Impact of Maternal HIV Infection on Cord Blood Passive Antibody Levels Against Protein and Polysaccharide Antigens in Human Immunodeficiency virus (HIV) Exposed Versus Unexposed Uninfected Infants

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Risks for Vaccine Preventable infections (VPI)- Complex phenomenon

- **Socioeconomic:**
  - **Compliance**
  - **Failure to seek prompt & adequate Rx**
  - **Risk exposure to VPI**
    - **HBV, measles, pertussis**
  - **↓ maternal Ab levels - quantitative/qualitative**
  - **Nutritional status**
    - **Multiple births**
    - **Prematurity**
    - **# Parity**

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Risks for VPI-
Complex phenomenon

- **Genetic:**
  - **Polymorphisms**
    - **Racial disparities**
- **Immunocompromising conditions:**
  - **HIV infection**
  - **Congenital ID**
  - **Secondary ID**

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VPI and low/ middle income countries (LMIC)

Even HIV- uninfected but exposed infants from areas (LMIC) with ↑ burden of infectious diseases (HIV &VPI) remain at ↑'er risk of suffering from infectious morbidity & mortality than their HIV-unexposed peers

Hypothetically, maternal immunization during pregnancy can boost maternal Ab levels & provide ↑'er infant levels to protect against infectious diseases in LMIC?

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Background

Some examples:

Viral- measles, varicella, rubella, influenza, polio and respiratory syncytial virus (RSV) infections

Bacterial- *Hemophilus influenzae* type b (Hib), *Streptococcus pneumoniae (SPN)*, *Clostridium tetani*, & *B. pertussis*

Infants born to HIV-infected mothers in Africa found to be 3.8x ↑'er at risk of acquiring measles & significant sequelae before vaccination (9 mos) compared to the uninfected group [1]

Even uninfected, HIV- exposed infants can suffer higher morbidities when infected with varicella virus, reflecting a clinical immunodeficiency[2]

- **1- Embree JE, Datta P, Stackiw W, et al. Increased risk of early measles in infants of human immunodeficiency virus type1- seropositive mothers. J Infect Dis 1992; 165: 262- 7**
- 2. Slogrove AL, Cotton MF, Esser MM. Severe infections in HIV-exposed uninfected infants: clinical evidence of immunodeficiency. *J Trop Pediatr.* 2010;56:75-81.

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Why is VPI higher in HIV- infected population?

Due to impaired humoral and cell mediated immunities, HIV-infected individuals have higher prevalence of VPI

HIV- infected mother with a defective immune system may not have adequate level of antibodies against VPI

Poor response to vaccines or maintenance of immunity (primary and secondary vaccine failures) in HIV- infected patients-

well documented

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Risk for VPI in HIV- infected or uninfected exposed Infants

Infants are prone to various infections during the neonatal period due to their relatively immature immune system

During this period, they are protected by passively transferred maternal antibodies

These antibodies are eventually replaced by the infant's own antibodies after contact with wild or vaccine strains of the pathogens- Basis for the timing of administration of vaccines

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Passive antibodies (Ab)

Protection against VPI in first few months of life prior to initiating active immunization =

Passive antibodies =

Maternal antibody levels (quantitative & qualitative)
And
Factors determining placental transfer

Placental transfer of maternal antibodies

- IgG class & subclass
  - Only IgG class crosses human placenta
  - Differential placental transfer: IgG1>IgG4>IgG3>IgG2 (1)
- Nature of antigen
  - ↓ transfer of thymus-independent Ab (e.g., encapsulated bacteria- *Hib,SPN*) compared to thymus-dependent (e.g., protein Ags – tetanus toxoid) (2)
  - ? Impact of maternal CD4 count (HIV infection) on Ab transfer of protein vs. polysaccharide Ags

References: 1. Costa-Carvalho. et.al. Transfer of IgG subclasses across placenta in term and preterm newborns. *Brazilian J of Medical and Biological Research.* 1996;29(2):201-204.

2. Okoko BJ. et.al. The transplacental transfer of IgG subclasses: influence of prematurity and low birth weight in the Gambian population. *Annals of Tropical Pediatrics.* 2002;22(4):325-332.

Placental transfer of maternal antibodies

- Maternal levels of total IgG and specific antibodies
  - Newborn IgG Abs correlate with maternal levels
    - Correlation indexes ‘er for thymus dependent than for thymus independent Ags
  - IgG placental transfer is mediated by FcRn (neonatal Fc receptors)
    - Down a concentration gradient of IgG (1)
  - However, non-specific maternal hypergammaglobulinemia (e.g., HIV infection) may impair placental transfer of specific Abs

References: 1. Radulescu L. et.al. Neonatal fc receptors discriminates and monitors the pathway of native and modified immunoglobulin G in placental endothelial cells. *Human immunology.* 2004;65(6):578-585.

Placental transfer of maternal antibodies

- Gestational age
  - Total IgG concentrations in newborn directly related to length of gestation
  - Sharp in IgG level occurs after 36 weeks gestation
  - Sharp decline occurs before 33 weeks
- Placental integrity
  - Placental injuries. e.g, HIV infection, malaria, ↓ Ab transfer (1,2)

References: 1. de Moraes-Pinto MI. et.al. Maternally acquired immunity in newborns from women infected by the human immunodeficiency virus. *Acta Pediatrica, International J of Pediatrics.* 1993;82(12):1034-1038.

2. Farquhar C. et.al. High maternal HIV-1 viral load during pregnancy is associated with reduced placcental transfer of measles igG antibody. *J of Acquired Immune Deficiency Syndromes.* 2005;40(4):494-497.

