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Review Article

Broadly neutralizing antibodies targeting HIV: Progress and challenges

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ABSTRACT

Anti-HIV broadly neutralizing antibodies (bNAbs) offer a novel approach to treating, preventing, or curing HIV. Pre-clinical models and clinical trials involving the passive transfer of bNAbs have demonstrated that they can control viremia and potentially serve as alternatives or complement antiretroviral therapy (ART). However, antibody decay, persistent latent reservoirs, and resistance impede bNAb treatment. This review discusses recent advancements and obstacles in applying bNAbs and proposes strategies to enhance their therapeutic potential. These strategies include multi-epitope targeting, antibody half-life extension, combining with current and newer antiretrovirals, and sustained antibody secretion.

1. Introduction

The global prevalence of HIV continues to pose a substantial public health challenge, with millions of individuals affected. Those living with HIV require lifelong antiretroviral therapy (ART), which may lead to considerable toxicity and an increased risk of non-AIDS-associated comorbidities [1]. ART cannot cure HIV infection, as viral rebound typically occurs shortly after withdrawal due to persistent latent reservoirs. Without an effective vaccine, developing innovative therapeutic approaches is crucial for HIV management, particularly in high-burden regions such as Africa and Asia.

Passive transfer of therapeutic antibodies has been a longstanding treatment protocol for various diseases, including diphtheria and tetanus. Infused monoclonal antibodies have also demonstrated efficacy in treating a diverse range of conditions, such as cancer, autoimmunity, and pathogenic toxins. Concerning HIV, cutting-edge single-cell antibody cloning technology has led to the isolation of numerous anti-HIV broadly neutralizing antibodies (bNAbs) [2]. Although eliciting such bNAbs through vaccination remains elusive, their potential as a treatment for HIV infection is highly promising. This review examines recent advances and challenges associated with the therapeutic use of bNAbs and proposes novel strategies for addressing these obstacles.

2. Passive transfer of anti-HIV bNAbs

In recent years, several studies have highlighted the therapeutic potential of bNAbs in HIV-infected humanized mice, non-human primates, and humans. Early investigations employed first-generation bNAbs, such as 2G12, 2F5, and 4E10, demonstrating their safety and capacity to reduce viral load in HIV-infected individuals [3,4]. However, enthusiasm waned due to the rapid emergence of escape mutants [5]. Despite this, two independent studies assessed the therapeutic potential of these early bNAbs in individuals undergoing analytical treatment interruption (ATI) of ART. These studies documented a significant delay in viral rebound, ranging from 3 to 24 weeks after ART withdrawal [6,7]. Regrettably, 2F5 and 4E10 exhibit autoreactivity [8], while 2G12 demonstrates limited potency, with resistance observed in most HIV subtypes within a typical global panel [9]. Consequently, the undesirable characteristics of these first-generation bNAbs rendered them less appealing for therapeutic application, but they still provided a foundation for future treatment modalities.

In 2009, the development of a high-throughput HIV viral neutralization assay [10] and single-cell antibody cloning techniques [2] led to the isolation of second-generation bNAbs with significantly improved neutralization breadth and potency (Table 1). These antibodies target the seven highly conserved major epitopes of the HIV envelope glycoprotein (Env) (Fig. 1), including the CD4 binding site (CD4bs), the V1V2 glycan region, the V3-glycan region, the gp120-gp41 interface, the gp120 silent face, the gp41 MPER, and the gp41 fusion domain. The discovery of these second-generation bNAbs has renewed interest in antibody-mediated treatment [11–14]. However, given the diverse range of HIV subtypes with varying levels of antibody sensitivity encountered by humans, clinical trials are necessary to determine efficacy. The administration of bNAbs has been deemed safe and tolerable

Abbreviations: bNAb, Broadly neutralizing antibody; ART, Antiretroviral therapy; ATI, Analytical treatment interruption; ARV, Antiretrovirals.

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Table 1
Neutralization profiles and genetic features of anti-HIV bNAbs.

