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Broadly-Neutralizing Antibodies (bNAbs) for the Treatment and Prevention of HIV Infection

Marina Caskey

Laboratory of Molecular Immunology, The Rockefeller University, New York, NY, USA

Abstract

Purpose of review: Several anti-HIV-1 broadly neutralizing antibodies (bNAbs) with exceptional breadth and potency and targeting different HIV-1 envelope epitopes have entered clinical trials. bNAbs are being evaluated for their potential as long-acting alternatives to antiretrovirals in HIV-1 prevention and therapy, and for potential role in strategies aiming at long-term viral remission. Here, we discuss recent findings from bNAb clinical studies.

Recent findings: bNAbs targeting distinct HIV-1 envelope epitopes have shown, in general, favorable safety profiles, and engineered bNAb variants have demonstrated improved pharmacokinetics. Single bNAb infusions transiently decreased viremia with subsequent selection of escape variants, while a combination of two bNAbs successfully maintained viral suppression in individuals harboring antibody-sensitive viruses after antiretroviral therapy (ART) was discontinued. Studies in animal models suggest that bNAbs can modulate immune responses and potentially interfere with the establishment or composition of the latent reservoir, and ongoing clinical studies aim to assess potential bNAb-mediated effects on HIV-1 persistence and host immune responses.

Summary: Early clinical studies support additional evaluation of bNAbs. Antibodies may offer advantages over standard ART for HIV-1 prevention and therapy, and as components of immunologic strategies to achieve sustained virologic control. The evaluation of engineered bNAbs with multi-specificity, extended half-lives and increased potency as well as alternative bNAb-delivery systems are being pursued.

Keywords

broadly neutralizing antibodies; clinical trials; HIV reservoir; HIV cure

Introduction

Combination antiretroviral therapy (ART) revolutionized the treatment of HIV-1 infection and showed efficacy in prevention. However, ART does not eradicate established infection and worldwide HIV incidence rates have continued to decline slowly [1]. The search for

Author of correspondence: Marina Caskey, MD. Laboratory of Molecular Immunology, The Rockefeller University, New York, NY 10065, USA. Tel:+1 212 327 7396; mcaskey@rockefeller.edu.

Conflicts of interest

The author has no conflicts of interest.

novel preventive and therapeutic interventions remains a high priority. Antibodies are an attractive new therapeutic modality against HIV because not only can antibodies directly target specific viral epitopes, but they also have the potential to harness host immune responses [2]. Single cell antibody cloning methods enabled the identification and subsequent characterization of bNAbs with remarkable potency and breadth in comparison to previously identified anti-HIV-1 neutralizing antibodies [3,4]. These highly potent new generation bNAbs are a promising new strategy against HIV-1 [5–7]. Several bNAbs with different envelope specificities have entered clinical evaluation in the last 5 years [8–15] (Table 1). Here we will focus on the clinical potential of anti-HIV bNAbs that have entered clinical trials. We will review available results of bNAb clinical trials, and discuss existing challenges to the clinical development of bNAbs.

Safety and Pharmacokinetics of New Generation Broadly Neutralizing Antibodies

Passive transfer of antibodies against HIV-1 was first tested clinically in the early 1990s with pooled polyclonal antibodies. Subsequently, a series of studies tested first generation monoclonal antibodies in the context of ongoing viremia or during ART interruption (reviewed in [16]). While generally safe, the antibodies showed limited antiviral activity, which led investigators to abandon passive bNAb immunotherapy for HIV-1 infection until highly broad and potent bNAbs became available. Several new generation bNAbs are undergoing clinical testing, including two phase 2b efficacy studies in HIV-uninfected individuals (NCT02716675, NCT02568215). The safety, pharmacokinetics and antiviral activity of antibodies targeting two non-overlapping epitopes on the HIV-1 envelope trimer, the CD4 binding site (3BNC117, VRC01, VRC01LS, VRC07–523LS) [8–10,12,13,15] and the base of the V3 loop (10–1074, PGT121) [11,14] have been reported to date. Antibodies targeting other neutralization epitopes, such as the V1/V2 loop (PDGM-1400; NCT03205917, NCT03721510) and the Membrane Proximal External Region (MPER; 10e8; NCT03565315), and another CD4bs antibody (N6LS; NCT03538626) have also entered clinical trials. In addition, studies evaluating a bi-specific (10E8.4/iMab, NCT03875209) [17] and a tri-specific antibody (SAR 441236, NCT03705169) [18] have also been initiated. To date, bNAbs have been evaluated in different populations and clinical scenarios, including HIV-exposed newborns [19], HIV-uninfected adults [8,9,11–13,20,21], and HIV-infected adults who initiated ART during primary infection [22], during ongoing viremia in chronic infection [8,10,14,15,23], during suppressive ART [8,10,11,23,24] as well as during ART interruption [3,24–26].