Purpose of our study

- Paucity of data regarding placentally transferred Abs in newborns of HIV-infected mothers in the US

- To determine Ab levels & prevalence of placentally transferred protective Abs in newborns of HIV- infected mothers & duration of these protective immunities

Subnormal Immunity to Measles and Varicella in HIV-Infected Mothers and Cord Bloods of Their Infants

Introduction

- Measles (MS) & VZV infections can cause significant morbidity & mortality, particularly in young & immunocompromised populations
- MS & VZV infections during pregnancy can be life threatening for both mother & infant
- Re-emergence of MS in the US

Child with measles

- Between 2001 and 2014, 78 reported **measles** cases resulted from transmission in **US** healthcare facilities, and 29 healthcare personnel were infected from occupational exposure, 1 of whom transmitted **measles** to a patient. The economic impact of preventing and controlling **measles** transmission in healthcare facilities was
- $19 000-$114 286 per case.

- Clin Infect Dis. 2015 15;61(4):615-8. doi: 10.1093/cid/civ387.



Child with measles

- Red blotchy rash involving Head and shoulder

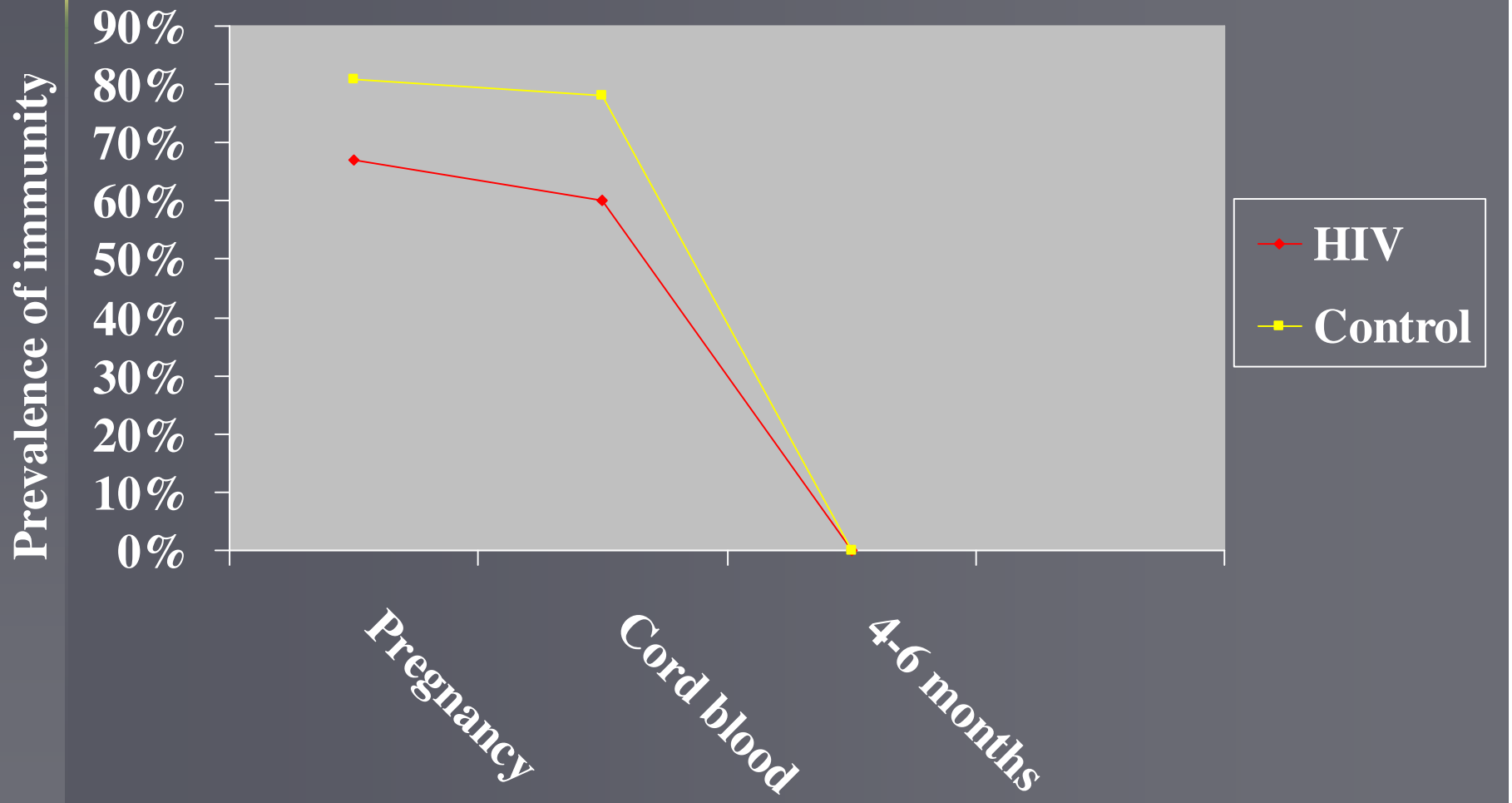


Child with measles

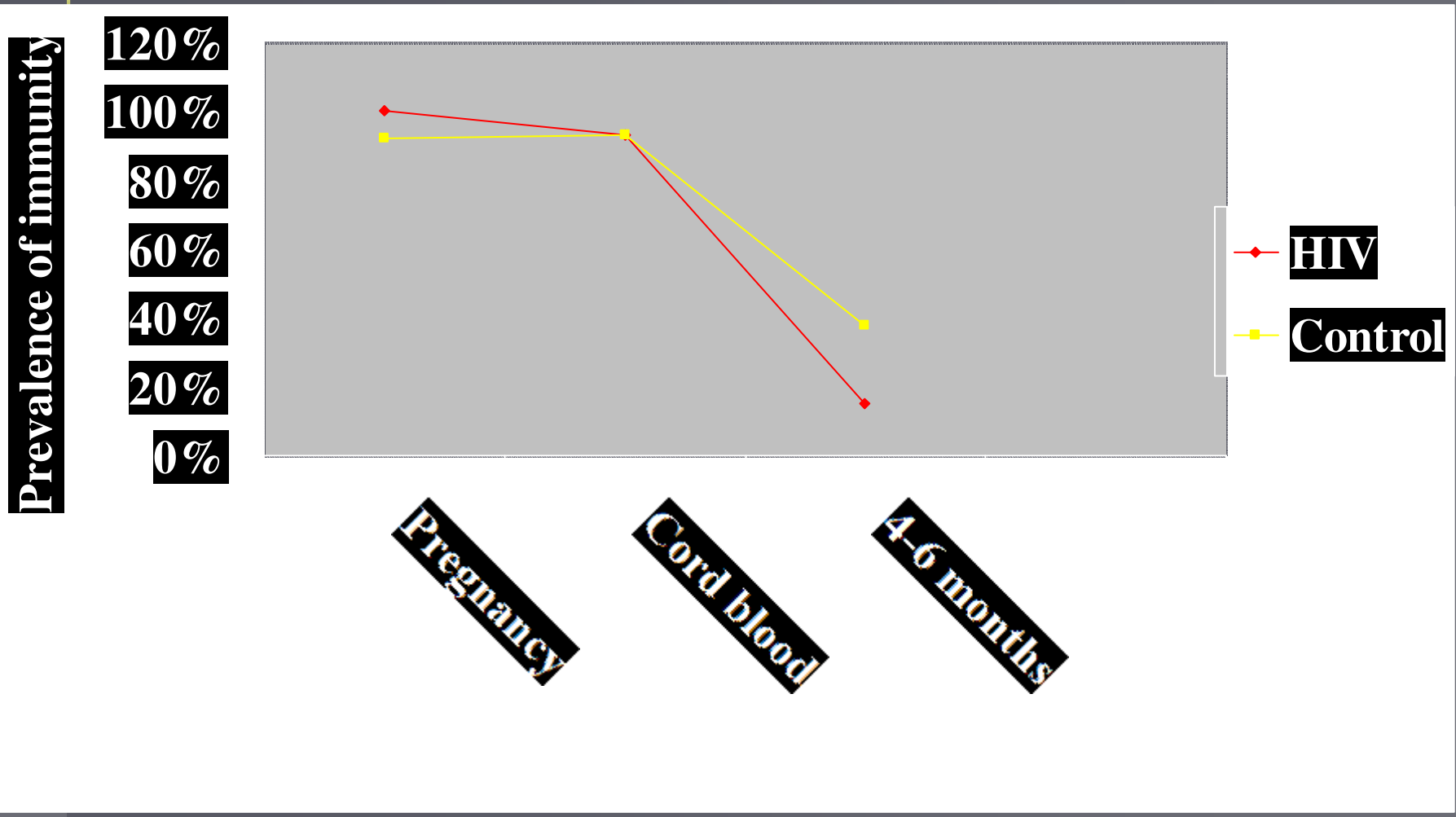
- Conjunctivitis



Subnormal waning immunity to measles
Protective level: ≥ 1.09 OD ratio

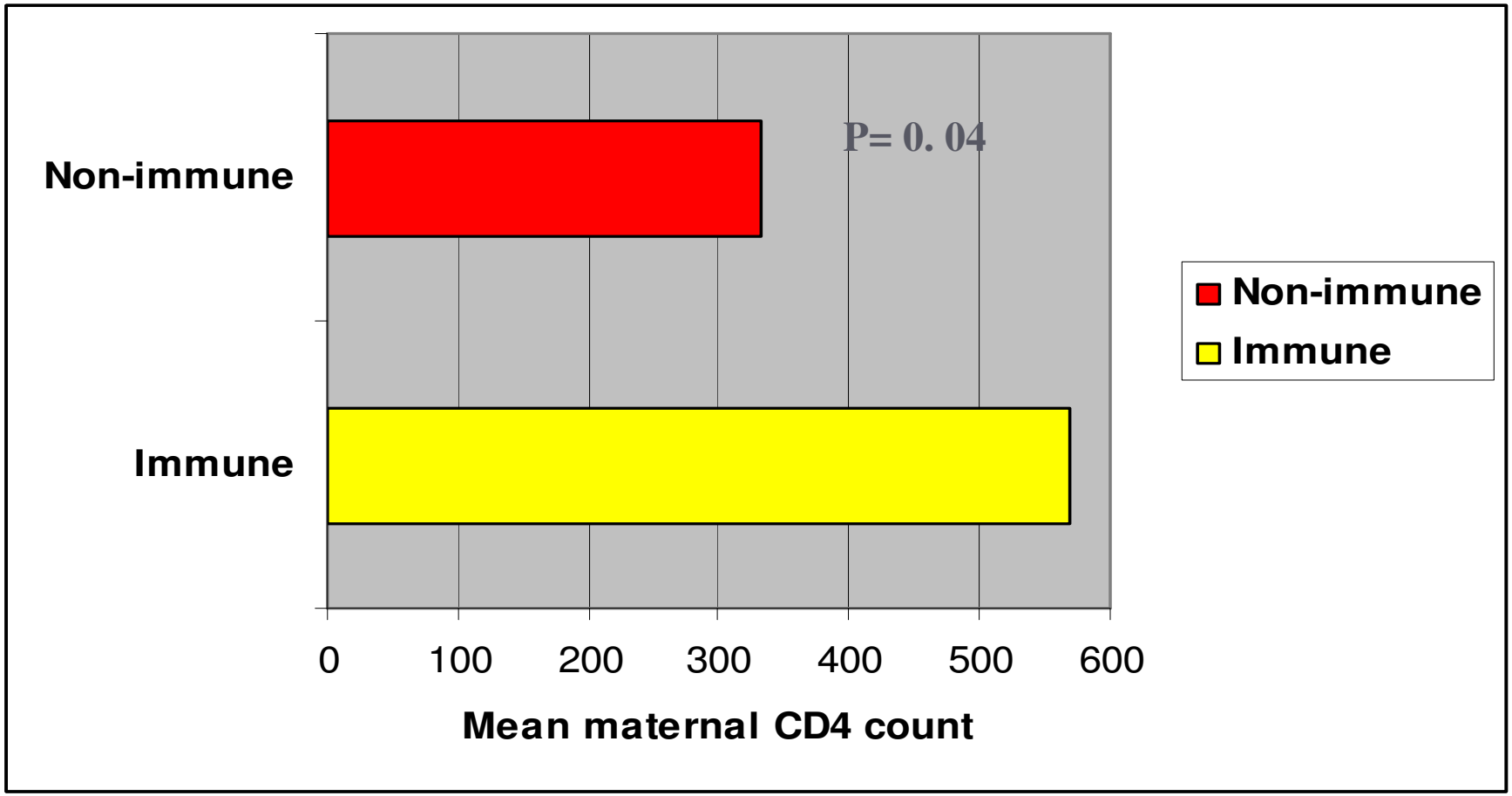


Subnormal waning immunity to varicella
Protective level ≥ 1:8



Mean CD4 Cell Counts in HIV-Seropositive Pregnant Women: Immune and Non-immune to Measles

