SARS-CoV-2 and HIV-1 — a tale of two vaccines

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The rapid development of COVID-19 vaccines and their deployment in less than a year is a scientific and medical triumph that has raised a key question. Why do we have several SARS-CoV-2 vaccines but do not have a single HIV-1 vaccine?

Vaccines are the major preventive tool for infectious diseases and their use improves survival rates, protects communities from emerging infectious agents and promotes societal productivity. A major component of vaccine-induced protective immunity for most viral infections is neutralizing antibodies, although non-neutralizing antibodies and $CD8^+$ T cells can add to vaccine protective efficacy. In December 2019, the WHO was notified of a cluster of viral pneumonia of unknown origin, and the first draft genome of the causative virus, SARS-CoV-2, was published in January 2020. By the end of 2020, several SARS-CoV-2 vaccines had been developed. Two of these were shown to be ~95% effective in preventing symptomatic COVID-19 in phase III efficacy trials and received approval by the FDA for deployment under Emergency Use Authorization before the end of the year. By contrast, four decades ago, in the summer of 1981, the first individuals with what would be known as acquired immunodeficiency syndrome (AIDS) were described, and, in 1983, the aetiological agent of AIDS, HIV-1, was isolated — yet, we still do not have a globally protective HIV-1 vaccine. A critical question is "Why was the SARS-CoV-2 vaccine made so quickly and the HIV-1 vaccine has been so difficult to make"? The answer lies in the immunobiology of the interactions of the viruses with their hosts.

HIV-1, a member of the *Retroviridae* virus family, and SARS-CoV-2, a coronavirus of the subgenus Sarbecovirus, are positive-sense single-stranded RNA viruses. A major difference between SARS-CoV-2 and HIV-1, however, is that a majority of individuals infected with SARS-CoV-2 clear the virus, while those with HIV-1 do not[1]. This is because SARS-CoV-2 is a slowly mutating, non-integrating virus, and the host can rely on a vaccine-primed secondary immune response to clear SARS-CoV-2-infected cells. By contrast, HIV-1 integrates into the host genome within ~72 hours of transmission. By the time a vaccine-primed secondary immune response to HIV-1 develops, an irreversible infection has occurred, with a latently infected $CD4^+$ T cell reservoir established with incorporated proviral double-stranded DNA. Thus, for a successful HIV-1 vaccine, high levels of protective neutralizing antibodies must be present at the time of transmission to completely prevent infection — which presents a very high bar[2].

The target of neutralizing antibodies to SARS-CoV-2 is the receptor-binding domain (RBD) of the spike (S) glycoprotein, whereas the target of HIV-1-neutralizing antibodies is the envelope (Env) glycoprotein. Both types of neutralizing antibody block the binding of virions to their receptors — angiotensin-converting enzyme 2 for SARS-CoV-2, and the CD4 molecule for HIV-1. All COVID-19 vaccines tested in phase III induced neutralizing antibodies targeted at the S protein and are highly protective from symptomatic disease. In monkeys, the correlates of protection are primarily neutralizing antibodies[3]. Traditional prime or prime and boost vaccine regimens with S glycoprotein immunogens have been extremely successful as COVID-19 vaccines (FIG. 1). Prior work on Middle Eastern respiratory syndrome spike protein[4], on modified mRNA encased in lipid nanoparticles[5], and on platforms and techniques from HIV-1 vaccine research[6] all enabled rapid COVID-19 vaccine development.

For HIV-1, two general strategies have been tested in vaccine efficacy trials: the induction of $CD8^+$ T cells that kill HIV-1-infected cells, and the induction of non-neutralizing antibodies that protect from HIV-1 transmission by Fc receptor-γ (FcRγ)-mediated antiviral effector functions. Like SARS-CoV-2-neutralizing antibodies, HIV-1 non-neutralizing antibodies are easily induced by any of a number of HIV-1 Env monomers or open trimers. However, out of seven HIV-1 vaccine efficacy trials carried out to date, six have failed. The seventh, called RV144, which was carried out in Thailand by the US Army, showed minimal protection of ~31%, and non-neutralizing antibodies with FcRγ-mediated antiviral effector functions served as correlates of decreased transmission risk[7]. Two additional efficacy trials targeted at inducing protective non-neutralizing Env-targeted antibodies and T cell responses are ongoing, with the hope that these will show a degree of protection.