Epitope	bNAb	Neutralization Profiles			Genetic Features			Ref.
		Viral Panel	Breadth (%)	Potency (μg/ml)	V_H Somatic mutation (%)	HCDR3 length (AA)	Auto/poly reactivity	
	N49P7	176	98	0.20	38	19	ND	[193]
	N6	173	98	0.07	31	15	No	[194]
	1–18	119	97	0.05	32	18	ND	[195]
	12A12	170	94	0.19	20	13	Yes	[196]
	CH235.12	162	90	0.69	26	15	No	[197]
	VRC01	176	90	0.36	32	14	No	[176]
	VRC07	175	93	0.15	31	16	No	[198]
	VRC02	134	89	0.31	32	14	No	[176]
	3BNC117	176	86	0.12	24	10	Yes	[196]
	VRC13	176	86	0.18	43	21	ND	[199]
	NIH45–46	175	85	0.15	33	18	Yes	[196]
	VRC-CH31	174	83	0.25	36	15	Yes	[200]
	CH103	176	80	1.76	16	15	Yes	[201]
	VRC-PG04	171	80	0.27	29	16	No	[200]
	PG20	140	77	0.18	24	15	No	[177]
	8ANC131	142	75	2.30	26	18	Yes	[196]
	VRC-PG04b	137	71	0.21	29	16	No	[200]
	b12	176	47	2.84	33	18	Yes	[202]
	VRC23	139	61	2.29	22	14	No	[203]
	1B2530	167	59	2.73	28	18	Yes	[199]
	IOMA	176	52	2.31	12	19	ND	[204]
	VRC03	174	52	0.62	30	16	No	[176]
	8ANC134	136	49	0.97	27	18	Yes	[199]
	b12	176	47	2.84	12	20	No	[205]
	HJ16	176	39	0.92	18	29	ND	[199]
	VRC06	146	34	1.74	31	17	No	[206]
CD4 binding site	179NC75	92	30	0.16	24	25	ND	[207]
	10–1074	96	100	0.08	16	26	NR	[208]
	PGT128	176	70	0.07	20	21	NR	[178]
	PGT121	176	68	0.05	20	26	NR	[178]
	PGT130	98	64	0.20	22	19	No	[178]
	BG18	91	63	0.04	21	21	ND	[209]
	DH270.6	162	56	0.16	13	20	ND	[210]
	PGDM12	86	52	0.14	32	21	ND	[211]
	VRC41.01	99	52	0.31	21	21	ND	[212]
V3 glycan region	PGDM21	86	47	0.13	22	20	ND	[211]
	PCDN-33 A	93	46	0.48	12	22	ND	[213]
	PGT125	94	45	0.06	21	21	NR	[178]
	PGT127	93	41	0.11	16	21	NR	[178]
	438-B11	97	38	0.10	25	21	ND	[214]
	PGT135	176	36	0.43	19	20	NR	[178]
	VRC24	50	34	1.36	23	26	NR	[203]
	VRC29.03	162	28	1.69	15	20	ND	[215]
	2G12	176	27	2.20	21	16	Yes	[216]
	PGDM1400	176	82	0.02	27	34	ND	[217]
	PG9	176	80	0.11	15	30	No	[177]
	PG16	176	77	0.05	15	30	No	[177]
	PGT145	173	75	0.13	17	33	NR	[178]
	CAP256-VRC26.25	173	66	0.01	12	36	No	[218]
	PGT142	154	57	0.05	16	34	NR	[178]
	VRC26.08	176	55	0.02	12	37	ND	[219]
	CH01	172	53	1.20	17	26	No	[220]
	CH02	94	45	0.89	14	26	No	[220]
	PCT64-35S	87	37	1.10	13	25	ND	[221]
	VRC38.01	174	29	0.55	18	16	ND	[222]
V1V2 glycan region	BG1	91	37	0.67	27	22	ND	[209]
	4E10	176	99	1.55	7	20	Yes	[179]
	10E8	176	99	0.41	21	22	No	[223]
gp41 MPER	DH511.2	173	98	0.88	18	23	ND	[224]
	LN01	90	93	0.97	26	20	No	[225]
	2F5	176	56	2.09	14	24	Yes	[226]
	M66.6	127	25	15.18	4	23	Yes	[227]
	8ANC195	176	70	1.20	28	22	Yes	[196]
	PGT151	176	72	0.02	21	28	No	[180]
gp120 -gp41 interface	35O22	176	62	0.13	35	14	ND	[228]
	PGT152	89	61	0.02	20	28	No	[180]
	VRC34.01 (Fusion peptide)	162	54	0.31	15	13	ND	[229]
	ACS202 (Fusion peptide)	63	49	0.12	43	24	ND	[230]
	SF12	106	61	0.22	17	23	ND	[231]
gp120 Silent face	VRC-PG05	176	41	2.34	9	17	ND	[232]

in healthy [15–23] and HIV-infected individuals [24–29], and the most promising second-generation bNAbs are currently undergoing clinical trials.

2.1. Temporary viral suppression following bNAb monotherapy

Initial phase 1 clinical studies in HIV-infected individuals involved bNAbs targeting either the CD4 binding site (3BNC117 and VRC01) or the V3-glycan region (10–1074 and PGT121). A single infusion of 3BNC117, VRC01, PGT121, or 10–1074 in viremic individuals with bNAb-sensitive viruses resulted in an average reduction of 1.48, 1.10, 1.77, and 1.52 log10 viral copies/ml, respectively, from their pre-infusion baseline [24–27]. In these studies, viremia remained suppressed for up to 28 days following 3BNC117, 10–1074, and PGT121 administration [24,26,27]. However, viral rebound was inevitable due to the emergence of escape mutants, as observed with other antiretrovirals (ARVs) [30].

2.2. bNAb monotherapy during analytical treatment interruption (ATI)

Despite the resistance to monotherapy observed in untreated patients, some participants with significantly lower viral loads maintained viral suppression for two to six months [24,26,27]. These findings were likely attributable to reduced viral diversity in the individual or fewer opportunities for escape mutants to emerge [31]. Consequently, lowering viral diversity *via* prior ART may enhance the efficacy of bNAb monotherapy [32], as it is evident that combinations of ARVs can significantly limit viral escape.

Researchers tested this combinatorial approach in ART-treated patients who received bNAbs before ART discontinuation. These promising studies demonstrated effective viremia control and delayed viral rebound for 4 and 10 weeks with VRC01 or 3BNC117 monotherapy, respectively [29,33–35]. The eventual viral rebound was associated with either pre-existing bNAb resistance variants or waning bNAb levels, and interestingly, rebound viruses primarily arose from a single provirus. Nevertheless, 30% of 3BNC117 participants remained virally suppressed. Emerging viruses in all but one of these individuals remained susceptible to 3BCN117, suggesting that 3BCN117 effectively prevents escape mutants for up to 19 weeks [33]. We conclude that 3BNC117 exerts significant selective pressure on emerging viruses during ATI in humans.

In summary, these findings demonstrated the efficacy and safety of bNAbs in HIV-infected individuals. However, it is also evident that individual bNAbs can select resistance variants, highlighting their inability to provide durable viral suppression when administered alone.

2.3. Combination bNAb therapy

Multiple combinations of antiretroviral medications limit viral escape. Similarly, bNAb combinations should provide broader antiviral coverage and be more effective than single bNAbs. As an initial proof-of-concept, several studies showed that a combination of bNAbs achieved durable viral suppression in animal models [36–38].