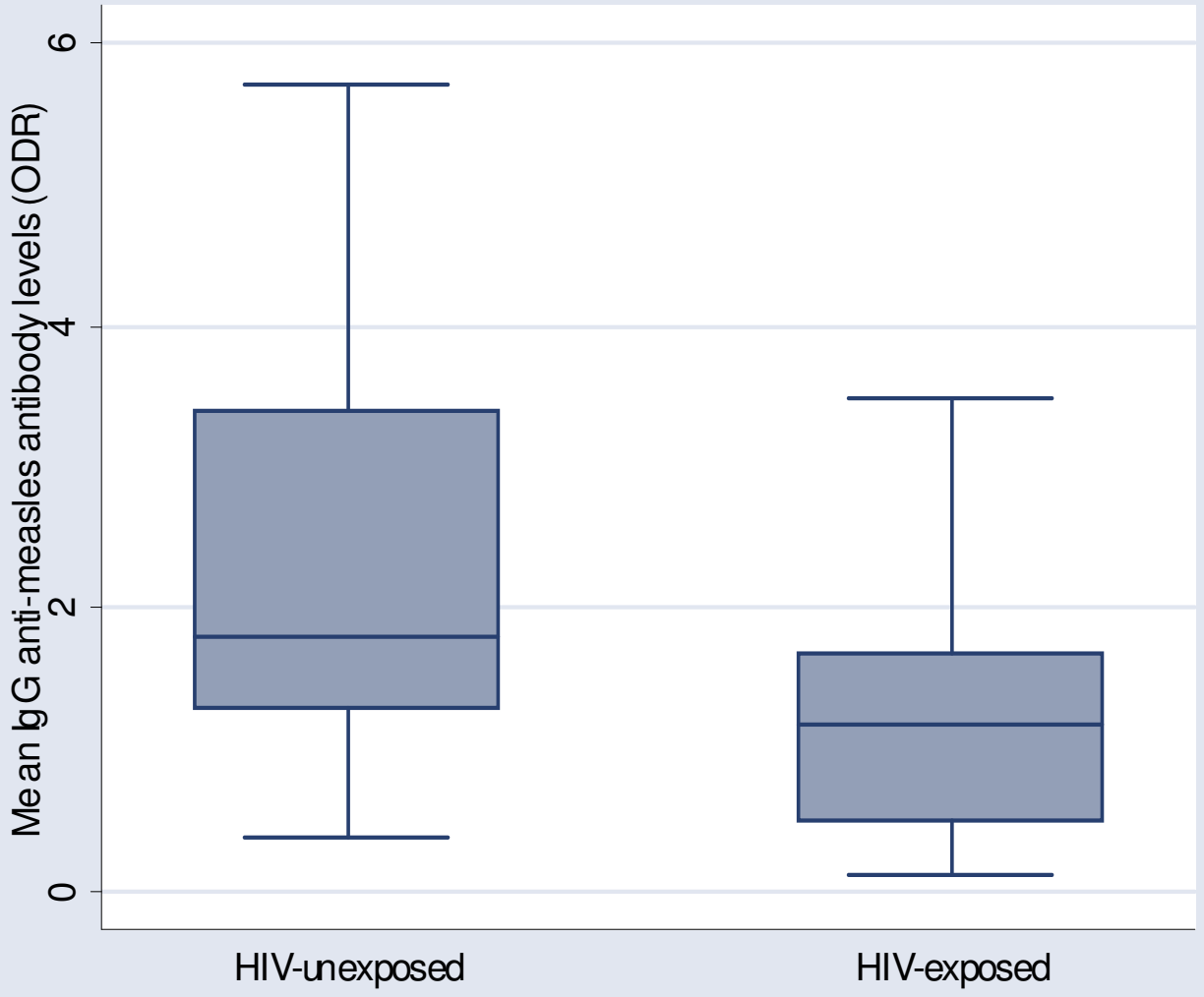
Immune level: ≥ 1.09 OD ratio



Anti- measles Ab levels in cord bloods: HIV-exposed and HIV-unexposed infants

Groups (n)	Anti-MS antibody GMT* (OD ratio) Mean (± SD)
HIV-exposed (14)	0.991 (1.095)
HIV-unexposed (27)	1.923 (1.524)
P value	0.04#

*GMT- geometric mean titer
Non-parametric test
OD- Optical Density



Measles and varicella conclusions

HIV-infected mothers & cord blood of their infants have significantly ↓'er level of Abs to measles compared to their uninfected counterparts

Significant waning maternal Abs to non-protective levels occurred for measles & varicella in HIV-exposed & unexposed infants equally before 6 months of age

HIV infected mothers with ↓'er CD4 counts are more likely to have ↓'er measles Abs in their infants compared to mothers with ↑'er CD4 counts

The above finding should concern health care providers

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Tetanus

Tetanus is a life threatening, but preventable disease

The disease primarily occurs in unvaccinated or inadequately vaccinated individuals

Immunocompromized individuals may remain at risk despite adequate vaccination

Immunogenicity to TT in previously vaccinated HIV-infected compared to uninfected pregnant women, passive Abs in cord bloods, & waning Abs in infants have not been well studied

Hypotheses and Specific Aims

Hypothesis

- **Lack of adequate maternal Abs result in inadequate Ab levels in the NB regardless of the newborn's HIV infection status**

