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Lessons from babies: inducing HIV-1 broadly neutralizing antibodies

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Abstract

A new study in infants shows that broadly neutralizing antibodies (bNAbs) against HIV can be found early in life, demonstrating for the first time that these antibodies can be induced by the infant immune system.

Subject terms

Antibodies; HIV infections

HIV-1 bNAbs are generated in the HIV-1–positive population in a continuum of potency and breadth. In general, these responses appear late, usually between the second and fourth years after infection. Work in infected adults has helped to define the pathway that orchestrates induction of bNAbs in individuals where both the virus and B cell responses can be studied from the time of transmission to the presence of bNAbs^{1, 2}. These studies have been done only in adults, and although they have uncovered conserved targets on the HIV-1 envelope for neutralization breadth, unidentified envelope neutralization targets may still exist, and multiple neutralizing antibody specificities that are not yet known may also be involved. Identifying HIV-infected patients and cohorts with substantial neutralization breadth and potentially new neutralization targets is important in defining new immunogen designs for vaccine-mediated induction of bNAbs. Recent studies have demonstrated the interplay between virus evolution and antibody maturation leading to the development of bNAbs^{1, 3} and have provided new insights on how B cell–lineage vaccine strategies might be able to mimic these pathways toward the maturation of bNAbs⁴.

Although neutralization breadth has been extensively characterized in HIV-1–infected adults, it has been unknown whether infants, who usually have higher viral loads and can

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Competing financial interests

B.F.H. has the following patent applications relating to HIV-1 vaccine immunogen design: “Antibody Evolution Immunogens,” “Swarm Immunization with Envelopes from CH505,” “B Cell Lineage Design,” “Synthetic Env Proteins” and “Polyvalent Vaccine.”

progress to AIDS quickly, can also develop bNAbs. In this issue of *Nature Medicine*, Goo *et al.*⁵ show that a subset of the HIV-1–infected infants studied developed varying levels of bNAbs within the first 24 months of infection (Fig. 1). As bNAbs can develop early in life, the findings demonstrate that the neonatal naive B cell and T helper repertoires are equipped to respond to HIV-1 envelope in a manner that can induce broadly reactive anti-HIV neutralizing antibodies.

The authors measured the neutralization breadth of antibodies in plasma samples collected at least after 12 months of birth from 28 HIV-1–infected infants from the Nairobi Breastfeeding Trial who were infected with clade A, C or D viruses either *in utero*, during delivery or via breastfeeding⁵. Maternally derived antibodies waned within the first 3 months of infection and predominantly targeted easy-to-neutralize viruses. Subsequent development of *de novo* cross-clade responses arose in some the infants by ~1 year after infection, with continued development of neutralization breadth in some infants by 20 months after transmission. Envelope-specific binding responses and viral load set point correlated with broad neutralization, consistent with a previous report in adults⁴ and suggesting that the high viral load found in HIV-infected infants may contribute to bNAb maturation.

Although only a small fraction of HIV-1–infected adults have broad and potent neutralization breadth, the overall neutralizing antibody response is a continuum, with many more infected individuals having some level of bNAbs than previously thought⁶. Single epitope specificities can be attributed to neutralization breadth in some individuals; however, other studies suggest the involvement of multiple specificities^{7, 8, 9, 10}. Goo *et al.*⁵ tested the known neutralization targets, the CD4 binding site, glycan-dependent V1–V2, glycan-dependent V3 and the membrane-proximal external region, using both experimental mapping and computational approaches¹¹ for defining neutralizing epitope specificities. However, no known bNAb epitope specificity could be ascribed to the infant plasma neutralization breadth, indicating that either a new neutralization target was involved or that multiple antibody specificities were contributing to the neutralization breadth. Indeed, recent studies have identified additional epitope targets for bNAbs involving the gp120 and gp41 regions in the native envelope spike^{12, 13, 14} that could be considered for measurement in follow-up studies to epitope map neutralization breadth in HIV-1–infected infants.

One path toward an efficacious HIV-1 vaccine strategy is the induction of antibodies that can neutralize a diverse range of circulating viruses in a population. In adults, the development of neutralizing antibodies has been reported to take 2–4 years after virus transmission¹⁵, and these antibodies are associated with unique characteristics such as high levels of somatic mutation¹⁶, long complementarity-determining region H3 (CDRH3) and polyreactivity and/or autoreactivity, among others¹⁷. The high level of somatic mutation and rare CDRH3 length is a formidable challenge for developing an HIV-1 vaccine based on bNAbs, as the goal is to generate bNAbs as soon as possible after vaccination and with the minimum number of immunizations possible. The findings in infants, taken together with others from studies in adults^{1, 18}, suggest that in some individuals, development of bNAbs can arise within the first 2 years, suggesting that there might be shorter pathways toward the development of bNAbs. The study by Goo *et al.*⁵ highlights how tracking the existence and

development of neutralizing antibodies in infants could provide insights into what hopefully will turn out to be new bNAb targets, thus potentially increasing the repertoire of potential bNAbs for vaccine development.

The time of development of bNAbs in infants⁵ is coincident with some studies on the earliest time of bNAb development reported for adults^{1, 18}. Whether induction of neutralization breadth is more commonly elicited earlier in infants than in adults was not rigorously addressed in this study, but the study by Goo *et al.*⁵ does raise this possibility. Additional side-by-side studies with larger numbers of patients would be needed to directly address how different the timing of neutralization breadth and potency is between adults and infants. However, this will be difficult to do because of the decline in perinatal HIV-1 transmission as a result of implementation of numerous prevention strategies and improved treatment interventions for infected infants.

Nonetheless, the demonstration by Goo *et al.*⁵ that infants can make bNAbs leads to a proof of concept for immunization of infants in that these responses can be generated early in life. Determining whether there is a benefit for infant vaccination over vaccination in adolescence or adulthood for the induction of bNAbs awaits the development of an immunization regimen that can safely induce bNAbs. This study at the very least proposes that successful infant vaccination against HIV-1 is plausible by demonstrating that the infant immune system is capable of generating the highly sought-after bNAbs.

These findings raise several questions regarding how bNAbs develop in infants. Do evolving virus quasispecies with sequential ‘sweeps’ of viruses drive bNAb development in neonates, as has been described in adults¹? Are bNAbs that develop in infants generated against different and perhaps new targets compared to those from adults? Are infant bNAbs polyreactive as in adults¹⁷? Finally, it remains unclear whether infant bNAbs are as highly mutated as adult ones, and if so, whether this somatic hypermutation in response to HIV-1 early in life occurs more rapidly than in adults.

Answering these questions to determine whether the infant immune system is uniquely poised to respond to HIV-1 compared to that of adults can further our understanding as to whether infant immunization would be better than immunization of adults in generating bNAbs—a key step in learning how to protect infants from HIV-1 transmission. Certainly, it is exciting to consider that understanding the ontogeny and specificity of bNAbs in the context of both the infant B and helper T cell repertoires may provide new insights into practical vaccination strategies toward induction of plasma neutralization breadth in all vaccinated individuals.

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Figure 1. Timing and class of bNAbs induced in HIV-1-infected infants

Initially after HIV transmission, there is limited or no *de novo* antibody neutralization of heterologous viruses; instead, antibody responses seem to be predominantly restricted to neutralization of maternally transmitted virus. Goo *et al.*⁵ now show that the infant antibody response can mature over time early in life to broadly neutralize multiple HIV-1 clades, demonstrating the infant B cell repertoire is capable of responding to HIV-1 antigens and generating cross-reactive neutralizing antibodies.

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