Single and repeated bNAb administrations have been generally well-tolerated with infrequent adverse events reported. The antibodies have maintained expected neutralizing activities in serum, and anti-drug antibody responses interfering with antibody activity or clearance rates have not been reported [9,20,21]. Two ongoing phase 2b studies are evaluating the protective efficacy of VRC01 in adults at risk to acquire HIV in sub-Saharan Africa and in the Americas. These studies enrolled over 4,000 participants to receive VRC01 or placebo on a bi-monthly basis over 18 months (NCT02716675, NCT02568215). Enrollment is completed and results are expected in 2020.

Naturally occurring antibodies tested to date have shown expected half-lives for IgG1s of 2 to 3 weeks in HIV-uninfected adults [8,9,11,20,21]. Available results also showed that decay curves are similar after repeated dosing and half-lives are maintained when antibodies are given in combination [20,21,27]. Reported half-lives were shorter in viremic HIV-infected individuals [8,10,11,23], likely as a result of more rapid clearance in the presence of antigen, but did not appear significantly shorter during suppressive ART or ART interruption [23,24,26].

Engineered antibodies designed to have extended half-lives and increased potency and breadth have also been evaluated. VRC01-LS is a modified version of VRC01 designed to extend serum half-life through increased binding affinity to the neonatal Fc receptor, which results in recirculation of antibody into serum following cellular endocytosis [28]. In HIV-uninfected individuals, VRC01-LS showed an elimination half-life of 71 +/− 18 days, which is more than 4-fold longer than the half-life of the unmodified antibody [12]. VRC07–523LS, another CD4-binding site antibody engineered for increased breadth and potency as well as longer half-life, showed serum half-life of 38 days after intravenous administration and 33 days after subcutaneous administration in HIV-uninfected individuals. Sera containing VRC07–523LS displayed equivalent or greater neutralization activity against a panel of genetically diverse pseudoviruses than sera containing VRC01 or VRC01LS even at lower serum concentrations, confirming its enhanced neutralization characteristics in vitro [13].

Long-term delivery of bNAbs through antibody gene transfer is another strategy to extend bioavailability. A recombinant adeno-associated virus (rAAV) vector encoding the gene for PG9, which targets the V2 loop of HIV-1 envelope, was evaluated in a phase 1 study and showed favorable safety profile. However, the construct tested led to low circulating antibody levels, while inducing anti-vector and neutralizing anti-PG9 antibody responses [29]. Whether the occurrence of anti-antibody responses was related to the specific antibody gene insert or to the level of antibody expression is unclear. This study highlighted the challenges of achieving sufficient protein expression while avoiding or limiting anti-vector or anti-antibody immune responses that abrogate antibody function. An ongoing phase 1 study is assessing a rAAV8 vector expressing the anti-HIV-1 CD4 binding site antibody VRC07 and results are expected soon (NCT03374202).