Nonetheless, the ultimate aim of HIV-1 vaccine development is induction of broadly neutralizing antibodies (bnAbs)[8]. Whereas SARS-CoV-2-neutralizing antibodies are easily induced within ~10 days of onset of COVID-19

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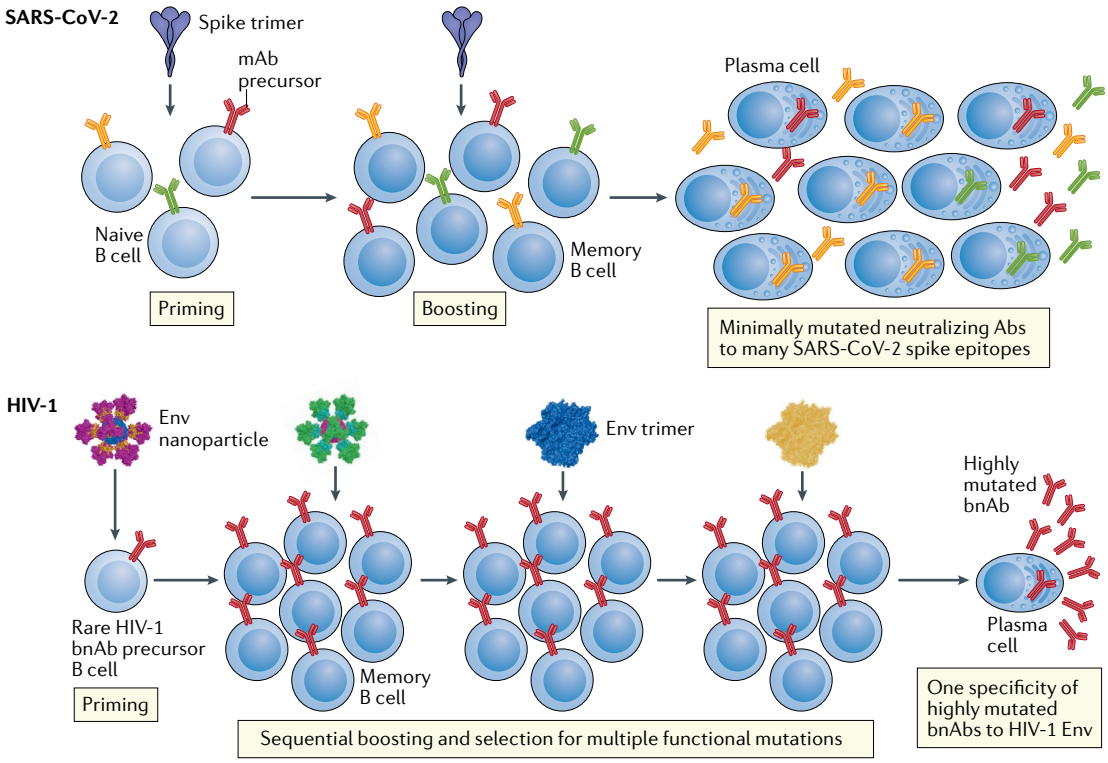

Fig. 1 | **Vaccine development for SARS-CoV-2 and HIV-1.** Ab, antibody; bnAb, broadly neutralizing antibody.

symptoms and within 2 weeks of vaccination, HIV-1 bnAbs are not readily induced by vaccination, nor in infection, and only occur at very high levels in ~10% of individuals infected with HIV-1 after years of infection. Roadblocks for the induction of HIV-1 bnAbs are the presence of a dense and poorly immunogenic Env glycan shield, molecular mimicry of Env epitopes that induce cross-reaction of antibodies with human proteins, and variable loop regions in Env that can induce competing non-protective antibodies. Most importantly, HIV-1 bnAbs have unusual traits such as autoreactivity, long third heavy chain complementary determining regions (HCDR3s) and are enriched in rare somatic mutations — all of which make bnAb precursors either very rare owing to immune tolerance deletion or difficult to activate[9,10].

These unusual traits of HIV-1 bnAbs have necessitated a strategy for HIV-1 vaccine design of first targeting rare naive B cell precursors of bnAbs, to expand the bnAb precursor pool. Next, sequential Env trimers are having to be specifically designed to select for intermediate bnAb B cell lineage members to have rare antibody mutations that are required for bnAb maturation[8–10] (FIG. 1). In addition, to avoid HIV-1 founder virus escape, a successful HIV-1 vaccine will need to induce B cell lineages to several of the seven bnAb binding sites on HIV-1 Env. The significance of successful germline-targeting and sequential HIV-1 immunogen design goes beyond making the long-awaited HIV-1 vaccine. Learning the rules for safely guiding bnAb B cell lineages should improve the development of other difficult-to-make vaccines, and also hold lessons with regard to avoiding undesired immune responses such as the development of pathogenic autoantibodies.

The SARS-CoV-2 vaccine effort marshalled extraordinary resources and unprecedented global cooperation. The scientific and medical triumphs of COVID-19 vaccines are now inspiring a renewed sense of urgency for this most difficult HIV-1 vaccine development effort.

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Competing interests
B.F.H. has patents submitted and pending on coronavirus spike protein designs, composition and methods for their use (US patent nos 63/147,998; 63/149,541; 63/167,390), compositions comprising modified HIV envelopes (US patent PCT/US2018/034,772), and compositions comprising HIV envelopes to induce HIV antibodies (US patent provisional 62/739,701).