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Broadly Neutralizing Antibodies for HIV Prevention

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Abstract

In the last decade, over a dozen potent broadly neutralizing antibodies (bnAbs) to several HIV envelope protein epitopes have been identified, and their in vitro neutralization profiles have been defined. Many have demonstrated prevention efficacy in preclinical trials and favorable safety and pharmacokinetic profiles in early human clinical trials. The first human prevention efficacy trials using 10 sequential, every-two-month administrations of a single anti-HIV bnAb are anticipated to conclude in 2020. Combinations of complementary bnAbs and multi-specific bnAbs exhibit improved breadth and potency over most individual antibodies and are entering advanced clinical development. Genetic engineering of the Fc regions has markedly improved bnAb half-life, increased mucosal tissue concentrations of antibodies (especially in the genital tract), and enhanced immunomodulatory and Fc effector functionality, all of which improve antibodies' preventative and therapeutic potential. Human-derived monoclonal antibodies are likely to enter the realm of primary care prevention and therapy for viral infections in the near future.

INTRODUCTION

Human immunodeficiency virus (HIV) remains a catastrophic public health concern, with an estimated global prevalence of 37.9 million HIV-infected persons worldwide. The World Health Organization (WHO) estimates that there were 1.7 million new HIV infections, including 160,000 in infants, and 770,000 deaths due to HIV worldwide in 2018 (1). Sub-Saharan Africa is seeing a resurgence in HIV incidence among its adolescent and young women populations, and the United States has tolerated 40,000 to 45,000 new infections yearly, essentially unnoticed by the press or public because of the asymptomatic nature of HIV acquisition (2). The global effort toward 90–90–90 (percent of HIV-infected individuals diagnosed, treated, and virally suppressed) has not achieved the significant reduction in transmission on a population basis required for epidemic control, and there is a lack of evidence that this is doable even in the most wealthy societies with low burden of disease (3–6). The stigma of mental illness, intravenous drug use, and marginalized men who have sex with men (MSM) populations limits the capacity for prompt diagnosis and the ability to maintain long-term antiretroviral therapy (ART) adherence. Access to services following HIV diagnosis, triage into early care, and maintenance on ART to stop the onward transmission of this infection have not been fully realized; even the proposed plan to eliminate mother-to-child transmissions has not been achieved for structural, social, and biological reasons (3–8). Thus, a biomedical HIV prevention approach that exhibits sustained activity in vulnerable persons over an extended time period, that has a safety profile acceptable for healthy individuals, and that is less dependent on individual adherence for its effectiveness is still needed. Passive immunization with broadly neutralizing antibodies (bnAbs) may fill this gap in HIV prevention approaches (7, 9–14).

HISTORY OF ANTIBODIES FOR PREVENTION

Passive immunization with protective antibodies has a long history in the field of infectious disease. In 1890, von Behring and Kitasato reported the discovery of specific antibodies, "antitoxins" administered as animal serum, that protected against diphtheria toxin. Serum therapy reduced morbidity and mortality from many infections and prevented others (15). Success relied on accurate microbiological diagnosis and serum administration either before or very shortly after exposure; serum antibody therapy was rarely effective for treatment of chronic infection. Importantly, there were challenges with the systemic administration of large amounts of animal proteins in sera: up to half of patients experienced hypersensitivity or "serum sickness," lot-to-lot variability was high, and serum was expensive (16).

Antibody purification methods introduced by the 1930s reduced serum-associated toxicity, but the introduction of sulfonamides in 1935 marked the advent of the antibiotic era and the concomitant decline of serum therapy. Early in this transition, antibody-rich sera and antibiotics were used in combination and synergistic effects were noted; for example, sulfonamides made pneumococci more susceptible to antibody-dependent phagocytosis. But by the 1940s, with the introduction of beta-lactam antibiotics, serum therapy was eclipsed almost entirely by antibiotic therapy, which had the advantages of lower cost, greater lot consistency, simpler administration, higher safety, and broader coverage for treatment and prevention of most bacterial diseases (16).

Antibodies re-emerged as an important antiviral prophylactic just a few years later, in 1945, when immunoglobulin against hepatitis A prevented infection in multiple outbreaks. Since then, antibody-mediated prophylaxis has been used for hepatitis A and B, for rabies, and, in select (e.g., immunosuppressed) populations, for cytomegalovirus, varicella zoster virus, measles, vaccinia, and respiratory syncytial virus (17, 18).

Notably absent from this list is HIV, though not for lack of effort. In the 1980s, it was noted that HIV-seropositive mothers with high anti-HIV antibody titers were more likely to have

uninfected babies (19–22). Similarly, healthy HIV-infected individuals were noted to have high titers of antiviral neutralizing antibodies, in contrast to undetectable titers in patients with AIDS. In one study of nine AIDS patients given monthly infusions of hyperimmune plasma from healthy HIV-infected patients, five initially demonstrated an improved clinical course. Infusions were well tolerated, viral load decreased, and autologous antibody titers increased. However, these salutary effects of polyclonal immunoglobulin waned quickly (23).

Fortunately, the development of phage display—an advance for which George Smith and Gregory Winter shared the Nobel Prize in Chemistry in 2018—rendered the identification of monoclonal antibody (mAb) candidates from combinatorial libraries more feasible, leading to the isolation of the first fully human mAb, b12, from a donor who was HIV-infected but asymptomatic for six years (24). This was the first of four mAbs identified in the 1990s: b12 bound to the CD4 binding site (CD4bs) on gp120 envelope protein (Env); 2G12 bound to a glycan cluster (25); and 4E10 and 2F5 bound to the membrane-proximal external region (MPER) (26–28). The study of these mAbs furthered understanding of HIV envelope protein structure and of the conformational epitopes to which they bound.

The potential of mAbs was demonstrated in several in vitro and nonhuman primate (NHP) studies, where they were evaluated alone and in combination with each other and with polyclonal HIV immunoglobulin. Combinations of antibodies, or of antibodies and HIV immunoglobulin, were more protective than single antibodies; and rates of protection were somewhat higher in mucosal challenge than in intravenous challenge. Furthermore, animals that became infected after receiving HIV immunoglobulin or an antibody alone exhibited a more benign clinical course than those that received a control preparation (29).

The challenge viruses utilized in these experiments were relatively easily neutralized in vitro, yet serum neutralization titers required for protection were high, and breadth was relatively narrow. Nevertheless, studies of the earliest neutralizing antibodies against HIV demonstrated the potential of antibody-mediated prevention of HIV and fueled the search for more potent antibodies (14, 30).