A combination of 3BNC117 and 10–1074 in HIV-negative individuals was safe and well-tolerated [20]. When administered to HIV-positive patients undergoing ATI, the combination of bNAbs 3BNC117 and 10–1074 resulted in a delayed viral rebound of 21 weeks in individuals with bNAb-sensitive viruses without developing bNAb resistance [39]. Importantly, the same combination of bNAbs delayed viral rebound for up to 3 months in untreated HIV-viremic patients without bNAb resistance [40]. These results indicated that the combination of 3BNC117 and 10–1074 offers some degree of viral suppression in patients with bNAb-sensitive viruses, provided sufficient concentrations are maintained. For broader coverage, a recent phase 1 study explored the safety and efficacy of a triple combination of bNAbs targeting non-overlapping epitopes, including the CD4bs antibody VRC07–523LS, the V3-glycan antibody PGT121, and the V1V2 glycan antibody PGDM1400. In this study, a single infusion of the three bNAbs in untreated viremic patients was safe and well-tolerated, reducing viremia by approximately 2.04 log10 copies per ml from their day 0 baseline. However, viral rebound seemed inevitable, with a median of 20 days post-infusion [28]. Viral rebound was associated with the rapid development of escape mutants evading V1V2 and V3-glycan bNAbs and the decay of serum bNAb concentrations [28]. These studies demonstrated that bNAb combinations are generally safe and well-tolerated and suggest that these antibodies can maintain viral suppression if a) pre-existing viruses are bNAb-sensitive and b) therapeutic levels are maintained. Accordingly, optimal bNAb combinations and concentrations are necessary to achieve durable viral suppression in HIV-infected individuals.

Identifying the right combination of bNAbs is challenging due to the continuous mutation of HIV (Fig .2) [41]. Interestingly, in rare cases, ARV resistance, such as the development of escape mutations, can be advantageous for different bNAbs therapies. For instance, escape variants resistant to the fusion peptide inhibitors enfuvirtide and C34 exhibited increased susceptibility to several bNAbs, including VRC01 and 10e8 [42]. The reasons for the increased bNAb susceptibility are unclear. Further studies are needed to identify specific viral mutations that lead to ART resistance while rendering the virus more susceptible to bNAbs. These findings could help inform future combinations of various antivirals to combat resistance.

3. bNAb challenges

3.1. Viral resistance

3.1.1. Viral diversity within the host

The transmitted/founder (T/F) virus establishes infection during the initial acute infection [43]. The virus then evolves, escaping the immune attack and reaching maximum diversity over time [44]. Drug resistance is also associated with viral evolution. The high viral replication rate and error-prone reverse transcriptase can generate multiple recombination events, contributing to viral diversity [45]. Consequently, bNAbs continuously encounter a highly diverse pool of quasi-viral species.

Numerous studies strongly suggest that developing broad and highly potent neutralizing antibodies involves multiple rounds of viral escape from autologous neutralizing antibodies [46–48]. This process is associated with increased genetic diversity in the envelope protein [49], accumulating antibody-resistant variants [50–52]. In fact, about half of individuals infected with HIV develop immune responses within 4 to 5 years that can neutralize roughly 50% of tested viral strains [53], with 21–36% targeting the V3 glycan region, 5–26% targeting the CD4bs, and 12–14% directed towards the V1V2 glycan domain [54–56]. Individuals who generated neutralizing antibodies against the V2 apex, the CD4bs, or the V3 glycan region exhibited escape mutations in the corresponding epitopes [48,57,58]. Expectedly, these mutations affected the efficacy of bNAb-based therapeutic interventions, particularly in individuals with chronic infections [25,59]. However, viruses from patients who initiated ART during the acute infection stage (Fiebig stage I-III) are more sensitive to bNAbs [32], as the drug regimen significantly reduced the number of viral escape mutants due to small viral reservoirs and low viral diversity [35].

Neutralization breadth is defined as the percentage of virus neutralized by the respective bNAb. Potency is defined as the geometric mean bNAb concentration required to neutralize a broad viral panel (IC_{50}). Neutralization data were captured from CATNAP, as of 2023 [233]. Antibody genetic features were obtained from the HIV Molecular Immunology Database [234]. ND = data not available; Viral Panel = number of viruses tested.

3.1.2. Global genetic diversity of HIV

HIV exhibits considerable genetic variability, with nine genetic subtypes and an increasing number of circulating recombinant forms (CRFs) that differ in prevalence across geographic regions [60]. Genetic diversity within a subtype can range from 15 to 20%, while diversity between subtypes can be as high as 24–35% [61].

The HIV genome consists of nine genes that encode fifteen viral proteins, among which the Env protein displays the greatest genetic diversity. A recent study reported median differences in Env amino acid sequences within and between subtypes at 22% and 27%, respectively [62]. Consequently, with ongoing viral evolution at the population level [63,64], neutralization resistance has increased over the decades and will likely present significant challenges to future bNAb-based immunotherapy [65]. To be effective within geographic regions, bNAbs must overcome this Env genetic diversity, preferably across all subtypes.

Each virus subtype possesses unique antigenic properties due to genetic diversity, resulting in subtype-specific geographically associated antibody neutralization sensitivity (Table 2). Thus, the selection of bNAbs for immunotherapeutic applications requires careful consideration. Combining bNAbs that target non-overlapping Env epitopes and pre-screening selected bNAbs for viral resistance can minimize the risk of immunotherapeutic failure [40,66].