Specific Aims

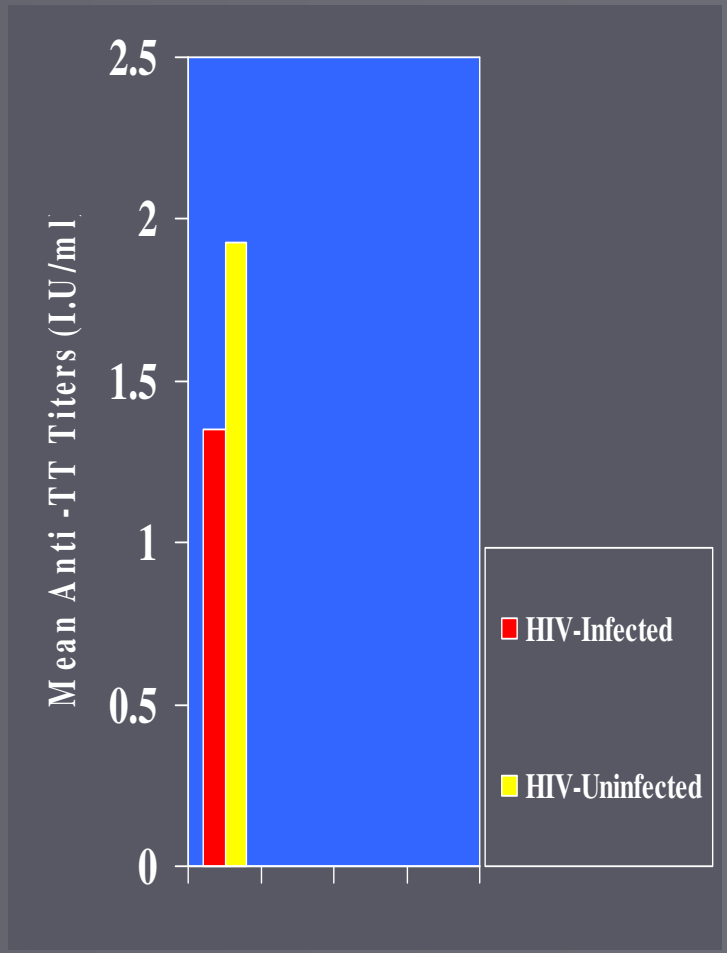
- **To determine & compare between HIV - infected and uninfected pregnant women & infants' cord blood:**
  - **Baseline and FU Ab levels**
  - **Correlation of virologic & immunologic parameters in pregnant mothers with the levels of Abs in their NBs**

Patient Population: Pregnant Women

	HIV-Seropositive (n)	HIV-Seronegative (n)
Age in years mean (range)	28 (18-40) (12)	26 (15-42) (24)
Vaccination records	none	none
Antiretroviral Rx N (%)	5 (62)	na
CD4 count/mm3	442 (256-786)	na
Viral load Copies/ml	28,456 (ND-159,917)	na

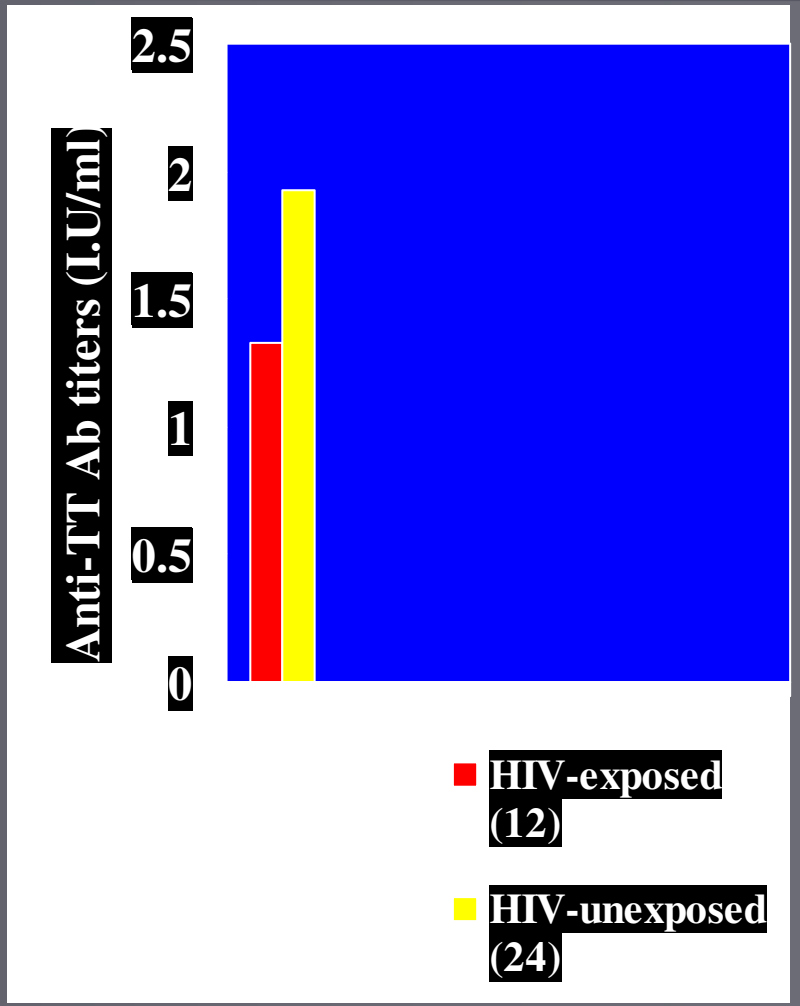
Anti-TT Antibody in Pregnant Mothers

Groups (n)	Anti-TT (IU/ml) Mean (± SE)
HIV- infected (8)	1.35 (0.56)
HIV-uninfected (24)	1.93 (0.45)
P*	ns
* Two-tailed Mann-Whitney U Test	