That search got a significant boost in 2009 with the application of single B cell sorting and cloning techniques coupled with the identification of individuals, largely from natural history cohorts created in the 1990s, exhibiting high levels of autologous neutralizing activity (14). Using the new platforms and building on information gleaned from b12 regarding gp120 structure, the first of a new generation of much more potent and broadly neutralizing HIV mAbs was identified in 2010: VRC01, which neutralized 90% of viruses in a panel of 190 HIV-1 Env viruses with a mean IC_{50} of 0.33 μg/ml, compared to b12's neutralization of 40% of viruses, with a mean IC_{50} of 1.79 μg/ml (31).

MODERN BROADLY NEUTRALIZING ANTIBODIES FOR HIV PREVENTION

Since the identification of VRC01, several other antibodies directed against the highly conserved CD4bs have been identified, the most clinically advanced of which are 3BNC117, VRC07–523LS, and N6. Other sites of gp120 vulnerability targeted by bnAbs currently in clinical trials include epitopes in the V3 loop and surrounding glycans (V3 glycan), which are bound by bnAbs 10–1074 and PGT121; the MPER, bound by 10E8; and the V1-V2 loop at or near the gp120 apex (V2 glycan), bound by PGDM1400 and CAP256-VRC26.25 (32).

All of the anti-HIV bnAbs currently in clinical trials exhibit greater breadth and potency than the mAbs of the 1990s. Potency–breadth curves and neutralization heatmaps (**Figure 1**) highlight this progression. The relative right-shift of curves for 2G12, b12, 2F5, and 4E10 and the blue

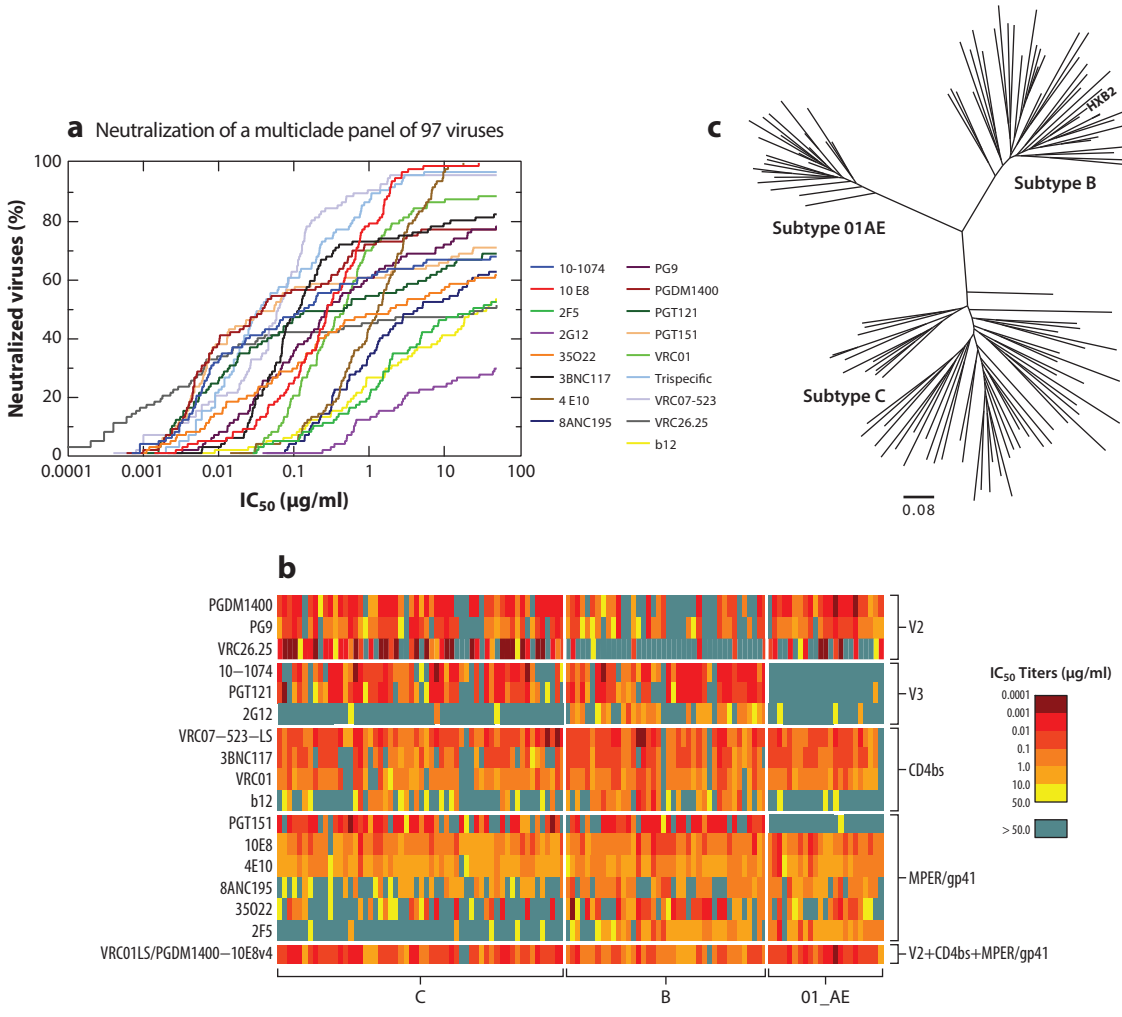

Figure 1

Potency–breadth curves for a panel of 97 viruses (*a*) and neutralization (IC_{50}) heatmap for a panel of 120 viruses (*b*) across three clades represented in the star phylogeny (*c*). In the heatmap, each block in the horizontal axis represents a different virus against which neutralization of the broadly neutralizing antibodies along the vertical axis, grouped by epitope, was evaluated in TZM-bl cells. **Figures 1*a*** and **1*b*** were created with data in the Los Alamos National Laboratory CATNAP database (33).

shades in the heatmap represent their higher IC_{50}, the inhibitory concentration at which 50% of individuals are protected upon exposure, reflecting their lower potency compared to the left-shifted curves (**Figure 1*a***) and orange and red shades (**Figure 1*b***) of most modern bnAbs. The blunting of the pre-2009 mAb curves at or below 50% of viruses neutralized and the quantity of blue-shading in the heatmap reflect their limited breadth.

