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REVIEW

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Clinical trials of broadly neutralizing monoclonal antibodies in people living with HIV – a review

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Abstract

Introduction HIV-1 remains a major global health challenge, impacting approximately 39 million people worldwide. Although antiretroviral therapy has substantially reduced HIV incidence and enhanced the quality of life for those living with HIV, adherence difficulties, limited access, and persistent stigma continue to exacerbate the disease burden. A curative or long-term immunological control strategy without continuous medication would significantly advance pandemic management. In the 2010s, technological progress led to the development of a new generation of broadly neutralizing antibodies (bNAbs) with improved potency and breadth, targeting conserved regions of the HIV-1 envelope and facilitating viral neutralization and clearance.

Methods This review evaluates the clinical outcomes and potential of bNAbs in people living with HIV, summarizing findings from a review of 154 registered trials, of which 62 met the inclusion criteria focusing on adult PLWH.

Results Early trials confirmed bNAbs' safety but revealed transient and limited viral suppression, often due to viral escape. Second-generation bNAbs like VRC01 and 3BNC117, as well as combination therapies such as 3BNC117 with 10-1074, extended viral suppression but continued to face resistance challenges.

Conclusion More recent trials that paired bNAbs with latency-reversing agents or combined multiple bNAbs demonstrated promising results, including delayed viral rebound and enhanced CD8 + T-cell responses. While bNAbs show potential as an adjunct or alternative to ART, obstacles such as viral resistance, high production costs, and scalability must be addressed. Continued research is crucial to developing more potent, durable, and affordable bNAbs for sustainable HIV treatment and potential remission.

Keywords Broadly neutralizing monoclonal antibodies, Clinical trials, Cure, Human immunodeficiency virus, Safety, Treatment

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Introduction

HIV-1 remains a major global health challenge, with 39 million people living with HIV (PLWH) worldwide [1]. Antiretroviral therapy (ART) has significantly reduced HIV-related morbidity and mortality, but lifelong adherence remains essential, as ART suppresses viral replication but does not eliminate the latent reservoir [2, 3]. This reservoir, primarily in resting memory CD4 + T cells, allows for rapid viral rebound upon treatment interruption [4, 5]. Even though long-acting ART formulations such as cabotegravir/rilpivirine and lenacapavir offer alternatives to daily therapy [6, 7], they do not address viral persistence, and lifelong treatment remains necessary [8].

Broadly neutralizing antibodies (bNAbs) represent an innovative strategy to enhance HIV therapy and potentially achieve sustained viral remission. Unlike ART, bNAbs target multiple sites on the HIV envelope, neutralizing circulating virus while also engaging the immune system to clear infected cells [9]. Studies suggest that bNAbs could suppress viremia without ART, delay viral rebound after treatment interruption, and reduce the size of the latent reservoir [10]. While stem-cell transplantation has resulted in HIV remission in rare cases [11], bNAb-based interventions offer a more scalable and less invasive approach. Optimizing bNAb combinations, dosing strategies, and host factors influencing response will be crucial in determining their role in long-term HIV control and cure strategies.

Between 1985 and 1995, infusions of pooled plasma from PLWH were investigated as a potential HIV treatment [12]. Three randomized, placebo-controlled trials were conducted during this period [13–16]. Although there was no statistically significant reduction in mortality [17] the data revealed a trend toward prolonged survival and a reduction in opportunistic infections among treated individuals [14, 18]. Additionally, there was evidence of transient declines in plasma HIV RNA levels [17, 19]. These findings, although limited, provided important early insights, suggesting that the infusion of HIV-specific antibodies could confer clinical benefits and laid the groundwork for future antibody-based therapeutic strategies [15].

Between 1995 and 2014, the first monoclonal antibodies (mAbs) and broadly neutralizing antibodies (bNAbs) were tested in humans, with trials primarily focusing on three specific antibodies: 2G12, 2F5, and 4E10 [20, 21]. These trials demonstrated that the mAbs were safe and well-tolerated in PLWH on ART [20]. However, despite their safety profile, combination mAb therapy did not prevent viral rebound after treatment interruption [22, 23]. Moreover, nearly all participants developed viral escape mutations, underscoring the low barrier to resistance of these antibodies [23], and highlighting the need for better antibodies and combination approaches. In the 2010s, technological advancements led to the development of a new generation of bNAbs, with increased potency and neutralization breadth against diverse HIV-1 strains [24]. These bNAbs were isolated from PLWH, termed 'elite neutralizers' by utilizing single memory B-cell isolation technologies [25]. These bNAbs target conserved epitopes on the HIV-1 Envelope spike (Env), including the CD4 binding site, V2-apex, the V3-glycan site, membrane-proximal external region (MPER), gp120/gp41 interface, and the silent face (Fig. 1) [26]. The Env protein is the only external target on HIV-1 and is expressed on the surface of infected cells.

BNAbs exhibit both neutralizing and non-neutralizing properties [27, 28]. This neutralizing function is mediated through a variable region of the antibody that binds to the antigen, known as the fragment antigen-binding (Fab) region. The non-neutralizing function of bNAbs include clearing of the virus by identifying and binding to infected cells, through functions such as antibody dependent cellular cytotoxicity (ADCC) and phagocytosis. The Fc domains [29] of these bNAbs mediate effector functions [30] through interactions with host immune cells, and also influence their half-life. BNAbs differ from traditional ART by directly targeting circulating viruses, recognizing HIV-1-infected cells expressing Env, and engaging with the host immune system. Passively administered bNAbs can also enhance the autologous antiviral immune response [31].

Both animal and human studies using bNAbs have demonstrated modest and transient suppression of HIV viremia [32–34]. Several bNAbs have entered clinical trials, and additional candidates are being considered for future clinical evaluations. Clinical studies have shown that single or repeated administrations of bNAbs are safe and well-tolerated [35]. In addition, therapy with bNAbs during, or prior to, ART interruption has been shown to boost HIV-1-specific CD8 + T cell responses [36, 37] and antibody breadth [38]. It is unclear whether these heightened T cell responses play a role in the viral control achieved by bNAbs [38]. BNAbs also present a promising immunotherapeutic strategy for HIV cure [39]. The "shock and kill" approach, which induces HIV-1 Env expression on latently infected cells, makes these cells vulnerable to bNAbs. These antibodies engage the host immune system to clear the infected cells. When combined with latency-reversing agents (LRAs), this method has demonstrated long-term viral suppression in some HIV-infected humanized mice and simian HIV-infected macaques [40].

