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VIEWPOINT

Broadly neutralizing antibodies, nonneutralizing antibodies and broadly effector antibodies to prevent HIV transmission?

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Broadly neutralizing antibodies (bNAbs), which are able to recognize a diversity of global strains, are an attractive prospect of HIV prevention. While less effective in the presence of a massive viral inoculum, HIV neutralizing antibodies can be exquisitely effective as a first-line block in the case of repeated, low-dose viral exposure, as is the case with transmission through breastfeeding [1]. The establishment of a cellular HIV reservoir occurs within a few days of infection and this short period postinfection represents a narrow window of opportunity for antibodies to protect against HIV persistence or at least to control the viral replication. It has been well demonstrated in a macaque simian/human immunodeficiency virus (SHIV) model, that a passive infusion of neutralizing immunoglobulin G (IgG) 6 h after systemic viral challenge protected three out of four animals, whereas an infusion 24 h after infection did not [2]. Using a similar nonhuman primate model, subsequent administration of neutralizing antibodies with infusions approximately 1 week after viral challenge functionally enhance cognate T-cell responses in several ways, most likely in an Fc-dependent manner, and confer long-lasting SIV/SHIV replication control [3,4].

Although not fully understood, viral neutralization mediated by the fragment antigen-binding (Fab) region of neutralizing antibodies results from inhibition of viral attachment to host cells, fusion, or both [5]. However, other first-line antiviral mechanisms engaging innate immune response exist, involving interactions of the fragment crystallizable (Fc) region of antibodies with various forms of Fc receptors on the host cell surface [6], and these functions are relatively less studied than neutralization. HIV-infected cells opsonized by antibodies can be recognized by FcγRIII (CD16) and destroyed by natural killer (NK) cells in a mechanism known as antibody-dependent cellular cytotoxicity (ADCC) [7]. Macrophages and other phagocytes can engage in antibody-dependent cellular phagocytosis (ADCP) by recognizing opsonized viral particles via FcγRI (CD64) and FcγRIIA (CD32) receptors, leading to lysis of viral particles and downstream antigen presentation of viral antigens at the cell surface [5]. Antibody-dependent complement-mediated lysis (ADCML) occurs when the Fc region of an antibody on the virion and/or cell surface activates the classical complement pathway starting with the complement complex C1q, resulting in lysis of viral

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particles or infected cells through the formation of a membrane attack complex at the cell surface. Other Fc-mediated effector functions of antiviral antibodies include trogocytosis, epitope unmasking and intracellular neutralization [6]. After infection with HIV, children mount a cross-reactive neutralizing response faster and more frequently than adults, and nonprogressor children living with HIV have antibodies that elicit a strong Fc-mediated, NK-associated response and a distinct Fc glycosylation pattern [8].

These Fc-mediated effector functions, capable of eliminating HIV-infected cells and virions, have been described in both neutralizing and nonneutralizing antibodies (nNAbs). In several viral models, Fc-mediated effector functions complement Fab neutralization, and in some cases, protection can be conferred in the absence of Fab neutralization [6]. Passive immunoprophylaxis with nNAbs protects against certain viral infections. In a pioneering experimental study – followed by several others involving other viral models including in SARS-CoV2 [6] –, a monoclonal nNAb directed against the E1 glycoprotein of the Sindbis virus was completely protective in a murine model [9]. After controlling for Env specific IgA antibodies, Fc-mediated functions of non-neutralizing antibodies were associated with the modest protective efficacy of the RV 144 HIV-1 vaccine observed in clinical trials [10]. Nonetheless, viral neutralization and Fc-mediated effector functions are not mutually exclusive, and several HIV bNAbs developed to date also display varying degrees of Fc-mediated effector functions [11]. bNAbs are capable of providing sterilizing immunity against HIV through Fab-mediated neutralization. Using the Fc receptor-binding deficient LALA (L234A/L235A) bNAb variant, which abolishes ADCC and phagocytosis, or the DEL (S239D/A330L/I332E) bNAb variant, which enhances ADCC and phagocytosis, it is possible to decipher the respective roles of Fab- and Fc-mediated antiviral activity of HIV bNAbs [12–14]. For some bNAbs, up to 50% of the antiviral efficacy in reducing HIV viral load is lost upon ablation of FcR binding activity [12,13]. Furthermore, for some bNAbs, such as VRC07-523LS, antiviral efficacy associated with Fc-mediated effector function is obtained at lower concentrations than Fab-mediated neutralization [13]. As direct neutralization does not fully explain the antiviral activity of the currently named bNAbs – nor is it a reasonable proxy – we propose to redefine bNAbs as antibodies having only broad spectrum Fab-mediated neutralizing properties, to define nNAbs as antibodies having only Fc-mediated properties and to more appropriately rename antibodies with both Fab- and Fc-mediated properties as broadly effector antibodies (bEAbs).

