Are HIV-1 antibodies useful biomarkers for pediatric cure studies?

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Two Decades of Early ART

- **Early/very early ART:**
  - **Is safe**
  - **Allows long term control of HIV replication**
  - **Preserves immune function**
    - **Normal CD4 counts and responses to childhood vaccines**
  - **Markedly reduces HIV-related mortality**
  - **US DHHS and WHO: Recommend early HIV diagnosis and ART**

Luzuriaga et al, NEJM 1997, 2004; J Virol 2000
Chadwick et al, AIDS, 2011; Judd et al, AIDS, 2011, Violari et al, NEJM, 2008

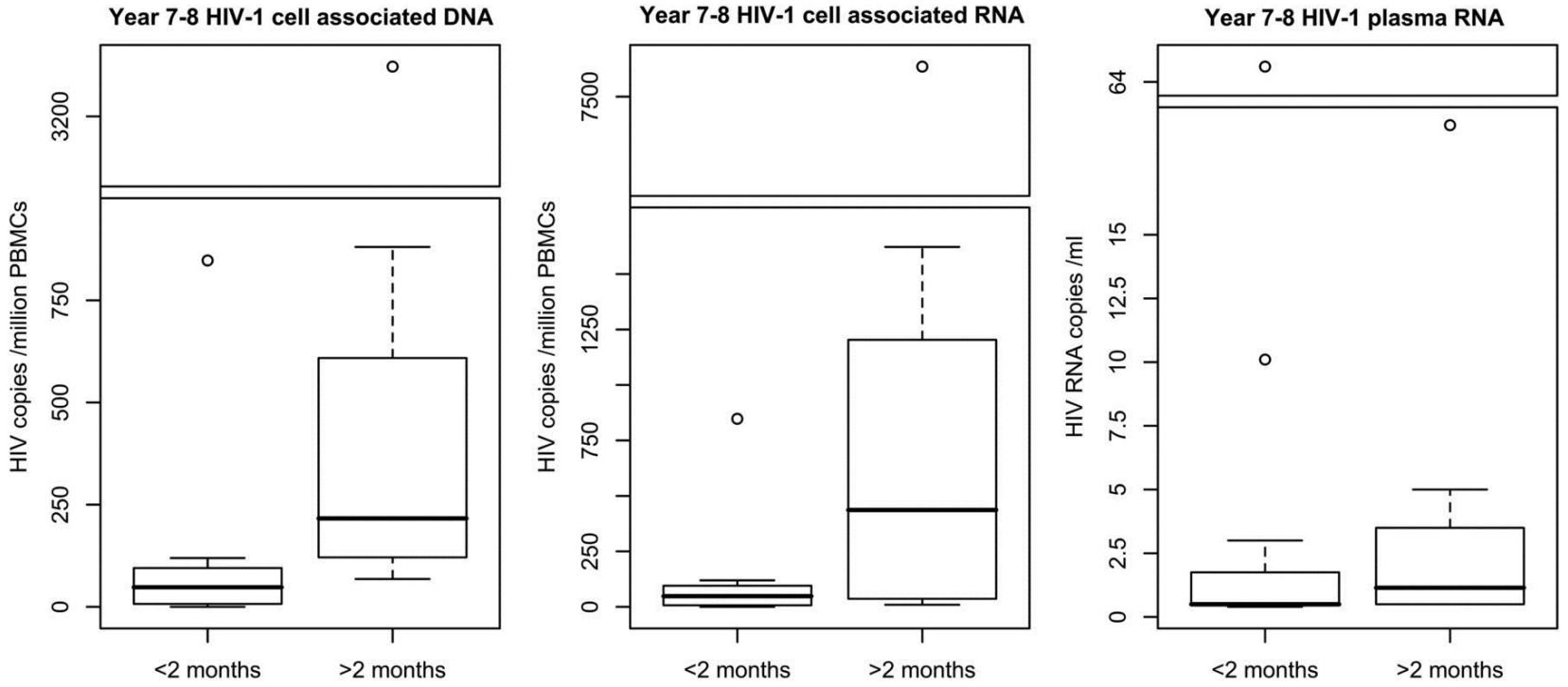
Early/very early ART limits HIV-1 persistence