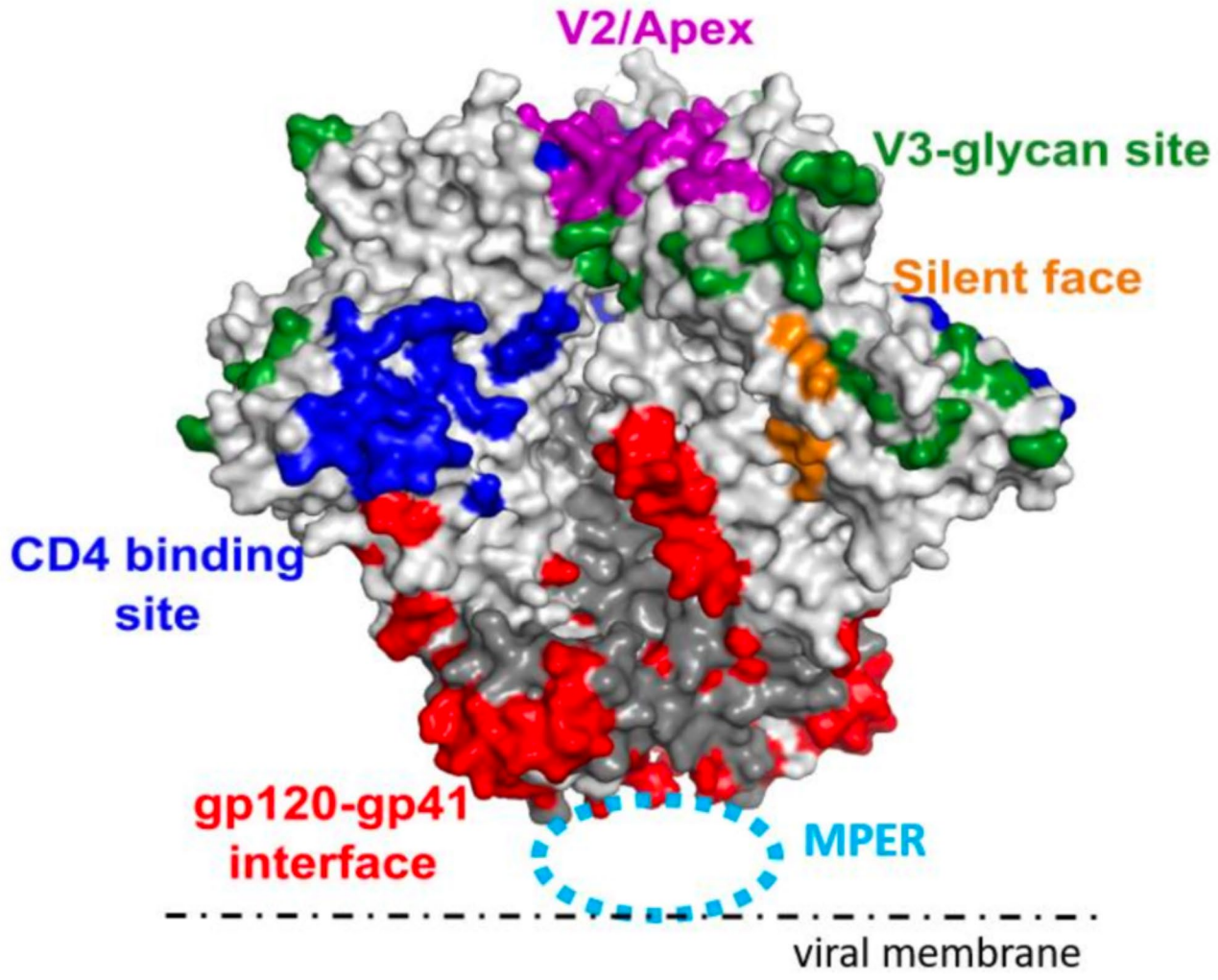

Fig. 1 Broadly neutralizing antibodies in clinical trials and their target sites on the HIV-1 envelope. Abbreviations: MPER = membrane-proximal external region (image generated by Elizabeth Venter)

Although clinical trials aimed at reversing HIV latency and depleting viral reservoirs have commenced, much more needs to be understood about eradication or durable control of HIV. Current efforts are focused on developing cellular or gene therapies to control or eliminate infection, strategies to permanently silence viral genomes, induce apoptotic death in infected cells, or achieve viral remission without complete eradication of the virus. This review summarizes current knowledge, clinical studies, and the potential future role of bNAbs in PLWH.

Methods

A comprehensive literature review was conducted to identify all relevant bNAb clinical trials. The primary search was performed in PubMed and Google Scholar, covering the period from January 2010 to June 15, 2024. Search terms included combinations of "broadly neutralizing antibody," "bNAb," "HIV," "clinical trial," along with specific antibody names (VRC01, VRC01LS, VRC01-N, VRC01.23LS, VRC07, VRC07-523LS, CAP256V2LS, PGT121, PGT121.414.LS, N6LS, 10E8, 10E8VLS, 3BNC117, 3BNC117-LS, 3BNC117-LS-J, 10-1074, 10-1074-LS, 1074-LS-J, PGDM1400, and SAR441236). This was supplemented by a search of the World Health Organization's International Clinical Trials Registry Platform using similar terms.

Two independent reviewers screened titles and abstracts for relevance. Full-text articles were then assessed for eligibility based on predefined criteria: (1) studies involving adult PLWH, (2) trials evaluating bNAbs for HIV treatment or cure, and (3) completed trials with published data. Disagreements were resolved through discussion with a third reviewer. To ensure comprehensive coverage, reference lists of included studies were also examined for additional

relevant articles. The final selection focused on bNAbs that have progressed furthest in clinical development pipelines.