3.2. The latent viral reservoir

Despite ART, cells harboring latent provirus can expand in tissues and remain stable for years [67], posing a significant barrier to a cure. Among these latently infected cells, tissue-resident memory CD4 T cells are a primary reservoir in gut-associated lymphoid tissues and lymph nodes (LNs), containing higher levels of HIV nucleic acids than peripheral blood CD4 cells [68]. This phenomenon is likely due to poor penetration of ARVs [69,70] or higher concentrations of follicular helper T cells in LN germinal centers (GCs), a major source of latently infected CD4 T cells [71]. CD8 T and NK cells mediate robust cellular antiviral responses against HIV-infected cells, and this response is associated with slower disease progression in elite controllers [72,73]. However, therapeutic strategies aimed at inducing cellular immune responses to HIV have failed to control viral replication due to escape mutants [74] and cellular exhaustion [75,76]. Yet, potential strategies that involve infusing dual anti-HIV CAR (Chimeric Antigen Receptor) -T cells, which are also genetically engineered to produce functional bNAbs, could present a promising immunotherapy solution.

3.3. bNAb decay

Maintaining a stable serum concentration of passively transferred bNAbs is crucial for determining their therapeutic efficacy. Rapid HIV rebound and the emergence of escape variants are associated with significant bNAb decay [28,35], which depends on antibody half-life. The half-life of passively transferred anti-HIV bNAbs is approximately 2–3 weeks in healthy individuals [20,22] and even shorter in HIV-infected viremic patients, with an average half-life of around 10 days [24–26], presumably due to the rapid clearance of antigen-antibody complexes [40]. Therefore, antibody engineering and gene transfer technologies should focus on producing longer antibody half-lives and sustained antibody release to achieve durable viral suppression.

4. Strategies to improve bNAb immunotherapy

4.1. Combinations of bNAbs with ART

Viral diversity poses a significant challenge to bNAb immunotherapy. Even with triple combinations of bNAbs, escape variants have emerged in clinical studies [28,39]. One strategy to overcome viral escape is to reduce viral diversity within the host by combining bNAbs with ART (Fig .2). ART substantially limits viral diversity in both circulating and latent viruses [31,77,78]. Studies have demonstrated that participants who initiated ART during the acute infection phase had significantly reduced genetic variants and were more susceptible to bNAbs [32,52]. Consequently, a significant reduction in the likelihood of escape mutants is expected when treated with bNAbs and ART. Two trials are currently in progress (NCT02591420, NCT05719441) to determine if bNAbs in combination with daily ART can prevent the emergence of escape mutants, providing long-term viral suppression in infected patients.

Recently, long-acting ARVs, cabotegravir and rilpivirine, have demonstrated durable viral suppression for up to 2 months in HIV-infected individuals when administered together [79]. A newer long-acting ARV, lenacapavir, has provided at least six months of HIV suppression as a standalone treatment [80]. Combining bNAb therapy with newer long-acting ARVs should enhance the efficacy of both modalities. Indeed, six monthly lenacapavir injections and a single infusion of bNAbs (10–1074-LS and 3BNC117-LS) maintained undetectable viral loads for 26 weeks in HIV-infected individuals [81]. Therefore, combining bNAbs with long-acting ARVs could represent a potent treatment strategy that provides patients with long-lasting viral suppression without requiring a daily drug regimen.

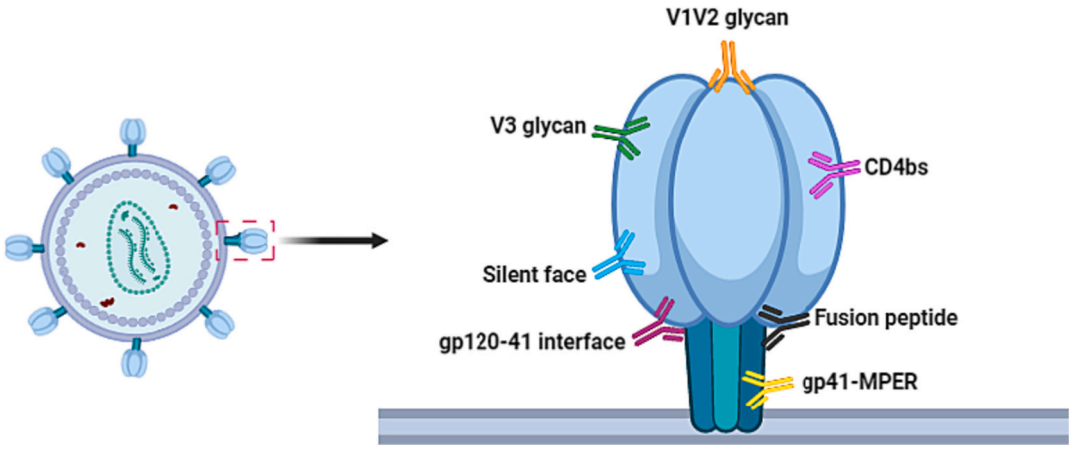

Fig. 1. HIV Env epitopes. bNAbs targeting the major Env epitopes are indicated as follows: V3 glycan–green; V1V2 glycan–orange; CD4 binding site (bs)–pink; fusion peptide- black; gp41 membrane proximal region (MPER)–yellow; gp120–41 interface-magenta and Silent face-blue. See Table 1 for references of anti-HIV bNAbs and their respective epitopes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