The Fc-mediated functions of nNAbs and bEAbs are particularly attractive as a means of blocking cell-to-cell transfer in the context of viruses evading neutralization, through multiple mechanisms. Cell-associated virus may be responsible for up to 40% of sexually transmitted HIV infections [15]. However, cell-cell transmission is probably of greatest relevance in vertical transmission through breastfeeding [16,17]. In an observational study of breast milk samples from women living with HIV with high HIV plasma viral loads, neutralizing antibodies were detected in only a minority (4 out of 19 samples) of the breast milk samples, while all had antibodies that mediated ADCC. Furthermore, ADCC activity in milk was inversely correlated with transmission risk, suggesting that a strong ADCC response in breast milk – but also in the infant's mucosal sites – is at least as important as neutralization [18]. Newborn macaques were experimentally fully protected against repeated, twice-weekly oral exposure to $SHIV_{SF162P3}$ by subcutaneous injections of PGT121-LS alone or in combination with VRC07-523LS, both antibodies with strong Fab-mediated neutralization functions and Fc-mediated properties against HIV-infected cells [19]. Intermittent dosing with a small volume of long-acting bEAbs administered subcutaneously to neonates and breastfed infants, together with limited or no toxicity, makes passive immune prophylaxis of vertical HIV transmission through breastfeeding one of the most promising indications for the use of bEAbs in humans [20,21]. This strategy may be particularly appropriate given that vertical transmission of HIV (mainly through breastfeeding) has not been eliminated, despite international efforts, and the number of new HIV infections in children per year has plateaued over the past decade (on average 150 000 new infections per year) [22].

Beside their potential application for HIV-1 prevention, currently named bNAbs are also promising as therapeutics. As an example, a recent report of a phase 1/2a trial shows that a triple combination of bEAbs (PGT121, PGDM1400 and VRC07-523LS) administered intravenously to adults with HIV is safe and, in some individuals, enables prolonged viral control [23]. In the development of new therapeutic/prophylactic antibodies, both neutralizing and nonneutralizing antibodies with Fc-mediated effector functions should be targeted [8]. Opportunities should be exploited to modulate currently named HIV bNABs for enhanced Fc-mediated functions by harnessing isotypes and allelic diversity. This could enable enhancement of the antiviral role of these antibodies, including elicitation of diverse inductor and effector sites of the mucosal immune system [24] Prophylactic anti-HIV antibodies to be investigated should be carefully selected according to the candidate's property profile and the known route-specific transmission mechanisms. bNAbs – or bEAbs – candidates for passive immune prophylaxis of HIV transmission during breastfeeding should be carefully selected among those with the strongest Fc-mediated properties (ADCC, ADCP) [11]. In phase 1 and phase 2 trials of these selected antibodies, the ability of these antibodies to mediate ADCC and ADCP should be monitored in addition to their Fab mediated neutralizing capacity.

