Poster 870

Maternal HIV-1 Envelope Variable Region 3-specific IgG and Neutralization Responses are Correlates of Risk of Perinatal HIV-1 Transmission

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Background

Globally, more than 250,000 infants become vertically-infected with HIV-1 annually, despite the availability of effective antiretroviral (ARV) prophylaxis regimens. Immunologic interventions, such as a maternal or infant vaccine, will likely be required to eliminate pediatric HIV-1. Immune correlates of risk of HIV-1 acquisition were identified in the moderately-successful RV144 HIV-1 vaccine trial, including Envelope (Env) variable regions 1 and 2 (V1V2) IgG and Env IgA responses.

➢**Do maternal Env-specific antibody responses predict the risk of mother-to-child HIV-1 transmission?**

Methods

- Utilized the Women and Infants Transmission Study (WITS) cohort of U.S., nonbreastfeeding HIV-infected mothers, which began enrolling prior to the availability of ARV[1]
- Selected untreated, HIV-transmitting mothers (**n = 83**); and a clinically-matched group of nontransmitting mothers (**n = 165**) with plasma samples available between 25 weeks gestation and 2 months postpartum.
  - Transmissions were 52% peripartum, 13% *in utero* and 35% unknown transmission mode
- A pilot study revealed no significant differences in the Env-specific humoral responses during this peripartum period.
- Utilized a multivariable logistic regression model to determine if the following plasma Env-specific antibody responses predicted the risk of MTCT:
  1. IgG Env-binding responses (including Env V1V2[2] and V3 regions)
  2. IgA Env-binding response score[2]
  3. Neutralization response score (TZM-bl, tier 1 and 2)[2]
  4. Env-binding avidity[2]
  5. Antibody-dependent cell cytotoxicity[3] (SF162-infected CEM target cells)
- Env-binding IgA, neutralization, and V3-binding IgG scores were calculated as a weighted combination of responses, with standard deviation scaled to one[2]
- Applied a significance cut off of $p < 0.05$ and a false discovery rate (q value) of < 0.20[2]

Results

Table 1. Clinical characteristics of matched cohort of transmitting and nontransmitting HIV-1 infected, untreated mothers

Variable	Transmission status	N[1]	Mean (Range)	SD	P value[2]
Plasma viral load (copies/ml)	Nontransmitters	160	62,906 (167 – 1,031,250)	139,273	0.22
	Transmitters	83	112,235 (699 – 3,101,258)	347,778	
CD4 Count (cells/µl)	Nontransmitters	170	553.3 (32 - 2330)	333.3	0.08
	Transmitters	83	488.5 (16 – 1792)	285.3	
Gestational Age (weeks)	Nontransmitters	170	37.8 (28 – 43)	2.8	0.18
	Transmitters	84	37.3 (26 – 42)	3.2	
Variable	**Transmission status**	**N**	**Percent**	**P value[3]**	
Birth type					
Vaginal birth	Nontransmitters	125/170	74%	0.74	
	Transmitters	64/85	75%		
Cesarean section	Nontransmitters	40/170	24%		
	Transmitters	17/85	20%		
Birth year					
1990	Nontransmitters	37/166	22%		
	Transmitters	14/83	17%		
1991	Nontransmitters	53/166	32%		
	Transmitters	23/83	28%		
1992	Nontransmitters	32/166	19%		
	Transmitters	20/83	24%		
1993	Nontransmitters	28/166	17%		
	Transmitters	18/83	22%		
1994-1998	Nontransmitters	16/83	9%		
	Transmitters	8/83	10%		
Visit					
25 weeks gestation	Nontransmitters	58/166	35%		
	Transmitters	8/83	10%		
34 weeks gestation	Nontransmitters	41/166	25%		
	Transmitters	33/166	40%		
Delivery	Nontransmitters	16/166	10%		
	Transmitters	38/83	46%		
2 months postpartum	Nontransmitters	51/166	31%		
	Transmitters	4/83	5%		

[1]Missing data from 85 transmitters and 170 clinically-matched nontransmitters included: 10 nontransmitters and 2 transmitters plasma virus load, and 1 transmitter infant gestational age. Two transmitters and 4 nontransmitters were removed from the study following matching due to lack of sample availability.
[2]P value calculated by student's t test
[3]P value calculated by Chi squared test

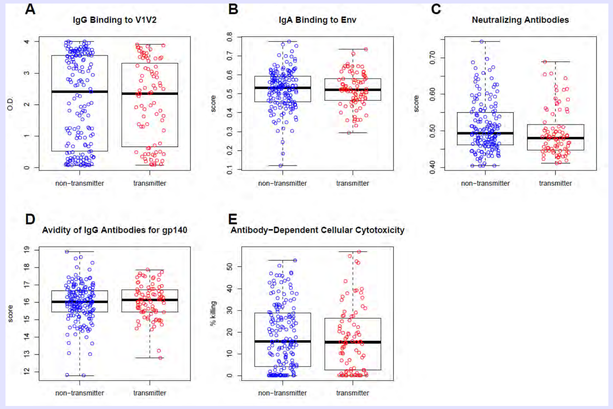


Figure 1. Comparison of the primary RV144 clade B-modified humoral immune responses in HIV-infected transmitting and nontransmitting women. Neither the maternal V1V2-specific IgG response (A), the clade B-modified Env-binding IgA score (B), clade B neutralizing antibody score (C), clade B gp140 avidity (D) or the ADCC response (E) correlated with the risk of MTCT. Nontransmitting women are shown on the left and transmitting women are shown on the right of the graph.

