

## Countering HIV — Three’s the Charm?

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Antibodies have grown in importance as medicines over the more than 40 years since Köhler and Milstein first produced monoclonal constructs.<sup>1</sup> However, the ability of human immunodeficiency virus (HIV) type 1 (HIV-1) to evade the humoral immune response has until recently thwarted the effective use of antibodies in this important disease. The extraordinary plasticity of the HIV envelope allows exceptional antigenic diversity, leading to the rapid escape of the virus from most antibody responses.

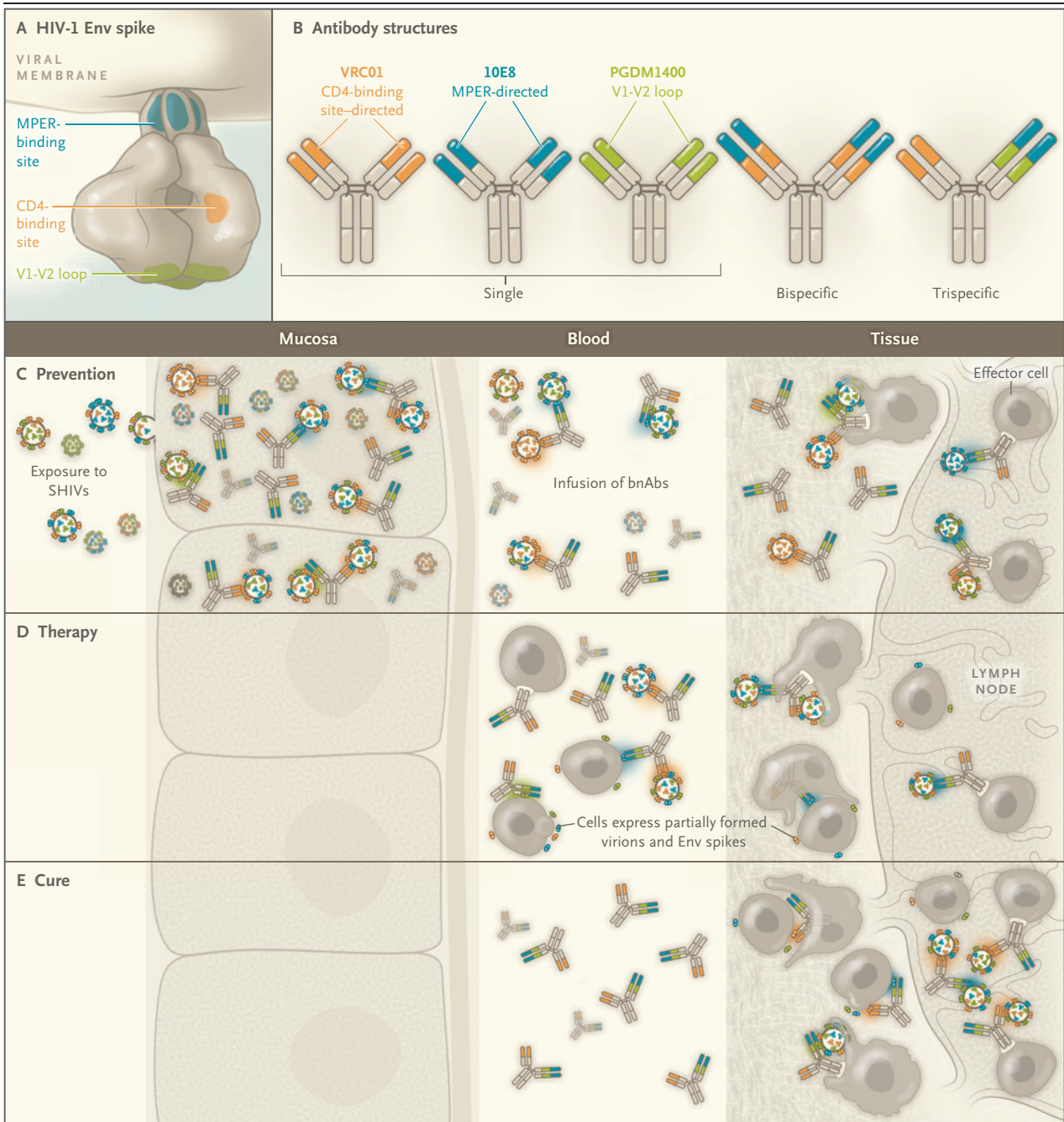
However, unique broadly neutralizing antibodies (bnAbs) can evolve over years in some HIV-infected people. These bnAbs can recognize a wide array of viral envelope sequences, and advances in high-throughput technologies have allowed the isolation and cloning of the genes encoding these rare antibodies.<sup>2</sup> Since these antibodies were identified, they have been intensively studied. They are thought to be akin to signposts, in the sense that they point to a path that might be followed by a future HIV vaccine strategy by means of the induction of bnAbs that are capable of preventing HIV infection.<sup>3</sup>