- **Lower levels of circulating cell-associated HIV-1 nucleic acids and smaller latent reservoir size in children who initiated ART < 3 months of age**

- **Levels of circulating cell-associated HIV-1 DNA directly correlate with:**
  - **Age at ART initiation**
  - **Time to virologic control**

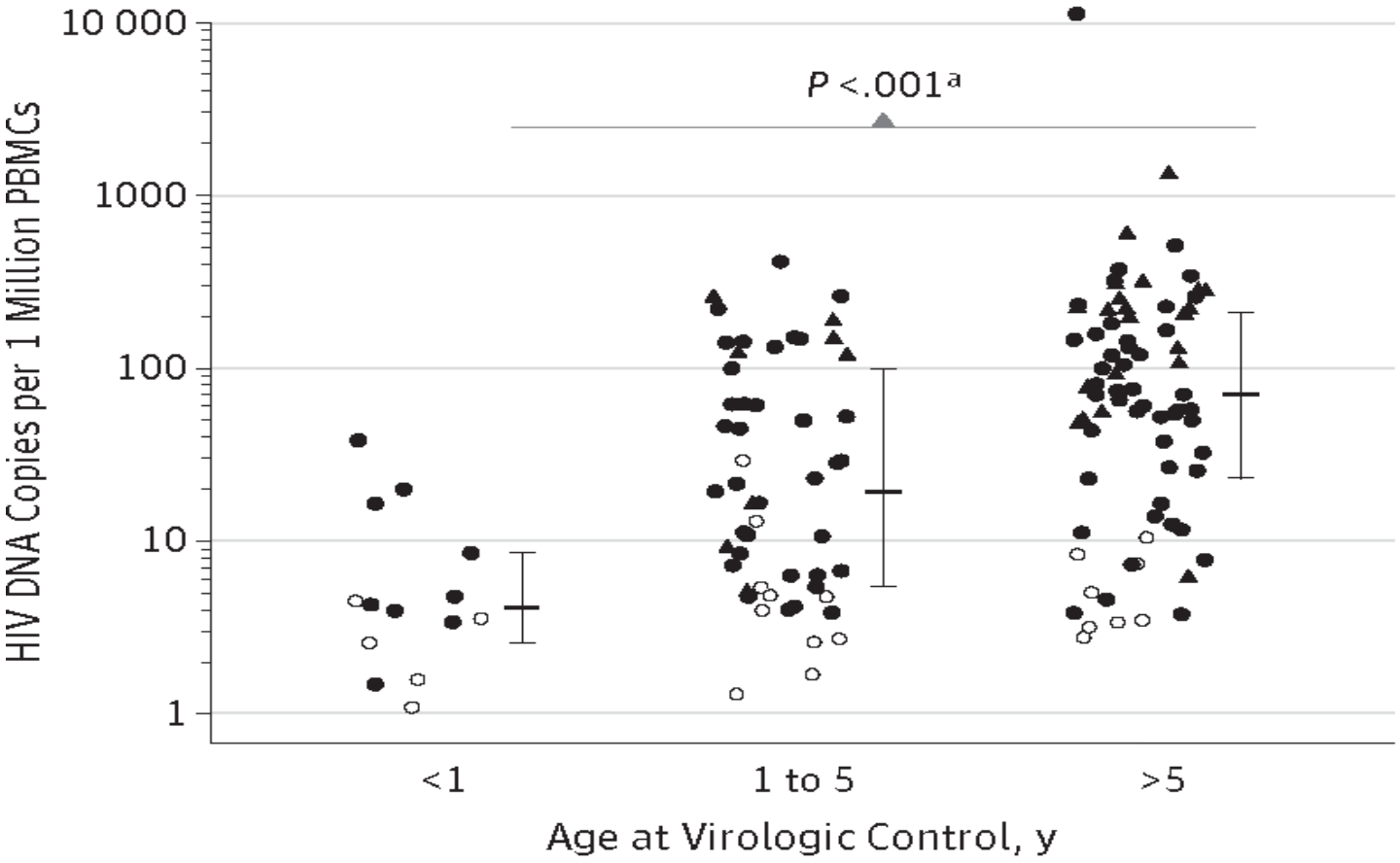
Luzuriaga, NEJM, 1997, 2004; Persaud, AIDS, 2012; Luzuriaga, JID, 2014; Persaud, JAMA Peds, 2014; Anaworanich, JAIDS, 2014; van Zyl, JID, 2014; Uprety, CID, 2015; Martinez-Bonet, CID, 2015.; Luzuriaga, PLoS One, 2016