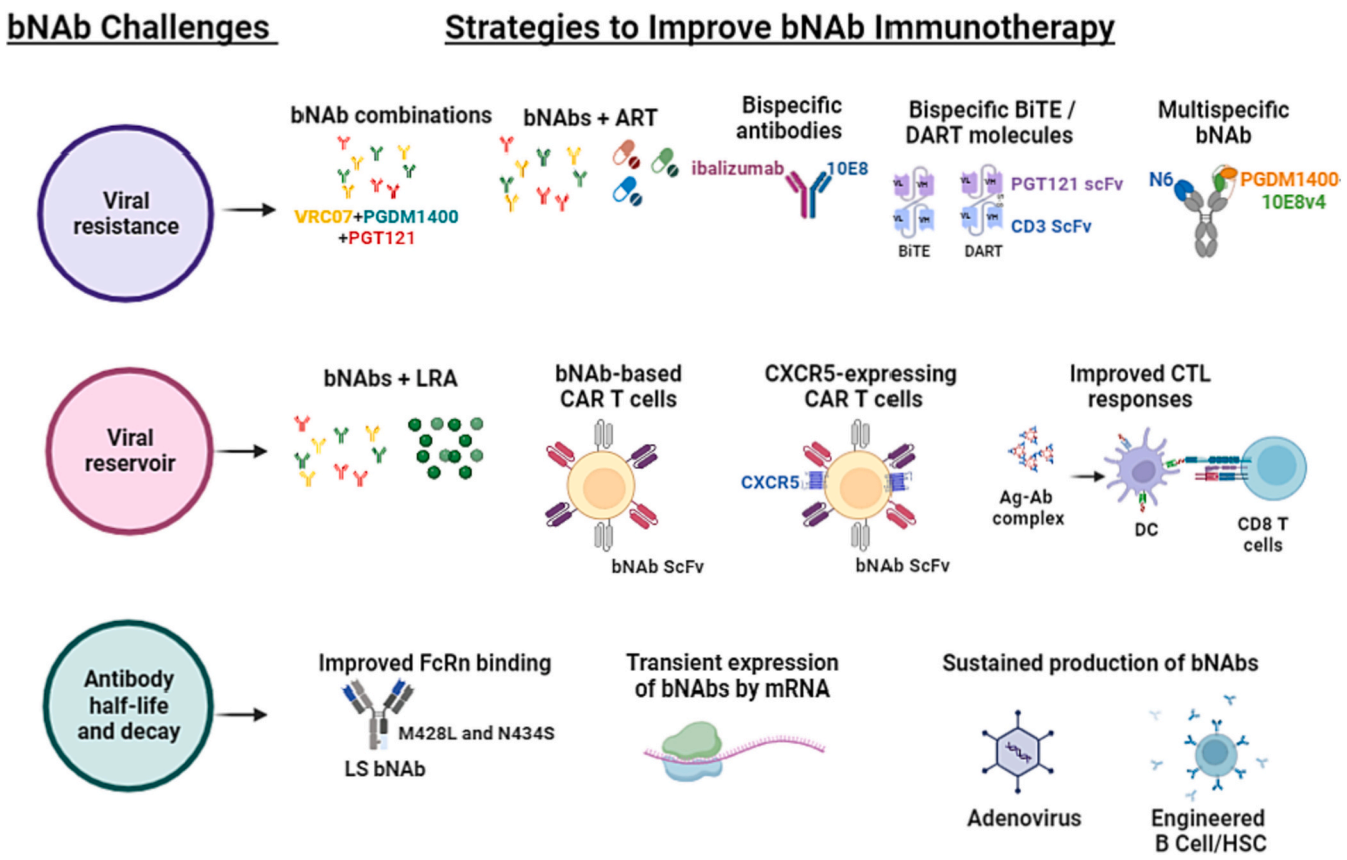

Fig. 2. Challenges of bNAbs and strategies for enhancing immunotherapy. The diverse challenges the virus presents could be overcome through combinations of bNAbs, multi-specific antibodies/molecules, LRAs, CAR T cells, and/or ART. FcRn = neonatal Fc-receptor; LS bNAb = modified bNAb which prefers the FcRn.

Table 2
Subtype-Specific anti-HIV bNAb Resistance.

bNAb	Env Target Domain	HIV bNAb Resistance	A.A. mutation	Ref.
3BNC117 and VRC01	CD4bs	30% subtype C viruses	G458Y	[235]
2G12, 10–1074 and PGT121	V3-glycan	96% CRF07_BC recombinant viruses and 40% subtype A viruses	Deletion of N332	[51,235]
PG9 and PG16	V1/V2-glycan	100% of CRF01_AE recombinant	Deletion of N160	[236]
CAP256. VRC26	V1/V2-glycan	85% subtype B viruses	E/D164 substitution	[218]

4.2. Multi-specific bNAbs

Multi-specific antibodies possess two or more binding arms that target different epitopes on the Env protein. CrossMAb technology enables the combination of heavy and light chains derived from two distinct antibodies to form human bispecific IgG antibodies without using an artificial linker [82]. Compared to a single parental bNAb, bispecific antibodies, such as VRC07/PG16, which target both the CD4bs site and the V1V2 region, exhibit greater efficacy [83]. Recently, a bispecific antibody, CAP256.J3LS, was designed by combining the light chain N-terminus of CAP256V2LS with either nanobody J3 or scFv fragments of 10E8 or VRC01, displaying improved viral neutralization breadth and potency compared to parental antibodies [84]. Furthermore, trispecific antibodies VRC01/PGDM1400-10E8v4 and N6/PGDM1400-10E8v4 achieved superior neutralization breadth and potency compared to single parental bNAbs and have demonstrated effectiveness in preclinical studies [38,85] with clinical trials now underway (NCT03705169) (Fig .2).

4.3. Antibodies targeting host receptors

HIV requires host cell receptors to enter cells and establish infection. Targeting HIV entry host receptors, such as CD4 and CCR5, offers an advantage over traditional ARVs. Host factors are relatively stable, and mutations in viral proteins targeting these host receptors are limited. Two host-targeting antibodies, anti-CD4 (ibalizumab) and anti-CCR5 (PRO140), have proven effective in clinical studies [86,87]. Ibalizumab targets domain 2 of human CD4 without compromising its functionality [88], while PRO140 binds to the conformational epitope between the N-terminus and ECL2, blocking viral entry [89]. Both ibalizumab and PRO140 are safe, well-tolerated, and effective in HIV-infected patients with multi-drug-resistant (MDR) mutations [86,90]. Other antibodies targeting LFA-1 [91] and $\alpha_4\beta_7$ integrin, found on human CD4 T cells, have demonstrated promising results in pre-clinical studies [92,93]. However, drug resistance inevitably emerged with ibalizumab monotherapy [90], indicating that combining these antibodies with other bNAbs or ARVs is necessary.