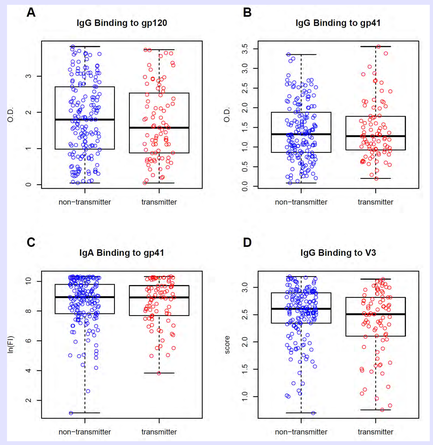


Figure 2. Comparison of the primary MTCT humoral immune responses in HIV-infected transmitting and nontransmitting women. Neither the maternal MN gp120-specific IgG binding (A), MN gp41-specific IgG (B) or IgA (C) responses predicted MTCT risk, however maternal V3 IgG-binding score predicted reduced risk of MTCT (OR: 0.64, p = 0.04, q = 0.15) Nontransmitting women are shown on the left and transmitting women are shown on the right of the graph.

Table 2. Odds ratios of perinatal HIV-1 transmission in multivariable analyses of the primary RV144-adapted and MTCT humoral immune correlate models

Humoral immune variables	Multivariate Logistic Regression		
	Odds Ratio (95% CI)	P[1] Value	Q[1] Value
RV144-clade B modified model			
IgG binding to V2	1.06 (0.80-1.42)	0.67	0.76
IgA binding	0.96 (0.72-1.27)	0.76	0.76
Neutralizing antibodies	0.76 (0.55-1.05)	0.1	0.48
Avidity	1.12 (0.83-1.51)	0.45	0.76
ADCC	0.94 (0.71-1.24)	0.65	0.76
MTCT model			
IgG binding to MN gp120	1.18 (0.69-2.03)	0.55	0.91
IgG binding to MN gp41	1.09 (0.72-1.65)	0.69	0.91
IgA binding to gp41	1.02 (0.76-1.36)	0.91	0.91
IgG binding to V3 (score)	**0.64 (0.42-0.97)**	**0.04**	**0.15**

[1] immune variable interactions with $p < 0.05$ and $q<0.2$ are bolded

Table 3. Five lowest odds ratios of vertical HIV-1 transmission in multivariate analyses of secondary humoral immune variables for entire MTCT cohort and peripartum transmission cohort.

Immune variables	Odds Ratio (95% CI[1])	P[1] value	Q[1] value
Entire MTCT cohort (n = 83 transmitters, 165 nontransmitters)			
Nab SF162	0.67 (0.50-0.90)	0.006	0.25
Nab MN3	0.71 (0.54-0.95)	0.02	0.4
B.V3 IgG	0.75 (0.58-0.98)	0.035	0.47
B.MNV3 gp70 IgG	0.78 (0.59-1.01)	0.061	0.49
M.V3 IgG	0.78 (0.59-1.01)	0.061	0.49
Peripartum transmission cohort (n = 42 transmitters, 84 nontransmitters)			
Nab MN3	**0.54 (0.35-0.83)**	**0.005**	**0.1**
Nab SF162	**0.54 (0.35-0.84)**	**0.005**	**0.1**
Nab BaL26	0.65 (0.43-0.98)	0.037	0.38
B.V3 IgG	0.67 (0.46-0.99)	0.042	0.38
A1con03 gp140 IgA	0.69 (0.47-1.01)	0.057	0.38

[1] immune variable interactions with $p < 0.05$ and $q<0.2$ are bolded

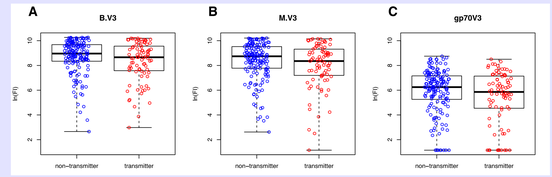


Figure 3. Comparison of Env V3-specific IgG responses in HIV-infected transmitting and nontransmitting women. Plasma IgG binding to consensus clade B (A) and group M (B) Env peptides, and scaffolded (gp70) B.MN V3 (C) in perinatal transmitting and nontransmitting mothers. Nontransmitting women are shown on the left and transmitting women are shown on the right of the graph

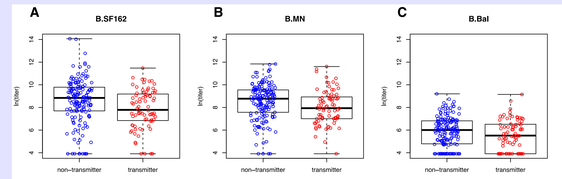


Figure 4. Comparison of clade-matched tier 1 virus neutralization responses in HIV-infected transmitting and nontransmitting women. Plasma neutralization responses against HIV-1 strains B.SF162 (A), B.MN (B), and B.Bal (C) in perinatal transmitting and nontransmitting mothers. Nontransmitting women are shown on the left and transmitting women are shown on the right of the graph

Conclusions

- In this cohort of untreated, U.S. HIV-1 infected women, high magnitude maternal plasma Env V3-specific IgG binding predicted reduced risk of MTCT
- High magnitude clade-matched tier 1, but not tier 2, virus neutralization predicted reduced risk of peripartum MTCT
- The magnitude of the maternal Env V1V2 IgG binding did not predict the risk of MTCT
- The responses that predicted the risk of MTCT (V3-binding IgG and tier 1 virus neutralization) may be reflective of an unmeasured humoral immune variable that contributes to protection of infants against HIV-1, such as autologous virus neutralization

Acknowledgements

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