Unique aspects of pediatric vs adult immune responses in HIV infection: Impact on Potential for HIV Cure/Remission in Pediatric Infection

Framework for Initiating Pediatric Studies of HIV Cure Interventions: Scientific Knowledge Gaps, Regulatory and Ethical Considerations
NIAID Conference Center | 5601 Fishers Lane | Room 1D13
Rockville, MD 20892

May 22-23, 2018

Unique aspects of pediatric vs adult immune responses in HIV infection:

- **Impact of immune ontogeny**

- **Impact of pediatric infection arising via transmission from the mother**

on cure potential in pediatric infection

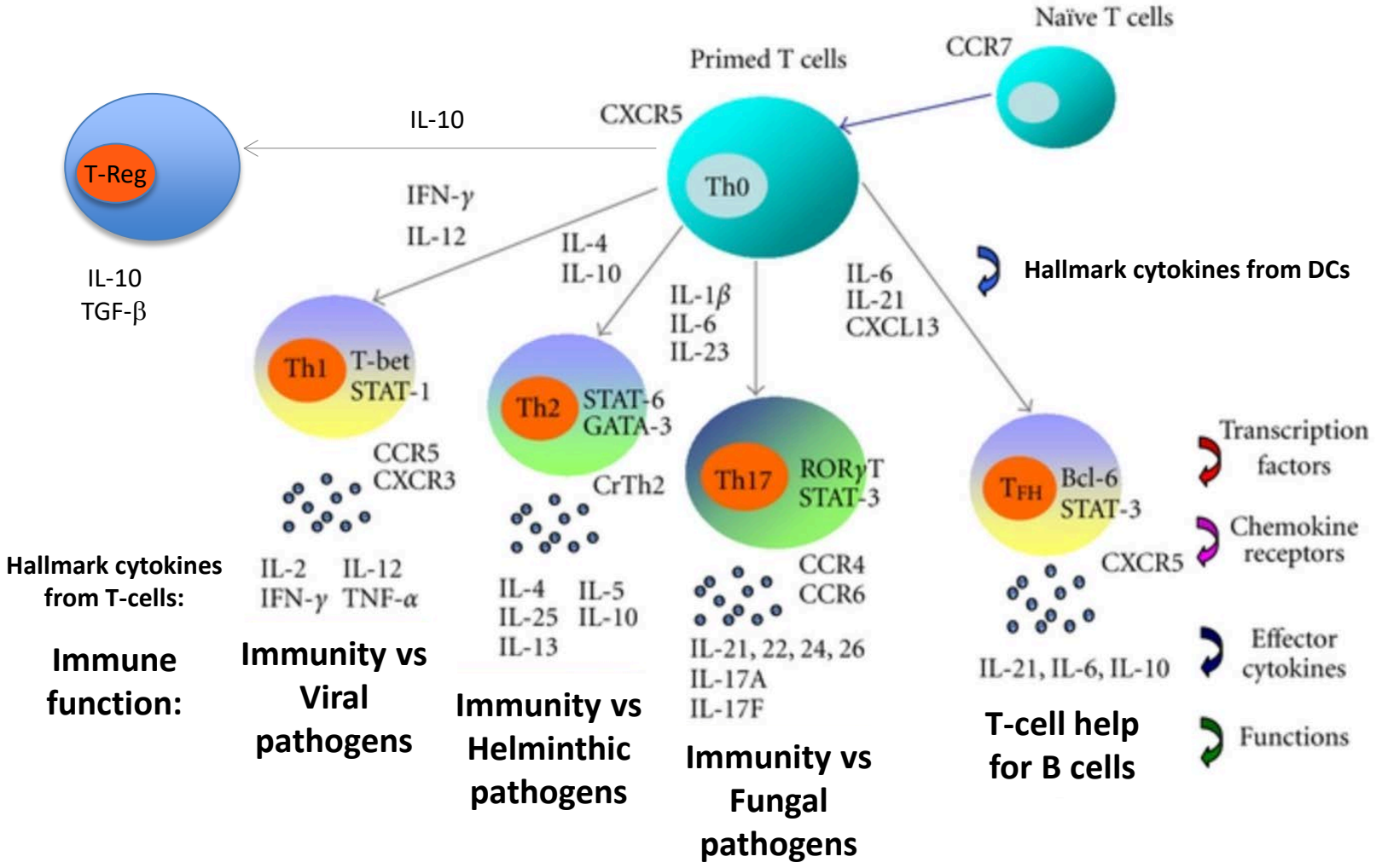
Impact of immune ontogeny on cure potential in pediatric infection:

- Size of initial reservoir, decay kinetics
- Ab and bnAb responses
- CTL responses
- Immune reconstitution on ART

Impact of immune ontogeny on cure potential in pediatric infection:

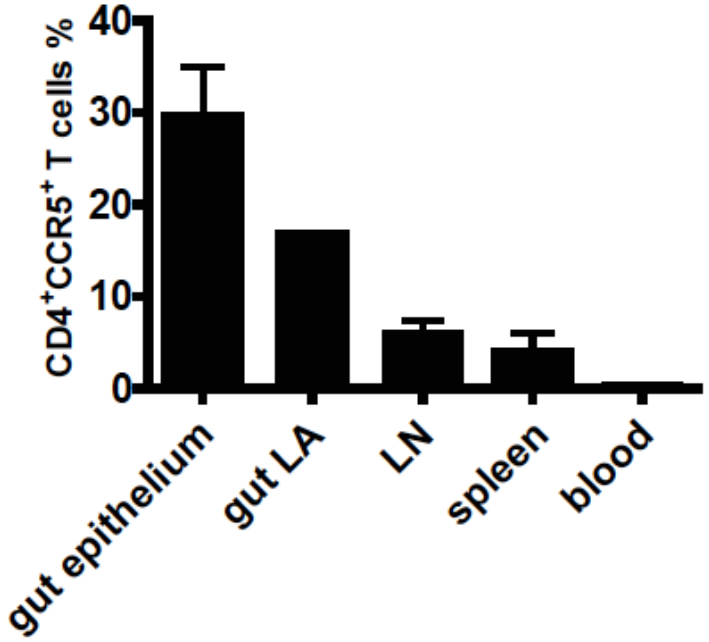
- **Size of initial reservoir, decay kinetics**
  - **Ab and bnAb responses**
  - **CTL responses**
- **Immune reconstitution on ART**

Innate immune responses support immune tolerance in early life vs aggression in adults



Tolerogenic immune environment → low immune activation → low CCR5 expression, low numbers of CD4 memory cells →hard to establish a reservoir of infection

