THE ROLE OF MATERNAL BROADLY NEUTRALIZING ANTIBODY ACTIVITY IN PERINATAL TRANSMISSION OF HIV-1

903

Krithika P Karthigeyan[1], Ashley Nelson[1], Dieter Mielke[3], Christian Binuya[1], Ria Goswami[1], John Isaac[1], Elena E. Giorgi[2], Justin Pollara[3], Joshua Eudailey[1], Megan Connors[1], Carolyn Weinbaum[1], Genevieve Fouda[1] , Feng Gao[2], Manish Sagar[4], Sallie R Permar[1]

[1]Weill Cornell Medicine, New York, NY,[2]Fred Hutchinson Cancer Research Center, Seattle, WA,[3]Duke University, Durham, NC,[4]Boston University, Boston, MA

BACKGROUND

- Despite increased availability to antiretroviral therapy (ART), up to 5% of women living with HIV (WLH) still transmit the virus to their infants.[1]
- While broadly neutralizing antibodies (bNAbs) are the immunologic goal of HIV-1 vaccine candidates, there are contrasting reports for the role of bNAbs during vertical transmission.[2,3] We have demonstrated escape of infant HIV variants in the presence of bNAbs targeting a single, dominant epitope in postnatal transmitters.[4]

HYPOTHESIS

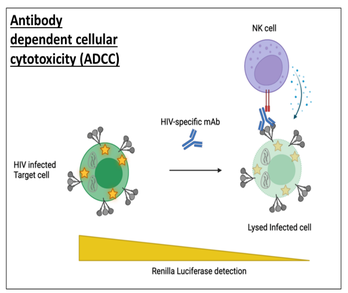
WLH with bNAb responses against single epitopes of the HIV envelope are at higher risk of **perinatal transmission** due to viral escape, and this impacts the development of a bNAb response in infants.

METHODS

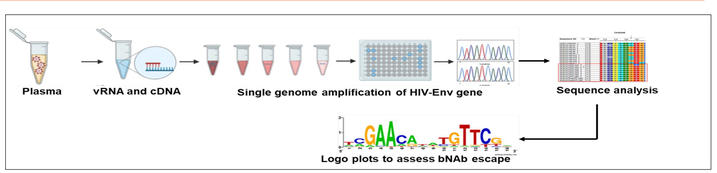
- **Neutralization** against a ten-virus, Tier 2 global panel was screened for transmitters (n = 23) and non-transmitters (n = 70) of the **perinatal MICS and NISDI cohorts** and paired infants with HIV of MICS cohort.
- **Antibody dependent cellular cytotoxicity (ADCC)** was assessed against cells infected with a transmitted/founder subtype B virus (WITO).
- **Single genome amplification** of the HIV envelope was done for two infants of paired transmitters with neutralization breadth, and the sequence was analyzed for the presence of bNAb escape mutation patterns.

Neutralization Screening Strategy

	Virus	Clade
Screen 1	25710	C
	TRO11	B
	X2278	B
	BJOX002000	CRF07
	246F3	AC
Screen 2	X1632	G
	CE1176	C
	CH119	CRF07
	CE0217	C
	CNE55	CRF01