4.4. Nanobodies

Certain animals, including llamas, camels, and sharks, naturally produce unique antibodies known as nanobodies. These nanobodies consist of a single variable domain from the heavy-chain-only (VHHs) [94]. Unlike typical antibodies, nanobodies can access and neutralize viruses by reaching hidden epitopes on the Env trimer thanks to their large CDR3 arm [95]. Several anti-HIV nanobodies, including NC-Cow1,

J3, A12, D7, and C8, have been isolated from llamas immunized with an HIV-1 Env immunogen [96–98]. Although these nanobodies demonstrated enhanced neutralization against a variety of viruses, their potency was limited. To enhance both the range and effectiveness of these nanobodies, a bi-specific nanobody called J3 + 2E7 was developed [99]. This nanobody targets both the CD4bs and gp41 regions on Env and has shown increased potency against various viruses. In general, nanobodies have a short half-life of 1–2 h. However, their half-life can be extended by fusing them with an anti-albumin nanobody or through Fc-engineering [100] [101].

4.5. Multi-specific antibodies

Multi-specific antibodies target both host and viral proteins, such as a combination of anti-CD4 or anti-CCR5 with an anti-HIV bNAb. Several bispecific antibodies, including 10E8v2/ibalizumab and N6/ibalizumab, are under investigation and have shown improved neutralization breadth and potency compared to individual antibodies, exhibiting efficacy in pre-clinical studies [102,103]. The 10E8v2/ibalizumab multi-specific antibody is currently in clinical trials (NCT03875209) (Fig .2).

4.6. bNAbs and latency-reversing agents (LRAs)

Rapid viral rebound following antiviral discontinuation presents a significant challenge in achieving viral remission with current drugs and bNAbs. Several approaches for a functional cure have been proposed and are under investigation in pre-clinical and clinical studies, including shock and kill [104,105], block and lock [106,107], and host genomic editing [108]. Using LRAs in combination with bNAbs for shock and kill strategies has provided ART-free HIV control in some patients [104,105] (Fig .2). However, this approach cannot entirely clear infected cells.

To address this issue, researchers designed Bispecific T-cell Engaging antibodies (BiTEs) with distinct specificities in each variable region, such as anti-CD3 and anti-HIV bNAb. After administration of an LRA, BiTEs target CD3 on naïve CD8+ T cells, bringing them into proximity to host cells where the HIV provirus has emerged and is expressing viral antigens. Once close to the infected cell, the CD8+ T cell is activated through its CD3 receptor, killing the target cell. *In vitro* studies have demonstrated that BiTEs VRC01 x CD3 and VRC07 x CD3 efficiently eliminated gp120-expressing cells [109,110].

To enhance the stability of BiTEs, disulfide bonds have been introduced between the two scFvs to form a Dual-Affinity *Re*-Targeting molecule (DART). *In vitro* evaluations of these DARTs, combining anti-HIV bNAb scFvs with anti-CD3 scFvs, demonstrated that PGT121 x CD3, 7B2 x CD3, and A32 x CD3 exhibited higher potency compared to other combinations, such as PGT145 x CD3, VRC01 x CD3, and 10e8 x CD3 when tested against diverse HIV isolates [111] and Simian HIVs [112]. Moreover, phase 1 clinical trials of A32 x CD3 (NCT03570918) and 7B2 x CD3 (NCT05261191) are in progress (Fig .2).

Apart from BiTEs and DARTs, a tandem bispecific antibody designed with a combination of bNAb scFvs from PGT128 and Hu5A8 fused with a modified IgG Fc demonstrated enhanced neutralization and killing when tested against a panel of 124 HIV viral strains, eliminating infected cells in mice [113]. Recently, the same tandem bispecific antibody significantly reduced peak viremia, achieving undetectable viral levels in 8 of 13 macaques and delaying disease progression for years [114]. Therefore, anti-HIV bNAb-based BiTEs and DARTs combined with LRAs could be employed in shock and kill strategies to achieve viral remission.

4.7. bNAb-based multi-specific CAR T cells

HIV evasion of CD8 T cells presents a significant barrier to clearing HIV-infected cells. HIV-specific CD8 CAR T cells incorporate CAR genes to express CD4 molecules on their surface, recognizing antigens without MHC I restriction. These cells are safe [115] and promote cytotoxic activity [116]; however, they are ineffective in controlling viremia and succumb to HIV infection *via* CAR-encoded CD4 molecules. Therefore, single-chain variable fragment (scFv)-based CAR T cells targeting different epitopes of the Env protein were generated and validated [117,118]. Adoptive transfer of these HIV-specific CAR T cells demonstrated durable viral suppression in animal models [119–121]. However, a single infusion of bNAb-based CAR T cells only resulted in transient viral suppression for a few weeks [122], associated with the relatively rapid emergence of escape variants in HIV-infected individuals. To address this issue, bi- and tri-specific bNAb-based CARs that combine two or three distinct bNAb scFvs with or without the CD4 domain were developed [123,124]. These multi-specific CAR-Ts were safe and effective in pre-clinical studies [124–126], and clinical trials (NCT03240328 and NCT03617198) are evaluating the safety and efficacy of these cells in patients (Fig .2).