Notably, different bnAb classes exhibit characteristic neutralization sensitivity profiles, often explained by mutations in amino acids or potential N-linked glycosylation sites on or around bnAb contact residues. For example, bnAbs in some classes, like CD4bs and MPER, tend to bind epitopes that are highly conserved across strains and carry high fitness costs to escape; these classes typically exhibit significant breadth, albeit often with lower potency for some CD4bs bnAbs. V3

glycan binding bnAbs are highly potent against some clade B and C viruses, but poorly neutralize CRF 01_AE strains, 96% of which shift N332, a key potential N-linked glycosylation site that is part of the V3 bnAb contact site, to N334 (34).

Additional bnAbs to the known regions of HIV vulnerability, and additional epitopes and antibodies that bind them, are being identified at a rapid pace. For example, the identification of bnAb PGT151 led to the recognition of vulnerable epitopes, conserved across many HIV strains, at the gp120–gp41 interface. This area is also targeted by 35O22 and, in a different conformation, by 8ANC195. Two recently identified bnAbs, ACS202 and VRC34, target this interface as well as the nearby Env fusion peptide. In 2018, the gp120 inner domain and the so-called silent face were also identified as sites of bnAb attachment on gp120 (32). This identification of new epitope binding sites increases the potential to optimize combinations of antibodies for therapeutic cocktails, similar to those developed for antiretroviral agents.

The identification of new bnAbs has been made possible by the technological advances, cohort development, and HIV Env structural understandings described above. But the increasing pace at which bnAbs are being discovered and moving into clinical trials has been inspired and sustained by their attractive side effect profiles, convenient administration possibilities, host immune engagement potential, and promising evidence of HIV prevention efficacy.

EVIDENCE OF PREVENTION EFFICACY OF BROADLY NEUTRALIZING ANTIBODIES

To date, bnAbs' HIV prevention efficacy has been evaluated definitively only in murine and NHP models. The first human efficacy trial of a bnAb for HIV prevention was initiated in 2016 and is anticipated to report results in late 2020.

The murine model relies largely on reconstitution of severe combined immunodeficiency (SCID) mice with human hematolymphoid engraftment (i.e., humanized mice), which allows for in vivo HIV replication and interaction of investigational mAbs with human immune cells (14, 35). While there are limitations to the murine model, mice contributed to the earliest proof of principle, demonstrating that both early-generation and recent bnAbs could prevent HIV infection (36–40).

NHPs provide a closer model for the study of HIV in humans. Many NHP species are naturally infected with simian immunodeficiency virus (SIV), which is in the same lentivirus family as HIV, and the relevance of the NHP model for HIV pathogenesis and prevention is vastly improved with the hybrid simian–human immunodeficiency virus (SHIV) model, in which SIV envelope protein is replaced by HIV envelope protein while preserving the internal SIV machinery responsible for virus replication in NHPs.

The main limitations of the SHIV challenge model are that infecting strains do not reflect the variability of HIV envelope proteins encountered in nature and that, in general, quite sensitive strains tend to be used in initial challenge studies. Furthermore, SHIV challenge strains are relatively homogeneous, unlike the HIV swarm to which humans are exposed, and many SHIV challenge studies use high doses that infect 100% of animals after a single exposure. Even low-titer, repeat-dose NHP challenge models infect up to 30% of animals per challenge, a significant difference from the 0.1–1% rate of infection per human exposure (14, 41, 42).

Despite these shortcomings, the NHP model remains the best available for preclinical efficacy assessment. All of the post-2009 bnAbs currently in clinical trials have demonstrated 100% protection in NHP models of oral, intrarectal, and intravaginal challenge and at doses ranging from 0.08 mg/kg to 20 mg/kg. Protection at the lowest doses is typically only observed for the most potent antibodies against sensitive challenge virus strains (43–55).

An important observation from these studies is the reduction in protection with increasing in vitro resistance to the antibody, leading to a requirement of higher doses for protection and, in some cases, no observed protection even from potent, but insufficiently broad, antibodies. Incomplete neutralization can be overcome by high doses of select, highly potent antibodies (49), and by the use of combinations of antibodies, including at least one bnAb to which the challenge strain is sensitive (48, 54). Protection can be complete when the two antibodies are administered together prior to challenge.

BROADLY NEUTRALIZING ANTIBODY COMBINATIONS: MULTIPLE SPECIFICITIES

As with combination ART, combinations of bnAbs are highly likely to enhance efficacy. Combinations of bnAbs binding different epitopes typically act additively to provide greater breadth, reduce levels of incomplete neutralization, and provide double or triple coverage, limiting early viral escape to effect protection (56).

Combinations of bnAbs are assessed against panels of HIV Env pseudoviruses, which are created from individual HIV envelopes from real-world isolates (including recently transmitted isolates) that are placed onto a uniform backbone. This allows bnAbs to be tested in a sensitive and highly reproducible fashion and ranked on their global or clade-specific breadth, neutralization potency, and rate of incomplete neutralization. It also allows classification of an individual isolate to a wide variety of bnAbs. In one such assessment, the CD4bs bnAb VRC07 provided the best single global bnAb coverage—83% of a multiclade 125-pseudovirus panel at an IC_{50} of 1 μg/ml. Global coverage increased to 89%, on average, for dual bnAb combinations and reached 98–100% for triple and quadruple bnAb combinations at a 1 μg/ml IC_{50} cutoff (56).

Combinations of bnAbs with independent epitopes are not generally impacted by neutralization resistance to one bnAb in the combination because the resistant viral subpopulations do not usually overlap. Thus, such combinations may overcome the incomplete neutralization that plagues some single bnAbs (57). Furthermore, combining bnAbs with independent epitopes improves potency and breadth more than combining bnAbs with overlapping epitopes (e.g., two CD4bs bnAbs) (58). Whether combinations with epitopes near each other, or even overlapping, offer enhanced protection is unclear. Theoretically, such an approach might enhance effectiveness by improving coverage of minor resistant variants among the quasispecies transmitted by chronically infected individuals (57, 59). Defining optimal combinations for global or regional use is an area of active investigation. Considerations such as manufacturability, cost, and effectiveness are all factors in defining what potential combinations will be tested clinically.