CCR5+ CD4 memory cells do exist in neonatal lymphoid tissues

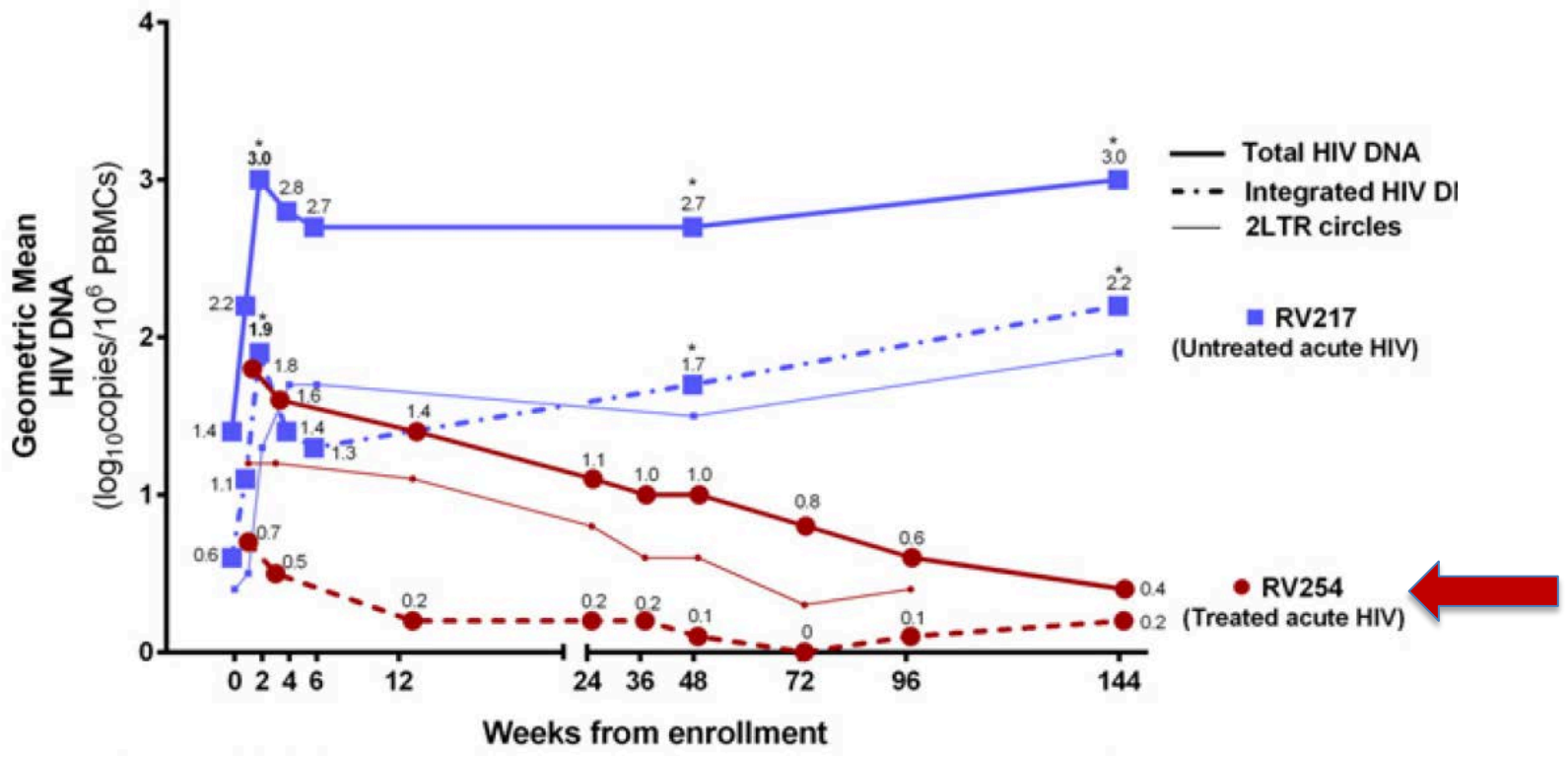


Bunders et al Blood 2012

In children vs adults:

- **Is the initial viral reservoir lower?**
- **Is the decay of the viral reservoir faster?**

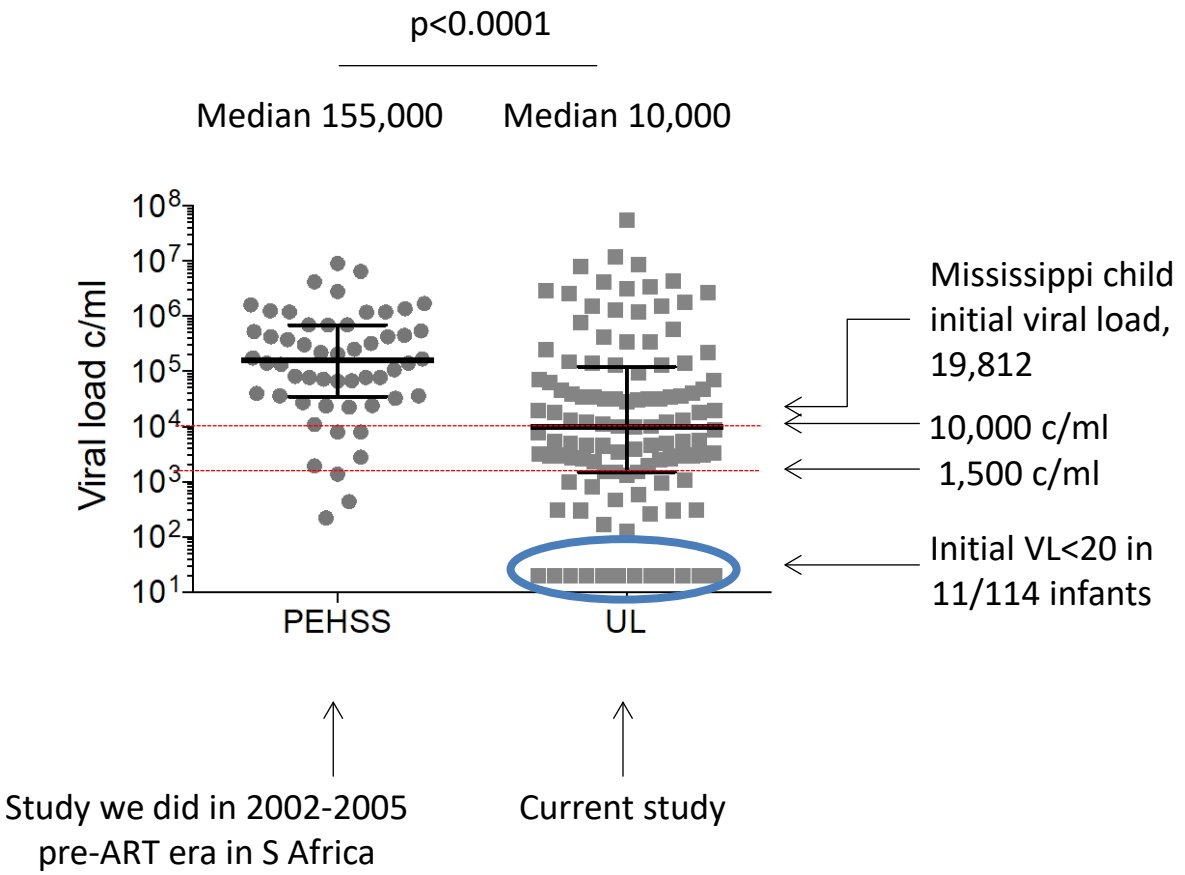
Adults treated in Fiebig I/II (<2wks from infection) have low HIV DNA cpm PBMC