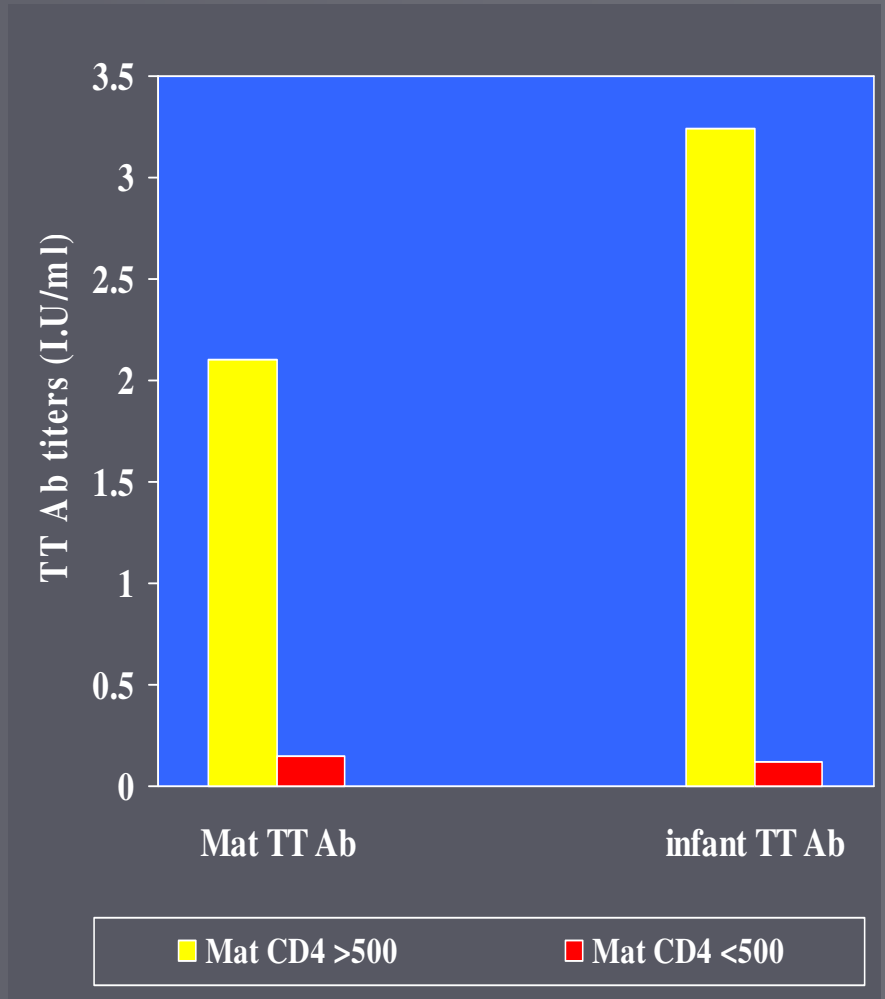
Anti-TT Antibody in Cord Blood of Infants

Groups (n)	Anti-TT (IU/ml) Mean (± SE)
HIV- exposed (12)	1.33 (0.45)
HIV-unexposed (24)	1.93 (0.45)
P*	ns
* Two-tailed Mann-Whitney U Test	



Relationship Between Maternal CD4 Counts During Pregnancy &TT Titers in HIV- Infected Mothers & Infants' Cord Bloods

	Mother TT Ab(IU/ml) Mean (± SE) (n)	Infant TT Ab(IU/ml) Mean (± SE) (n)
CD4 >500/mm^3	2.1 (±0.56) (4)	3.24 (±0.51) (4)
CD4 <500/mm^3	0.15 (±0.04) (4)	0.12 (±0.02) (4)
P* Two-tailed Mann-Whitney U	0.01	0.0009 Not M-I pairs



Tetanus Conclusions

Evidence of documentation of last TT vaccination was not available on any subject

Babies born to HIV -infected women have Ab levels to TT lower than that of HIV-unexposed

Pregnant HIV- infected women (CD4 counts < 500/mm^3) & infants have significantly ↓'er Ab levels compared to those mothers with CD4 counts > 500/mm^3

Tetanus Recommendations

Neonatal and Intrapartum/ Postpartum tetanus in HIV - infected women with CD4 counts < 500/mm^3 should remain a concern to health care providers in the US

It may be recommended that HIV-infected women with CD4 counts < 500/mm^3 have tetanus boosters during pregnancy to prevent neonatal & intrapartum/postpartum tetanus in the US and elsewhere in the world

Passive antibodies to *Streptococcus pneumoniae* and *Hemophilus influenzae* type b

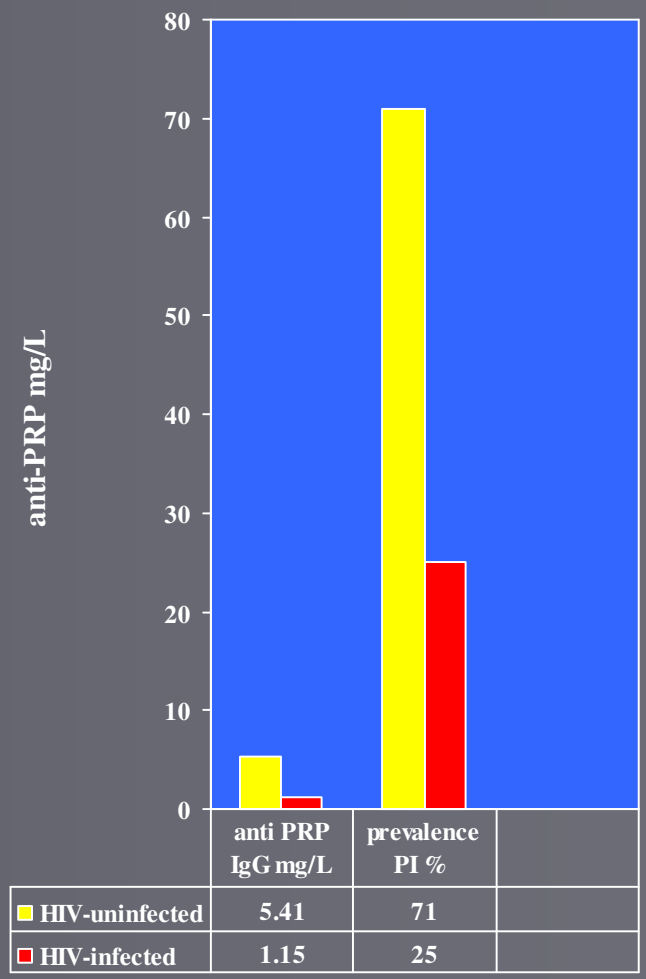
The purpose of the study was to assess and compare passive Ab levels (cord blood) to the polysaccharide Ags in HIV-exposed versus unexposed uninfected infants