Antiviral Activity of New Generation Broadly Neutralizing Antibodies

Single bNAb infusions have led to transient decline in viremia in the range of 1.5 $\log_{10}$ copies/ml in most evaluated participants (range 3BNC117: 0.8–2.5 $\log_{10}$ copies/ml, VRC01: 1.1–1.8 $\log_{10}$ copies/ml, 10–1074: 0.9–2.1 $\log_{10}$ copies/ml). Following 3BNC117, viremia levels remained significantly lower than baseline levels for 28 days after infusion (mean decline 1.48 $\log_{10}$ copies/ml) [8]. Similar antiviral activity was observed with 10–1074 (mean decline of 1.52 $\log_{10}$ copies/ml), which targets a non-overlapping epitope on HIV-1 envelope [11]. VRC01, which targets the same site as 3BNC117, produced similar but somewhat less pronounced results (median decline 1.35 $\log_{10}$ copies/ml) [10]. Selection of resistant variants were reported in all three studies, however it appeared to occur more readily and in all participants following 10–1074 administration. In these first studies, full

viral suppression was only achieved transiently in participants with low starting viral load levels (viral load (VL) < 1,000 copies/ml). Two other phase 1 studies recently evaluated PGT121, which binds to the base of the V3 loop as 10–1074, and VRC07–523LS in viremic individuals and final results are expected in the near future [14,15].

bNAb monotherapy was also tested in the context of analytical treatment interruption (ATI). Two studies evaluated 3BNC117 monotherapy in chronically-infected individuals who achieved viral suppression on ART and another study evaluated VRC01. In contrast to previous studies [30,31], the two 3BNC117 studies showed delay in viral rebound in comparison to historical controls (8.4 and 5.5 weeks [24,32]) and restriction of viral populations emerging from the reservoir. Moreover, a small number of the participants maintained viral suppression until 3BNC117 levels fell below 20 μg/ml suggesting that selection of pre-existing escape variants or development of *de novo* resistance to 3BNC117 did not occur. In contrast, the effects of VRC01 were more limited (median time to VL > 200 copies/ml was 4 weeks) and reflected the prevalence of pre-existing resistance to VRC01 in this cohort of participants not selected for bNAb sensitivity [25]. A recently reported study evaluating VRC01 monotherapy in Thai adult participants who initiated ART during acute HIV-1 infection (i.e. Fiebig stages I–III) showed very similar results. The median time to plasma HIV-1 RNA > 1,000 copies/ml was 33 days in the group receiving VRC01, and not statistically different from the median time of 14 days in the placebo group [22]. These bNAb monotherapy studies led to the overall conclusion that while these antibodies have significant antiviral activity, they resemble small molecule antiretroviral drugs in that monotherapy with either modality selects for HIV-1 resistant variants.

The idea that bNAb combinations will provide broader antiviral coverage and therefore be more effective against HIV-1 than monotherapy was tested in the context of viremia and analytical treatment interruption using 3BNC117 and 10–1074, which target non-overlapping sites on the HIV-1 envelope. Seven viremic participants received one or three infusions of 3BNC117 and 10–1074. The 4 individuals with sensitive viruses experienced a more pronounced decline in viremia than observed during monotherapy, an average of 2.05 $\log_{10}$ copies/ml, and viremia remained significantly reduced for 3 months. However, complete suppression was only seen in one participant with low starting viral load (730 copies/ml). Interestingly, none of the 4 participants who were initially sensitive to the two antibodies developed *de novo* resistance to 3BNC117, despite residual viremia for several weeks and frequent recombination events between circulating viruses. In keeping with the previously reported shorter half-life of 3BNC117, there was a period of 10–1074 monotherapy at the end of the observation period which coincided with the emergence of 10–1074 resistant variants. Thus, dual bNAb combination therapy was more effective than monotherapy in viremic individuals, but it did not completely suppress viremia in participants with high baseline viral loads [23].

