microbial cell

Review

www.microbialcell.com

Neutralizing the threat: harnessing broadly neutralizing antibodies against HIV-1 for treatment and prevention

Juan C Becerra, Lauren Hitchcock, Khoa Vu and Johannes S Gach*

Department of Medicine, Division of Infectious Diseases, University of California, CA, 92697, Irvine, Irvine, USA

*Corresponding Author:
Johannes S Gach, Department of Medicine, Division of Infectious Diseases, University of California, Irvine, Irvine, CA 92697, USA; E-mail: jgach@uci.edu

ABSTRACT Broadly neutralizing antibodies (bnAbs) targeting the human immunodeficiency virus-1 (HIV-1) have played a crucial role in elucidating and characterizing neutralization-sensitive sites on the HIV-1 envelope spike and in informing vaccine development. Continual advancements in identifying more potent bnAbs, along with their capacity to trigger antibody-mediated effector functions, coupled with modifications to extend their half-life, position them as promising candidates for both HIV-1 treatment and prevention. While current pharmacological interventions have made significant progress in managing HIV-1 infection and enhancing quality of life, no definitive cure or vaccines have been developed thus far. Standard treatments involve daily oral anti-retroviral therapy, which, despite its efficacy, can lead to notable long-term side effects. Recent clinical trial data have demonstrated encouraging therapeutic and preventive potential for bnAb therapies in both HIV-1-infected individuals and those without the infection. This review provides an overview of the advancements in HIV-1-specific bnAbs and discusses the insights gathered from recent clinical trials regarding their application in treating and preventing HIV-1 infection.

doi: 10.15698/mic2024.07.826
Received originally: 17. 10. 2023;
in revised form: 06. 05. 2024,
Accepted: 15. 05. 2024
Published: 03. 07. 2024

Keywords: HIV1, bnAbs, prevention, treatment, viral reservoir

Abbreviations:
ADCC - antibody-dependent cellular cytotoxicity,
ADCP - antibody-dependent cellular phagocytosis
ART - antiretroviral therapy
bnAbs - broadly neutralizing antibodies,
CDC - complement-dependent cytotoxicity,
CDCP - complement-dependent cellular phagocytosis,
HIV-1 - human immunodeficiency virus-1,
IgG - immunoglobulin G.

INTRODUCTION

Antibody-mediated immunity is essential for the host defense system by eliminating disease-causing pathogens such as viruses or bacteria and preventing them from infecting human cells [1]. Antibodies of the immunoglobulin G (IgG) isotype are the most abundant in humans and can recognize antigens with one or two Fab regions and interact with Fc gamma receptors (FcγRs) through the immunoglobulin Fc region [2, 3]. IgG plays a vital role in the protection against human immunodeficiency virus-1 (HIV-1) infection, as demonstrated by numerous non-human primate studies [4, 5].

HIV-1 envelope spikes (**Figure 1A**), responsible for mediating the attachment and fusion between viral and host cell membranes [6], represent the primary targets of neutralizing immune responses in HIV-1-infected individuals [7, 8]. However, HIV-1 has evolved evasive mechanisms by displaying major sequence variations on the envelope spike as well as a dense array of host-derived, immunologically "self", N-linked glycans that efficiently shield the underlying protein from host antibody responses [9, 10]. Moreover, HIV-1 virions typically exhibit a limited quantity of intact or functional envelope spikes on their surface, averaging seven to 14 spikes per viral particle [11–13]. As a result, multivalent engagement with B cell receptors and, consequently, the B cell immune response against HIV-1 is limited [14, 15].

Furthermore, low spike numbers decrease the likelihood of bivalent antibody binding that might otherwise enhance neutralization [8, 16] or other antibody-mediated effector functions [17]. In addition to the sparse number of functional envelope spikes, a high prevalence of non-functional forms of envelope, acting as decoys [18, 19], is present, which include soluble monomeric gp120 (**Figure 1B**) and fusion-incompetent gp41 stumps on the viral surface (**Figure 1C**). These non-functional forms of envelope succeed in diverting the immune responses toward immunodominant, non-neutralizing, epitopes rather than to the less accessible neutralizing epitopes [20]. Accordingly, the first autologous neutralizing antibodies emerge relatively late following HIV-1