Results

A total of 154 trials registered on the International Clinical Trials Registry Platform and Pan African Clinical Trials Registry were identified. Of these, 91 trials did not meet the eligibility criteria (Fig. 2). The excluded trials involved bNAb studies conducted in HIV-negative individuals for HIV prevention, trials not designed for an HIV indication, trials not employing bNAbs for HIV treatment or cure, or trials not conducted in adults. Consequently, 62 trials met the inclusion criteria. Among these, 31 trials were completed, and 7 were suspended due to reasons such as failure to achieve the required sample size, protocol withdrawal, inconsistent contact with participants, and withdrawal of funding from the trial sponsor. Of the 31 completed trials, 20 had published data and were included in this review (Supplementary Table S1). Additionally, data from 3 conference abstracts were incorporated to ensure comprehensive coverage (Table 1).

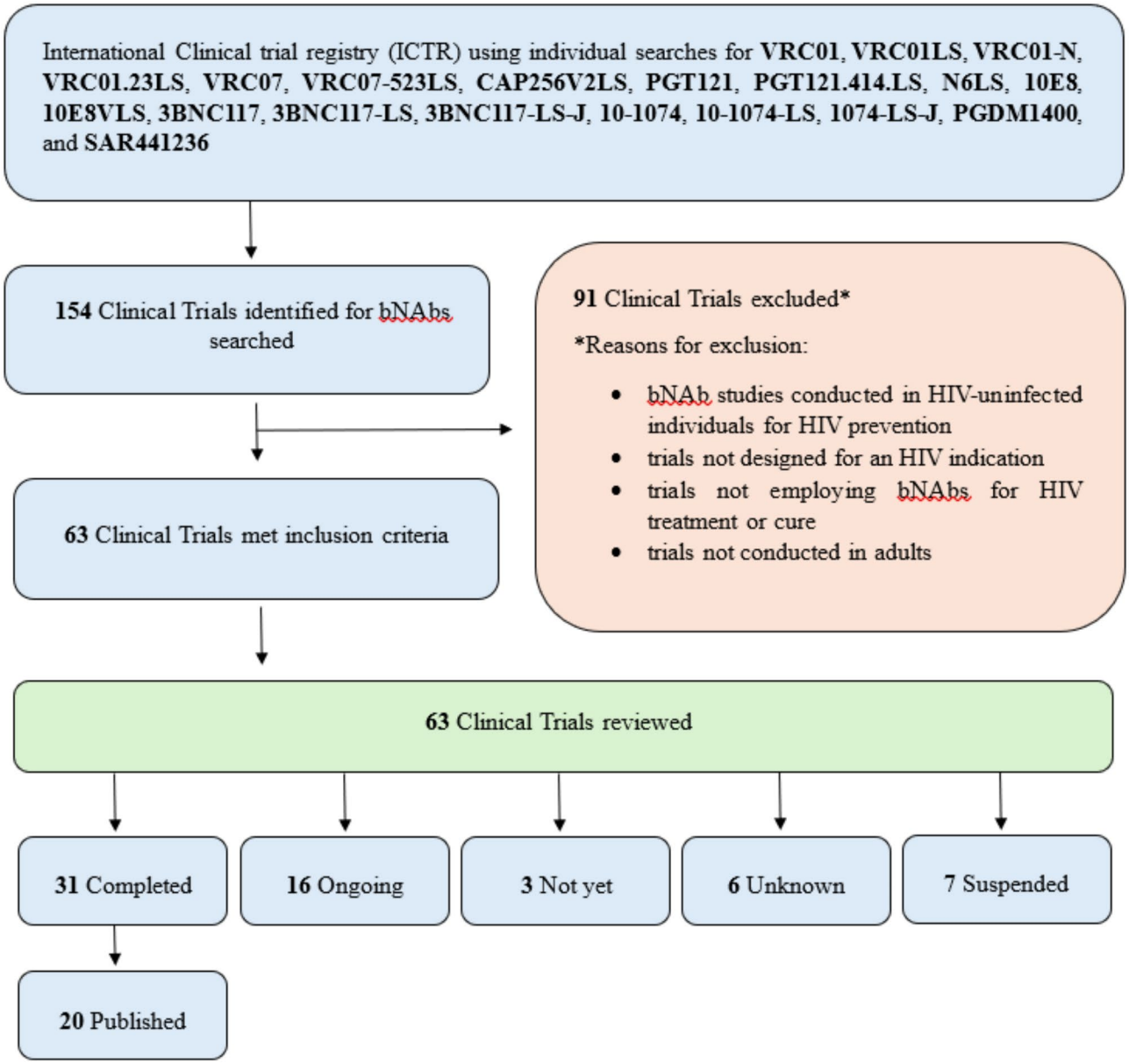

Fig. 2 Investigative methodology and search results. Abbreviations: ICTR = International Clinical trial registry; bNAbs = broadly neutralizing antibodies; HIV = Human Immunodeficiency Virus

Table 1 Clinical trials of broadly neutralizing monoclonal antibodies for human immunodeficiency virus

Study Product	Clinical Trial Identifier	Study population numbers (*N*)	ATI	Virus sensitivity testing	Plasma HIV RNA levels	Time to VL rebound (weeks)	Location	Trial status	Publication
VRC01	NCT02411539	40	No	Virus sensitivity testing was not performed	No significant change	N/A	United States	Completed	Riddler et al. 2018. PMID: 30364428
	NCT02463227	14	Yes	Sensitive and resistant	No significant change	Median: 5,6	United States	Completed	Salantes et al. 2018. PMID: 29911997
	NCT02664415	23	Yes	Sensitive and resistant	Increased; rebound in all but one participant	≤ 24	Thailand	Completed	Crowell et al., 2019. PMID: 31000477 Cale et al. 2020. PMID: 32182219
	NCT02471326	10	Yes	Sensitive and resistant	No sustained decrease	Median: 4	United states	Completed	Bar et al. 2016. PMID: 27959728
	NCT02591420	24	No	-	-	-	Kenya Tanzania Thailand Uganda	Completed	-
	NCT03831945	27	Yes	-	-	-	United States	Terminated	-
	NCT01950325	27	No	Sensitive and resistant	Decreased in six of eight participants	N/A	United States	Completed	Lynch et al. 2015. PMID: 26702094
	NCT04801758	18	Yes	-	-	-	Peru Brazil United States	Completed	-
	NCT04860323	39	Yes	-	-	-	Malawi Botswana Zimbabwe South Africa	Active, not recruiting	-
	NCT03729752	15	No	N/A	N/A	N/A	United States	Completed	Beckford-vera et al. 2022. PMID: 35264559
VRC01LS	NCT02840474	16	No	-	-	-	United states Puerto Rico	Completed	-
VRC07	NCT03374202	8	No	Sensitive and resistant	-	-	United States	Active, not recruiting	Casazza et al. 2022. PMID: 35411076

