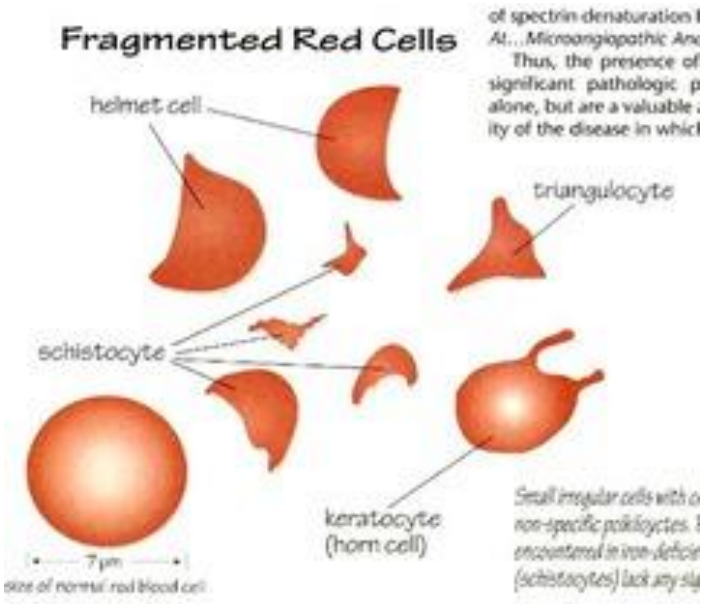
- Increasing burden of MDR-TB (~500 000 cases) and treatment desitute XDR-TB
- Slow development of new TB drugs and need for complex regimens
- Could IVIg have an immunomodulatory benefit?



Roy E et al *Infection and Immunity* 2005
Olivares N et al *Tuberculosis* 2009

Thrombotic thrombocytopaenic purpura (TTP)

- Pentad: thrombocytopenia, microangiopathic HA, neurological abnormalities, renal failure and fever
- Low platelets, fragments and elevated LDH sufficient
- Usually in the context of advanced immunosuprresion (ART-naïve)
- 44 patients (1996-2003) in single hospital - GSH



Novitsky N et al *BJ Haematology* 2005

TTP treatment in SA

- Plasma exchange or plasma infusion (60-90% survival of acute episodes)
- Prednisone 1mg/kg and cryoprecipitate-poor FFP at 30ml/kg/d
- If unable to cope with fluid load, or no improvement on plasma infusions then plasmapheresis
- Responders – decrease FFP infusions by 320ml every third day

Table III. Response to therapy according to HIV infection status.

	ALL ($n = 44$)	HIV− ($n = 23$)	HIV+ ($n = 21$)
All patients			
Complete response (%)	39 (89)	19 (78)	20 (95)
Alive (%)	33 (75)	18 (78)	15 (71)
Died of TTP (%)	6/44 (16)	5 (21)	1 (5)
Overall number of FFP Units* used; median (range)	36 (30–186)	55 (30–186)	33 (30–93); ($P = 0{\cdot}0046$)
Days to platelets $>150 \times 10^9$/l; median (range)	6 (5–21)	7·5 (5–21)	6 (5–16); ($P = 0{\cdot}03$)
Days to normal LDH; median (range)	22 (10–42)	24·5 (21–42)	21 (10–42); ($P = 0{\cdot}01$)
FFP Units* used to normalize platelet count; median (range)	36 (30–186)	54 (30–186)	33 (30–93); $P = 0{\cdot}0046$)
Patients undergoing Apheresis ($n = 10$)			
Median (range) number of procedures to response		5 (3–9)	
FFP units* used to normalize platelet count, median (range); apheresis		96 (70–186) ($P = 0{\cdot}004$)	
Number of patients responding		6/10	
Patients not undergoing apheresis (responded to FFP infusion; $n = 34$)			
FFP units* used to normalize platelet count, median (range); FFP infusion only		41 (30–74) ($P = 0{\cdot}1$)	33 (30–93)

Novitsky N et al *BJ Haematology* 2005

Conclusions

- Number of PDMPs important for treatment of HIV-related diseases
- Cost a major barrier to expansion of indications
- Areas of active research are accelerated aging in HIV-infected patients on longterm ART (chronic immune activation) and sepsis