Combining antibodies is not without challenges. Each bnAb has unique pharmacokinetic, formulation, and stability characteristics, adding complexity to coadministering multiple different antibodies. However, recent advances in antibody engineering are addressing these challenges, facilitating structural modifications to the antigen-binding fragment (Fab) to create single immunoglobulin molecules with multiple specificities and preserved IgG architecture, typically with an IgG1 backbone. In some cases, bi- or trispecific molecules exhibit neutralization potency that exceeds the additive potency of each parental bnAb (60–62).

Bispecific antibodies exhibit two epitope specificities, one on each Fab of an antibody with one crystallizable fragment (Fc) (**Figure 2*a***). Each Fab may bind an HIV Env epitope (e.g., the CD4bs and the V2 glycan region), recapitulating optimal combinations of two different bnAbs, or they may bind an Env and a host epitope. An example of the latter, 10E8v4/iMab, entered clinical trials in early 2019. 10E8v4 is a variant of the 10E8 MPER-binding bnAb; ibalizumab (iMab) binds to the human CD4 receptor. This bispecific combination exhibited substantially greater

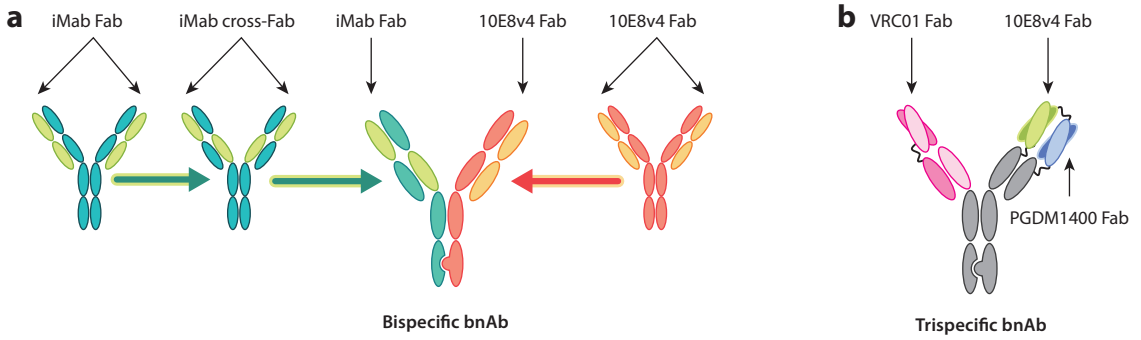

Figure 2

Schematic of multispecific broadly neutralizing antibodies (bnAbs). Bispecific bnAbs like 10E8v4/iMab are created by combining two bnAbs. (*a*) The antigen-binding fragment (Fab) of one of the two bnAbs here is engineered in a cross-Fab fashion before combining with another bnAb. Adapted from Reference 61 with permission. (*b*) The trispecific bnAb combines three Fabs, as shown, utilizing novel structural engineering, described in Reference 65. Both of these multispecific bnAbs utilize knob-in-hole heterodimerization of the Fc.

potency in vitro on a multiclade 118-virus panel than the 10E8 parental bnAb or variants, possibly due to iMab-mediated concentration of the 10E8v4 Fab at the site of attempted viral entry and increased avidity from the simultaneous binding of both Fabs to antigen (i.e., bivalency) (60, 63). A 10E8/iMab variant showed enhanced in vitro coverage and potency as compared to even the best combinations of two separate bnAbs across clade A, C, and D viruses and performed even better when combined with another single antibody in a three-epitope combination (64). These in vitro data are as yet unproven predictors of clinical efficacy; and toxicity and enhanced clearance are possible with antibodies targeting abundant host receptors like CD4. These possibilities are being assessed in ongoing clinical trials.

The first trispecific bnAb to enter clinical trials, SAR441236, includes one Fab with VRC01 and another Fab with linked 10E8v4 and PGDM1400 (**Figure 2*b***). Preclinically, the trispecific bound each epitope sequentially, exhibited greater potency and breadth than the single parental bnAbs or any bispecific combination of them, and yielded higher protein levels and greater solubility than bispecific analogs. It protected eight of eight NHPs when infused five days before high-dose rectal SHIV challenge and has entered early clinical testing (65). While demonstrating impressive in vitro potency, the bi- and trispecific antibodies require greater amounts of engineering to achieve their structural optimization than the parental bnAb selected from a human donor. Whether such engineering leads to significant side effects or antidrug activity remains to be determined.

PHARMACOKINETICS AND DELIVERY OF BROADLY NEUTRALIZING ANTIBODIES

Most mAbs in current therapeutic use are delivered intravenously, often over extended time periods, making them difficult to use for prevention of infection/disease. In addition, antidrug antibodies (ADAs) can arise, which can shorten half-life or totally abrogate activity. ADAs appear much less commonly to mAbs to infectious agents that are derived from human B cell cloning than to humanized mouse mAbs, which are commonly used for autoimmune and cancer chemotherapy. ADAs have been, to date, an uncommon observation in clinical trials of naturally derived anti-HIV bnAbs.

Most bnAbs are initially tested on a common IgG1 backbone, and hence the half-life is usually from 20 to 40 days, necessitating relatively frequent (e.g., every 2–4 months) administration. Of