Table 1 (continued)

Study Product	Clinical Trial Identifier	Study population numbers (*N*)	ATI	Virus sensitivity testing	Plasma HIV RNA levels	Time to VL rebound (weeks)	Location	Trial status	Publication
VRC07-523LS	NCT03721510	19	No	-	-	-	United States	Completed	Julg et al. 2024. PMID: 39266747
	NCT03803605	15	No	Sensitive	Decreased	-	United States	Completed	Gay et al. 2022. PMID: 34562096
	NCT05281510	21	No	-	-	-	South Africa	Active, not recruiting	-
	NCT05890963	20	No	-	-	-	Tanzania	Recruiting	-
	NCT04983030	36	Yes	-	-	-	United States	Recruiting	-
	NCT04340596	46	Yes	-	-	-	United States	Recruiting	-
	NCT03739996	75	No	-	-	-	United States; Puerto	Completed	-
	NCT03205917	29 (24 PLWoH*; 5 PLWH#)	No	Sensitive and resistant	Decreased and/or increased	20 days post-nadir	United states	Complete	Julg et al. 2022. PMID: 35551291
	NCT04144335	0	No	-	-	-	United States	Withdrawn	-
	NCT05769569	0	Yes	-	-	-	Thailand	Withdrawn	-
	NCT05719441	48	No	-	-	-	United States Peru Brazil	Not yet recruiting	-
	NCT04357821	11	Yes	-	-	-	United States	Active, not recruiting	-
	NCT05275998	90	Yes	-	-	-	United States	Active, not recruiting	-
CAP256-V2LS	PACTR202309578224660	30	Yes	-	-	-	South Africa	Recruiting	-
	PACTR202003767867253	76 (62 PLWoH*; 14 PLWH#)	No	Sensitive and resistant	-	-	South Africa	Recruiting HIV positive arm groups. recruitment for HIV negative arm groups has been completed	Mahomed et al. 2023. PMID: 37001964
PGT121	NCT02960581	48 (20 PLWoH*; 28 PLWH#)	No	Sensitive and resistant	Decreased and/or increased	28	United States	Completed	Stephenson et al. 2021. PMID: 34621054

Table 1 (continued)

Study Product	Clinical Trial Identifier	Study population numbers (*N*)	ATI	Virus sensitivity testing	Plasma HIV RNA levels	Time to VL rebound (weeks)	Location	Trial status	Publication
N6LS	NCT04871113	63	No	-	Decreased	-	United States Argentina Brazil Canada Mexico Peru	Completed	-
3BNC117	NCT03468582	6	N/A	N/A	N/A	N/A	Switzerland	Completed	-
	NCT02446847	13	Yes	Sensitive and resistant	Group a: increased; Group b: increased in 3 out of 7 participants	Median: 8,4 (all participants)	United States	Completed	Scheid et al. 2016. PMID: 27338952
	NCT03719664	80	No	-	-	-	United States	Unknown status	-
	NCT02588586	15	Yes	Sensitive and resistant	Initial decrease followed by an increase after ATI	2–17 weeks after ATI	United States	Completed	Cohen et al. 2018. PMID: 30072495
	NCT02850016	22	Yes	Sensitive and resistant	Increased (only one individual maintained suppression until day 84 of the ATI)	By day 35 of the ATI; median time: 18 (3BNC117 plus romidepsin group), 28 days (romidepsin-only group)	United States Germany Denmark	Completed	Gruell et al. 2022. PMID: 35544074
	NCT04560569	20	No	-	-	-	United States	Unknown status	-

Table 1 (continued)

Study Product	Clinical Trial Identifier	Study population numbers (*N*)	ATI	Virus sensitivity testing	Plasma HIV RNA levels	Time to VL rebound (weeks)	Location	Trial status	Publication
	NCT02018510	29 (12 PLWoH*; 17 PLWH#)	No	Sensitive and resistant	Decreased in PLWH# who received 10 or 30 mg/kg of 3BNC117; Transient changes in viremia in individuals who received 1 or 3 mg/kg, temporary decrease followed by a rapid return to baseline	Median: 7 days	Germany United States	Completed	Schoofs et al. 2016. PMID: 27199429 Caskey et al. 2015 PMID: 25855300
	NCT03571204	19	Yes	Sensitive and resistant	Active comparator group 1: decreased; placebo group: increased	33,0.4 (bNAb arm); 8 (vl > 200 copies/ml in bNAb group); 8 (placebo group)	United States	Terminated	Sneller et al. 2022. PMID: 35650437
	NCT03063788	17 (4 PLWoH*, 8 PLWH# viremic, 5 PLWH# aviremic)	No	Sensitive	Decreased in viremic participants who received a 3 mg/kg dose of 3BNC117	3BNC117 delayed the return of detectable viremia; exact time frame is not provided	Australia	Completed	Mcmahon et al. 2021. PMID: 33640794
	NCT03526848	26	Yes	Sensitive and resistant	Decreased in 76% of participants; increased after serum concentration of the antibodies dropped below a specific threshold	Group 1: 28.5; 32 (median) for those who received all seven infusions of the bNAbs; group 2: 7 (median)	United States	Completed	Gaebler et al. 2022. PMID: 35418681
	NCT04819347	24	Yes	-	-	-	China	Unknown status	-
	NCT03837756	46	Yes	Sensitive and resistant	Decreased and/or increased	Details not provided	United States Denmark Australia Norway	Completed	Gunst et al. 2023. PMID: 37696935
	NCT02825797	15	Yes	Sensitive	Decreased when antibody concentrations remained high; rebound occurred in lower concentrations	21	United States Germany	Completed	Mendoza et al. 2018. PMID: 30258136 Bar-on et al. 2018. PMID: 30258217
	NCT03041012	60	Yes	Sensitive and resistant	Decreased	Details not provided	Denmark United Kingdom	Unknown status	Gunst et al. 2022. PMID: 36253609
	NCT03588715	14	Yes	Sensitive	Decreased	8 and 14 (2 of 12 participants)	United States	Unknown status	https://www.croiconference.org/abstract/a-first-in-human-study-of-the-trispecific-hiv-1-broadly-neutralizing-antibody-sar441236/.