Early therapy (< 2 mo) and continued viral suppression limits cell-associated HIV-1 DNA and RNA



van Zyl, JID, 2015

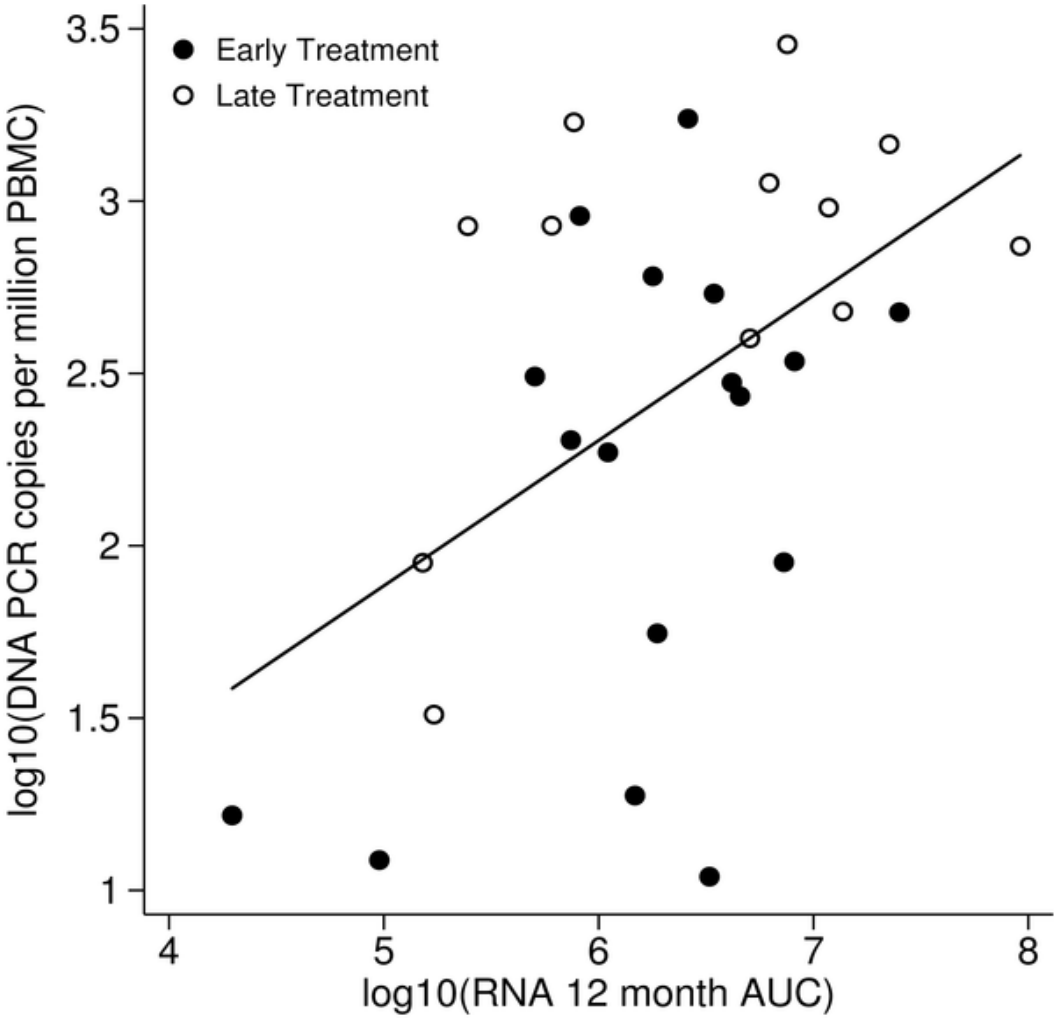
Lower Circulating HIV-1 DNA Levels with Younger Age at Virologic Control