In contrast to active viremia, the combination of 3BNC117 and 10–1074 maintained full viral suppression in ART-treated individuals who harbored bNAb-sensitive viruses when they discontinued ART and received combination antibody infusions over 6 weeks. The median time to rebound for 7 of the 9 antibody-sensitive participants who experienced viral rebound during the study period was 21 weeks (range 15–26 weeks). The two remaining

participants maintained viral suppression for over 30 weeks. The average 3BNC117 serum concentration at the time of rebound in the sensitive participants was 1.9 μg/ml. In contrast, the average serum concentration of 10–1074 at rebound was 14.8 μg/ml. As seen in the viremic cohort, the difference in antibody concentrations at the time of rebound is again consistent with the longer half-life of 10–1074 which resulted in a period of 10–1074 monotherapy and selection for resistance. However, there was no emergence of double-resistant viral variants. These results demonstrate that the combination of 3BNC117 and 10–1074 is effective in maintaining suppression for extended periods of time in individuals harboring HIV-1 strains sensitive to the antibodies [26]. Ongoing and planned studies will evaluate if the period of bNAb-mediated viral suppression can be extended further, by repeated administration of the parental antibodies (NCT03526848, NCT03571204) or by long-acting variants. In addition, different combinations including bNAbs with specificity for three distinct epitopes on the envelope trimer (e.g. PGT121, PDGM1400 plus VRC07–523LS, and VRC07–523LS plus 10–1074) are undergoing clinical evaluation (NCT03205917, NCT03721510, NCT03707977). Two engineered antibodies, one with specificity for CD4 and the MPER (10E8.4/iMab, NCT03875209) [17] and the second with specificity for the CD4bs, V2 loop and MPER (SAR441236, which contains the anti-HIV binding domains of VRC01, PDGM1400 and 10e8; NCT03705169)[18] are being tested in viremic individuals. The expected advantages of these multi-specific antibodies are that they will provide broader and more potent antiviral coverage, at a lower overall cost, and will have a more streamlined clinical development path than single-specificity antibody combinations [33]. It will be interesting to see if these engineered molecules will maintain the favorable safety profiles of the naturally occurring bNAbs tested to date and will not induce clinically significant anti-antibody responses that affect half-life and activity.

Effects on the Latent Reservoir and on anti-HIV-1 Host Immune Responses

In addition to their direct antiviral activity and potential role in HIV-1 prevention and treatment, anti-HIV-1 bNAbs are also being explored in cure strategies. Antibodies are among the key modulators of immunity and differ from ART in that they can recruit immune effector functions through their Fc domains [2]. Antibodies accelerate clearance of viruses and infected cells, and antigen-antibody immune complexes are potent immunogens that can foster development of host immune responses [2,34,35]. Studies in humanized mice and non-human primates have explored the possibility that bNAbs might induce prolonged HIV-1 remission or cure [36–38]. Nishimura et al. evaluated the effects of the combination of 3BNC117 and 10–1074 in the absence of ART during early $SHIV_{AD8}$ infection. In contrast to ART, 6 of 13 animals achieved long-term viral control, and an additional 4 became elite controllers. Infusion of a T-cell-depleting anti-CD8β monoclonal antibody led to the rapid reappearance of viremia. These results demonstrate that immunotherapy can facilitate the emergence of potent CD8+ T cell immunity that can durably suppress virus replication [37]. Related results were obtained in $SHIV_{SF162.P3}$-infected animals who initiated ART seven days after infection, and were subsequently treated with a combination of PGT121 and a TLR 7 agonist during ART suppression. After a bNAb wash out period, ART was discontinued and animals with higher initial levels of $SHIV_{SF162.P3}$ viremia maintained viral suppression by a CD8+ T cell mediated mechanism. In contrast, animals

with the lowest initial viral loads appeared to clear the infection entirely. Whether or not CD8+ T cells contributed to infection clearance could not be determined [38].

Limited data is available on the effects of bNAbs on the latent HIV-1 reservoir in humans. Two infusions of VRC01 or 3BNC117 administered during ART suppression did not interfere with reservoir size or composition [10,24,39]. Similarly, repeated infusions of 3BNC117 and 10–1074 during analytical treatment interruption did not lead to statistically significant changes in the reservoir. Although different viral clones expanded and contracted over time, these fluctuations did not appear related to the bNAb infusions [26]. It is possible that more prolonged treatment with potent bNAb combinations will affect the latent HIV-1 reservoir. Alternatively, since engagement of Fc-mediated effector functions requires sustained cell surface binding of bNAbs to Env [40], the immunomodulatory effects of bNAbs may require their use in combination with potent latency reversing agents, or other immunomodulatory strategies, such as toll-like receptor agonists, cytokines, checkpoint blockade inhibitors or therapeutic vaccines. In parallel, modified antibodies with enhanced Fc functions [41] and bi-functional antibodies, which bind to HIV-1 envelope while also engaging other cellular receptors such as CD3 [42,43], are also being considered.