Ananworanich et al EBioMed 2016
Buzon et al JV 2014

Initial HIV DNA cpm PBMC and reservoir decay kinetics in *in utero* infected children receiving ART in first days of life

Initial viral loads >1 log_{10} lower than in pre-ART era; 10% have VL<20c/ml



HIV DNA decay in early treated infants vs adults

Adults: Half-life 21d in first 2 weeks, 198d over next 2.7yrs
Infants: Half-life 17.5d in first month, 58d over next 11m

Ananworanich et al EBioMed 2016
Veldsman et al AIDS 2018
Uprety et al CID 2015

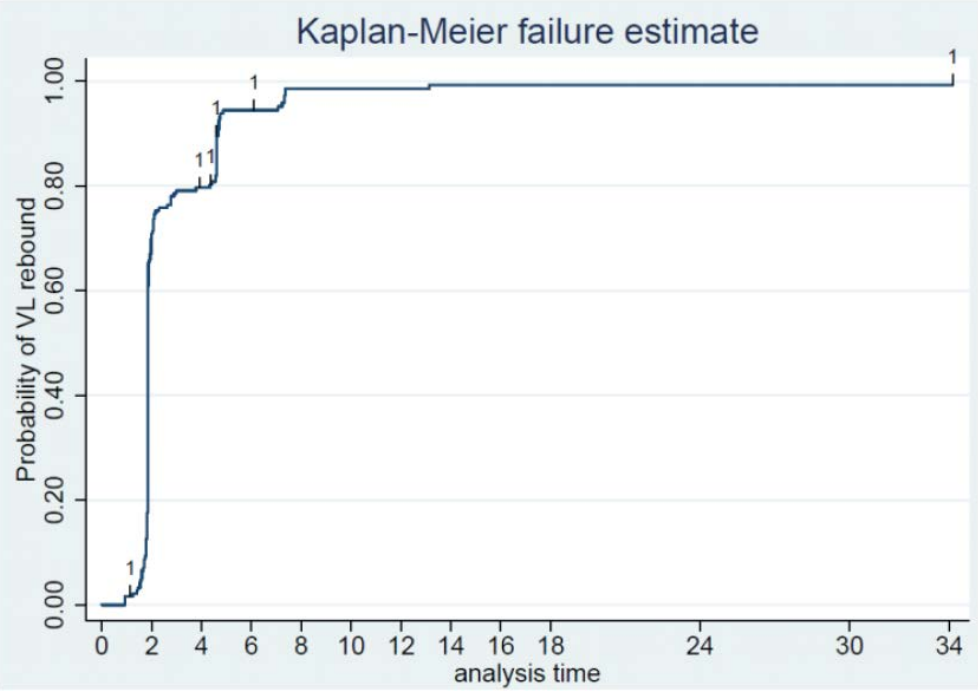
Viral rebound post treatment interruption: SPARTAC vs RV411

SPARTAC Adults receiving 48wks ART
Cumulative probability of viral rebound after ART interruption
68% (95% CI 58, 78) at 12 wks
86% (78, 93) at 52 wks
95% (89, 98) at 104 wks

RV411 Fiebig I (n=8)
Median time to rebound 26d (range 13-48d)

Stohr et al PLoS ONE 2013
Ananworanich pers comm

CHER study -



♦ **Overall estimated cumulative probability of rebound (95% CI) after ART interruption at:**

- **2 months** = 70% (63,76)
- **4 months** = 80% (74, 85)
- **6 months** = 94% (90,97)
- **8 months** = 99% (96,100)

Violari, Cotton et al CROI 2018

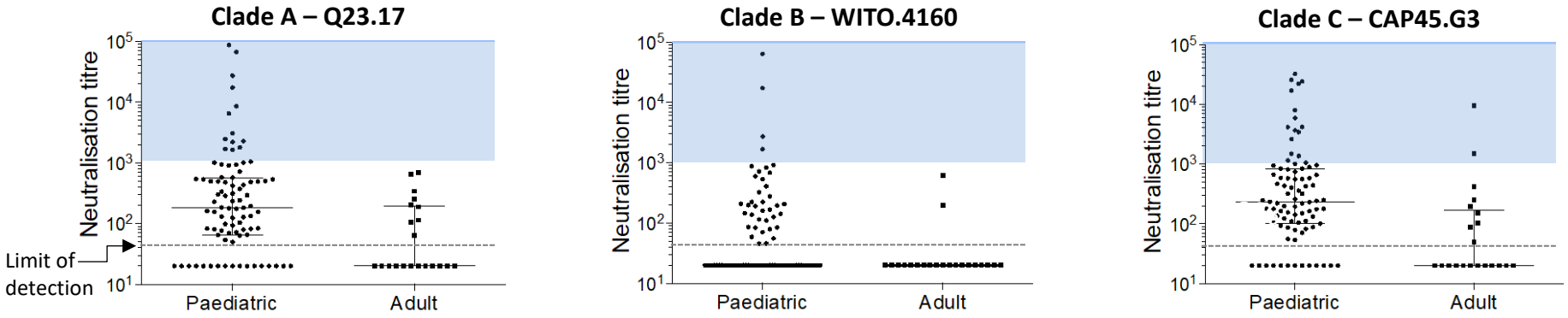
Impact of immune ontogeny on cure potential in pediatric infection:

- Size of initial reservoir, decay kinetics
- **Ab and bnAb responses**
- CTL responses
- Immune reconstitution of T-cell function on ART

Children make higher magnitude and more broadly neutralizing Ab responses than adults

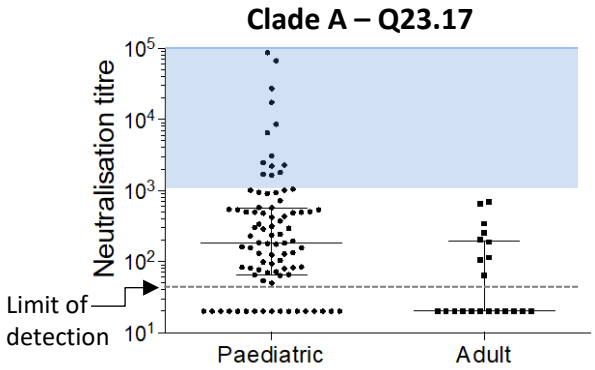
- Fouda et al JID 2015
- McGuire et al JV 2018
- Goo et al Nat Med 2014
- Simonich et al Cell 2016
- Muenchhoff et al Sci Transl Med 2016