Median 4.2 **19** **71**

Persaud et al, JAMA Ped, 2014

Higher PBMC DNA levels at Year 1 with greater exposure to viral replication

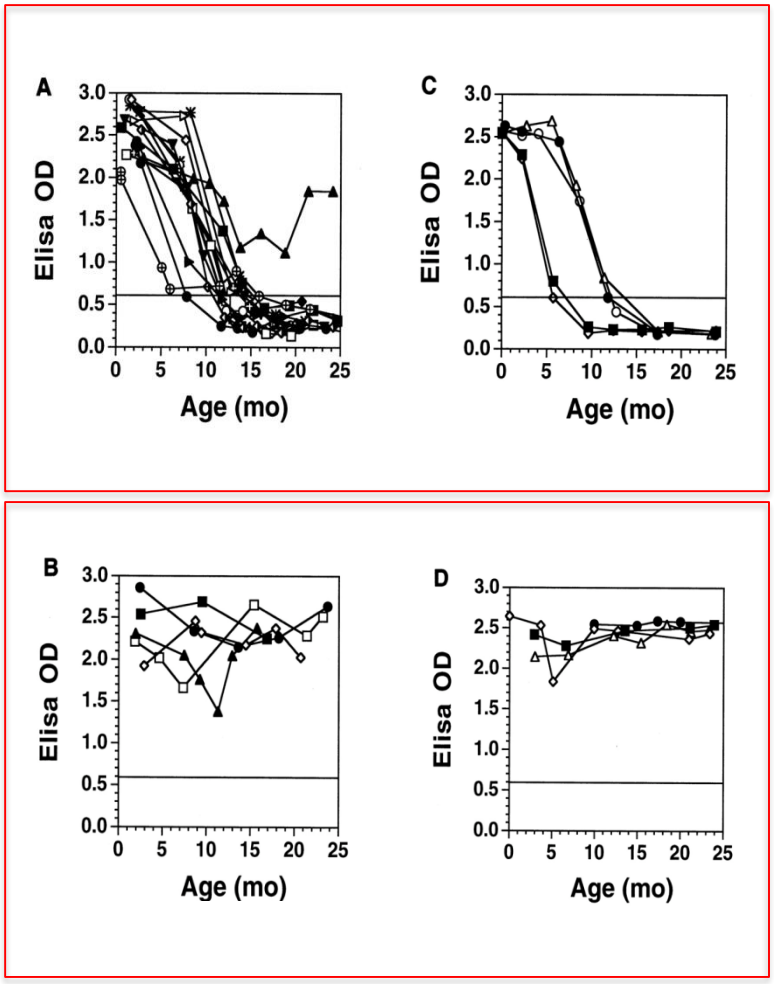


p = 0.004

McManus et al, .PLoS ONE, 2016

PLOS ONE

Clearance of HIV-specific Antibodies is a Hallmark of Early Effective cART in Infants



EIA negative at 15 months:

