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The Use of Broadly Neutralizing Antibodies (BnAbs) for HIV-1 Treatment

Abstract:

Background: Known as "the plague of the 21st century", HIV-1 remains a major global health issue. Thus far, researchers have unsuccessfully been working on a sterilizing cure. Nonetheless, antiretroviral therapy, ART, has managed to effectively suppress viral load to undetectable levels, allowing it to be untransmittable. However, factors such as the daily- and life-long need for medication in ART, adherence, drug-resistance, social stigma and the increasing criminalization of same-sex relations contributes to the need for a longer-lasting, more potent therapeutic approach. Additionally, ART is not able to eradicate the virus completely, and thus viral rebound occurs within a few weeks of ART-cessation. Broadly Neutralizing Antibodies are therefore of interest as studies have shown that they provide sterilizing protection in nonhuman primates. Here, we sought to investigate the use and efficacy of BnAbs for HIV-treatment in humans – in order to determine whether they could be used as an alternative or adjuvant to ART.

Methods: A comprehensive literature search of recent clinical trials (in various phases) investigating the clinical effects of different BnAbs were compared to the effects of ART in humans – including mono- and combination-therapy with either solely BnAbs or BnAbs with latency-reversing agents.

Results: Recent clinical trials in humans indicate that monotherapy with BnAbs does not have sufficient breadth to prevent viral rebound nor the occurrence of antibody-resistant HIV-1 viruses, thus suggesting a potential benefit of combination-therapy. Combination-therapy of BnAbs shows greater efficacy compared to ART and monotherapy in both viral suppression and delaying viral rebound, especially in patients with antibody-sensitive HIV-1 strains.

Conclusion: BnAbs offer a more potent and durable suppression of viral load compared to ART. Thus, BnAbs in combination-therapy do hold certain advantages over current ART, although complete eradication of latent reservoirs using BnAbs have not been achieved in clinical trial as of yet. The main reasoning for using BnAbs would be its potential for a sterilizing cure of HIV-1, which is one of the major shortcomings of current ART. Therefore, further studies are needed to determine the optimal use of BnAbs in HIV-1 treatment.

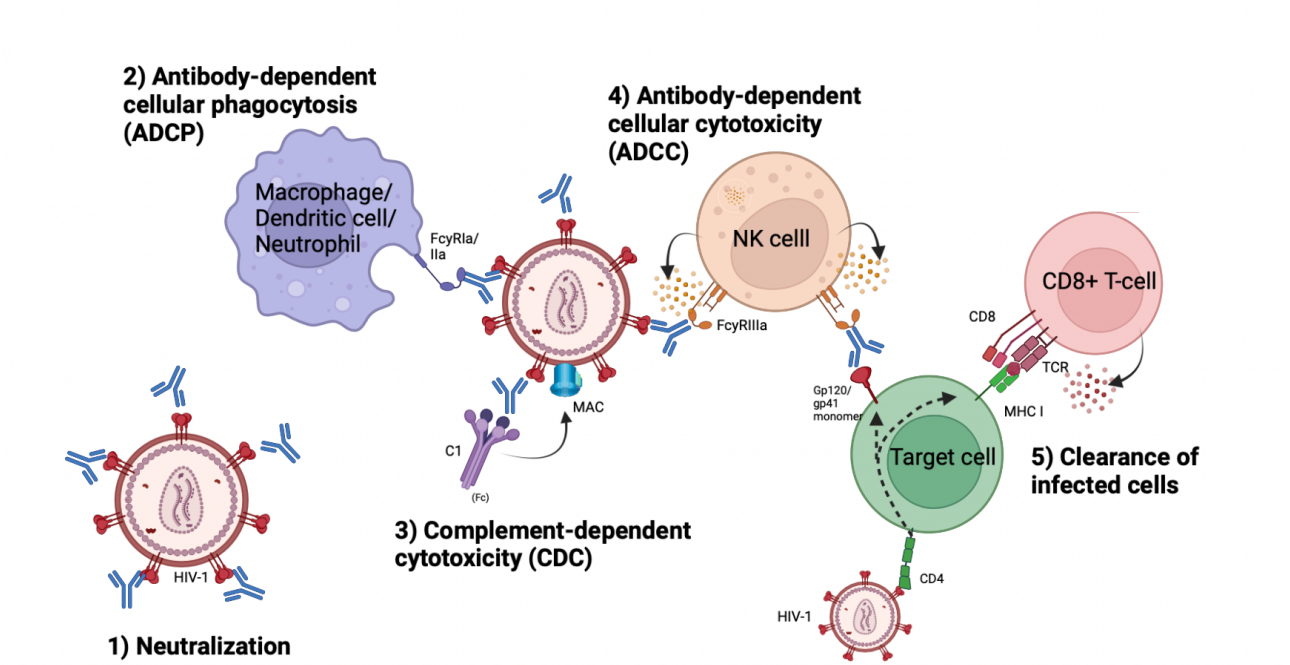

Figure 1: Effector functions of broadly neutralizing antibodies. The main function of antibodies includes their ability to neutralize the virus. The effector functions of antibodies mediated through their Fc-region leads to ADCC, ADCP, CDC and potentially clearance of infected target-cells. Antibodies can interact with macrophages and neutrophiles through FcγRIa and FcγRIIa, which leads to ADCP (antibody-dependent cellular phagocytosis), and with NK-cells and CD8+ T-lymphocytes through FcγRIIIa, leading to ADCC (antibody-dependent cellular cytotoxicity). In addition, antibodies can mediate activation of the classical complement pathway leading to CDC (complement-dependent cytotoxicity). Lastly, clearance of HIV-1 infected cells is enhanced by BnAbs by NK cells or macrophages/neutrophiles. ADCC-mediated clearing is depicted in fig. 1, meanwhile ADCP- and CDC-mediated clearing of infected cells is not depicted but are nonetheless equally important effector-functions.

** The figure is made in "BioRender" and inspired by figure 1 from Phelps et al.'s "Contribution to HIV Prevention and Treatment by Antibody-Mediated Effector Function and Advances in Broadly Neutralizing Antibody Delivery by Vectored Immunoprophylaxis" with additional effects of BnAbs added.