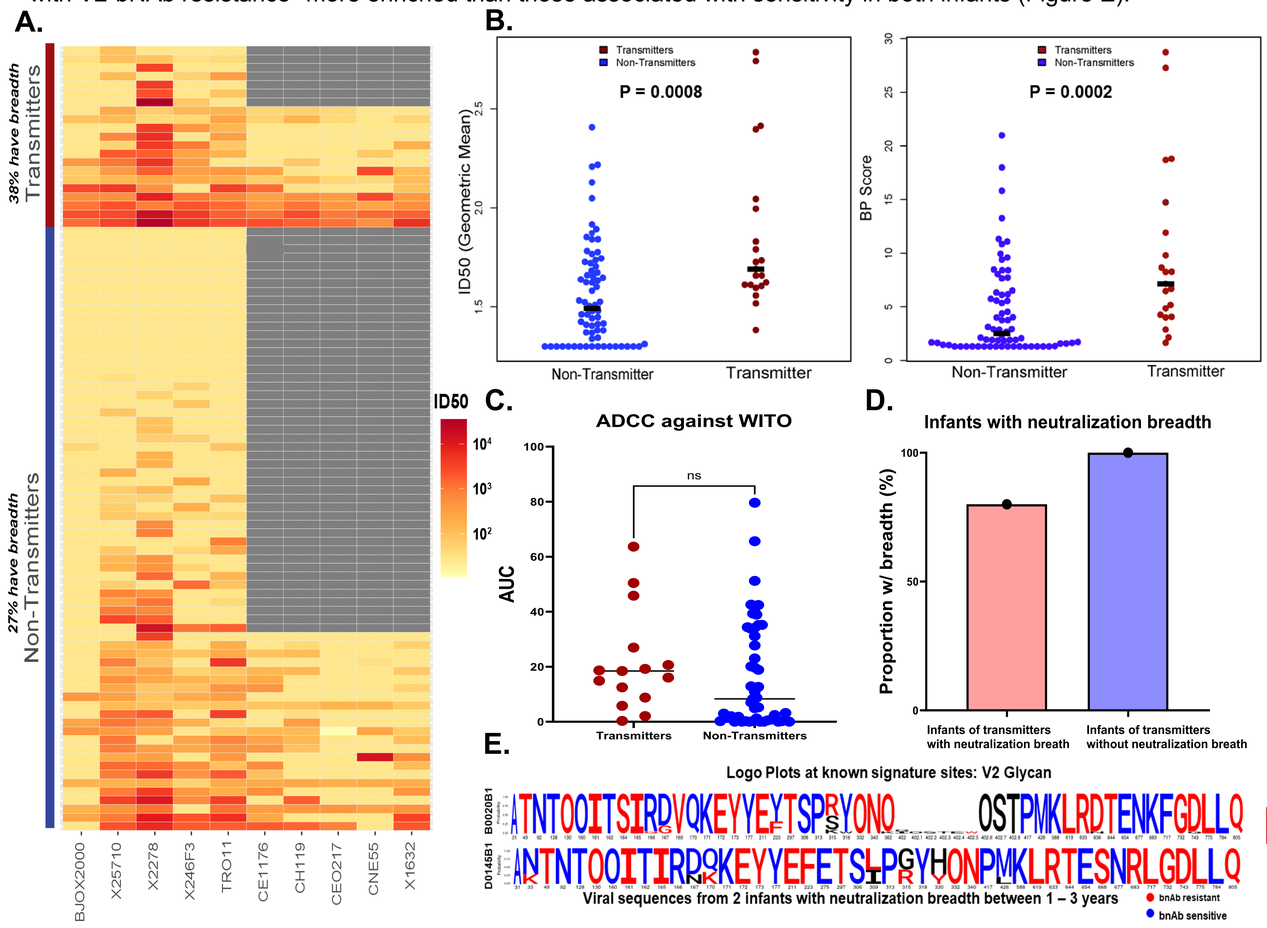


Neutralization is defined as an ID50 of at least 40 post background subtraction (2x-MLV ID50). Breadth is defined as neutralizing at least 5 out of 10 viruses



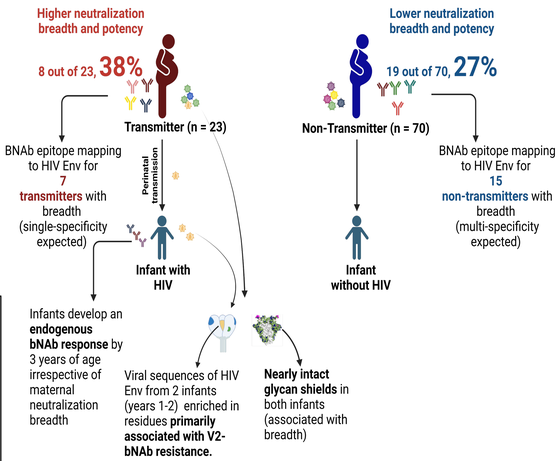
RESULTS

- **A significantly higher proportion of perinatal transmitters (8 out of 23, 38%) had neutralization breadth and potency compared to non-transmitters (19 out of 70, 27%) (Figures A-B).**
- Transmitters of the MICS cohort (n = 15) trended towards higher ADCC against WITO (Figure C).
- Infants developed an endogenous neutralization response between 1-3 years of age irrespective of maternal neutralization breadth (Figure D). Signature site analysis of two infant sequences with breadth revealed that both infants carried a combination of residues associated with either resistance or sensitivity, with the sites associated with V2-bNAb resistance[5] more enriched than those associated with sensitivity in both infants (Figure E).



A.Plasma neutralizing antibody breadth in transmitters (n = 21) and non-transmitters (n = 70) was measured against a global panel of 10 viruses. Grey indicates neutralization was not assessed **B.** Transmitters had higher magnitude of neutralization (p=0.0008, geometric means reported) and significantly higher breadth-potency scores[3] (p=0.0002) **C. ADCC against WITO** was assessed for the MICS cohort **D. Neutralization breadth** was compared for paired infants of transmitters with and without breadth. **E.** Logo plots from viral sequences of two infants with neutralization breadth depicting signature sites for the V2 Glycan bNAb epitope; residues associated with resistance shown in red and those associated with sensitivity shown in blue. O indicates a glycosylation motif.

CONCLUSIONS



- Our findings support the existence of increased bNAb activity in transmitters, which could lead to emergence of bNAb-resistant viral variants that can be transmitted perinatally to the infant, which in turn may contribute to endogenous bNAb responses.
- Thus, bNAb-based pediatric HIV prevention and treatments that are synergistic with ART will likely need to be multi-specific to effectively eliminate and cure pediatric HIV.

FUTURE DIRECTIONS

- Epitope mapping of bnAbs from transmitters and non-transmitters with neutralization breadth.
- Sequence *env* variants from transmitter-infant pairs using single genome amplification (SGA).
- Generate Env pseudoviruses from maternal and T/F infant pairs to measure susceptibility to neutralization by autologous plasma.[5]

ACKNOWLEDGEMENTS

- All Study Participants and sample collection through the NICHD Data and Specimen Hub (DASH).
- Funding from the NIH R01 5250074901.

REFERENCES

1. Joint United Nations PoHA. UNAIDS Data 20182018
2. Bongertz V, et al., Neutralization titres and vertical HIV-1 transmission.Scand J Immuanol. 2002.
3. Ghulam-Smith M,et al. Maternal but Not Infant Anti-HIV-1 Neutralizing Antibody Response Associates with Enhanced Transmission and Infant Morbidity. MBio. 2017
4. Tu Jjet al., Vertical HIV-1 Transmission in the Setting of Maternal Broad and Potent Antibody Responses. J Virol. 2022
5. Bricault CA et al.,HIV-1 Neutralizing Antibody Signatures and Application to Epitope-Targeted Vaccine Design. Cell Host Microbe. 2019 Jan 9;25(1):59-72.e8. doi: 10.1016/j.chom.2018.12.001. Erratum in: Cell Host Microbe. 2019 Aug 14;26(2):296. PMID: 30629920; PMCID: PMC6331341.