4.8. CXCR5-expressing CAR T cells

Another challenge for CAR T cells is the inaccessibility to viral reservoirs in secondary lymphoid organs. Inserting the CXC chemokine receptor 5 (*CXCR5*) gene into CAR designs would enable these CAR T cells to access germinal centers (GCs) and further target viral reservoirs [127]. Several groups have reported that a specialized population of CD8+ T cells expressing CXCR5 migrate into GCs and control viral replication in mice or primates [128,129]. HIV-specific CXCR5-expressing CD8+ T cells also control viremia in humans [130]. Some natural killer (NK) cells naturally express CXCR5 and can migrate to GC follicles in HIV-infected individuals [131], a process associated with viral control in SHIV infection [132]. Lastly, macaques treated with CAR T cells engineered to express CXCR5, exhibited reduced viremia during SHIV infection [119] (Fig .2). However, researchers have yet to test this approach in humans.

4.9. Challenges to CAR T cell therapy

The effectiveness of CAR T cells is impacted by excessive *ex vivo* stimulation and expansion, often leading to exhaustion [133]. Utilizing stem/progenitor cells in CAR designs can result in a more durable response and expression in multiple cell types, including T-cells, B-cells, and NK cells [134]. Alternatively, PD-1 signaling blockade [135,136] or adding IL-7 and IL-15 to *ex vivo* stimulation cultures may help prevent exhaustion [137].

CAR T cell therapy can also result in significant adverse events, including cytokine release syndrome (CRS) [138], immune effector cell-associated neurotoxicity syndrome (ICANS) [139], off-target effects [140], anaphylaxis [141], macrophage activation syndrome (MAS) [142], coagulation disorders [143], and cytopenia [144]. Consequently, strategies to mitigate these risks, such as synNotch receptors [145,146] and inhibitory CARs (iCARs), are being tested [147]. Recently, newly designed convertible CAR T cells recognized various epitopes when multiplexed with bNAbs, efficiently mediating antiviral activity [148].

Notably, no current anti-HIV CAR T cell designs minimize adverse events and overcome pre-existing or escape mutations, functional exhaustion, or home to secondary lymphoid organs. Therefore, substantial studies are warranted to further optimize CAR T cell designs and provide safe and durable viral suppression.

4.10. bNAbs plus natural CD8 T cells

Apart from neutralization, antibodies and antigens form immune complexes, potent immunogens that promote host cellular immune responses [149]. In non-human primates, the combined anti-HIV bNAbs, 3BNC117 and 10–1074, conferred long-term viral suppression and enhanced CD8 T cell responses [13,150]. HIV-infected patients with the same bNAb combination also displayed similar results [33,151]. Escape mutants were not detected [151], possibly due to enhanced CD8 T cell responses [152]. The efficacy of LRAs administered with bNAbs is also

currently under investigation. Infusion of bNAbs plus a TLR 7 agonist during ART resulted in viral clearance in SHIV-infected macaques [153]. Separately in humans, the combination of romidepsin and 3BNC117 led to faster decay of viremia, decreased transcriptionally active infected cells, and improved gag-specific CD8 T cell responses [104] (Fig .2).

Thus, strategies combining antibodies targeting non-overlapping Env epitopes or host receptors, multi-specific antibodies, and multi-specific CAR T cells combined with LRA, bNAbs, and ART should overcome escape mutations and augment CD8 T cell responses.

4.11. bNAb bioavailability

The half-life of an antibody is crucial to the therapeutic efficacy of antibodies. By modifying the Fc-domain to have a higher affinity for the neonatal Fc receptor [154], the half-life of bNAbs can be improved (Fig .2). For example, the M428L and N434S ("LS") mutations prolong antibody half-life without compromising functionality [155]. These modifications have been integrated into several bNAbs and demonstrated in clinical trials to increase the antibody's half-life without impairing its functionality (Table 3). Further, single-dose administration of half-life-enhanced bNAbs is sufficient to control viremia for 6 to 12 months [14]. Increasing antibody half-life may enable more effective and affordable treatment by allowing smaller dosages and less frequent administrations.

4.12. mRNA encoded bNAbs

The use of mRNA as a genetic delivery platform has emerged as a powerful new class of therapeutic agents [156,157]. This approach provides a potential therapeutic solution to deliver multiple bNAbs as a single drug product. In humans, the first phase 1 mRNA-based trial demonstrated that mRNA-generated antibodies protected against chikungunya disease [158]. A recent study in mice showed an mRNA-lipid nanoparticle (LNP) platform expressing full-length N6 IgG, single-chain PGDM1400, and PGT121 with expected breadth and potency targeting multiple HIV pseudoviruses [159]. Several reports have described potential adverse events associated with the use of mRNA, including acute myocardial infarction [160], Bell's palsy [161], cerebral venous sinus thrombosis [162], myocarditis/pericarditis [163], pulmonary embolisms, and stroke [164]. Expressing multiple bNAbs for an extended duration in a single cell using mRNA is possible [165], but potential adverse events must be thoroughly examined (Fig. 2).

4.13. Adenoviral delivery

Among the many gene transfer methods, the adeno-associated virus (AAV) vector has demonstrated safety and efficacy in humans with rare incidences of vaccine-induced thrombotic thrombocytopenia [166]. Preclinical studies showed that AAV-based transfer of 3BNC117 and 10–1074 bNAbs demonstrated viral suppression up to 3 years after rAAV inoculation in SHIV-infected macaques [167] and HIV-infected humanized mice [168]. However, a phase 1 clinical trial showed that although the rAAV1-PG9DP vector was well-tolerated, only low levels of PG9 bNAbs were detected and were associated with ADAs [169]. A more recent study showed robust production of VRC07, lasting up to 3 years, after administering the AAV8-VRC07 vector to HIV-infected individuals [170], validating the use of AAV vectors for bNAb secretion (Fig .2).

