ody escape during HIV-1 mother-to-child transmission involves conformational masking of distal epitopes in envelope.

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Abstract:

HIV-1 variants transmitted to infants are often resistant to maternal neutralizing antibodies (NAbs), suggesting that they have escaped maternal NAb pressure. To define the molecular basis of NAb escape that contributes to selection of transmitted variants, we analyzed 5 viruses from 2 mother-to-child transmission pairs, in which the infant virus, but not the maternal virus, was resistant to neutralization by maternal plasma near transmission. We generated chimeric viruses between maternal and infant envelope clones obtained near transmission and examined neutralization by maternal plasma. The molecular determinants of NAb escape were distinct, even when comparing two maternal variants to the transmitted infant virus within one pair, in which insertions in V4 of gp120 and substitutions in HR2 of gp41 conferred neutralization resistance. In another pair, deletions and substitutions in V1 to V3 conferred resistance, but neither V1/V2 nor V3 alone was sufficient. Although the sequence determinants of escape were distinct, all of them involved modifications of potential N-linked glycosylation sites. None of the regions that mediated escape were major linear targets of maternal NAbs because corresponding peptides failed to compete for neutralization. Instead, these regions disrupted multiple distal epitopes targeted by HIV-1-specific monoclonal antibodies, suggesting that escape from maternal NAbs occurred through conformational masking of distal epitopes. This strategy likely allows HIV-1 to utilize relatively limited changes in the envelope to preserve the ability to infect a new host while simultaneously evading multiple NAb specificities present in maternal plasma.