A. **Durable HIV RNA suppression to < 400:**
   11 (85%) of 13 infants

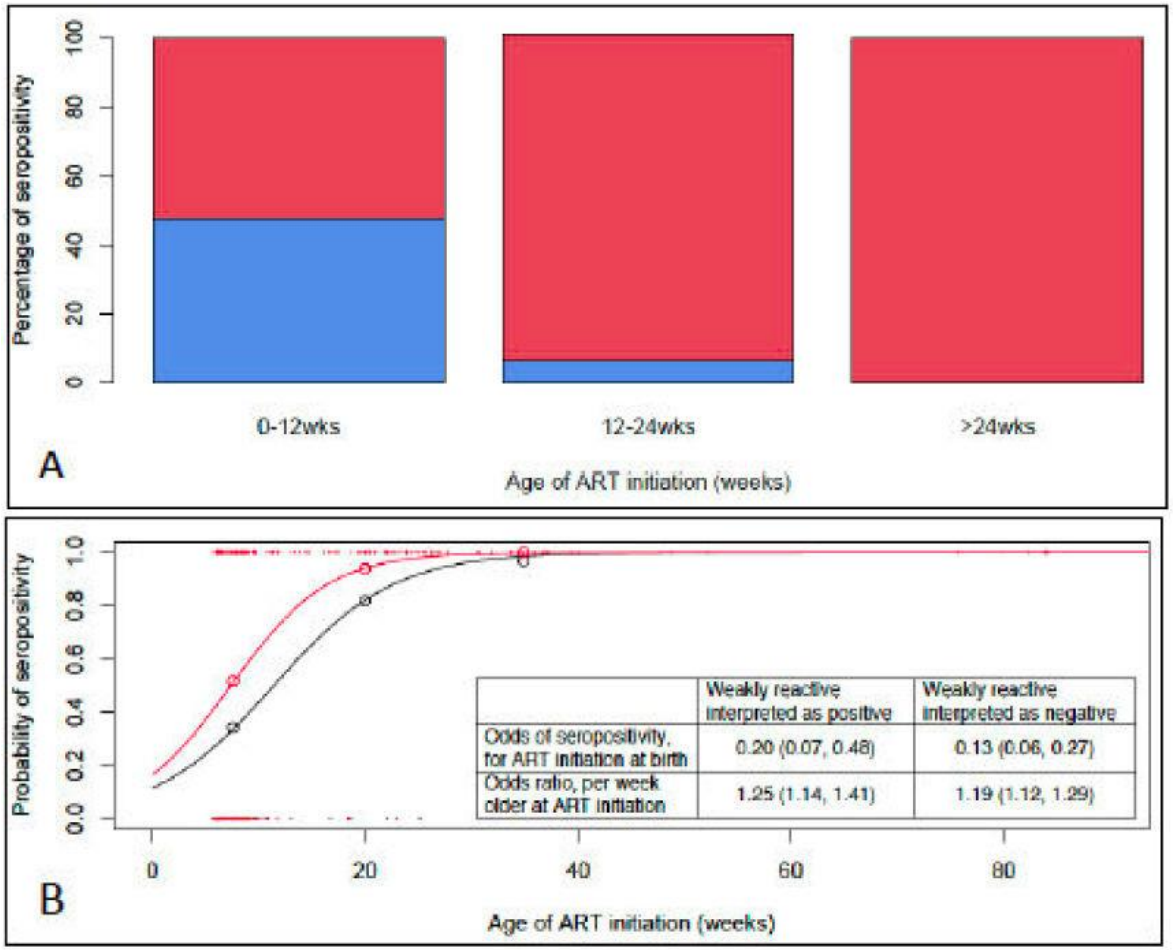
B. **Early tx, incomplete /transient suppression:**
   None (0%) of 5