4.14. Combined humoral and cellular strategies

An alternative to passively transferred bNAbs is engineering immune cells to express bNAbs directly. This strategy would allow memory B cell formation, somatic affinity maturation, class-switch recombination, and plasma cell generation, secreting bNAbs in response to virus coevolution [171]. CRISPR/Cas9 genome editing is one approach to insert a bNAb gene *ex vivo*. This strategy has already succeeded in mice, where CRISPR/Cas9-edited B cells expressed HIV-specific bNAbs [172]. Two other studies recently established that engineered memory B cells could secrete VRC01 and BNC117 bNAbs [173,174]. In addition, these engineered B cells migrated to germinal centers (GCs), class-switched, underwent somatic hypermutation (SHM), and clonally expanded, differentiating into plasmablasts following Env immunization. These

Table 3
Clinical efficacy of anti-HIV engineered bNAbs.

bNAb	Half-life (days)			Clinical Outcomes			
	Parental Ab	Ab with LS mutation	Ref.	Therapy	Viral Load	TVR (days)	Safety
VRC01	HIV$^-$ individuals: 15 HIV$^+$individuals: 12	71	[21,23]	Mono	0.5-fold reduction in 43% of participants [237].	ND	Yes
				Combined (VRC-01 LS + 10–1074)	<40 copies /ml in 44% of participants [238].	168	
VRC07–523	HIV$^-$ individuals: 29 HIV$^+$individuals: 10	40–66	[15,198] [19,239]	Mono	1.2-fold reduction in 89% of participants [237].	ND	Yes
				Combined (PGDM1400 + PGT121 + VRC07523 LS)	2.0-fold reduction [28].	20	
N6	ND	44	[240]	Mono	1.7-fold reduction in 93% of participants [241].	35	Yes
				Combined	ND	ND	ND
3BNC117	HIV$^-$ individuals: 17 HIV$^+$individuals: 09	62	[24,242]	Mono	ND		ND
				Combined (3NBC117 LS + 10–1074 LS)	1.1–2.5-fold reduction in 100% of participants [242].	ND	Yes
10–1074	HIV$^-$ individuals: 24 HIV$^+$individuals: 12	80	[26,242]	Mono	ND		ND
				Combined (3NBC117 LS + 10–1074 LS)	1.1–2.5-fold reduction in 100% of participants [238,242].	ND	Yes
CAP256V2	ND	43	[238]	Mono Combined	ND	ND	ND
PGT121	HIV$^-$ individuals: 23 HIV$^+$individuals: 13	74	[27,243]	Mono Combined	ND	ND	ND

ND = data not available, TVR = Time to viral rebound; HIV$^+$ individuals = Viremic patients without ART; LS = M428L and N434S.

findings demonstrated that when transferred, engineered B cells could express and secrete bNAbs (Fig. 2).

However, the current state of B cell reprogramming is insufficient to functionally cure HIV, as latent reservoirs activated in the presence of LRAs release additional free viruses and enable direct cell-to-cell transmission of the virus, circumventing bNAb neutralization. ART and bNAbs can clear free viruses, but a different set of engineered cells, CAR T cells, are required to target infected host cells. Advancements in CAR T cell methods have made expressing multiple proteins from a single vector feasible. *Ex vivo* engineering of HIV antigen-specific T cells to express functional bNAb genes demonstrates that such cells can neutralize free viruses and kill infected cells [175]. These findings suggest that combining two distinct immunotherapeutic strategies, humoral and cellular, may allow for synergy that broadens CAR T cells' ability to clear free and cell-associated viruses.

4.15. Challenges with sustained bNAb expression

Most bNAbs currently tested in clinical trials were isolated from HIV-infected individuals [176–180]. However, these bNAbs are associated with unusual characteristics, such as extended heavy-chain complementarity-determining region 3 (CDR—H3), high levels of SHM, and poly- or autoreactivity [181,182], all needed for higher Env affinity and neutralization breadth [183,184]. For instance, the bNAbs VRC01, VRC02, CH106, and CH103 strongly bind to human ubiquitin ligase E3A [181]. Thus, long-term expression of anti-HIV bNAbs may induce autoimmune responses, an undesirable side effect. Consequently, strategies to limit bNAb expression might mitigate some autoimmune concerns.

Repeated infusion or sustained expression of antibodies can result in anti-drug antibodies (ADAs) [185,186], limiting their efficacy [187]. Although anti-HIV bNAbs are primarily isolated from human B cells, most are highly somatically mutated and could be immunogenic [188]. Previous research has demonstrated that ADAs can occur when human bNAbs are administered to macaques, inducing a xenoresponse [167,189–191]. Even after repeated infusions of VRC01 in humans, however researchers did not detect ADAs [22]. Moreover, while 4 out of 18 participants had detectable ADAs, the effectiveness of bNAbs 3BNC117 and 10–1074 mainly remained unaltered [20].

Compared to passive infusion, ADAs are more commonly associated with sustained bNAb delivery methods, such as AAV-based gene delivery methods, reducing their clinical utility [167,189]. ADA responses generally range from insignificant to detrimental, rarely impacting patient safety [192]. bNAbs will typically need to be administered multiple times or delivered continuously *via* viral vectors to maintain viral suppression. However, the generation of ADAs does pose safety concerns, and their emergence should be monitored carefully in future clinical trials.

5. Conclusion

Anti-HIV bNAbs hold considerable potential for achieving viral control, with a functional cure on the horizon through combining bNAbs, CAR T cells, and ART. Furthermore, enhancing bNAb half-life and developing bi- and tri-specific antibodies would be advantageous. When choosing specific bNAbs for therapy, it is crucial to consider the resident HIV strains within the patient to minimize the risk of escape variants and provide a personalized treatment plan.

Gene therapeutic approaches can facilitate the long-term expression of desired proteins; however, the autoreactivity of these proteins may introduce potential complications. Therefore, it is essential to conduct long-term studies to assess the safety of continuous bNAb expression in humans. We anticipate that bNAbs, in conjunction with other modalities, will play a significant role in the treatment of HIV.

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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