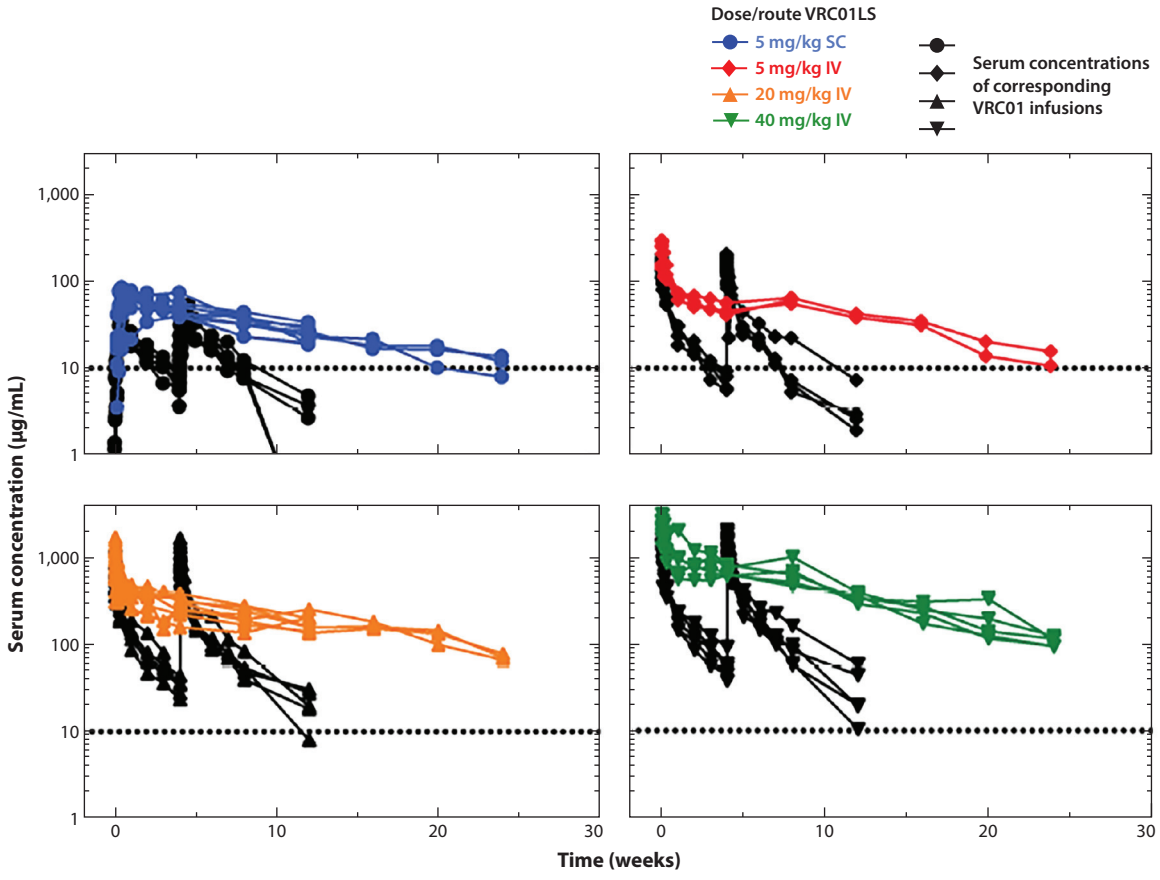

Figure 3

Enhanced pharmacokinetic profile of a monoclonal antibody containing the LS variant (VRC01LS) versus its non-LS form (VRC01). At all evaluated doses and routes, the half-life of VRC01LS (represented by the blue, red, orange, and green symbols) exceeds that of VRC01 (represented by the black triangles) by more than fourfold. Black symbols indicate serum concentrations of corresponding VRC01 infusions (97). Adapted from References 67 and 97 with permission. Abbreviations: IV, intravenous; SC, subcutaneous.

course, the durability of the effectiveness of a mAb is influenced by its potency; the more potent the antibody, the longer the threshold titer required for efficacy is maintained, and the more likely it is that dosing intervals can be extended for long time periods.

A recent advance for the field of mAb delivery is the observation that antibody half-life can be extended by antibody recirculation (e.g., through Fc engineering). Fc modifications like the two-amino-acid mutation in LS bnAb variants are, so far, the most successful approach to extend antibody half-life, enhancing affinity for the neonatal Fc receptor (FcRn) and thus increasing antibody recirculation (66). In human trials, the LS-modified variant of the VRC01 CD4bs bnAb, VRC01LS, was safe and well tolerated; it exhibited no antidrug responses and a half-life of over 70 days, more than four times that of VRC01 (**Figure 3**) (67). The FcRn is found in high concentrations in the mucosa, and since antibodies engineered with an Fc LS modification bind the FcRn with high avidity they exhibit enhanced mucosal localization. This observation is credited, in part, for the improved protection observed in NHP trials of VRC01LS (50, 68). Formulation of dimeric IgA1 bnAbs and bnAb formulation for topical mucosal application have also been proposed for optimal mucosal bnAb distribution (68, 69).

Antibody pharmacokinetics (PK) can also be improved by advances in drug formulation, including formulating for increased antibody stability, solubility, and concentration. This enables administration of higher doses in lower volumes, thus facilitating subcutaneous administration. Subcutaneous fixed dosing, rather than the weight-based dosing currently used for bnAb-mediated HIV treatment or prevention, is another advance that could simplify antibody manufacturing and delivery and could, as with chemotherapeutic mAbs, produce drug exposure comparable to that achieved with dosing based on weight or body surface area (70).

Another approach for achieving long-term concentrations of antibodies is to develop in vivo antibody expression. The latter is possible with mRNA, DNA, or vectored gene transfer, as with the insertion of bnAb genes into an adeno-associated virus (AAV) vector injected into muscle, where it provides constitutive bnAb production for extended systemic circulation (71, 72). The first clinical trial of an AAV-vectored anti-HIV bnAb, rAAV1-PG9DP, demonstrated some of the challenges of vectored immunoprophylaxis. While the regimen appeared safe and well tolerated, the concentrations of antibody in serum were minimal and anti-bnAb and antivector antibodies, often with associated T cell responses, were evident in over half of the rAAV1-PG9DP recipients (73, 74). Recent innovations in nonviral gene delivery may provide a second-generation approach to delivering mAb therapy for extended time periods.

MECHANISMS OF PROTECTION: NEUTRALIZATION

Antibody-mediated virus neutralization entails the binding of the bnAb Fab to viral antigen, thereby blunting viral replication by blocking virus attachment or preventing viral penetration of a host cell membrane (**Figure 4**). The titer at which this occurs in sufficient magnitude appears to be a primary correlate of bnAb-mediated protection (44, 47, 75).

Neutralization of both cell-free and cell-associated HIV, including inhibition of cell-to-cell transmission, is likely important for optimal bnAb-mediated HIV prevention (76). Disruption of cell-to-cell transmission can occur at several points, including inhibition of virologic synapse formation, viral fusion or the formation of conjugates between infected and uninfected cells, and viral transfer between cell conjugates (77). Neutralizing potency of mAbs is typically lower against cell-associated virus and cell-to-cell transmission than against cell-free virions, with some studies suggesting that bnAb concentrations required to prevent cell-to-cell transmission are 10–20 times higher than those required for neutralization of cell-free virions. This may be due to steric hindrance at the virologic synapse, the high number of viral particles (i.e., high multiplicity of infection) associated with cell-to-cell viral propagation, and the epitopes, conformation, and stability of Env or Env-bnAb complexes at the infected cell surface (76–78).

