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REVIEW

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Antibody-mediated prevention and treatment of HIV-1 infection

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Abstract

Novel broadly neutralizing antibodies targeting HIV-1 hold promise for their use in the prevention and treatment of HIV-1 infection. Pre-clinical results have encouraged the evaluation of these antibodies in healthy and HIV-1-infected humans. In first clinical trials, highly potent broadly neutralizing antibodies have demonstrated their safety and significant antiviral activity by reducing viremia and delaying the time to viral rebound in individuals interrupting antiretroviral therapy. While emerging antibody-resistant viral variants have indicated limitations of antibody monotherapy, strategies to enhance the efficacy of broadly neutralizing antibodies in humans are under investigation. These include the use of antibody combinations to prevent viral escape, antibody modifications to increase the half-life and the co-administration of latency-reversing agents to target the cellular reservoir of HIV-1. We provide an overview of the results of pre-clinical and clinical studies of broadly HIV-1 neutralizing antibodies, discuss their implications and highlight approaches for the ongoing advancement into humans.

Keywords: HIV-1 broadly neutralizing antibodies, Immunotherapy, Passive immunization, (S)HIV animal models, Clinical trials, Neutralization, Fc-mediated activity

Background

Pathogen-specific antibodies are a hallmark of an effective immune response following infection or vaccination [1, 2]. Their development is the result of a cascade of events ranging from antigen uptake and presentation to B cell induction and antibody production [3]. Passive immunization, i.e., the administration of immunoglobulins, bypasses these steps. As such, it is an effective concept for immediate but transient protection from infections including hepatitis A, hepatitis B and rabies [4]. Moreover, the principle of antibody-mediated immunotherapy of infectious diseases has long been established by the use of toxin-specific antibodies to treat diphtheria or tetanus [5].

Advances in antibody production technology have enabled the development of highly active and specific clinical products. Antibodies have gained widespread medical use at an accelerating pace, with more than half of the >70 available monoclonal antibodies and derived constructs having been approved over the span of the past 5 years [6]. Most of these antibodies are used in the treatment of malignant or autoimmune diseases. In contrast, approval of monoclonal antibodies that target infectious pathogens or pathogen-derived substances has been limited to antibodies against the respiratory syncytial virus and toxins produced by *Clostridium difficile* or *Bacillus anthracis*. Recently, the antibody ibalizumab has been approved for the treatment of multidrug-resistant HIV-1 infection [7]. While ibalizumab does not directly interact with the circulating virus or HIV-1-infected cells, it targets an extracellular CD4 domain and therefore interferes with the binding of HIV-1 to its primary receptor on target cells [7].

Despite being proposed early on [8], the idea of neutralizing antibody-mediated immunotherapy of HIV-1 infection was long abandoned because of limited activity in animal models and early clinical trials [9–14]. However, the isolation of highly potent broadly neutralizing anti-HIV-1 antibodies (bNAbs) has renewed enthusiasm about the potential application of these antibodies and

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resulted in numerous clinical trials investigating different concepts of bNAbs for HIV-1 infection.

Main text

First monoclonal HIV-1 neutralizing antibodies

Most HIV-1-infected individuals develop limited neutralizing serum activity. Accordingly, facing the enormous diversity of HIV-1, passive transfer of plasma or purified immunoglobulins from HIV-1-infected donors resulted in inconsistent or no detectable treatment effects in humans [15–18]. Similarly, the first monoclonal anti-HIV-1 antibodies failed to demonstrate significant antiviral effects in early clinical trials [19–23]. Limitations in potency and breadth remained for the first generation of broadly neutralizing antibodies [24–26]. However, proof-of-concept studies in non-human primates (NHPs) and humanized mice demonstrated that monoclonal antibodies can protect from infection with chimeric simian/human immunodeficiency virus (SHIV) and HIV-1 [27–41]. Nevertheless, these antibodies were not generally considered applicable for clinical use in HIV-1 prevention mainly because of an overall low neutralizing activity against the majority of viral strains. The bar for treatment of established infection proved even higher, as combinations of these early antibodies failed to significantly suppress viremia or prevent the development of resistance in animals and humans [9–14]. Thus, the results of these experiments reinforced the need for more potent antibodies that cover a wide spectrum of viral strains to facilitate bNAb-mediated prevention and treatment of HIV-1 infection.