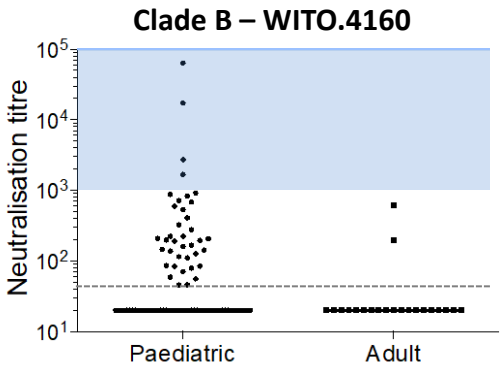
Children make higher potency Ab responses than adults

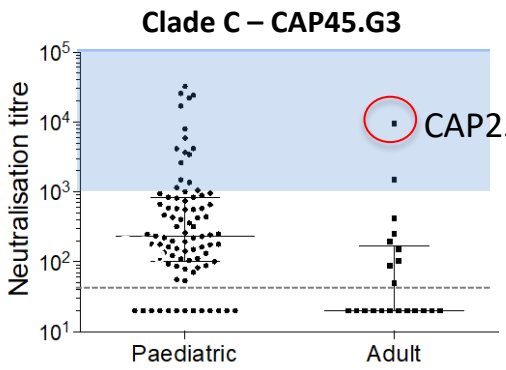


Muenchhoff et al Sci Transl Med 2016

Children make higher potency Ab responses than adults

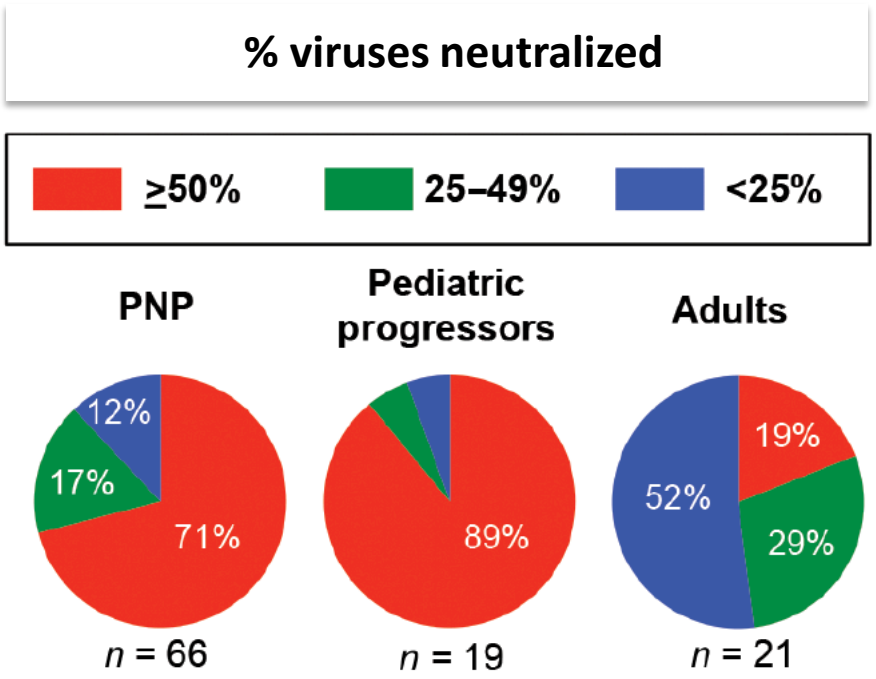






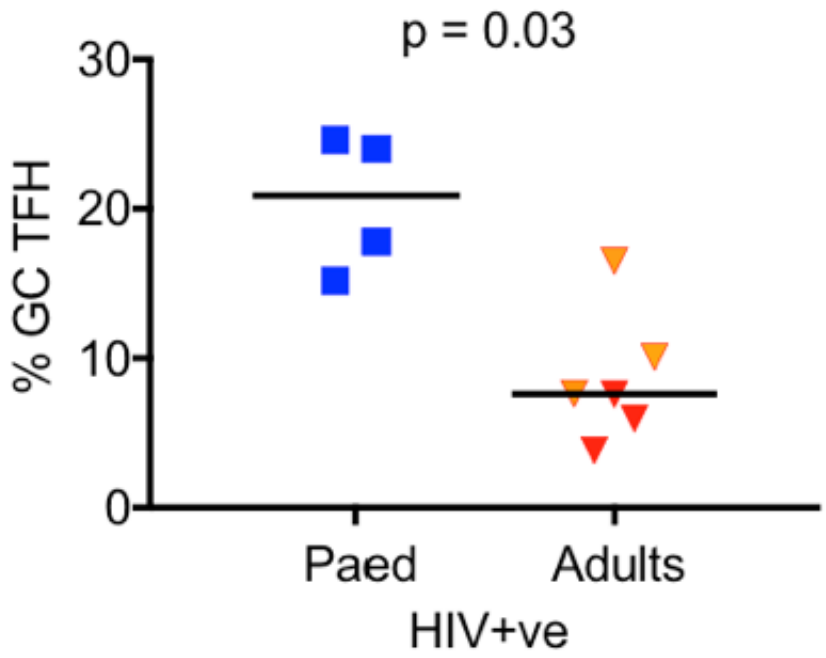
Muenchhoff et al Sci Transl Med 2016

Children make a higher frequency of bnAbs



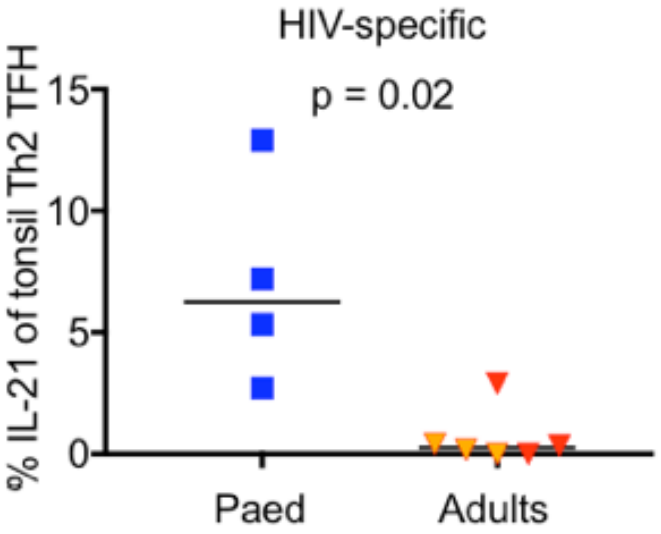
Muenchhoff et al Sci Transl Med 2016

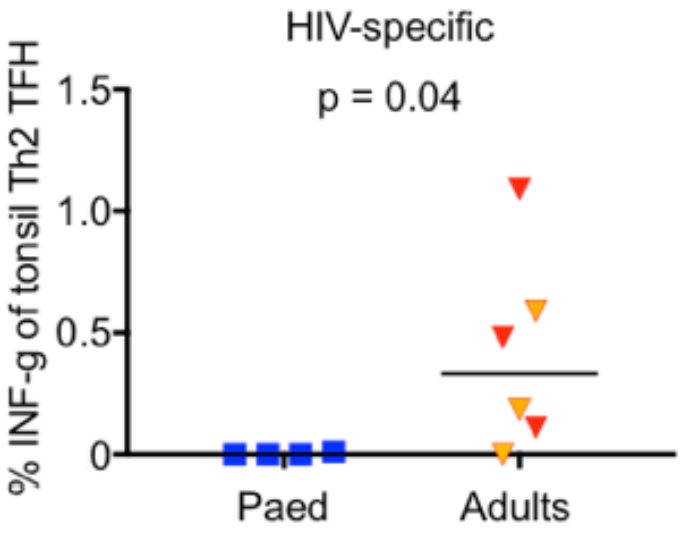
Tfh responses in children vs adults: Higher frequency in children in lymphoid tissue



Roider et al, unpublished