A forewarning of the impact of this issue may be the recent meta-analysis of antibody-mediated prevention in NHP models with experimental SHIV infection. This analysis of 274 rhesus macaques in 18 studies using a wide variety of mAbs identified viral neutralization as the single independent correlate of protection irrespective of mAb epitope specificity (75). The median neutralization titer (the ID_{50} or inhibitory dilution at which 50% neutralization is observed) required to protect 50% of animals was 100, a reasonably high titer. 90% protection required a titer of >400, much higher than predicted from in vitro sensitivity testing.

MECHANISMS OF PROTECTION: FC EFFECTOR FUNCTIONALITY

Overcoming insufficient neutralization potency against cell-associated virus and augmenting neutralization-mediated prophylaxis against cell-free virus require mechanisms beyond neutralization (76). Such mechanisms are clearly often at work in bnAb-mediated activity: neutralization

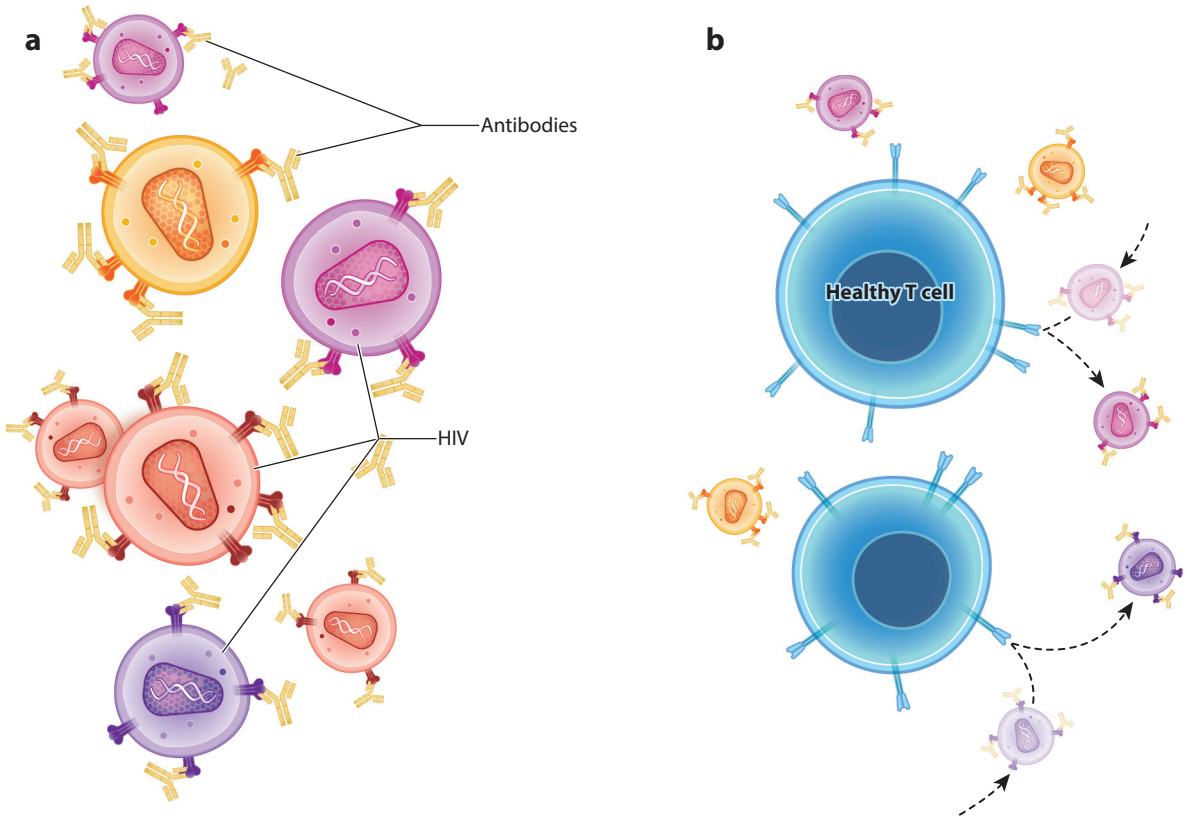

Figure 4

Schematic of bnAb-mediated viral neutralization. BnAbs mediate protection from (S)HIV acquisition primarily through neutralization, (*a*) binding to HIV envelope proteins of many HIV strains and (*b*) preventing receptor binding, viral entry, and infection of target cells. Abbreviations: bnAb, broadly neutralizing antibody; HIV, human immunodeficiency virus; SHIV, hybrid simian–human immunodeficiency virus.

titers in serum do not always correlate with protection from infection or disease; some antibodies appear to provide greater in vivo protection than predicted by in vitro neutralization; NHP models reveal apparent bnAb-mediated clearance of distal (i.e., lymphatic) virus via innate and antiviral immune responses; and mAb FcγR engagement clearly correlates with treatment outcomes in oncology and rheumatology models (79, 80). A major research focus in the mAb field is on using genetic engineering to improve non-neutralizing activity, including enhancing T cell responses by optimizing the Fc-mediated functions of the antibodies.

The Fc portion of bnAbs, particularly of IgG1 subclass bnAbs, binds to complement, mediating complement-dependent cytotoxicity and phagocytosis. The Fc portion also binds to Fc receptors (e.g., FcγRIIa and FcγRIIIa) on innate immune cells such as macrophages, natural killer cells, and dendritic cells, mediating antibody-dependent cellular phagocytosis, cellular cytotoxicity, and innate and adaptive immune activation. When multiple Fabs are bound to Env on cell-free virions or infected cells, forming an immune complex, Fc-FcγR binding avidity is increased, stimulating more potent effector functionality (**Figure 5**) (80–83).