Studies have also begun to explore potential effects of bNAbs on anti-HIV-1 immune responses. In chronically-infected participants, a single infusion of 3BNC117 transiently reduced viremia and was associated with increased breadth and potency of host humoral immunity to HIV-1 [44]. However, the effects of bNAbs on cellular immune responses has not yet been clearly demonstrated. During short periods of ART interruption, 3BNC117 monotherapy did not appear to expand T cell responses while viral suppression was maintained [32]. The combination of 3BNC117 and 10–1074 led to longer periods of viral suppression after ART discontinuation, including two individuals that continued to maintain suppression for over 30 weeks. Whether antibody-enhanced T cell responses contributed to the prolonged control in these two participants and whether this effect can be enhanced by immune modulators or other strategies remains to be determined [26].

Challenges and Future Directions

Emerging data has suggested that current bNAbs may not be as broad or potent as predicted by in vitro assays [25,26,32,45], and this is an important potential limitation to this strategy. Moreover, while available data suggest that escape from CD4bs antibodies may be harder to achieve than escape from antibodies targeting the V3 loop [8,11,23,24,26,44], it is not yet known if antibody combinations targeting a specific subset of Env vulnerability sites will show superior efficacy. Therefore, reliable clinical assays to predict antibody resistance, and additional antibody combinations or antibody plus long-acting ARV combinations will be required for this type of therapy to become generally applicable.

On a more practical level, in order for bNAbs to be widely adopted for the treatment, prevention, and possibly eradication of HIV-1 infection, production and distribution costs will need to be reduced. A number of strategies are currently being investigated, including bNAbs with modifications of the Fc domain to extend bioavailability, antibodies with multi-

specificity and alternative delivery systems. Advances in manufacturing methods may also significantly reduce the production and distribution costs of monoclonal antibodies.

Conclusion

BNAbs may offer advantages over standard ART for both the prevention and treatment of HIV-1 due to their favorable safety and pharmacokinetic profiles, which might allow bi-annual or less frequent dosing. In addition, monoclonal antibodies alone or in combination with other immunomodulatory strategies may enhance HIV-1 immunity leading to long term viral remission, as seen in cancer immunotherapy. The available preclinical and clinical data support additional studies of novel bNAbs and bNAb combinations to elucidate the mechanisms underlying protection and sustained virologic control, and establish the role of bNAbs in the clinical management of HIV-1.

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Key Points

- Early clinical trials have demonstrated that naturally occurring new generation broadly neutralizing anti-HIV-1 antibodies (bNAbs) are safe, have half-lives of approximately 2–3 weeks, and reduce viremia by approximately 1.5 $\log_{10}$ copies/ml. However bNAb monotherapy selects resistant escape variants.
- Current bNAbs may not be as broad and potent as predicted by in vitro assays. New screening methods to better predict in vivo bNAb sensitivity are needed.
- A combination of two bNAbs successfully maintained viral suppression in participants harboring viruses sensitive to both antibodies, and prevented the selection of de novo resistance.
- Unlike ART, bNAbs can engage the host immune system through Fc effector functions, which may allow for the clearance of latently infected cells. Clinical studies have not yet demonstrated significant effects on the latent reservoir or clear modulation of cellular immune responses.
- Combinations of bNAbs and/or multi-specific antibodies with extended half-lives and increased potency are promising new strategies to the prevention, treatment, and possibly cure of HIV-1.

Table 1.