A new generation of antibodies targeting HIV-1

Advances in antibody isolation and cloning methods, combined with the identification of subjects with exceptional neutralizing serum activity, resulted in the isolation of a new generation of anti-HIV-1 bNAbs [42–47]. These antibodies are orders of magnitude more potent than those isolated before and neutralize the majority of viral strains [48]. All bNAbs recognize the HIV-1 envelope glycoprotein (Env) by targeting defined vulnerable epitopes on its surface [49, 50]. Among them, antibodies against the CD4 binding site (3BNC117, VRC01) and the V3 loop (10-1074) have progressed beyond first-in-human trials to studies focusing on potential strategies for treatment and prevention of HIV-1 infection (Fig. 1). Additional antibodies targeting the CD4 binding site (N6-LS and VRC07-LS), the V3 loop (PGT121) or other epitopes (V1/V2 loop, PGDM1400; membrane proximal external region (MPER) of gp41, 10E8V-LS) are being investigated in early phase studies (Fig. 1). Indeed, more than 30 clinical trials have been initiated and will result in the enrollment of over 4000 study participants receiving one or a combination of novel broadly neutralizing antibodies (Fig. 1).

Paving the way for prevention

Members of the new generation of highly potent bNAbs can protect from infection in parenteral, vaginal, rectal and/or oral viral challenge models [51–71]. In fact, bNAbs have been shown to prevent (S)HIV infection by high titer virus mucosal challenge across a number of animal studies investigating different bNAbs, viral strains and/or routes of transmission [55–67]. While mucosal application of high titer virus ensures robust infection after a single challenge, this model does not reflect the limited frequency of transmission seen for a single sexual contact or breastfeeding [72, 73]. Thus, it may underestimate the efficacy of bNAbs to prevent HIV-1 transmission in humans. Low-dose repeated mucosal challenge mimics clinical scenarios more closely. In such models, the administration of a single bNAb can significantly delay the time to infection [68–71]. For example, macaques intrarectally challenged with $SHIV_{AD8}$ were protected from infection after a single administration of 10-1074, 3BNC117 or VRC01 until the median serum antibody concentrations declined to 0.17–1.83 μg/ml [70]. These levels were approximately 3-fold higher than the IC_{50}s determined against the challenge virus in vitro [70]. Higher ratios of protective serum antibody concentrations and in vitro IC_{50}s were observed for first-generation bNAbs in low-dose challenge models [68, 69]. However, these differences might be accounted for by the use of different virus strains, challenge routes and other conditions including the experimental thinning of epithelia in vaginal transmission models. Nevertheless, if the results from low-dose rectal challenge in NHPs hold true in humans, bNAb serum levels of 10 μg/ml are likely to be sufficient to prevent infection from a large fraction of circulating viruses [74]. When infused intravenously (i.v.), 3BNC117, VRC01 and 10-1074 showed mean half-lives of 11–24 days in healthy individuals [75–79]. Following an infusion of either antibody at a dose of 20–30 mg/kg, bNAb levels of >10 μg/ml were measured for approximately 8–16 weeks [75–77]. Importantly, this period can be substantially extended by antibody modifications discussed below.

In contrast to the challenge with selected monoclonal viruses in animal models, humans are exposed to a wide range of viral strains with different antibody sensitivities. Thus, whether bNAbs can afford a meaningful degree of protection from HIV-1 infection in humans can only be demonstrated in clinical trials. Two large placebo-controlled studies aim to answer this question using the CD4 binding site antibody VRC01. To this end, VRC01 is given at 10 or 30 mg/kg every 2 months