Patient Population: Pregnant Women

	HIV-Seropositive (n)	HIV-Seronegative (n)
Age in years mean (range)	28 (18-40) (12)	26 (15-42) (24)
Vaccination records	none	none
Antiretroviral Rx N (%)	5 (62)	na
CD4 count/mm3	442 (256-786)	na
Viral load Copies/ml	28,456 (ND-159,917)	na

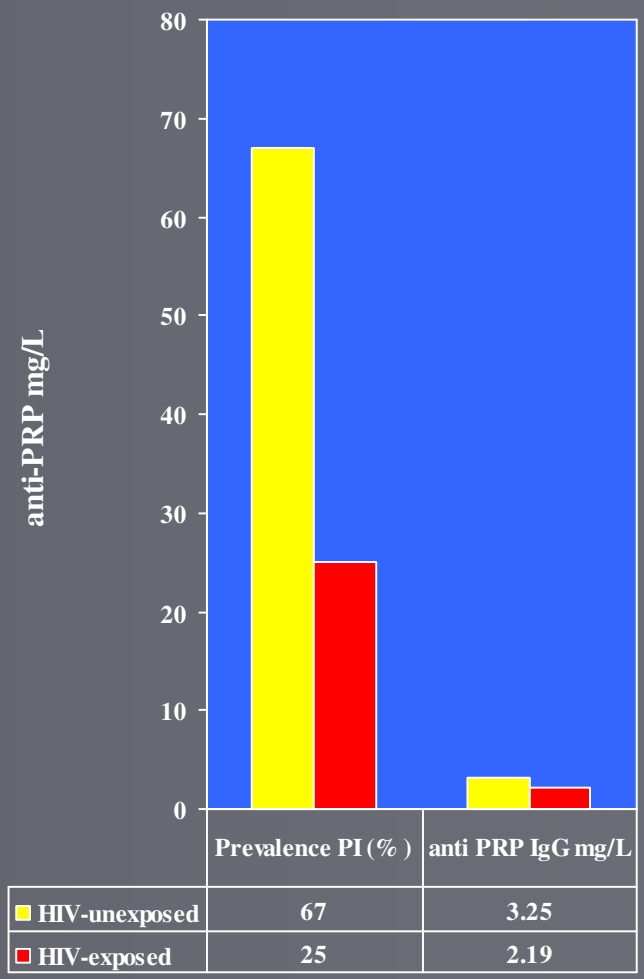
Anti PRP (Hib): mothers

Groups	Prevalence of protective immunity ≥ 1 mg/L (%)	Anti-PRP IgG mg/L mean (± SD)
HIV infected (n)	2/8 (25%) (8)	1.15 (± 1.41) (8)
HIV uninfected (n)	17/24 (71%) (24)	5.41 (± 6.25) (24)
P*	0.03	ns 0.06
	*Two-tailed Fisher's Exact test	* two-tailed ttest



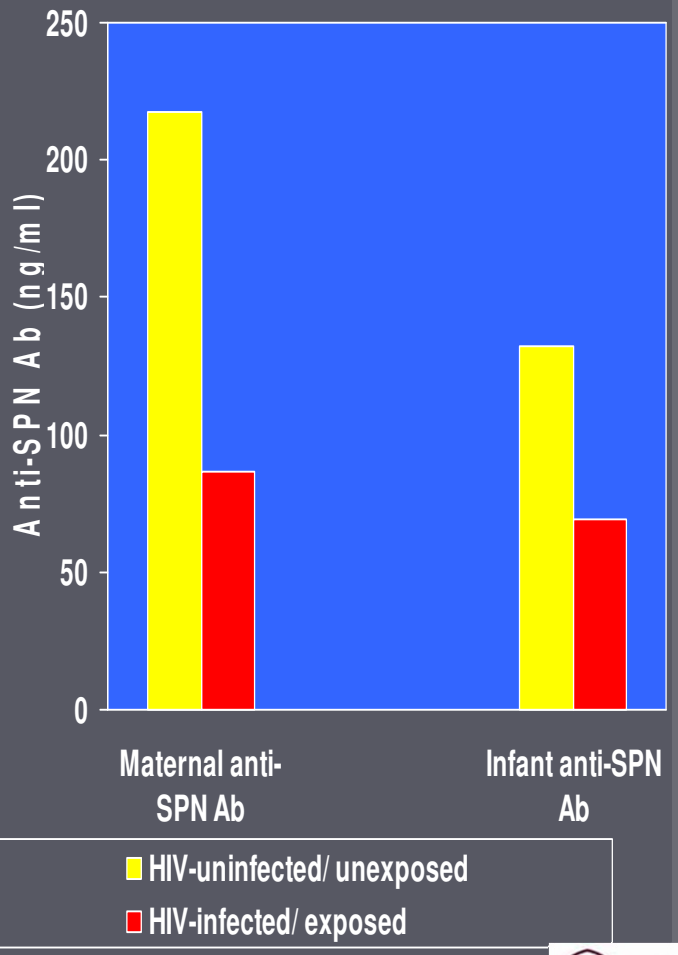
Anti PRP (Hib): infants (cord blood)

Groups	Prevalence of protective immunity (PI) ≥ 1 mg/L (%)	Anti-PRP IgG mg/L mean (± SD)
HIV exposed (n)	3/12 (25%) (12)	2.19 (± 4.39) (12)
HIV unexposed (n)	16/24 (67%) (24)	3.25 (± 3.14) (24)
P*	0.03	ns
	*Two-tailed Fisher's Exact test	* two-tailed ttest