Table 1 (continued)

Study Product	Clinical Trial Identifier	Study population numbers (*N*)	ATI	Virus sensitivity testing	Plasma HIV RNA levels	Time to VL rebound (weeks)	Location	Trial status	Publication
	NCT04720742	0	Yes	-	-	-	Italy Netherlands Spain	Withdrawn	-
3BNC117-LS	NCT03254277	43 (28 PLWoH*, 15 PLWH#)	No	-	-	-	United States	Completed	-
	NCT03554408	11 PLWH#	No	-	-	-	United States	Completed	-
	NCT04250636	6	No	-	Decreased	-	United States	Completed	-
	NCT05612178	200	No	-	-	-	United States	Recruiting	-
	NCT05245292	36	Yes	-	-	-	United States	Recruiting	-
	NCT05079451	0	Yes	-	-	-	United States	Withdrawn	-
	NCT06205602	135	No	-	-	-	No location data	Not yet recruiting	-
	NCT04319367	72	Yes	-	-	-	Denmark United Kingdom	Recruiting	Lee et al. 2022. PMID: 35382844
	NCT05300035	69	Yes	-	-	-	France	Recruiting	-
	NCT06071767	45	Yes	-	-	-	United States Brazil	Recruiting	-
	NCT04811040	21	Yes	Sensitive and resistant	Decreased	Details not provided	United States	Completed	Eron et al. 2024. PMID: 38307098
	NCT05729568	83	No	-	-	-	United States Australia Canada Puerto Rico	Active, not recruiting	-
3BNC117-LS-J	NCT06031272	48	Yes	-			Botswana Malawi South Africa	Not yet recruiting	-
10-1074	NCT02511990	33 (14 PLWoH* and 19 PLWH#)	No	Sensitive and resistant	Decrease	Details not provided	United States Germany	Completed	Caskey et al. 2017. PMID: 28092665
	NCT03619278	12	No	-	-	-	No location data	Unknown status	-
SAR441236	NCT03705169	52	No	-	Decreased	Details not provided	United States	Terminated	https://www.croiconference.org/abstract/a-first-in-human-study-of-the-trispecific-hiv-1-broadly-neutralizing-antibody-sar441236/
10E8	NCT03875209	8 PLWH#	No	-	-	-	United States	Completed	-

*PLWoH = People living without HIV

#PLWH = People living with HIV

Safety

First-generation bNAbs were generally safe and well-tolerated [41]. Some bNAbs, such as 2F5 and 4E10, showed autoreactivity [42, 43], raising safety concerns. Second-generation bNAbs have demonstrated a favourable safety and tolerability profile across intravenous (IV), subcutaneous (SC), and intramuscular (IM) administration routes, with most adverse events (AEs) being mild (Grade 1–2) and transient.

Safety profile consistency was seen in both single and multiple infusions, in PLWH [25]. In IV infusion trials, infusion-related symptoms such as mild chills or myalgia occurred in a small percentage of participants (~1–3%), with no serious AEs reported [44]. SC administration had a higher frequency of injection-site reactions, affecting ~ 50–73% of participants in some studies, though these were mild to moderate and resolved quickly [45]. IM administration showed a similar pattern, with most participants experiencing short-lived local pain or tenderness but no severe systemic effects [46]. Across all delivery methods, moderate AEs were infrequent, and severe AEs were rare or nonexistent, except for isolated cases (e.g., 10E8VLS causing a severe injection reaction in 1 of 8 participants [47]).

Generally, there was no detection of anti-drug antibodies (ADAs) against the bNAbs, with one notable exception, where 4 out of 15 healthy HIV-1-negative participants developed specific anti-bNAb responses [48]. However, these responses did not affect elimination half-life or resulted in adverse events. In a phase 1 trial evaluating the use of adeno-associated viral (AAV) vectors to deliver bNAbs, the vector was safe, but three participants developed ADAs, leading to decreased serum VRC07 in two of these participants [49]. The favourable safety profiles of second-generation bNAbs are likely due to their high specificity and affinity for HIV-1 viral targets, reducing the risk of unexpected adverse effects.

Effect on viremia and reservoir

Study populations in these trials consisted of PLWH on ART who were virologically suppressed and had acute or chronic infection. Newly diagnosed, ART naïve, PLWH were also included. In some trials volunteers underwent an analytical treatment interruption (ATI) to evaluate whether the bNAb had an effect on viral control. The endpoints in these trials were centred around time to viral rebound and/or the impact on the HIV-1 reservoir.

Results from single bNAb trials

VRC01

NCT01950325 was a phase 1 study evaluating safety, pharmacokinetics, and impact on HIV-1 reservoir in 27 PLWH (15 on ART, 8 off ART) [50]. Participants received two VRC01 infusions (1–40 mg/kg IV or 5 mg/kg SC) 28 days apart. VRC01 did not reduce the viral reservoir in ART-treated participants with undetectable viremia. In ART-untreated individuals, 75% (6/8) showed decreased plasma viremia (1.1 to 1.8 $\log^{10}$ reduction). Viral load was decreased by 12- to 59-fold in these individuals. Two participants with low viral loads achieved undetectable levels for over 20 days.

NCT02411539 was a phase 1 trial assessing VRC01 effects on HIV-1 persistence in 40 ART-treated individuals with chronic infection [51]. VRC01 (40 mg/kg) showed no significant effect on plasma viremia, cellular HIV-1 RNA/DNA levels, or stimulated virus production from CD4 + T-cells [51].

NCT02664415 was a phase 2 trial evaluating VRC01 for HIV remission in 23 virally suppressed adults who started ART during acute infection and underwent an ATI [52] Participants received VRC01 (40 mg/kg) or placebo during the ATI. Despite high serum antibody concentrations, viral rebound occurred after a median of 33 days in all but one participant.