BnAb variants engineered with Fc mutations that enhance or reduce FcγR binding have illuminated the potential contributions of Fc effector functionality. In one study, NHPs that received

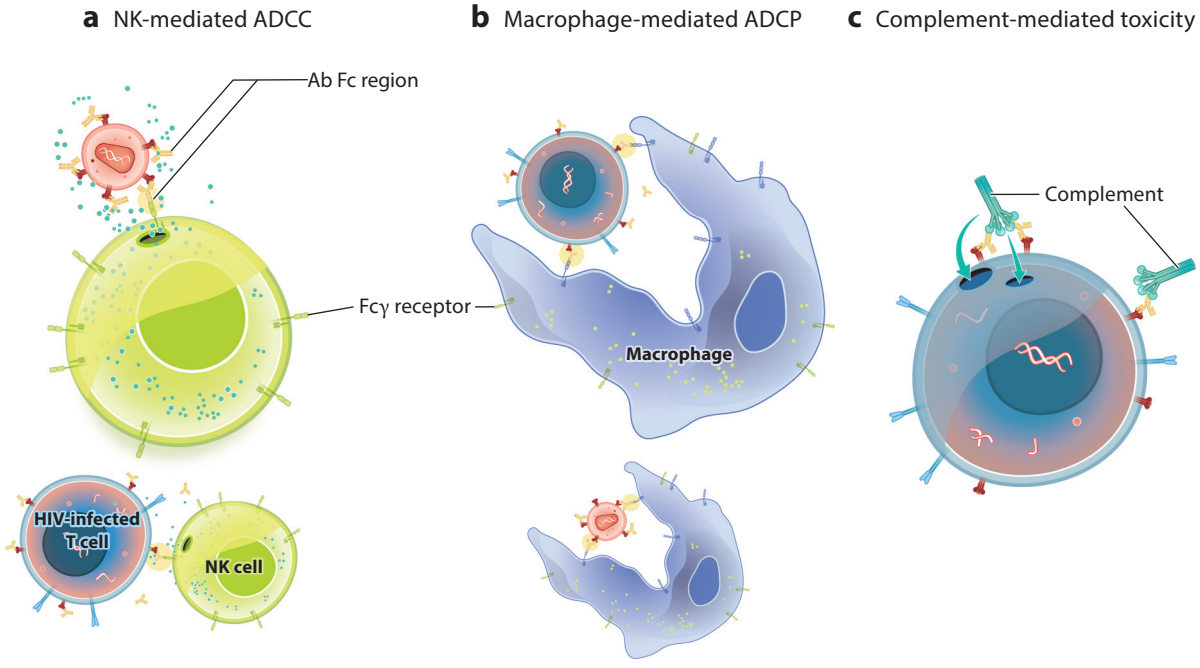

Figure 5

BnAb-mediated Fc effector functionality complements neutralization to mediate protection from (S)HIV acquisition. NK cells (*a*) and macrophages (*b*) bind to the bnAb Fc, recognizing immune complexes of cell-free and cell-associated virus coated in bnAbs. Complement recognizes bnAb bound to infected cells (*c*). The macrophages, NK cells, and complement then mediate antibody-dependent or complement-mediated cellular phagocytosis and cytotoxicity. Abbreviations: Ab, antibody; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; bnAb, broadly neutralizing antibody; HIV, human immunodeficiency virus; NK, natural killer; SHIV, hybrid simian–human–immunodeficiency virus.

a b12 bnAb variant (LALA) engineered with reduced FcγR and complement binding were more likely to become infected and exhibited higher peak viremia than animals treated with wild-type b12 with intact effector functionality (84, 85). The virus may escape from b12 neutralization with a low fitness cost, and Fc effector functionality may then be necessary to clear escape mutants, especially when neutralization potency is low (79, 86).

The importance of effector functions was also demonstrated in an NHP experiment in which 24 NHPs received 2 mg/kg PGT121 or an isotype-matched sham control antibody one day prior to vaginal challenge; serial postchallenge necropsies showed low and declining levels of viral RNA and DNA in tissues distal to the inoculation in >75% of animals receiving PGT121, primarily in draining lymph nodes and gastrointestinal tissue. By 10 days postchallenge, no viral DNA was detected in any tissues from PGT121-treated NHPs but was detected at high levels in all evaluated tissues in the sham controls. Notably, transcriptomic profiles suggest that activation of innate immunity and antiviral activity was associated with the observed distal viral clearance (87). Similarly, distal clearance was observed in infant macaques administered a combination of PGT121 and the CD4bs bnAb VRC07–523 within 24 hours after oral $SHIV_{SF162P3}$ challenge (45).

Enhanced cellular responses in the presence of bnAbs—including accelerated clearance of HIV-infected cells, increased $CD8^+$ T cell virus inhibition, and decreased $CD8^+$ and $CD4^+$ cell exhaustion—are all potential factors contributing to these observations (88, 89). One hypothesis for these improved T cell responses is the induction of bnAb–Env immune complexes that

stimulate improved antigen processing and presentation, stimulating broad cellular proliferation and a more effective response to ongoing or later antigen (re)exposure, a cascade referred to as a "vaccinal effect" (**Figure 6**) (82, 83).

ENGINEERING IMPROVED BROADLY NEUTRALIZING ANTIBODIES FOR PROTECTION

One of the unique features of HIV is the scarcity of gp160 trimers on the outer envelope. Thus, both Fabs on a single bnAb with a single epitope specificity rarely, if ever, bind simultaneously (90, 91). However, such bivalency enhances avidity and, thus, neutralization potency; bispecific bnAbs that can simultaneously bind two epitopes are typically more potent than their monovalent parental bnAbs. Structural engineers have worked to enhance avidity potential even in the absence of multispecificity. Approaches in development include the creation of longer and more flexible IgG hinges (e.g., modified IgG3 hinge regions) (61), single-chain variable (scFv) domains connected by flexible linkers (62), and Fc fusion peptides (92).

Other structure-based modifications enhance the stability of a preferred conformation, decreasing steric clashes between antigen and antibody, or add non-native functions to bnAbs, as with the conjugation of antibody with small molecules that inhibit viral entry (69, 93).

CLINICAL TRIALS OF BROADLY NEUTRALIZING ANTIBODIES FOR PROTECTION

Early-phase clinical trials of over a dozen anti-HIV bnAbs have demonstrated the safety and PK of bnAbs administered alone and in combination via subcutaneous, intravenous, and intramuscular routes in HIV-infected and HIV-uninfected adults and infants. Population PK assessments have demonstrated limited interindividual variability after accounting for body weight, and, with the exception of AAV-vectored bnAbs, no antidrug antibodies have been observed. All of the anti-HIV bnAbs evaluated thus far are fully human molecules and have exhibited reassuring safety profiles, with rare mAb reactions such as generalized pruritis or rash (67, 74, 94–99).