Mother-Infant Pairs Placental Transfer Anti-*Hib* Abs: HIV-Infected and Uninfected Groups

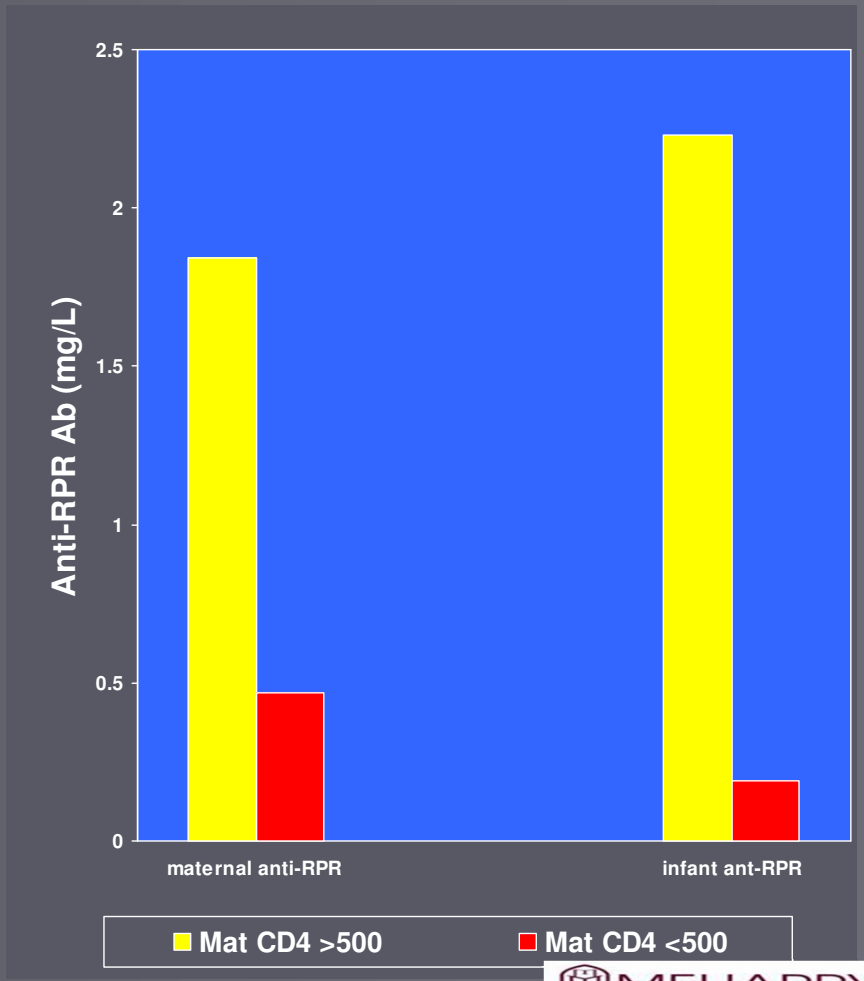
	HIV-infected/ exposed	HIV-uninfected/ unexposed
Mother Anti-*Hib* Ab (mg/L) Mean (± SD)	1.26 (± 1.49)	5.88 (± 6.48)
(n)	(7)	(20)
Infant Anti-*Hib* Ab (mg/L) Mean (± SD)	1.50 (± 2.33)	3.39 (± 3.15)
(n)	(7)	(20)
P* Two-tailed t-test	ns	0.03 Reflects placental transfer



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Relationship Between Maternal CD4 Counts & Anti-*Hib* Antibody in HIV- Infected Mothers & Infants' Cord Bloods

	Mother Anti- *Hib* Ab (mg/L) Mean (± SD) (n)	Infant Anti-*Hib* Ab (mg/L) Mean (± SD) (n)
CD4 >500/mm^3	1.84 (±1.82) (4)	2.23 (±3.03) (4)
CD4 <500/mm^3	0.47 (± 0.28) (4)	0.48 (±0.19) (4)
P* Two-tailed t test	4-fold Ns	4-fold Ns



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Streptococcus pneumoniae & *Hemophilus influenzae* type b conclusions

Ab levels or prevalence of protective immunity to above infections is significantly ↓'er in HIV-infected mothers & their infants compared to their uninfected counterparts

Anti-*SPN* abs were non-protective in > 98% mothers & infants

Concerns remain for invasive *SPN* and *Hib* infections during the neonatal period, particularly in areas with ↑ prevalence of HIV & VPI

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Summary Conclusions

There is significantly ↓'ed transplacental transfer of Abs against polysaccharide antigens, namely *SPN* and *Hib* in the HIV-unexposed infants

Similar finding was not observed for the HIV- exposed group, most likely due to small sample size

Lower maternal CD4 count had a negative impact on passive antibody transfer across placenta of the T cell dependent Abs only (namely protein antigens, measles and tetanus)

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Concerns

These results raise concerns that:

HIV-exposed, even uninfected infants from areas (LMIC) with ↑ burden of infectious diseases (HIV and VPI) may remain at risk of suffering from significant morbidity & mortality of VPI

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Solution to the concerns

These results support maternal immunization during pregnancy to boost maternal antibody levels and provide higher infant antibody levels to protect against infectious diseases, particularly in areas with high burden of HIV infection and VPI (LMIC)

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Overall Recommendations

- **Maintain integrity of immune system in HIV-infected pregnant women thru highly active antiretroviral therapy**
- **HIV-infected women with CD4 counts < 500/mm^3 have tetanus boosters during pregnancy to prevent neonatal & ntrapartum/ postpartum tetanus in the US and elsewhere in the world**
- **Infants should be considered for vaccination with measles & varicella at 6 months in areas with high prevalence of HIV & measles/ varicella infections**
- **HIV infected mothers with CD4 count > 500/mm3 can be considered for measles vaccination during the postpartum period prior to hospital discharge**

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Other Recommendations

It is important to conduct studies on larger sample sizes to examine transplacental transfer of antibodies against polysaccharide antigens (*SPN & Hi*b), to justify maternal immunization during pregnancy in areas with high burden of HIV and VPI

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