

# Broadly Neutralizing Antibodies Antagonize Diverse HIV-1 Subtypes

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GMR Deyter

HIV-1 continues to wreak havoc on human health worldwide. One of the reasons why the spread of HIV-1 is so difficult to contain has been the inability to generate a vaccine against HIV-1. Although neutralizing antibodies are a common feature of successful vaccines against other pathogens, antibodies that effectively target HIV-1 have proven difficult to elicit. Firstly, multiple HIV-1 subtypes exist that produce subtly different proteins, so epitopes that an antibody recognizes in one strain may be absent from another strain. Secondly, the HIV-1 genome changes rapidly during replication. These genomic changes produce viral proteins that escape the human immune response and propagate the infection.

However, broadly neutralizing antibodies (bNAbs) have been discovered and they can protect in passive immunization and challenge studies in non-human primates. The bNAbs identified to date target diverse epitopes, especially on the HIV-1 envelope glycoprotein called Env, and they can control the spread of many HIV-1 subtypes. The immunogens recognized by the bNAbs, then, might be useful agents in the development of an HIV-1 vaccine.

HIV is endemic to sub-Saharan Africa populations, where a significant percentage of new infections are caused by mother-to-child transmission (MTCT). In order to gain further insight on the protective value of bNAbs, Dr. Julie Overbaugh's lab studied the ability of a panel of bNAbs to neutralize several HIV-1 subtypes during MTCT. The envelope variants (envs) tested in this study were obtained from mothers and infants enrolled in the Nairobi breastfeeding clinical trial, and Dr. Ruth Nduati from the University of Nairobi contributed to the research.

Although previous studies had revealed that neutralizing antibodies protect against select subtype B HIV-1 infection, Mabuka and colleagues wondered whether bNAbs might help prevent MTCT of the major global HIV-1 variants including subtypes A, C and D that are prevalent in Africa. The authors analyzed the ability of seven newly identified bNAbs to neutralize a total of 107 envs. Their work revealed that all variants were neutralized by at least two of the bNAbs and several were sensitive to six of the seven bNAbs tested. However, their assays revealed similar sensitivities of the viruses

transmitted to infants (acute infection) to bNAbs compared to variants from their infected mothers (chronic infection). Thus, on average, infant variants were not more resistant to the bNAbs than maternal variants.

Additional analyses by Mabuka *et al.* showed that bNAbs were more effective at neutralizing viruses from non-transmitting mothers than transmitting mothers. Also, the mode by which HIV-1 is transmitted appears to be sensitive to specific bNAbs: two of the seven bNAbs tested were more effective at neutralizing MTCT variants compared to variants from acute heterosexual transmission (newly infected women).

The researchers also examined the ability of the bNAbs to neutralize different subtypes of HIV-1. They found that bNAbs that target the CD4 binding site of env showed more neutralization activity against subtype A variants versus variants C and D. Moreover, nonsubtype A variants and especially subtype C appeared to be more sensitive to bNAbs that target one of the variable regions of env that exists outside of the CD4 binding region.

The work performed by Mabuka and colleagues has revealed that diverse HIV-1 variants can be neutralized when bNAbs are combined to target independent epitopes of env. This type of bNAbs-promoted neutralization is not limited to chronic infection but can also influence acute infection given their activity against infant HIV-1 variants. This research highlights the importance of using multiple bNAbs to limit the spread of HIV-1, and offers clues to how an effective HIV-1 vaccine might be generated by targeting multiple critical epitopes on HIV-1 env.

[Mabuka J, Goo L, Omenda MM, Nduati R, Overbaugh J.](#) 2013. HIV-1 maternal and infant variants show similar sensitivity to broadly neutralizing antibodies, but sensitivity varies by subtype. *AIDS*. Jun 19;27(10):1535-44.



Dr. Julie Overbaugh

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