Definitive evidence of bnAbs' prevention efficacy in humans awaits clinical trial results that are anticipated in late 2020 from two phase IIb proof-of-concept prevention efficacy studies: the Antibody-Mediated Prevention (AMP) trials, being conducted by the HIV Vaccine and HIV Prevention Trials Networks (HVTN and HPTN) funded by the National Institute of Allergy and Infectious Diseases. The AMP cohorts include 1,900 heterosexual women at risk of HIV infection in sub-Saharan Africa and 2,700 MSM and transgender individuals at risk of HIV in North and South America and Europe. Participants receive intravenous infusions of VRC01 (10 or 30 mg/kg) or normal saline placebo every 8 weeks for a total of 10 infusions and have monthly HIV diagnostics. The trials are powered to detect at least 60% prevention efficacy of VRC01 and to correlate neutralization and serum concentration with protection (100). Accrual is complete and early reports show safety and tolerability and high rates of trial retention and drug adherence; final results are anticipated in late 2020 (101, 102).

NEXT STEPS

The pace of investigation using human-derived mAbs as therapeutic agents and for disease prevention has increased exponentially in the last five years. These antibodies, derived directly from persons who have HIV, have advantages in their epitope specificities and potential safety and durability compared to antibodies derived from nonhuman sources.

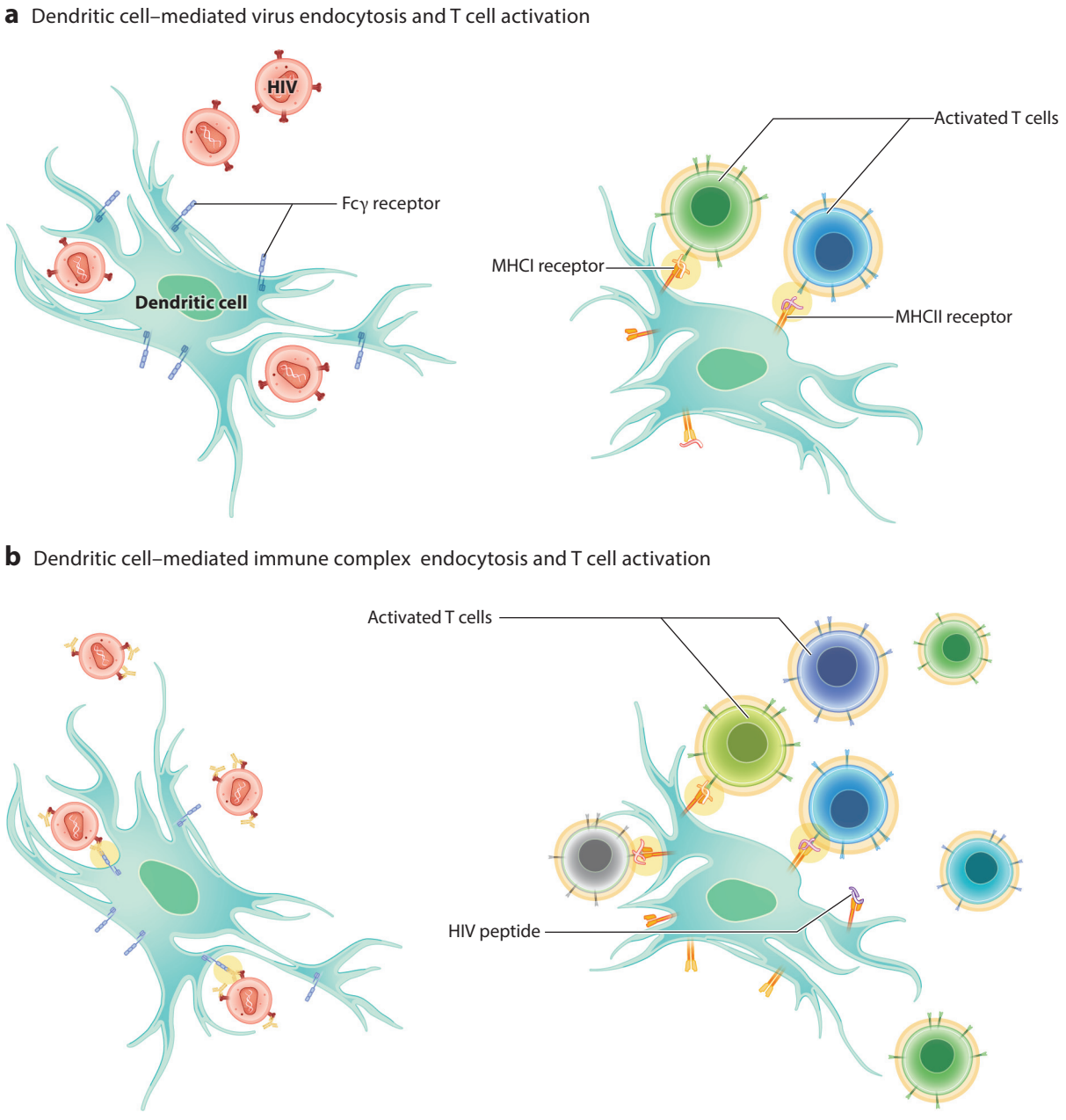

Figure 6

Vaccinal effect. In the absence (*a*) and presence (*b*) of bnAb–Env immune complexes, dendritic cells are among the first responders of the innate immune system, engulfing HIV and processing and presenting HIV antigens to activate T cells. The vaccinal effect is the phenomenon of bnAbs mediating a longer-lasting and broader T cell response than that observed in the absence of bnAbs, possibly due to Env–bnAb immune complexes facilitating enhanced antigen processing and presentation. Abbreviations: bnAb, broadly neutralizing antibody; MHC, major histocompatibility complex.

Advances in cell engineering to develop high-yield producer cell lines, in combination with synthetic biology to improve PK and effector function, are providing the impetus to make these antibodies reasonably priced potent agents useful for prevention of infection and perhaps for therapy. Formulation advances to allow self-administered long-acting (every 3–6 months) subcutaneous therapy are already in clinical trials. Whether these alterations can achieve the vaccinal effect described above remains to be seen.

The cost of bnAb manufacturing is an often-cited disadvantage that, even with optimization of PK profiles and antibody delivery, some argue renders bnAbs unrealistic as a prevention tool, particularly in the low- and middle-income countries bearing the brunt of the HIV pandemic. However, as demonstrated at the advent of the ART era, technological innovation and the pressures of a competitive market can reduce costs dramatically. It is, in the authors' opinion, highly likely that long-lasting mAbs will emerge as important tools for prevention of HIV as well as a wide variety of other important infectious diseases in the next decade. BnAb cocktails are likely to become an important part of the physician's armamentarium.

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