MATERNAL BROADLY NEUTRALIZING ANTIBODY ACTIVITY AND PERINATAL TRANSMISSION OF HIV-1

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BACKGROUND

- Over 150,000 children live with HIV-1 every year despite increased availability to antiretroviral therapy (ART), and up to 11% of women with HIV still transmit the virus to their infants[1].
- **Broadly neutralizing antibodies (bnAb)** are the primary focus of vaccine and therapeutic strategies and **have been shown to have contrasting roles in vertical transmission of HIV**[2,3], thus making further characterization of their role essential to mitigate vertical transmission.

HYPOTHESIS

People living with HIV with neutralizing antibody breadth and bnAbs targeting a single epitope may be at high risk of viral escape leading to vertical transmission.

METHODS

Neutralization against a ten-virus, Tier 2 global panel was screened for the two postnatal cohorts described below[4] as well transmitters of the perinatal MICS cohort. Non-transmitters have so far been screened against five viruses.

Perinatal Cohorts	Postnatal Cohorts
MICS (Mother-Infant Cohort Study) • US-based cohort • Enrollment period: 1986-1991 • **Pre-ART cohort**	**BAN (Breastfeeding, Antiretroviral, and Nutrition Study)** • Malawi-based cohort • Enrollment period 2004-2010 • Combination ART administered for 1 week post-delivery
NISDI (NICHD International Site Development Initiative study) • Latin American cohort • Enrollment period: 2002-2007. • ART administered around delivery, but only in less than half of enrolled women.	**CHAVI 009 (Center for HIV/AIDS Vaccine Immunology 009)** • Malawi-based cohort • Enrollment period: 2007-2009 • Nevirapine administered once at delivery

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

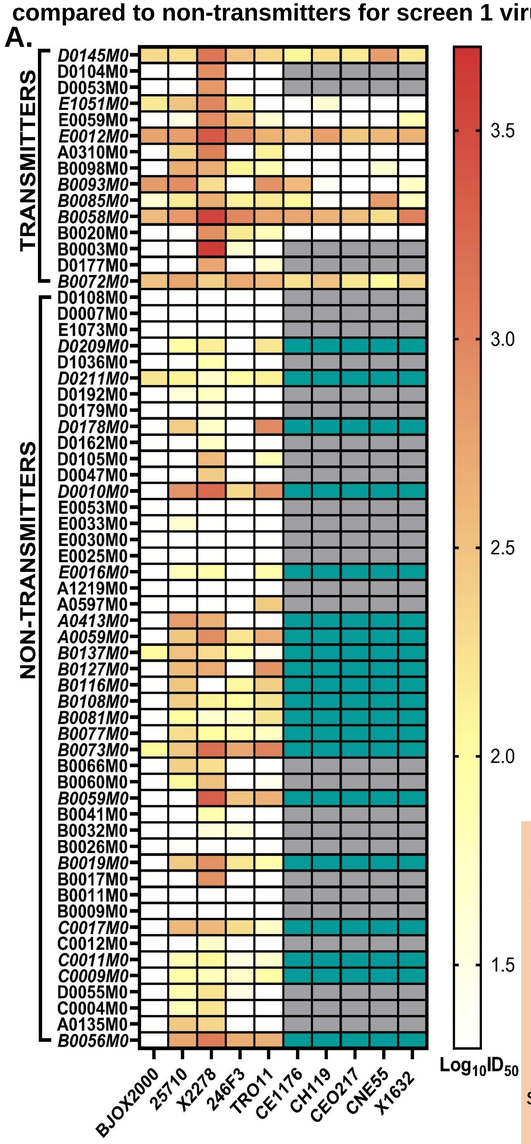
Neutralization is defined as an ID50 of at least 40 post background subtraction (2x-MLV ID50). Breadth is defined as neutralizing at least 5 out of 10 viruses, or 3 out of 5 viruses for Screen 1 alone.