VRC01 (40 mg/kg) was also evaluated in 18 individuals with acute HIV infection and underwent an ATI [53]. All 18 participants experienced viral rebound, with a median delay of 29 days in the VRC01 group compared to 14 days in the placebo group. Furthermore, participants with viruses most sensitive to VRC01, or those showing slower VRC01 decay rates in serum, exhibited a longer time to rebound. The reservoir viral diversity remained limited after early ART initiation, and there was no evidence of increased resistance to VRC01 following ATI.

NCT02463227 and NCT02471326 assessed VRC01 (40 mg/kg) in 24 participants during an ATI [54, 55]. Participants were not screened for VRC01 sensitivity and received 3–8 infusions. Median time to plasma viral rebound was 4 and 5.6 weeks, compared to the historical control for time to plasma rebound of 11 to 28 days. VRC01 recipients did not achieve viral suppression beyond 8 weeks due to pre-existing or induced resistant viruses.

NCT03729752 was a ImmunoPET imaging study conducted in 15 individuals who received radiolabeled VRC01 [56]. The study suggests that bNAbs preferentially accumulate in tissues with persistent HIV burden, such as the gut and lymphoid nodes in people living with HIV (PLWH), even during ART suppression. This finding supports the idea that these tissues serve as key HIV reservoir sites and that bNAbs may actively engage with these reservoirs, making them a potential tool for targeting persistent infection in cure strategies. Additionally, the study highlights the utility of ImmunoPET imaging in tracking bNAb distribution and reservoir localization in vivo. The study indicated the potential for non-invasive assessment of persistent HIV infection.

VRC01 was evaluated in an abstract presented at the 12th International AIDS Society (IAS) Conference in 2023 [57]. The study investigated the impact of VRC01 in combination with ART on HIV rebound and control. The 30 participants were 13 African women and 17 Peruvian men. Participants received either 10 mg/kg or 30 mg/kg VRC01 or placebo. Virological control was observed in two African women for 33 weeks, while most participants experienced viral rebound. 28 participants met the ART re-initiation criteria, with ART use during ATI discovered in three participants. The median time to ART re-initiation was 13.7 weeks in African women, and 8 weeks in Peruvian men, with no significant difference noted between the VRC01 and placebo groups. Assay data (cellular responses, binding and neutralizing antibody responses, reservoir characterization and rebound virus sequencing) is pending for this study.

VRC07-523LS

NCT03803605 was a study combining VRC07-523LS (40 mg/kg) with vorinostat, an LRA, in 8 virologically suppressed PLWH [58]. Two cycles of treatment were administered at 0 and 8-week timepoints. No substantial reductions in the HIV reservoir were achieved. Significant decreases in rolling circle amplification (rca)-RNA levels were observed in four participants after the second cycle.

NCT03374202 was a phase 1 trial evaluating the use of AAV vectors to deliver bNAbs. VRC07 was administered by the AAV (AAV8-VRC07) in eight PLWH on ART [49]. Doses ranged from 5×10^{10} to 2.5×10^{12} vector genomes/kg IM. There were no significant changes in CD4 + T-cell counts or viral loads.

3BNC117

NCT02018510 was a phase 1 trial assessing 3BNC117 (1–30 mg/kg IV) in PLWH and uninfected participants [38, 59]. A single 30 mg/kg infusion reduced viral load by 0.8–2.5 $\log^{10}$ for up to 28 days in PLWH. 12 participants had viral strains sensitive to 3BNC117 and 3 had viral strains resistant to 3BNC117.

NCT02446847 was a phase 2a trial evaluating 3BNC117 (30 mg/kg) during an ATI in 13 PLWH [60]. Multiple infusions delayed viral rebound by 5–19 weeks compared to historical controls of viral rebound data from 52 participants who participated in four ACTG ATI studies without additional interventions (ACTG 37132, A502433, A506834, and A519732). Increased resistance to 3BNC117 was reported in 8 of 13 participants.

NCT02588586 was a trial assessing 3BNC117 in 15 ART-suppressed PLWH, with 3BNC117-sensitive viruses, followed by an ATI [61]. Two to four infusions (30 mg/kg) were given. Infusions delayed viral rebound for an average of 8.4 weeks vs. historical controls of 52 participants who underwent ATI without intervention in trials performed by the ACTG group. Rebound viruses were often recombinants of latent reservoir variants, with low diversity, and resistance to 3BNC117 in most participants.

NCT03063788 was a study exploring latent reservoir imaging using 64Cu-radiolabeled 3BNC117 with PET/CT scans in 4 PLWoH, 8 viremic PLWH, and 5 aviremic PLWH [62]. Despite no adverse effects or significant tissue uptake differences, the technique could not detect HIV-1 env expression, suggesting the need for longer half-life radiolabels.

10-1074

NCT02511990 was a study evaluating 10-1074 among 33 participants of whom 19 were PLWH [63]. In viremic participants receiving 30 mg/kg, 11/13 showed bNAb sensitivity with a 1.52 $\log^{10}$ decline in viral load, though resistant viruses emerged.

PGT121

NCT02960581 was a phase 1 trial of PGT121 in 48 participants (20 HIV-uninfected, 15 PLWH suppressed on ART and 13 viremic PLWH [64]. Single infusions (3–30 mg/kg IV or 3 mg/kg SC) were evaluated. PGT121 reduced plasma HIV RNA in viremic participants. In those with high baseline viral loads, there was a 1.77 $\log^{10}$ drop with rebound resistant virus in 5/9 responders. In those with low baseline viral loads, two participants experienced prolonged ART-free viral suppression > 5 months.

NCT04871113 evaluated GSK3810109A (long-acting version of N6 that targets the gp120 protein on the HIV envelop in viremic PLWH) and NCT02840474 evaluated VRC01LS and VRC07-523LS administered to PLWH in a phase 1 trial. These trials have been completed with no results available yet.