Despite the breadth and potency of bnAbs, no single bnAb has been able thus far to protect against the vast array of viral variants that are present in infected persons. However, the work recently reported by Xu and colleagues<sup>4</sup> represents an advance in the implementation of anti-HIV bnAbs. The investigators methodically created hybrid anti-HIV molecules containing at first two, and then three, broadly neutralizing domains that bind the HIV envelope (Env) protein (Fig. 1). Xu and colleagues found that a trispecific broadly neutralizing HIV antibody that encodes three bnAb domains — targeting the site within the HIV envelope that is used to bind the CD4 receptor, the membrane-proximal external region at the base of the envelope stalk, and the heavily

glycosylated V1 and V2 variable envelope loops — could mediate potent protection in macaques that were challenged with an infectious hybrid simian–human immunodeficiency virus (SHIV) with an HIV envelope gene.

There are several advantages, and some potential pitfalls, to this novel approach. A single entity is easier to test, produce, and implement than a mixture of three antibodies. Additional engineering of the triple antibody — the introduction of variants into the genic region encoding the Fc portion of the antibody — could augment its binding to the neonatal Fc receptor. High affinity is associated with a longer half-life. However, the engineered nature of these antibodies has a downside: over the course of weeks, the recipient’s immune system may treat this novel molecule as foreign and produce anti-antibodies that reduce the desired immunotherapeutic effect. If this risk does not prove to be limiting, the trispecific antibody could come to play an important role in grappling with the trifecta of unmet needs in the HIV pandemic: prevention, treatment, and cure.

Xu et al. modeled the use of bnAbs to prevent the acquisition of HIV-1 infection using a non-human primate model. Five days after the infusion of the trispecific bnAb into eight macaques, a mixture of SHIVs was introduced intrarectally. None of the primates became infected, in contrast to one quarter to one third of the animals that were given single bnAbs. In complementary work, Julg and colleagues<sup>5</sup> found that primates were fully protected from a challenge with a mix of two SHIV strains by the coadministration of two singly specific bnAbs, in which each virus was sensitive to one of the antibodies. Much work remains in order to examine bnAbs as prophylaxis in the face of different routes of HIV challenge and in different populations and to compare



**Figure 1. A Three-Pronged Attack against the Human Immunodeficiency Virus (HIV).**

Xu et al.<sup>4</sup> recently found that infusing nonhuman primates with a trispecific antibody prevented infection on exposure to a hybrid simian–human immunodeficiency virus (SHIV) with an HIV envelope gene. VRC01, PGDM1400, and 10E8 are potent antibodies that recognize different regions of the HIV envelope (Env) spike (Panel A) across a broad range of unique viral isolates. Their binding domains were combined into bispecific and trispecific antibodies (Panel B). Trispecific antibodies engage a broader range of viral particles than do monospecific and bispecific antibodies. They may also block infection more efficiently at mucosal surfaces and within deeper tissue (Panel C), neutralize a wider range of viral particles and cells in which the virus replicates (thus blocking viremia; Panel D), and identify persistently infected cells that have been induced to present antigen, allowing the clearance of these cells (Panel E). Xu et al. found that a trispecific broadly neutralizing antibody (bnAb) that encodes three bnAb domains targeting the site within the HIV envelope that is used to bind the CD4 receptor, the membrane-proximal external region (MPER) at the base of the Env stalk, and the heavily glycosylated V1 and V2 variable envelope loops could mediate potent protection in macaques that are challenged with the virus.

the relative success of this strategy with that of emerging long-acting antiretroviral drugs that are in development for the same purpose. Indeed, the first clinical trial of a single bnAb to prevent the acquisition of HIV is under way (ClinicalTrials.gov number, NCT02568215). It is conceivable that the two approaches might be used in combination.

Similarly, broadly active and long-acting antibodies may contribute to the deployment of long-acting antiretroviral therapy for the suppression of viremia in HIV-infected people, relieving the burden of adherence to a daily medication regimen in selected clinical situations. It may be more difficult for antibody therapy to totally contain viral replication once HIV infection is fully established, a situation that could allow antibody-escape mutations to develop over time. However, the availability of such bnAbs may contribute importantly to the long-acting armamentarium, which currently consists of only a handful of small-molecule drugs.

Finally, in the emerging field of HIV cure research, tools to clear persistently infected cells are widely sought. Again, broad and potent anti-Env antibodies that are capable of recognizing HIV-infected cells *in vivo* could direct effector cells to clear the latent reservoir, where viral

antigens may be intermittently expressed or revealed by specific HIV latency-reversing agents.<sup>6</sup> The ability of engineered antibodies to allow the simultaneous engagement of multiple epitopes is intriguing. In the case of the evasive HIV envelope, three may be the charm.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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