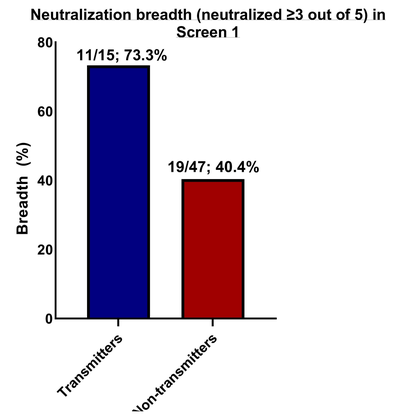
RESULTS

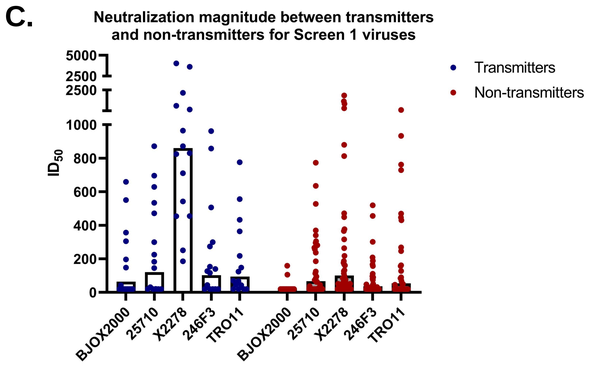
7 out of 15 (47%) people in the MICS cohort who transmitted HIV neutralized at least 50% of viruses of a heterologous, 10-virus global panel after correcting for non-specific neutralization activity (MLV).

While this rate is higher than that reported in adults living with HIV (20-30%), high neutralization breadth was also found among people who transmitted HIV postnatally in the BAN and CHAVI cohorts (18 of 24, 75%) indicating that transmission during perinatal and postnatal settings may involve a similar high rate of maternal bnAb responses that could lead to viral escape**.**

Transmitters in the perinatal MICS cohort also had higher neutralization breadth and magnitude compared to non-transmitters for screen 1 viruses.

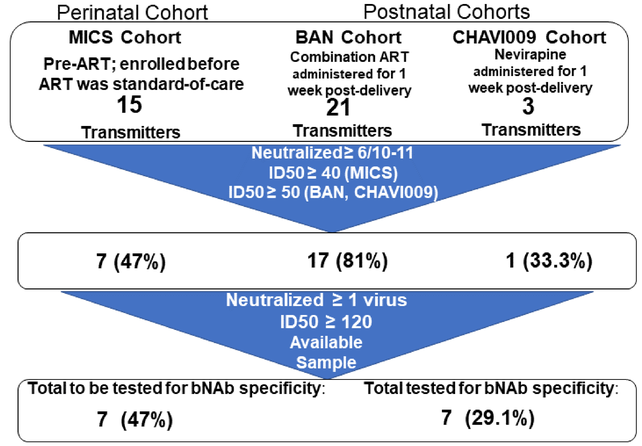






A.Plasma neutralizing antibody breadth in transmitters (n = 15) and non-transmitters (n = 47) was measured against a global panel of 5-10 viruses. Italicized participant IDs indicate breadth, grey indicates neutralization was not assessed, and turquoise indicates neutralization to be assessed for participants with breadth in Screen 1. **B.** Neutralization breadth and **C.** magnitude comparison between transmitters and non-transmitters. The ID50 geometric means over the screen 1 viruses were statistically significantly higher in the transmitters compared to non-transmitters (p = 0.000748)

CONCLUSIONS



- The finding of higher plasma bnAb rates in people who transmitted HIV perinatally than people who did not transmit HIV is similar to that observed in postnatal transmission settings[3,4] and might indicate a role for viral escape of neutralization in perinatal transmission.
- BnAb-based interventions during pregnancy and/or infancy to eliminate infant HIV acquisition will likely need to include mutispecific bnAbs.

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) and generate Env pseudoviruses from maternal and T/F infant pairs to measure susceptibility to neutralization by autologous plasma.
- Compare magnitude of Fc-mediated effector antibody responses such as ADCC between transmitters and non-transmitters.

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