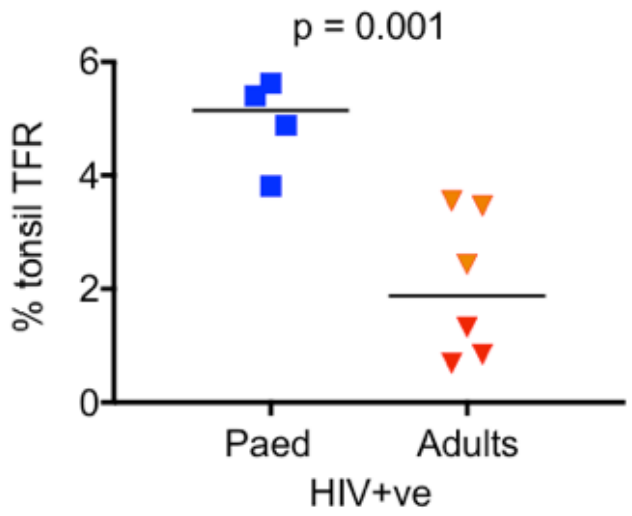
Tfh responses in children vs adults: IL-21 vs IFN-g production





Roider et al, unpublished

Higher frequency of follicular regulatory T cells in lymphoid tissue in children vs adults



Roider et al, unpublished

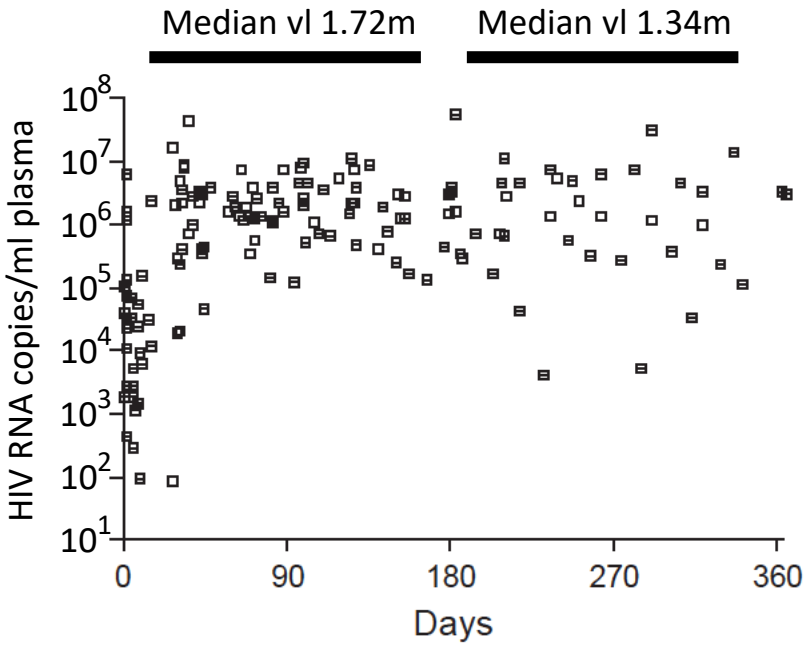
Conclusion:

Optimal time to induce bnAbs to protect adults from infection is in childhood

Impact of immune ontogeny on cure potential in pediatric infection:

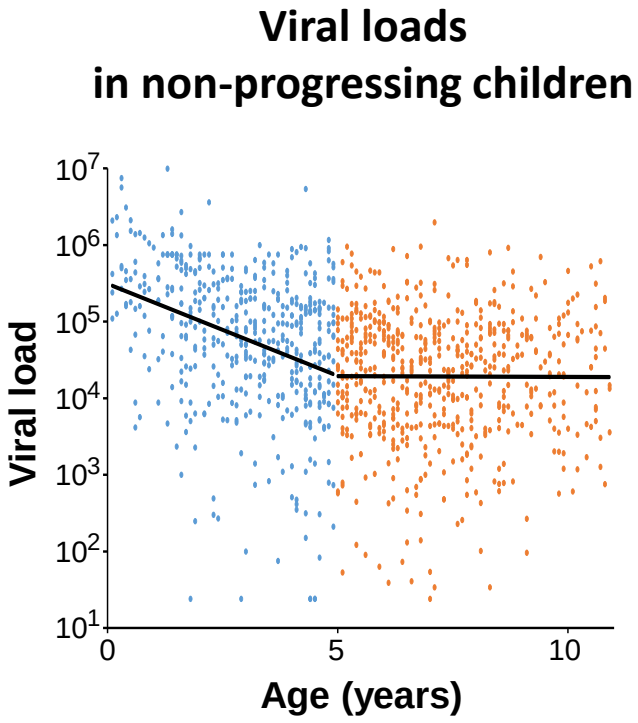
- Size of initial reservoir, decay kinetics
- Ab and bnAb responses
- **CTL responses**
- Immune reconstitution of T-cell function on ART