Combination bNAb trials

3BNC117 and 10-1074

NCT02825797 was a phase 1b trial evaluating 3BNC117 and 10-1074 (30 mg/kg each) administered to 15 PLWH on ART [65]. Viral suppression occurred in nine participants with sensitive virus, lasting 15 to more than 30 weeks. No resistance was observed [66]. In viremic individuals with dual-sensitive viruses, the combination of 3BNC117 and 10-1074 significantly reduced viral load by an average of 2.05 $\log^{10}$ copies/mL, with prolonged suppression lasting up to 3 months. There was no development of resistance to either of the bNAbs. However, some participants with pre-existing resistance to one or both bNAbs had less pronounced reductions in viral load. The bNAbs did not eradicate the viral reservoir.

NCT03571204 was a two-part trial evaluating 3BNC117 and 10-1074 (30 mg/kg) in early infection and ART-naive viremic controllers [67]. Up to 8 infusions were administered monthly over 24 weeks. Antibodies maintained viral suppression up to 43 weeks post-ATI in participants with sensitive viruses. BNAbs also suppressed virus in 2/5 ART-naïve PLWH, if they had sensitive virus.

NCT03526848 was a trial of 3BNC117 and 10-1074 in 26 ART-suppressed PLWH [68]. Participants received seven doses of 3BNC117 and 10-1074 (30 mg/kg) over 20 weeks in the presence or absence of ART. Thirteen out of seventeen participants maintained virologic suppression for at least 20 weeks off ART. Two of the individuals who received all seven antibody doses-maintained suppression after one year. Reservoir analysis performed after six months of antibody therapy revealed changes in the size and composition of the intact proviral reservoir.

PGT121, PGDM1400, and VRC07-523LS

NCT03205917 was a safety and efficacy study of single, dual, and triple bNAb combinations of PGT121, PGDM1400, and VRC07-523LS. The study was conducted in two parts. In part 1, PGDM1400 was evaluated alone (at intravenous doses of 3 mg/kg, 10 mg/kg and 30 mg/kg), and in combination with PGT121 (three intravenous doses of 3 mg/kg, 10 mg/kg and 30 mg/kg each). In part 2, PLWH received a single intravenous dose of PGDM1400, PGT121 and VRC07-523LS at 20 mg/kg each or PGDM1400 and PGT121 at 30 mg/kg each [69]. In five viremic participants, a single infusion of 20 mg/kg of each of the three antibodies reduced plasma HIV RNA by 2.04 $\log^{10}$ copies per millilitre, but viral rebound occurred within 20 days. Rebound viruses showed varying levels of resistance.

NCT03721510 evaluated the effect of PGT121, PGDM1400, and VRC07-523LS in PLWH undergoing an ATI. 12 PLWH interrupted ART and received up to six monthly infusions of PGT121, PGDM1400, and VRC07-523LS (20 mg/kg each). BNAbs maintained viral suppression for at least 28 weeks in 10 of 12 individuals and for at least 38–44 weeks in 5 of 12 participants, even as serum bNAb concentrations declined to undetectable levels. Early viral rebound in two participants was associated with baseline resistance to PGT121 and PGDM1400 [70].

CAPRISA 095 (NeutART) (PACTR202309578224660) is evaluating CAP256V2LS, a V2- apex antibody and VRC07-523LS (20 mg/kg each) administered in 30 PLWH. In 10 participants, CAP256V2LS and VRC07-532LS will be administered in combination with ART at enrolment; in 10 participants CAP256V2LS and VRC07-523LS will be administered at enrolment followed by ART at one week, and in 10 participants, only ART will be administered. A planned ATI will take place after 12 months to determine effect on viremia and the HIV-1 reservoir.

Combination bNAb trials with other agents

NCT02850016 (ROADMAP) was a phase 2a trial combining 3BNC117 (30 mg/kg) with romidepsin, another LRA, in ART-suppressed PLWH [71]. The combination was ineffective in reducing the viral reservoir or delaying viral rebound during an ATI. NCT03041012 (eCLEAR) was a phase 1b/2a study comparing ART alone or with 3BNC117, romidepsin, or both, in 55 newly diagnosed, ART-naive PLWH [72]. 3BNC117 treatment with or without romidepsin enhanced viral decay rates (16.9% for the ART + RMD + 3BNC117 group) compared to ART alone (10%). 3BNC117 accelerated clearance of infected cells compared to ART alone. There was a lower reservoir and increased CD8 + T cell immunity in treated groups. ART-free virologic control was observed among 4 of 5 (80%) participants with 3BNC117 sensitive viruses during the 12-week ATI.

NCT04811040 was a phase 1b proof-of-concept study combining lenacapavir, a long-acting capsid inhibitor with teropavimab (3BNC117-LS) and zinlirvimab (10-1074-LS) in 21 ART suppressed adults [73]. Participants received lenacapavir with either 30 mg/kg or 10 mg/kg IV doses of teropavimab (3BNC117-LS) and zinlirvimab (10-1074-LS) after ART discontinuation. The combination maintained HIV-1 suppression for at least 26 weeks in most participants, with only one experiencing viral rebound.

NCT03588715 (BEAT-2) was a trial combining pegylated interferon alpha 2b with 3BNC117 and 10-1074 (30 mg/kg each) in 14 ART-suppressed PLWH undergoing an ATI [74]. The combination maintained viral suppression for 26 weeks in most participants. Two participants experienced viral rebound during immunotherapy. Ten participants completed the 26-week study period. Although baseline sensitivity testing identified strains affected by 3BNC117 and 10-1074, this did not predict rebound time following ART interruption.

NCT03837756 (TITAN) was a phase 2a trial comparing lefitolimod, a TLR9 agonist, and/or 3BNC117 (30 mg/kg) and 10-1074 (20 mg/kg) in 43 ART-suppressed PLWH [75]. Participants were randomized into four groups: placebo/placebo, lefitolimod/placebo, placebo/bNAbs, or lefitolimod/bNAbs. BNAb groups showed delayed viral rebound (12.5 weeks for the placebo/bNAb group and 9.5 weeks for the lefitolimod/ bNAb group) compared to placebo. Despite subtherapeutic bNAb levels, 36% (4/11) PLWH in the placebo/bNAb group maintained virologic control after a 25-week ATI, compared to none in the placebo/placebo group. Lefitolimod showed no added benefit.

