More than just escaping neutralization

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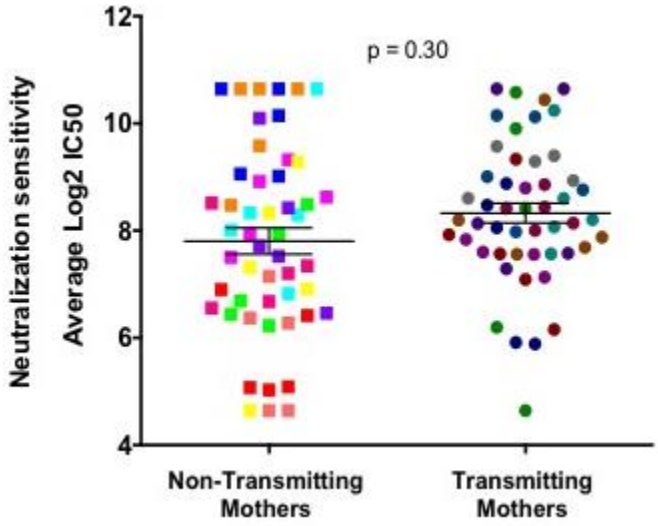

Autologous neutralizing antibody responses of nontransmitting and transmitting mothers. IC50s of nontransmitting and transmitting mothers are color coded by mother. Each square or dot represents the IC50 of an individual envelope variant tested against contemporaneous autologous plasma. Data are shown as raw IC50s on a log2 scale higher Log2IC50 suggests a more neutralization-sensitive virus variant; black bars represent medians and IQRs, and the dotted line represents an IC50 of 25 (resistant to neutralization at a 1:50 dilution).

Figure provided by Caitlin Milligan.

As of June 30th of last year, the fight against HIV reached another milestone: Cuba became the first country where HIV mother-to-child transmission (MTCT) was declared eliminated. While we expect other countries to reach the same milestone soon, we are aware that in many realities, achieving this goal will require more work and resources. In fact, although it has been demonstrated that a large proportion of MTCT occurs during breastfeeding, not every country has the ability to ensure that infected mothers have access to potable water and breast milk substitutes. In these situations, effective strategies to avoid transmission are still sought.

Evidence obtained from human and non-human primate studies suggests that neutralizing antibodies (NAbs), which inhibit viral infection, might play a role in decreasing HIV MTCT. Consistent with this, infants are usually infected with a single virus variant, one that is in general more resistant to neutralization than other maternal virus variants. Therefore, it is possible that maternal transmission risk correlates with a higher frequency of neutralization-resistant viruses.
To test this hypothesis, Caitlin Milligan and others from the Overbaugh Laboratory (Public Health Sciences and Human Biology Divisions) at Fred Hutch compared the viral populations of HIV transmitting and nontransmitting mothers for their sensitivity to neutralizing antibodies. The samples for the study were collected in the mid-1990s before antiretroviral therapies to prevent MTCT were available. The results of the study were recently published in the journal *MBio*.

The cohorts were chosen in order to achieve a clear answer: only breastfeeding mothers with high viral loads (thus higher probability of transmitting HIV), whose newborn children were HIV negative at birth were selected for the study. Moreover, the HIV status of children was monitored regularly to precisely determine the time of infection. The study tested maternal antibody and envelope (Env) variants at a time point shortly before seroconversion of the children. For each mother, five different clones encoding for Env were tested for sensitivity to neutralization by paired maternal plasma. Viruses carrying Envs cloned from transmitting and non-transmitting mothers showed a range of neutralization sensitivities (as shown in the figure). The overall sensitivities were comparable in the two groups when the most concentrated plasma dilutions were used, while when lower dilutions, comparable to those demonstrated to protect against infection in non-human primates, were tested, non-transmitting mothers unexpectedly had higher percentages of neutralization-resistant viruses.

This study shows that both nontransmitting and transmitting mothers have neutralization-resistant viruses, suggesting that the presence of these viruses alone does not predict transmission risk. "These results suggest that HIV mother-to-child transmission in the early breastfeeding period is not solely due to the presence of neutralization resistant viruses and likely involves multiple factors", said Milligan. Identification of other factors associated with the risk of MTCT may help elucidate mechanisms that can be targeted to prevent transmission and infection in other populations.

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Milligan C,Omenda MM,Chohan V,Odem-Davis K,Richardson BA,Nduati R,Overbaugh J. 2016. Maternal Neutralization-Resistant Virus Variants Do Not Predict Infant HIV Infection Risk. *MBio*. 7(1): e02221-15. Doi: 10.1128/mBio.02221-15.