C. **HIV-uninfected infants born to HIV-infected women:**
   5 (100%) of 5

D. **HIV- infected infants first treated > 12 mo:**
   None (0%) of 4

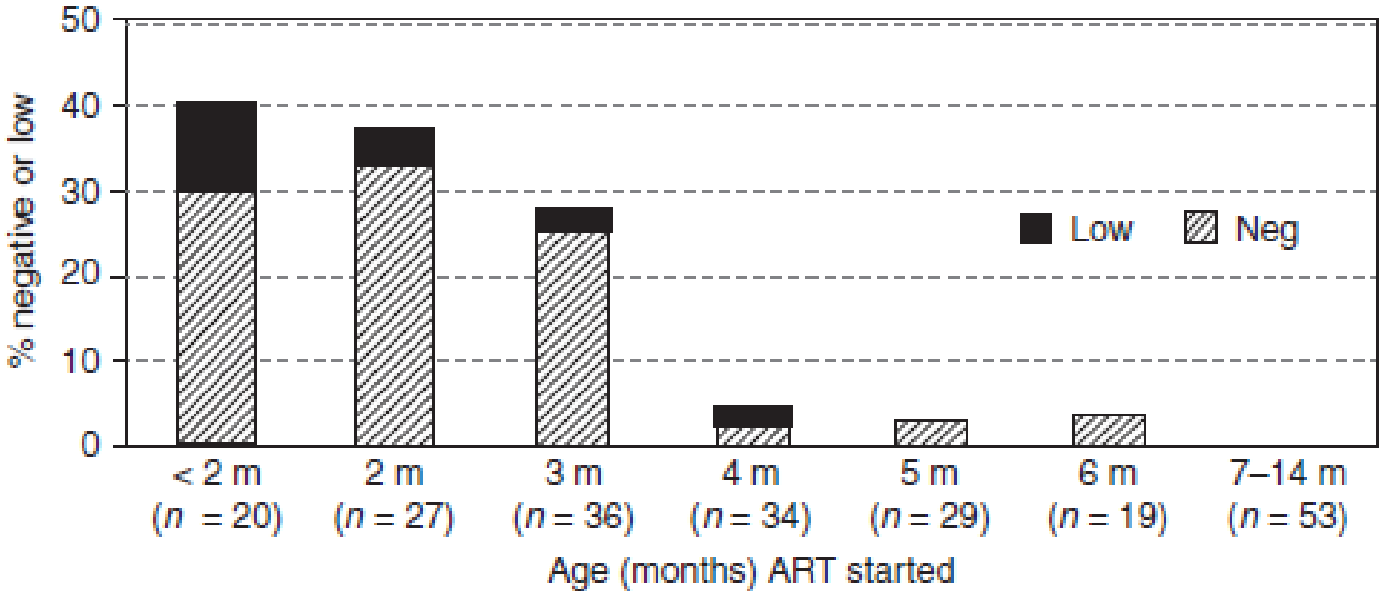
Luzuriaga et al, J Virol, 2000

HIV-1 antibody serostatus: CHER trial @ 84 weeks (~2 years of age)