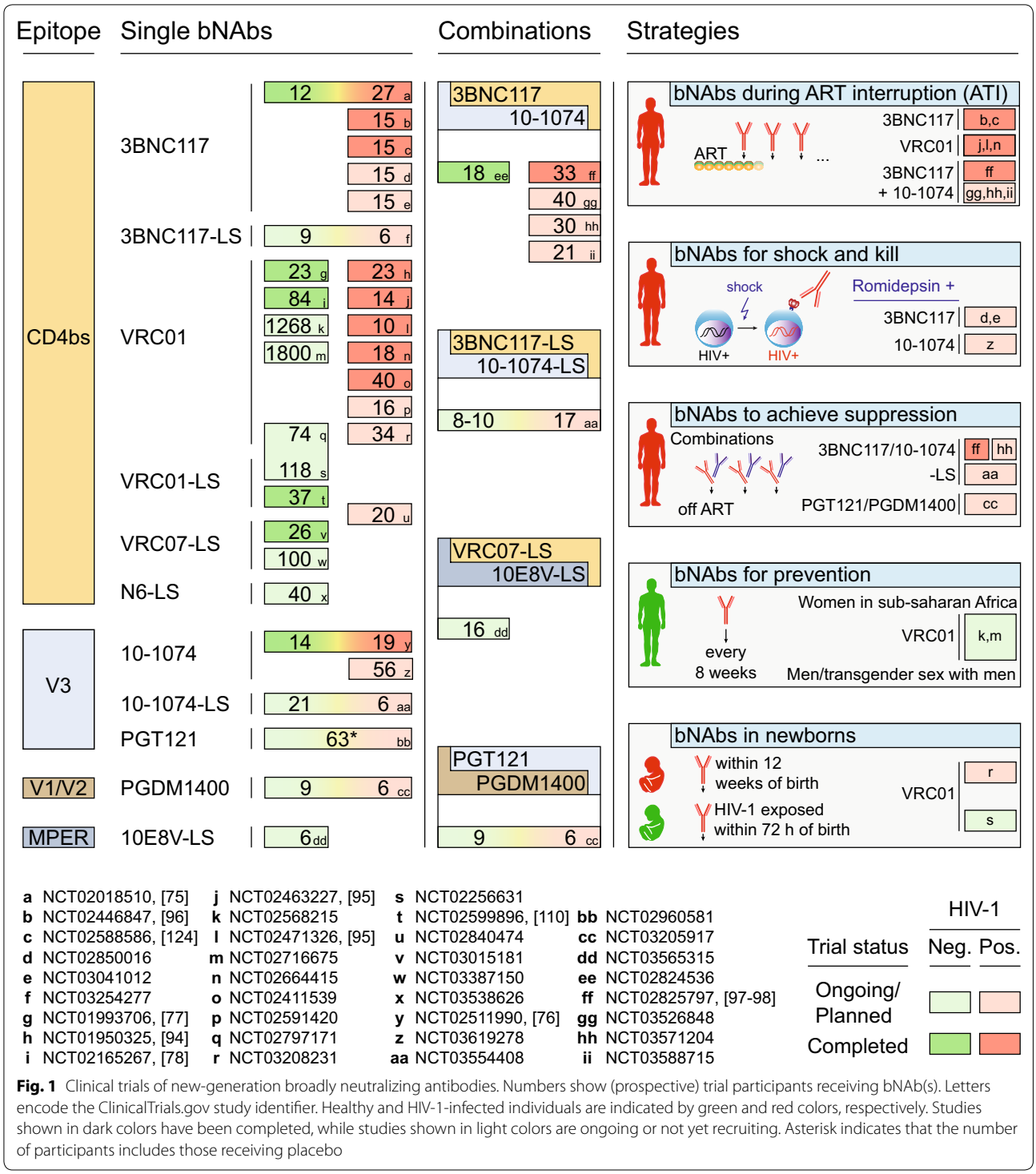

Fig. 1 Clinical trials of new-generation broadly neutralizing antibodies. Numbers show (prospective) trial participants receiving bNAb(s). Letters encode the ClinicalTrials.gov study identifier. Healthy and HIV-1-infected individuals are indicated by green and red colors, respectively. Studies shown in dark colors have been completed, while studies shown in light colors are ongoing or not yet recruiting. Asterisk indicates that the number of participants includes those receiving placebo

to individuals at high risk of acquiring HIV-1 infection (NCT02568215, women living in sub-Saharan Africa; NCT02716675, men and transgender persons who have sex with men) [78, 80]. These are critical proof-of-concept studies, however, more potent antibodies or bNAb combinations may provide more effective options for prevention.