Anti-HIV-1 broadly neutralizing antibodies in clinical development

Products		Target Site	Study Enpoints being Evaluated	References and/or Clinicaltrials.gov registry numbers [NCT]
Single Antibodies	**VRC01**	CD4bs	Safety and PK in HIV− and HIV+ adults and exposed infants	[9, 10, 19, 20, 22, 25, 39]
			Antiviral activity during viremia and analytical treatment interruption	[NCT02716675, NCT02568215, NCT02256631]
			Efficacy to prevent sexual transmission	
	3BNC117	CD4bs	Safety and PK in HIV− and HIV+ adults	[8, 24, 32]
			Antiviral activity during viremia and analytical treatment interruption	
	10–1074	V3 loop	Safety and PK in HIV− and HIV+ adults	[11]
			Antiviral activity during viremia	
	PGT121	V3 loop	Safety and PK in HIV− and HIV+ adults	[14]
			Antiviral activity during viremia	
	PDGM-1400	V2 loop	Safety and PK in HIV− and HIV+ adults	[NCT03205917]
			Antiviral activity during viremia	
	VRC01-LS	CD4bs	Safety and PK in HIV− and HIV+ adults and exposed infants	[12, 15]
			Antiviral activity during viremia	[NCT02256631]
	VRC07–523LS	CD4bs	Safety and PK in HIV− and HIV+ adults and exposed infants	[13, 15]
			Antiviral activity during viremia	[NCT02256631]
	3BNC117-LS	CD4bs	Safety and PK in HIV− and HIV+ adults	[NCT03254277]
	10–1074-LS	V3 loop	Safety and PK in HIV− and HIV+ adults	[NCT03554408]
	10E8VLS	MPER	Safety and PK in HIV− adults	[NCT03565315]
	N6LS	CD4bs	Safety and PK in HIV− adults	[NCT03538626]
Antibody combinations	**3BNC117** & **10–1074**	CD4bs, V3 loop	Safety and PK in HIV− and HIV+ adults	[21, 23, 26]
			Antiviral activity during viremia and analytical treatment interruption	[NCT03526848, NCT03571204]
	PGT121 & **PGDM1400**	V3 loop, V2 loop	Safety and PK in HIV− and HIV+ adults	[NCT03205917]
			Antiviral activity during viremia	
	3BNC117-LS & **10–1074-LS**	CDbs, V3 loop	Safety and PK in HIV− and HIV+ adults	[NCT03554408]
	VRC07–523LS & **10E8VLS**	CD4bs, MPER	Safety and PK in HIV− adults	[NCT03565315]
	VRC01-LS & **10–1074**	CD4bs, V3 loop	Safety, PK in HIV+ children	[NCT03707977]
			Antiviral activity during analytical treatment interruption	
	VRC01 & **10–1074**	CD4bs, V3 loop	Antiviral activity during sequentiall ART interruption periods	[NCT03831945]
	VRC07–523LS & **10–1074**	CD4bs, V3 loop	Safety and PK in HIV− adults	[NCT03928821]

Products		Target Site	Study Enpoints being Evaluated	References and/or Clinicaltrials.gov registry numbers [NCT]
	VRC07–523LS & **PGT121**	CD4bs, V3 loop	Safety, PK in HIV− adults	[NCT03721510]
	VRC07–523LS & **PGT121** & **PGDM1400**	CD4bs, V3 loop, V2 loop	Safety, PK in HIV− and HIV+ adults	[NCT03721510, NCT03205917, NCT03928821]
			Antiviral activity during viremia and analytical treatment interruption	
Multi-specific antibodies	**SAR441236**	CD4bs, V2 loop, MPER	Safety, PK in HIV+ adults	[NCT03705169]
			Antiviral activity during viremia	
	10e8.4/iMAb	CD4, MPER	Safety, PK in HIV− and HIV+ adults	[NCT03875209]
			Antiviral activity during viremia	
Antibody gene transfer	**AAV1-PG9**	V2 loop	Safety, PK in HIV− adults	[29]
	AAV8-VRC07	CD4bs	Safety, PK in HIV+ adults	[NCT03374202]