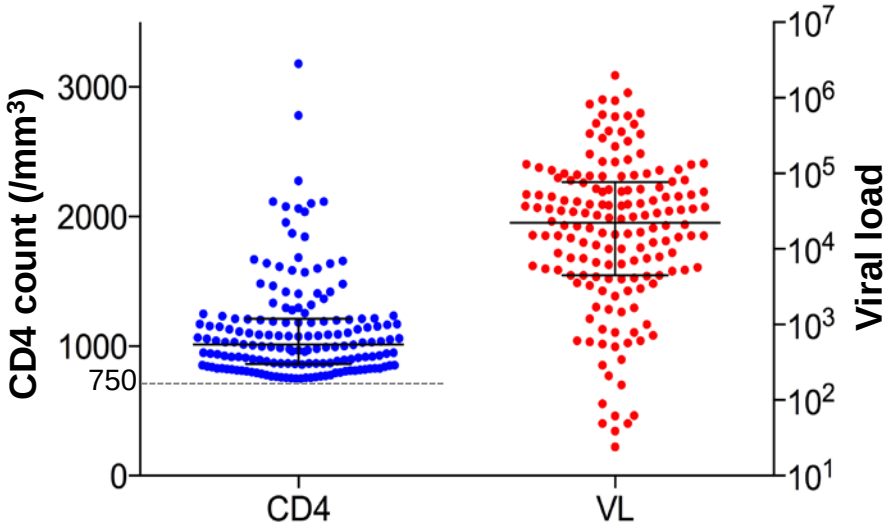
Very little decline in viral load in the first year of life



Mphatswe *et al, AIDS,* 2007

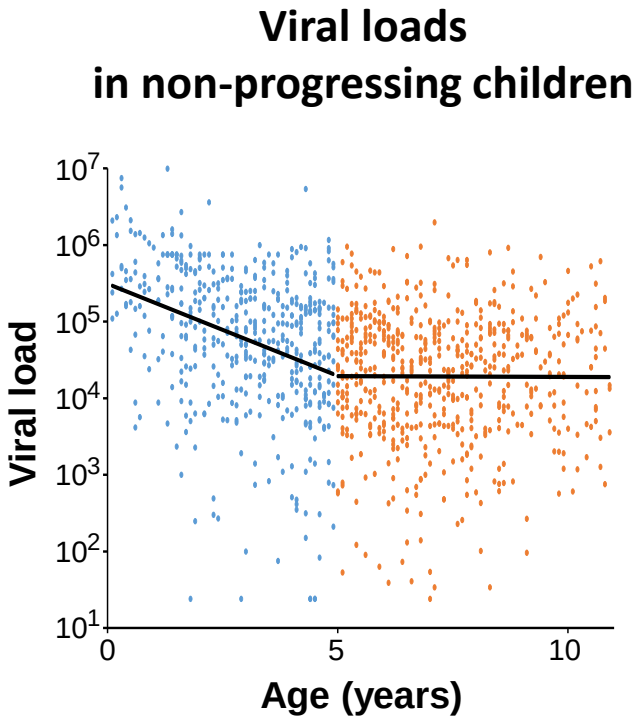
Pediatric non-progressors reach setpoint of ~30,000 c/ml after ~5 years

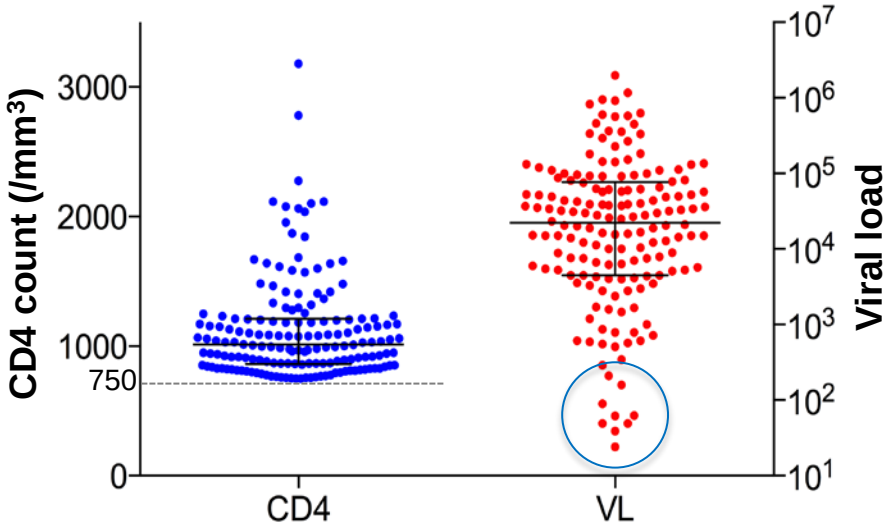




n=170

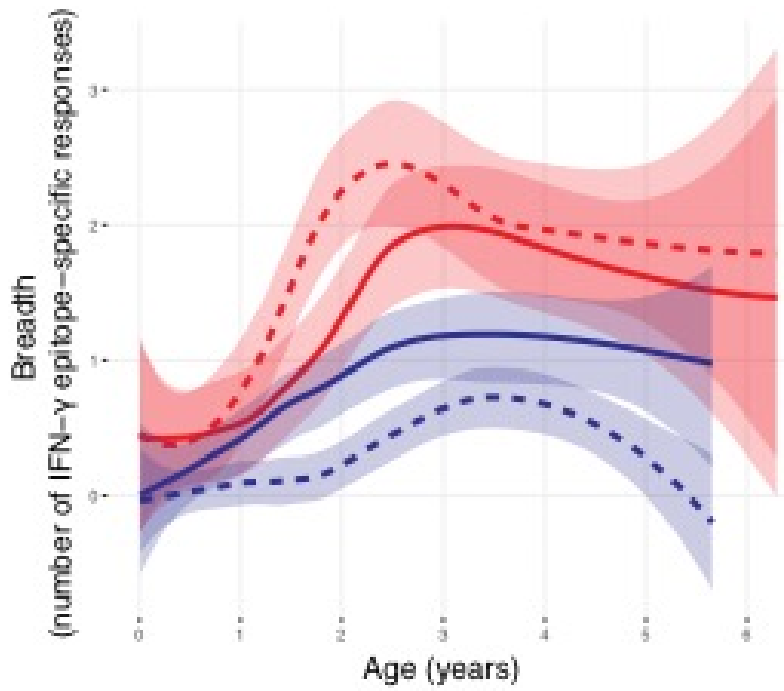
Pediatric non-progressors reach setpoint of ~30,000 c/ml after ~5 years





n=170

Gag/Pol preferentially targeted by controllers
Env/Nef-Acc-Reg targeted by non-controllers