Passively administered bNAbs need to be applied repeatedly to maintain levels above a threshold concentration required for effective protection. Transgenic

bNAb expression could be a feasible approach to overcome this limitation. For example, administration of adeno-associated viruses (AAVs) can result in sustained transgene expression, and their safety has been demonstrated throughout a number of clinical trials [81]. In humanized mice, AAV-mediated bNAb expression can protect from HIV-1 infection by repeated mucosal viral challenge [82, 83]. To investigate this concept of vectored immunoprophylaxis in humans, phase I studies of AAVs encoding for the anti-V1/V2 loop antibody PG9 or the CD4 binding site antibody VRC07 have been initiated (NCT01937455, NCT03374202).

Gaining traction for treatment

The identification of novel highly potent bNAbs prompted the re-assessment of antibody-mediated therapy of established infection in humanized mice and non-human primates [67, 84–91]. Treatment of HIV-1-infected mice with single bNAbs resulted in the rapid emergence of mutations at antibody target sites that were associated with viral rebound [84–86, 88, 89]. However, in contrast to earlier bNAbs, combinations of new-generation bNAbs targeting non-overlapping epitopes effectively maintained suppression of viremia [84, 85, 87]. Sequence analyses of viruses obtained during and after treatment demonstrated the lack of concurrent escape mutations at all antibody target residues [84, 87]. Thus, similar to combinations of classical antiretroviral drugs, combination antibody therapy can prevent the development of viral resistance in humanized mice.

In SHIV-infected non-human primates, the duration and magnitude of viral suppression during bNAb monotherapy appeared to be more pronounced than in humanized mice [67, 90, 91]. These differences might be explained by the fully functional immune system that is present in non-human primates but absent in humanized mice. Indeed, host immunity does play a critical role for the antiviral activity of HIV-1 neutralizing antibodies as demonstrated for Fc-mediated effector functions in both animal models [51, 52, 92, 93]. Underlining the impact on bNAb-mediated antiviral activity, the combination of bNAbs in NHPs prolonged suppression of sensitive SHIV strains and limited the development of viral resistance compared to single bNAbs [67].

bNAb monotherapy in humans

Early phase clinical trials started translating these findings to HIV-1-infected humans, beginning with the CD4 binding site antibodies 3BNC117 [75] and VRC01 [94], and followed by the V3 loop antibody 10-1074 [76]. Importantly, the administration of these antibodies was found to be safe and very well tolerated across all trials completed to date [75–78, 94–98]. Moreover, infusion of either 3BNC117, VRC01 or 10-1074 at a dose of 30–40 mg/kg to sensitive viremic individuals resulted in rapid reduction of viremia by an average of 1.5, 1.1 and 1.5 $\log_{10}$, respectively [75, 76, 94]. However, suppression of viral load below the limit of detection was only rarely achieved, and viral rebound generally occurred within 4 weeks. Rebound was associated with increased resistance against the administered bNAbs in most cases, although the extent differed between antibodies. Following the administration of the V3 loop antibody 10-1074, a rapid selection of fully resistant escape variants was observed in all study participants [76]. In contrast, infusion of the CD4 binding site antibodies 3BNC117 or VRC01 resulted in a general trend of reduced viral sensitivity, but was not consistently associated with the development of full resistance [75, 94]. For example, in six sensitive viremic individuals receiving 3BNC117 at a single dose of 10 or 30 mg/kg, autologous culture outgrowth viruses remained partially sensitive to 3BNC117 with an increase of the geometric mean IC_{50} against 3BNC117 from 0.2 μg/ml to only 1.7 μg/ml [75]. These findings might indicate that antibodies with similar effects on the viral load differ in their capacity to restrict viral escape. Importantly, the envelope protein targeted by broadly neutralizing antibodies has a critical function in the viral replication cycle, and escape from some bNAbs has been associated with reductions in viral fitness [76, 99, 100]. For example, in vitro studies of naturally occurring mutations that confer resistance against the CD4 binding site antibody VRC01 showed a negative impact on the viral replicative capacity that could, however, be restored through compensatory mutations [99].