Discussion

Passive immunization with single bNAbs against HIV-1 has demonstrated a complex and varied impact on viral control. Some bNAbs, such as 3BNC117 and VRC01, have shown extended viral suppression and enhanced host immune responses [38, 54]. However, these effects are often transient and insufficient for sustained viral control. Resistance remains a major challenge for bNAb-based therapies. Clinical studies have shown that individuals who do not respond to bNAb therapy often harbour resistant viral populations before treatment [76]. Additionally, even participants with sensitive viral strains can experience viral rebound with resistant variants after bNAb infusion [50, 77]. This can occur either due to pre-existing resistant variants or through mutations in sensitive viral strains in response to bNAb pressure [77].

Another critical insight from clinical studies is that rebound viruses do not typically exhibit cross-resistance to other antibodies targeting the same epitope on the HIV Env protein, which could have implications for selecting antibody combinations to reduce the likelihood of resistance development. This suggests that combinations of two or more bNAbs targeting distinct sites are likely to yield more robust and sustained antiviral effects by increasing both breadth and potency and preventing the emergence of viral resistance [25]. Combination therapy with two or more bNAbs demonstrates extended viral suppression and delayed rebound during ATI in individuals with antibody-sensitive strains [25]. The combination of 3BNC117 and 10-1074 has demonstrated significant viral suppression and delay in viral rebound in both viremic [68] and virally suppressed PLWH [65–67] with antibody-sensitive strains. Sustained viral suppression for up to 43 weeks was observed in PLWH who initiated ART during acute/early HIV-1 infection and had no antibody resistant strains at baseline. This combination also resulted in a reduction of the intact proviral reservoir but not the defective proviral reservoir and was also associated with increased HIV-1 Gag-specific CD8 + and CD4 + T-cell responses during the ATI.

Despite these promising results, challenges remain. Viral escape continues to be an issue even with dual bNAb therapy. Research has shown that viral rebound occurs when bNAb concentrations fall below certain levels, such as 10 μg/mL for the 3BNC117 and 10-1074 combination. To address these challenges, researchers have engineered longer acting and more potent antibodies and have begun exploring triple-bNAb therapy. A single infusion of PGDM1400, PGT121 and VRC07-523LS in viremic, ART-naïve PLWH showed rapid but transient viral load reduction. However, viral rebound was associated with pre-existing partial resistance and bNAb titer decay [68].

Screening for bNAb sensitivity before therapy could help tailor treatment regimens, optimizing efficacy by reducing the number of bNAbs required and minimizing the likelihood of resistance development. The use of assays like the PhenoSense HIV nAb assay [78] could play a crucial role in identifying bNAb-sensitive strains. Additionally, the development of bi-specific and tri-specific bNAbs, which target multiple sites simultaneously are being evaluated.

Another significant challenge is the relatively short half-life of bNAbs, which in PLWH tends to average around 10 days or less. Enhancing both the potency and the half-life of bNAbs could extend the periods of viral suppression and improve their clinical efficacy [77]. Ongoing research is focusing on evaluating longer acting and more potent bNAbs. The "RIO" study (NCT04319367) [79] is assessing 3BNC117-LS and 10-1074-LS in early-treated individuals, while the RHIVIERA-02 trial examines the combined effects of ART with long-acting bNAbs in newly diagnosed early-stage infections.

Early clinical evidence indicates that bNAbs may influence the intact proviral reservoir and modify anti-HIV immune responses. Studies suggest that bNAbs contribute to the elimination of HIV-infected cells, with potential effects on clearing viral foci established early in infection [31]. These findings are particularly relevant for strategies targeting the latent HIV reservoir. However, current studies have limitations, including short observation periods, a low number of antibody infusions, and a focus on individuals with chronic HIV infection.

Targeting the latent reservoir effectively may require the combination of bNAbs with LRAs. For instance, romidepsin has been shown to induce transient viremia in ART-treated individuals, but further research is needed to explore its combination with bNAbs. Other strategies may include using multiple LRAs or incorporating additional drugs like interferon-alpha [77, 80]. Non-human primate models have demonstrated promising results using immunologic approaches that combine bNAbs with vaccines, Toll-like receptor (TLR) agonists, and cytokines. Ongoing clinical trials, such as the HIV-CAR trial (NCT03619278) and others (NCT04357821, NCT05281510), are exploring combination immunotherapies involving bNAbs, vaccines, and LRAs. These studies, including the ACTG A5386 trial (NCT04340596), aim to evaluate the potential of inducing HIV control during an ATI by combining bNAbs with agents such as interleukin IL-15 superagonists. The recent success of lenacapavir for HIV prevention [81], may also help inform future bNAb therapy strategies in PLWH.

Conclusion

Despite these advancements, the clinical implementation of bNAbs faces significant challenges. One major hurdle is the production and distribution cost of bNAbs, as biological molecules are more expensive to produce than chemical-based antiretrovirals. This poses a substantial barrier to widespread clinical use. Scientific advances are being made to reduce the cost of bNAb production, which could make them more accessible in the future [26]. The persistence of the latent reservoir, the potential for viral resistance and the limited half-life of bNAbs collectively represent significant obstacles to their use as a sustainable HIV treatment option. While there are still challenges to overcome, the potential for bNAbs to serve as a valuable adjunct or alternative to traditional ART is significant. Continued research and development of more potent, durable, and cost-effective bNAbs will be essential to advancing HIV treatment, potentially contributing to long-term remission or even a functional cure for HIV.

Abbreviations

AAV	Adeno-associated viral
ADA	Anti-drug antibodies
AE	Adverse event
ART	Antiretroviral therapy
ATI	Analytical treatment interruption
bNAbs	broadly Neutralizing monoclonal antibodies
HIV	Human Immunodeficiency Virus
IM	Intramuscular
IV	Intravenous
LRA	Latency reversing agents
mAbs	Monoclonal antibodies
PLWoH	People living without HIV
PLWH	People living with HIV
RNA	Ribonucleic acid
SC	Subcutaneous

Supplementary Information

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Supplementary Material 1: Supplementary Table 1: Broadly neutralizing monoclonal antibodies previously or currently indicated for the treatment or cure of Human Immunodeficiency Virus. This supplementary provides detailed information pertaining to the clinical trials analyzed in this review.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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