Payne et al, Lancet ID, 2015

HIV-1 Serostatus:
218 HIV-1 infected children suppressed on ART for ~ 4 years



Kuhn et al , AIDS, 2015

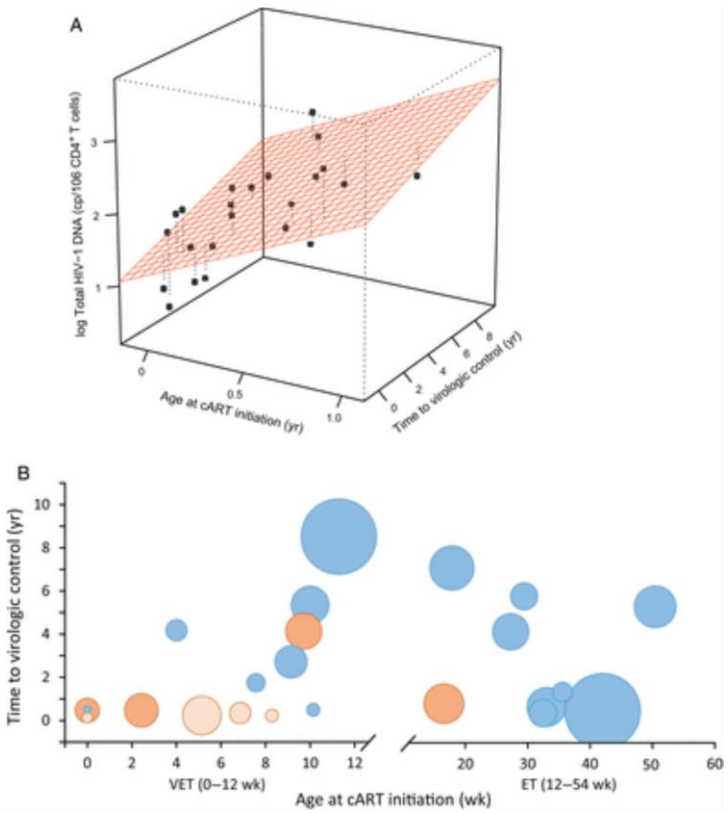
Higher CD4 percentage prior to ART initiation and lack of intermittent viremia ("blips") predictive of negative antibody results.

Immune parameters that differ between infants and adults

Immune parameter	Infants	Adults	Reference(s)
NK cell activity	CD16 expression similar to adult cells but lower cytotoxic capacity	Lower no. of NK cells than infants	8, 9
Dendritic cells	Higher ratio of plasmacytoid to monocyte-derived DCs than that in adults	Higher response to stimulation by CPG motifs than infant DCs	4, 5
$CD4^+$ T cell responses	Th2 bias	Th2 and Th1 responses	15
T_{reg}	High levels of T_{reg} compared to adults	Normal T_{reg} levels	12
Memory B cell formation	Lower markers of memory B cells, impaired bone marrow homing markers	High expression of memory B cell markers	20, 21
IgG subclass	IgG1 and IgG3 attain adult levels earlier than IgG2 and IgG4; low levels of IgG2 to polysaccharide antigens	IgG2 responses to polysaccharide antigens	18, 19
Maternal antibodies	Interference with development of B cell but not T cell responses in infants	Not present	34–38