Compared to active viral replication in viremic individuals, ART-mediated suppression at the onset of bNAb therapy may impede the development of escape mutations. In agreement with this idea, single antibodies were more effective in maintaining viral suppression in HIV-1-infected humanized mice following an initial period of antiretroviral therapy [85]. To test this concept in humans, monotherapy with the bNAb 3BNC117 or VRC01 was administered to HIV-1-infected individuals undergoing analytical treatment interruption (ATI) of antiretroviral therapy [95, 96]. While 3BNC117 or VRC01 delayed the time to viral rebound to 10 or 4 weeks, respectively, rebound did occur in the presence of high bNAb serum levels in most cases and was associated with increased antibody resistance [95, 96].

Taken together, first clinical trials demonstrated the safety and significant antiviral activity of novel broadly neutralizing antibodies targeting HIV-1. However, the emergence of viral escape variants has highlighted the limitations of antibody monotherapy.

Combining antibodies for HIV-1 therapy

Based on the well-established concept of preventing viral escape through combinations of antiretroviral drugs and similar results for bNAbs in pre-clinical studies, clinical trials that combine new-generation bNAbs were initiated (Fig. 1). In the first study, the combination of 3BNC117 and 10-1074 showed similar safety and pharmacokinetic profiles to either antibody alone [97, 98]. In four viremic individuals determined to be infected with viruses sensitive to both antibodies, treatment with up to three infusions of 3BNC117 and 10-1074 resulted in an average drop in viremia of 2.0 $\log_{10}$ copies/ml [97]. In most of these individuals, reduced viral loads were maintained for as long as both of the administered antibodies were detectable in the serum (8–12 weeks after the last antibody infusion) [97]. Moreover, in contrast to 10-1074 monotherapy [76], antibody escape did not develop in all instances [97]. However, despite the significant reduction of the viral load, full suppression was only achieved in study participants with relatively low levels of viremia (below 3000 copies/ml) [97].

More pronounced effects were observed in individuals infected with antibody-sensitive viruses undergoing ATI. These participants received the antibody combination at 0, 3 and 6 weeks after stopping ART. In contrast to the time to rebound without intervention (2.4 weeks, historical controls) or 3BNC117 monotherapy (9.9 weeks) [96], the combination of 3BNC117 and 10-1074 maintained viral suppression for a median of 21 weeks or nearly 4 months after the last antibody infusion [98].

Of note, 12 out of 13 individuals (4 viremic, 9 undergoing ART interruption) with viruses sensitive to 3BNC117 and 10-1074 did not experience viral rebound as long as both antibodies had serum concentrations above 10 μg/ml [97, 98]. Thus, combinations of new generation bNAbs at sufficient antibody concentrations are effective in maintaining viral suppression in humans infected with sensitive viruses.

Preparing for practice

Antiretroviral drugs are highly effective in treating HIV-1 infection and reducing the risk of infection when used as pre-exposure prophylaxis. Moreover, they are well-established, easily distributable, increasingly available in generic form and long-acting injectable drugs are at the final stages of development [101]. Clinical implementation of broadly neutralizing antibodies will therefore not only require safe and highly active products, but also depend on the ease of administration, cost-effectiveness and well-designed strategies for their use.

Neutralizing potency and breadth are the most obvious prerequisites for the activity of bNAbs in vivo. In addition, the capacity to restrict viral escape is likely to be an equally critical parameter for the efficacy of bNAbs. Results from bNAb monotherapy trials indicate that combinations of antibodies are required to reduce the development of viral resistance. All current combination studies target two non-overlapping epitopes (CD4 binding site and V3 loop; V1/V2 loop and V3 loop; CD4 binding site and MPER of gp41) (Fig. 1). Strategies that target more than two epitopes may further impede the development of viral resistance as well as increase the probability of capturing partially resistant variants. As an alternative to antibody combinations, bi- or tri-specific antibody-like molecules have been demonstrated to have similar or enhanced antiviral activity and clinical trials are about to be initiated [53, 64, 102, 103]. Finally, combinations of antibodies that bind to overlapping epitopes may restrict escape pathways for the given target [87]. This may be particularly effective for antibody target sites that are limited in their capacity to accommodate mutations.