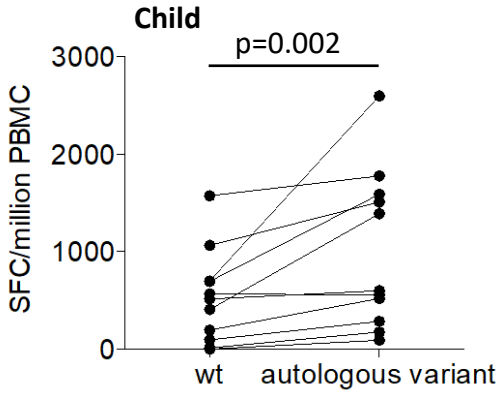
Viraemic Non-Controller

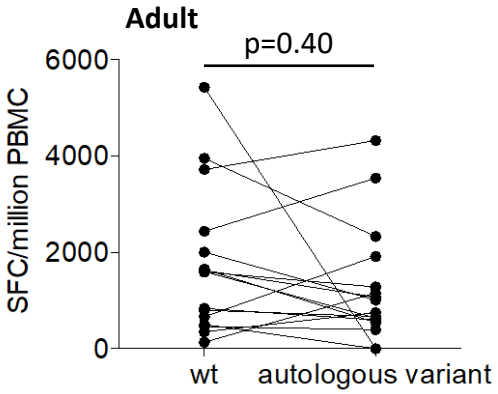
Antigen:
Gag/Pol
Env/Nef/Acc-Reg

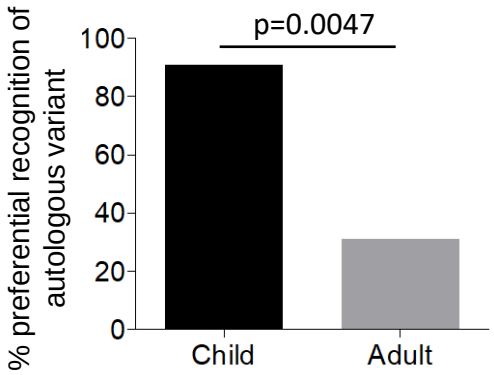
Viraemic Controller

Leitman/Thobakgale/Adland *et al, JEM* 2017

Preferential recognition of autologous variant in pediatric but not adult infection







Leitman, Thobakgale *et al, JEM* 2017

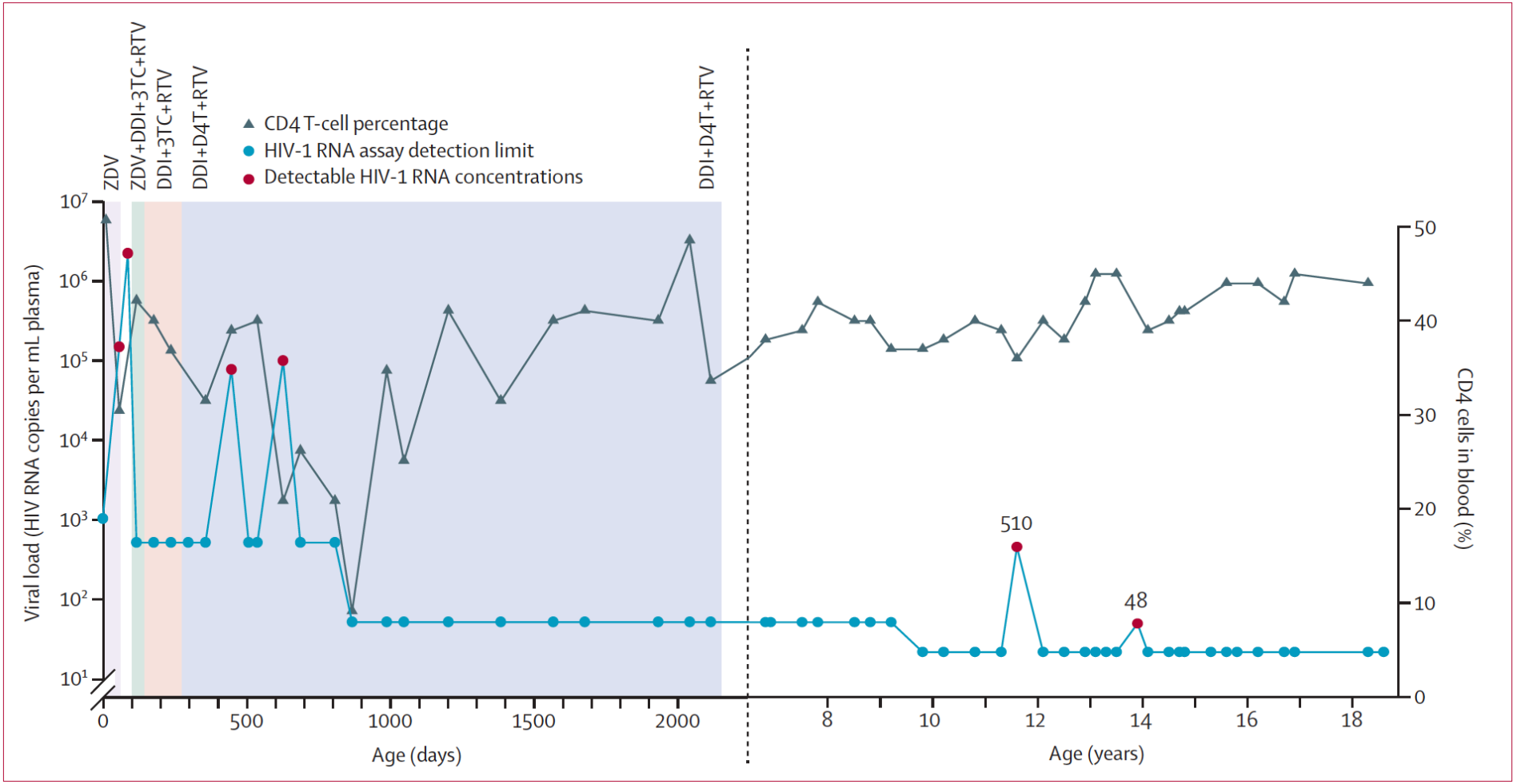
Summary on CTL:

- CTL vaccine should focus the response on Gag/Pol
- Optimal timing of a CTL vaccine or TI designed to generate CTL responses is >2yo
- Children have the capacity to generate variant-specific CTL responses

Impact of immune ontogeny on cure potential in pediatric infection:

- Size of initial reservoir, decay kinetics
- Ab and bnAb responses
- CTL responses
- **Immune reconstitution on ART**

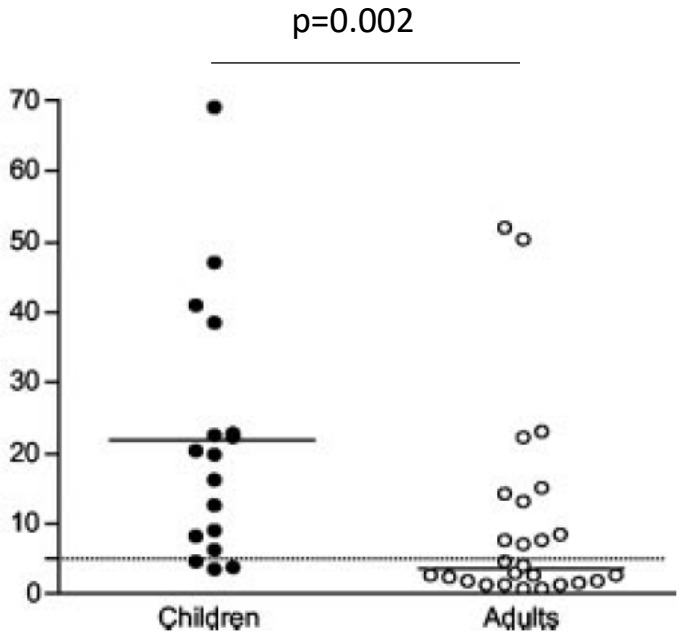
VISCONTI child



Frange *et al Lancet HIV* 2016

Immune reconstitution on ART

Gag-specific CD4 T-cell proliferative capacity (p24 SI)