Martinez et al, Clin Vaccine Immunol, 2015

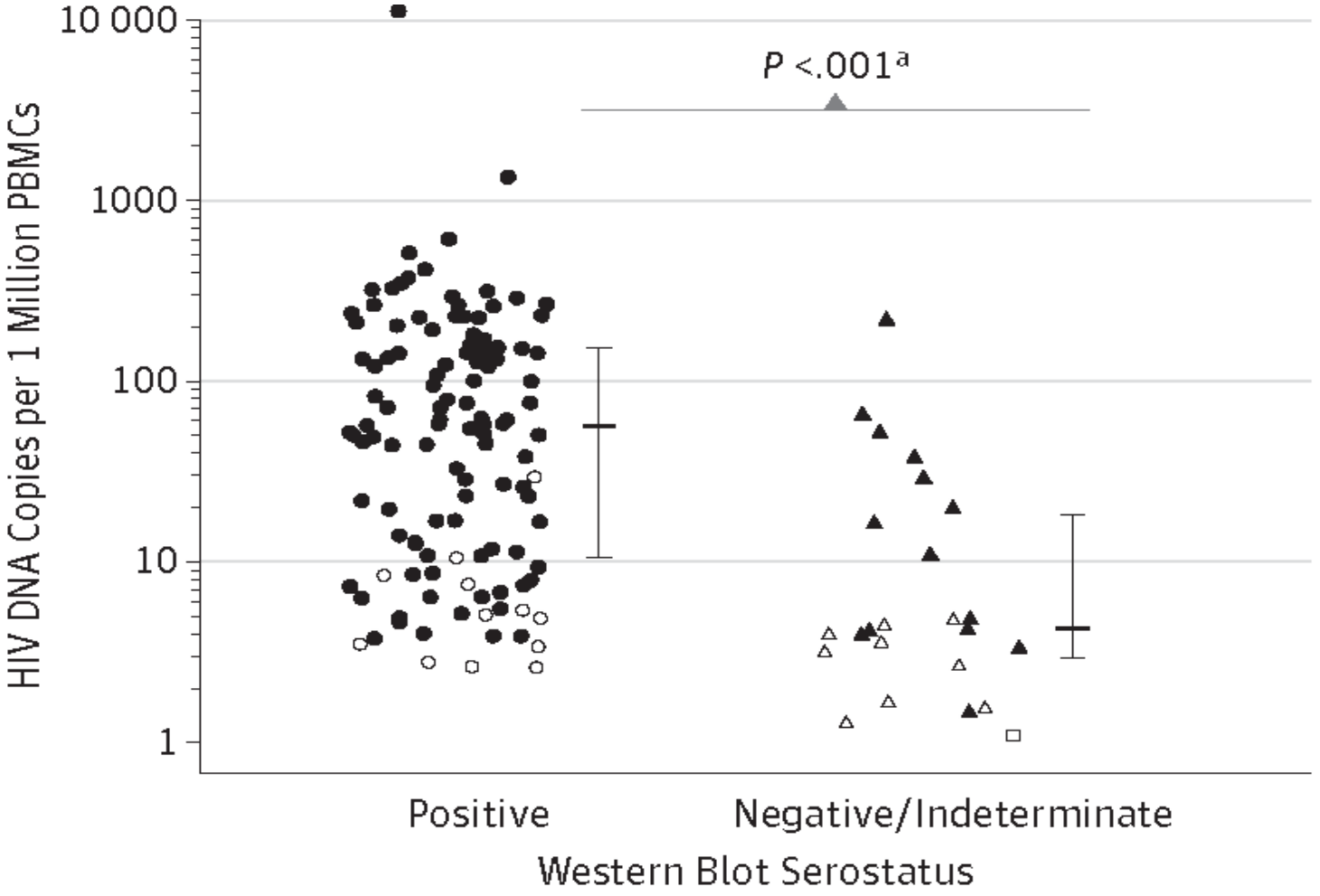
***Is there a relationship between HIV-1 serostatus and circulating HIV-1 DNA levels*?**



***Did not account for duration of virologic control at sampling*.**

***Martinez-Picado et al, Clin Infect Dis, 2015*.**

Low Proviral DNA Loads in Children with HIV-1 Negative or Indeterminate Wb



Persaud et al, JAMA Pediatr, 2014.

SUMMARY

- **Loss of HIV-1 antibodies with durable virologic suppression on ART**
  - **ART < 3 mo**
    - **Curtailed generation and persistence of HIV-1 specific antibodies**
    - **Higher likelihood of HIV-1 seronegativity after 2-4 years if CD4 higher at ART initiation, rapid suppression of HIV-1 replication, no subsequent viral blips.**
  - **ART > 3 mo**
    - **Reduction in Ab titers over time**
    - **Clearance of some bands on Wb over time**
  - **Relationship between HIV-1 antibody status and size of HIV-1 reservoir needs to be better defined**
    - **Timing of ART initiation, time to suppression, duration of suppression**
    - **Quantitative measures of HIV-1 antibodies**

Are HIV-1 antibodies useful biomarkers for pediatric cure studies?

- **HIV-1 seronegative status > 2 years is a marker for early, durable suppression of HIV-1 replication and children with smaller residual HIV-1 reservoirs**

- **HIV-1 infected seronegative children and youth with prolonged suppression of HIV replication are excellent candidates for additional strategies aimed at remission, particularly therapeutic vaccines:**
  - **Limited viral diversity**
  - **Normal immune responses to childhood vaccines**
  - **Lack of HIV-1 specific immune responses**
    - **Facilitates detection of vaccine-elicited responses**
    - **? potentially easier to focus T cell responses on conserved proteins**