Viral strains differ in their sensitivity to antibodies. Moreover, the HIV-1 envelope protein diversifies in response to the autologous immune response and different viral variants co-exist within one person. Thus, the selection of bNAbs needs to be tailored to an individual's viral quasispecies to prevent treatment failure. Phenotypic sensitivity assays of viruses derived from bulk T cell outgrowth cultures fail to detect pre-existing resistant variants in a relevant number of cases [75, 76, 96–98]. Limiting dilution outgrowth assays increase the sensitivity, however, they are time-consuming and costly [98, 104]. In contrast to phenotypic testing, antiretroviral therapy is mostly guided by prediction models based on viral sequences [105]. Similar approaches based on *env* sequences are under development but will need to be confirmed in prospective settings [106, 107].

While terminal elimination half-lives of most antiretroviral drugs range between a few hours to 2 days, the half-lives of bNAbs are measured in weeks and result in long periods of effective plasma concentrations after a single administration. Notably, these periods can be further extended by modifications of the antibody Fc domains that enhance the affinity to the neonatal Fc receptor [108]. For example, the M428L and N434S ("LS") mutations prolong antibody half-life without compromising antigen-binding or other Fc-mediated functions [109]. Indeed, the LS variant of VRC01 demonstrated a half-life of ≈70 days in healthy individuals, which is a nearly 5-fold increase compared to the unmodified VRC01 [110]. The extended half-life of LS variants is also reflected in prolonged protective activity in pre-clinical studies [70, 71]. Thus, LS-modified bNAbs may facilitate dosing every few weeks to several months for treatment or even less frequently for prevention.

Compared to the ease of oral application of most regular antiretroviral drugs, the intravenous route employed in most clinical trials of bNAbs can be impractical. Subcutaneous (s.c.) injection, however, allows for easy (self-) administration and bNAbs have shown similar half-lives when given s.c. or i.v. [77, 78, 94, 110]. While antibody peak concentrations are lower after s.c. application and injection volumes pose restrictions, these limitations can be compensated by advances in antibody formulations and extended half-lives. Finally, antibodies can be administered topically and vaginal application of anti-HIV-1 bNAbs was generally safe in clinical trials [111, 112]. In proof-of-concept studies, this strategy protected animals from infection [113–115]. While these findings would need to be confirmed in humans, adherence to repeated and timely administration is a critical and potentially limiting factor for the efficacy of topically applied antibodies [116].

Going forward and beyond neutralization

Despite substantial differences in their modes of action, both antiretroviral drugs and bNAbs suppress viremia. Thus, bNAbs may provide a treatment option for individuals infected with ART-resistant viruses as well as for individuals suffering from side effects or toxicities caused by ART. Effective ART with three active drugs leads to rapid reduction of high viral loads to levels undetectable by standard clinical assays. Whether this can be equally achieved by bNAb combinations remains to be determined. However, first results suggest that bNAb-mediated therapy is particularly effective in individuals with low or suppressed starting viral loads [95, 96, 98]. Therefore, an initial phase of ART followed by bNAb-mediated therapy is a promising strategy for long-term control of the virus. For all of these approaches, as well as for the potential application of bNAbs for pre-exposure prophylaxis, the long half-life of bNAbs can significantly reduce the burden of daily medication and the need for meticulous adherence.

Broadly neutralizing antibodies differ from classical antiretroviral drugs in that they directly target the circulating virus, recognize HIV-1-infected cells expressing HIV-1 Env and can engage with the host immune system. Indeed, Fc-mediated interactions have been demonstrated to be important for effective bNAb-mediated (S)HIV control and prevention in animal models [51, 52, 92, 93]. In addition, passively administered bNAbs can influence the extent of the autologous antiviral immune response. For example, a single infusion of 3BNC117 was associated with the development of enhanced host neutralizing antibody activity in HIV-1-infected individuals [117], corroborating similar observations made in SHIV-infected animals [118–121]. Moreover, bNAb therapy has been associated with enhancement of cellular immune responses [93, 122, 123]. Notably, administration of bNAbs 3BNC117 and 10-1074 during early SHIV-infection resulted in long-term viral suppression. As demonstrated by rapid viral rebound after $CD8^+$ T cell depletion, viral suppression was effectively mediated by T cells when the antibodies were no longer detectable in the serum [123]. Whether these effects can be exploited for an improvement of clinical outcomes in humans remains to be determined. In particular, the potential effects of bNAbs given during acute or early infection will be important to investigate in clinical trials.