Feeney *et al JID* 2003
Adland *et al AIDS* 2018

Unique aspects of pediatric vs adult immune responses in HIV infection:

- Impact of immune ontogeny on HIV-specific immunity

- **Impact of pediatric infection arising via transmission from the mother**

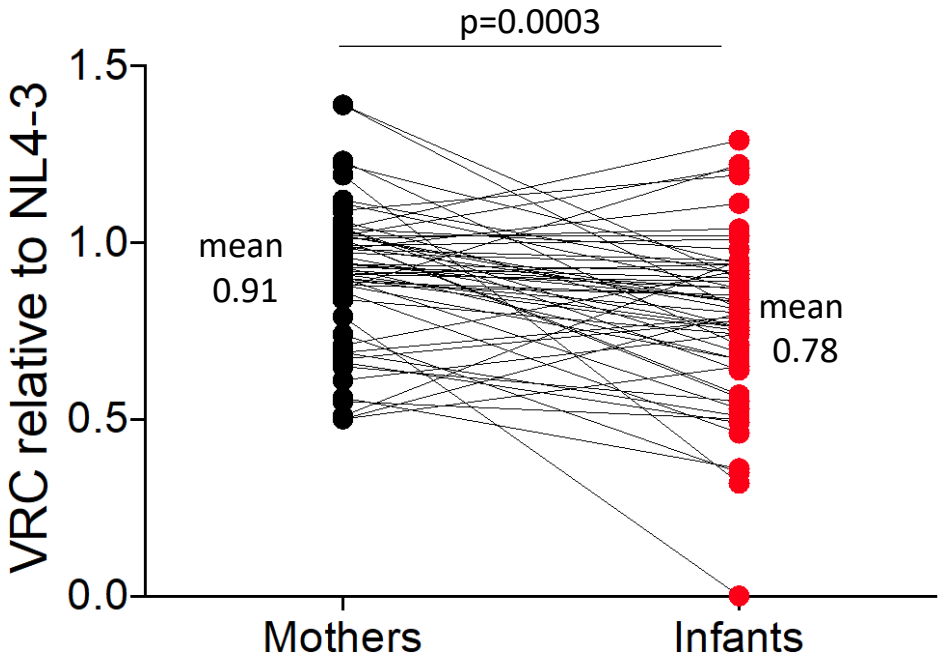
Impact of paediatric infection arising via MTCT:
(1) HLA

- **Children tend not to carry protective HLA**
  - **Pre-adaptation of virus to host HLA**

Goulder *et al Nature* 2001
Adland *et al PLoS Path* 2015
Carlson *et al Nat Med* 2016

Impact of pediatric infection arising via MTCT:

(2) Viral replicative capacity 1.2-fold lower in child than mother



In adults VRC is 1.4-fold higher in the recipient

Iyer *et al PNAS* 2017

Impact of pediatric infection arising via MTCT:

(3) Maternal antibodies

Transmitted/founder viruses in child are resistant to maternal neutralizing antibodies

Potentially could mediate ADCC

Kumar *et al PloS Path* 2018

Conclusions (1)

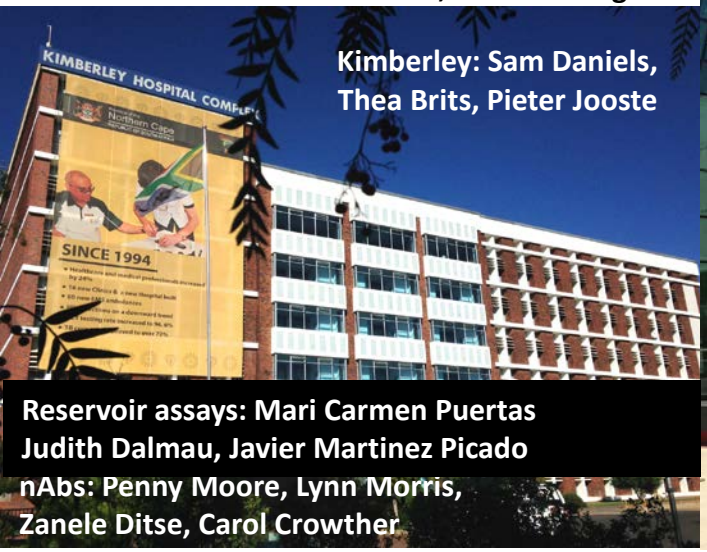
1. Low initial viral reservoirs, low replicative capacity of T/F virus, immunotolerant early life environment = high cure potential
2. Optimal timing for active immunization to induce bnAbs for prevention of adult infection is in childhood
3. Passive bnAb therapy should work better in early treated children vs adults

Conclusions (2)

4. CTL unlikely to be effective in cure strategies unless TI arises at age >2yrs
+/- Gag/Pol focused T-cell vaccine
5. Immune reconstitution in children means cure potential not limited to those receiving therapeutic interventions at birth

Acknowledgements

Oxford: Emily Adland, Anna Csala, Ellen Leitman, Chloe Tsai, Amna Malik, Reena Dsouza, Philippa Matthews, Masa Mori
London: Gareth Tudor-Williams, Delane Shingadia



Kimberley: Sam Daniels, Thea Brits, Pieter Jooste
Reservoir assays: Mari Carmen Puertas Judith Dalmau, Javier Martinez Picado
nAbs: Penny Moore, Lynn Morris, Zanele Ditse, Carol Crowther

HPP: Angeline Moonswamy, Khei Koofhethile, Jane Millar, Christina Thobakgale, Max Muenchhoff, Bruce Walker, Thumbi Ndung'u
AHRI: Julia Roider, Callum McGregor, Henrik Kloverpris, Al Leslie

Ucwaningo Lwabantwana Team: Zodumo Mvo, Vuyo Ntlantsana, Nomonde Bengu, Ken Sprenger, Yeney Graza, Constant Kapongo, Malini Krishna, Roopesh Bhoola, Jeroen van Lobenstein, Vinicius Vieira. Jane Miller

Funders: Wellcome Trust, NIH, Royal Society, Fell Fund, K-RITH/AHRI