Similarly, efforts to define correlates of protection should extend beyond the current focus on neutralization, as it is currently not known at what minimal Ab concentration ADCC and ADCP may protect and how persistent the responses are. Harnessing the full potential of multifunctional HIV antibodies such as bEAbs for HIV prevention may help to provide important insights into the protective efficacy of Fab- versus Fc-mediated functions and correlates of protection. Lessons can also be learned for the prevention of the many other viral infections that are amenable to passive immunoprophylaxis and immunotherapy with immunoglobulins.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Lewis GK. **The first 24 h: targeting the window of opportunity for antibody-mediated protection against HIV-1 transmission.** *Curr Opin HIV AIDS* 2016; **11**:561–568.
2. Nishimura Y, Igarashi T, Haigwood NL, Sadjadpour R, Donau OK, Buckler C, *et al*. **Transfer of neutralizing IgG to macaques 6 h but not 24 h after SHIV infection confers sterilizing protection: implications for HIV-1 vaccine development.** *Proc Natl Acad Sci USA* 2003; **100**:15131–15136.
3. Iseda S, Takahashi N, Poplimont H, Nomura T, Seki S, Nakane T, *et al*. **Biphasic CD8+ T-cell defense in simian immunodeficiency virus control by acute-phase passive neutralizing antibody immunization.** *J Virol* 2016; **90**:6276–6290.
4. Nishimura Y, Gautam R, Chun TW, Sadjadpour R, Foulds KE, Shingai M, *et al*. **Early antibody therapy can induce long-lasting immunity to SHIV.** *Nature* 2017; **543**:559–563.
5. Hessell AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, *et al*. **Fc receptor but not complement binding is important in antibody protection against HIV.** *Nature* 2007; **449**:101–104.
6. Chandler TL, Yang A, Otero CE, Permar SR, Caddy SL. **Protective mechanisms of nonneutralizing antiviral antibodies.** *PLoS Pathog* 2023; **19**:e1011670.
7. Bruel T, Guivel-Benhassine F, Amraoui S, Malbec M, Richard L, Bourdic K, *et al*. **Elimination of HIV-1-infected cells by broadly neutralizing antibodies.** *Nat Commun* 2016; **7**:10844.
8. Muenchhoff M, Chung AW, Roider J, Dugast AS, Richardson S, Kløverpris H, *et al*. **Distinct immunoglobulin Fc glycosylation patterns are associated with disease nonprogression and broadly neutralizing antibody responses in children with HIV infection.** *mSphere* 2020; **5**:e00880-20.
9. Schmaljohn AL, Johnson ED, Dalrymple JM, Cole GA. **Non-neutralizing monoclonal antibodies can prevent lethal alphavirus encephalitis.** *Nature* 1982; **297**:70–72.
10. Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM, *et al*. **Immune-correlates analysis of an HIV-1 vaccine efficacy trial.** *N Engl J Med* 2012; **366**:1275–1286.
11. Rossignol ED, Dugast AS, Compere H, Cottrell CA, Copps J, Lin S, *et al*. **Mining HIV controllers for broad and functional antibodies to recognize and eliminate HIV-infected cells.** *Cell Rep* 2021; **35**:109167.
12. Parsons MS, Chung AW, Kent SJ. **Importance of Fc-mediated functions of anti-HIV-1 broadly neutralizing antibodies.** *Retrovirology* 2018; **15**:58.
13. Asokan M, Dias J, Liu C, Maximova A, Ernste K, Pegu A, *et al*. **Fc-mediated effector function contributes to the in vivo antiviral effect of an HIV neutralizing antibody.** *Proc Natl Acad Sci USA* 2020; **117**:18754–18763.
14. Sips M, Krykbaeva M, Diefenbach TJ, Ghebremichael M, Bowman BA, Dugast AS, *et al*. **Fc receptor-mediated phagocytosis in tissues as a potent mechanism for preventive and therapeutic HIV vaccine strategies.** *Mucosal Immunol* 2016; **9**:1584–1595.
15. Zhu T, Wang N, Carr A, Nam DS, Moor-Jankowski R, Cooper DA, Ho DD. **Genetic characterization of human immunodeficiency virus type 1 in blood and genital secretions: evidence for viral compartmentalization and selection during sexual transmission.** *J Virol* 1996; **70**:3098–3107.
16. Becquart P, Petitjean G, Tabaa YA, Valéa D, Huguet MF, Tuaillon E, *et al*. **Detection of a large T-cell reservoir able to replicate HIV-1 actively in breast milk.** *AIDS* 2006; **20**:1453–1455.
17. Van de Perre P, Rubbo PA, Viljoen J, Nagot N, Tylleskär T, Lepage P, *et al*. **HIV-1 reservoirs in breast milk and challenges to elimination of breast-feeding transmission of HIV-1.** *Sci Transl Med* 2012; **4**:143sr3.
18. Mabuka J, Nduati R, Odem-Davis K, Peterson D, Overbaugh J. **HIV-specific antibodies capable of ADCC are common in breastmilk and are associated with reduced risk of transmission in women with high viral loads.** *PLoS Pathog* 2012; **8**: e1002739.
19. Rosenberg YJ, Jiang X, Cheever T, Coulter FJ, Pandey S, Sack M, *et al*. **Protection of newborn macaques by plant-derived HIV broadly neutralizing antibodies: a model for passive immunotherapy during breastfeeding.** *J Virol* 2021; **95**:e0026821.
20. Van de Perre P, Goga A, Ngandu N, Nagot N, Moodley D, King R, *et al*. **Eliminating postnatal HIV transmission in high incidence areas: need for complementary biomedical interventions.** *Lancet* 2021; **397**:1316–1324.
21. Van de Perre P, Scarlatti G, Moore PL, Molès JP, Nagot N, Tylleskär T, *et al*. **Preventing breast milk HIV transmission using broadly neutralizing monoclonal antibodies: One size does not fit all.** *Immun Inflamm Dis* 2024; **12**:e1216.
22. UNAIDS. The path that ends. UNAIDS global AIDS update. 2023. Available at: https://thepath.unaids.org.
23. Julg B, Walker-Sperling VEK, Wagh K, Aid M, Stephenson KE, Zash R, *et al*. **Safety and antiviral effect of a triple combination of HIV-1 broadly neutralizing antibodies: a phase 1/2a trial.** *Nat Med* 2024; **30**:3534–3543.
24. Brandtzaeg P. **The mucosal immune system and its integration with the mammary glands.** *J Pediatr* 2010; **156**:S8–S15.