Additionally, bNAbs contribute to the elimination of HIV-1-infected cells [93]. This activity may also extend to the clearance of viral foci established early after exposure [58, 66]. The capacity of antibodies to mediate the elimination of HIV-1-infected cells will become particularly relevant in strategies that target the HIV-1 reservoir. However, no significant changes in the size of the circulating latent reservoir were observed after the infusion of 3BNC117 or VRC01 to individuals on ongoing suppressive ART, or after the combined administration of 3BNC117 and 10-1074 during interruption of ART [94, 98, 124]. However, these studies had relatively short observation periods (up to a few months), involved only a low number of antibody infusions and mainly included individuals with chronic HIV-1 infection. All of these factors may have limited bNAb-mediated effects on the viral reservoir or their detection.

Stimulation and induction of HIV-1 Env expression on the surface of latently infected cells make them an approachable target for bNAbs that can mediate their clearance by engaging the host immune system (so-called shock and kill approach). Indeed, when bNAbs were combined with latency-reversing agents (LRAs), long-term viral suppression was observed in a fraction of (S)HIV-infected humanized mice and macaques [52, 125]. To investigate this concept in humans, the histone deacetylase inhibitor romidepsin is being studied in combination with 3BNC117 (NCT02850016, NCT03041012) as well as in combination with 10-1074 and experimental therapeutic vaccines (NCT03619278). When given to ART-treated individuals, romidepsin has been shown to result in transient viremia [126]. While the effects of romidepsin given in combination with bNAbs will be important to determine, latency-reversing strategies will likely require further optimization such as combinations of LRAs or use of additional drugs (e.g., interferon alpha [127]).

Conclusions

Newly identified highly potent broadly neutralizing anti-HIV-1 antibodies have rapidly advanced from pre-clinical experiments to clinical trials that have demonstrated their safety and significant antiviral activity. Moreover, these studies have improved our understanding on how to establish bNAb interventions for clinical practice.

Preventing the development of viral resistance is a key factor for effective bNAb-mediated therapy and, similar to antiretroviral drugs, combinations of antibodies or poly-specific antibody variants will be required to increase the barrier for HIV-1 escape. In determining optimal combination partners, factors beyond mere HIV-1 coverage will be relevant and are likely to include the efficacy in restricting viral escape pathways. Equally important, improved and reliable screening methods are needed to guide clinicians in bNAb selection and the identification of candidates for effective bNAb therapy.

Ongoing and planned trials will aid in the development of effective treatment and prevention strategies. In particular, bNAbs appear to be especially useful in maintaining viral suppression in a setting of ART interruption. Moreover, antibodies may contribute to a reduction in the reservoir of HIV-1-infected cells as part of future cure strategies. Finally, modified antibody variants with substantially increased half-lives facilitate infrequent dosing of antibodies, and improved formulations will allow for alternatives to i.v. application that will be of particular interest for the use of bNAbs in prevention.

By limiting disease progression and reducing viral transmission, antiretroviral drugs have profoundly affected the course of the HIV-1 pandemic. With highly potent broadly neutralizing antibodies now demonstrating their impressive potential in pre-clinical and clinical settings, novel agents for the treatment and prevention of HIV-1 infection have come into the reach of clinical reality. Delineating the critical factors for successful application of bNAbs will be essential to exploit the unique capabilities of antibodies to benefit HIV-1-infected patients and those at risk of acquiring HIV-1 infection.

Abbreviations

AAV: adeno-associated virus; ART: antiretroviral therapy; ATI: analytical treatment interruption; bNAb: broadly neutralizing antibody; Env: envelope protein; Fc: fragment crystallizable; HIV: human immunodeficiency virus; IC: inhibitory concentration; iv: intravenously; LRA: latency-reversing agent; MPER: membrane proximal external region; NHP: non-human primate; sc: subcutaneously; SHIV: simian/human chimeric immunodeficiency virus.

Authors' contributions

Both authors wrote the manuscript, and prepared the figure. Both authors read and approved the final manuscript.

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