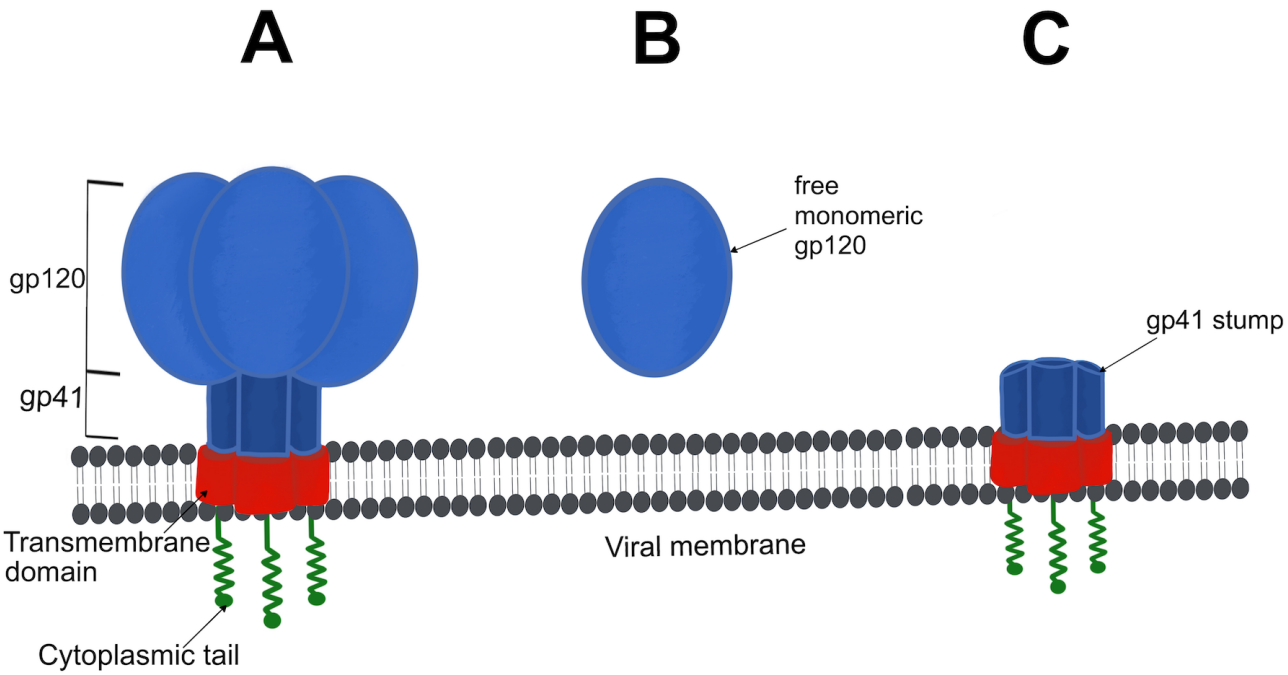

FIGURE 1 ● **Examples of potential forms of HIV-1 envelope on the viral surface.** (**A**) Intact envelope spikes consist of three non-covalently bound gp120/gp41 heterodimers embedded in the viral membrane via a transmembrane domain and a cytoplasmic tail. (**B**) Free monomeric gp120, released through envelope shedding. (**C**) Shaved gp41 stumps on the viral surface.

transmission (i.e., ~ twelve or more weeks) [21]. These initial autologous strain-specific neutralizing antibodies are capable of blocking viral entry and preventing further host cell infection to some extent by (i) interfering with the engagement of CD4 receptors or co-receptors CCR5 and CXCR4, (ii) stabilizing the pre-fusion envelope spike to prevent membrane fusion, or (iii) accelerating envelope spike decay thereby applying selection pressure on cell-free HIV-1 virions [22].

Nevertheless, once HIV-1 enters and integrates into the host genome the error-prone viral reverse transcriptase, with a mutation rate of 5.4 x 10^{-5} per base per replication cycle [23], introduces random mutations into the envelope gene that can affect antibody-binding epitopes contributing neutralization-resistant variants that can continue infecting new cells [24]. As a result, high mutation rates, combined with a short replication cycle and a tendency for recombination, induce quasispecies and generate viral diversity within an individual over the course of HIV-1 infection [25]. A study that followed HIV-1 quasispecies generation in an infected couple revealed that, during the early stages, the distribution of virion varieties formed relatively tight phylogenetic clusters, becoming increasingly dispersed over time, with a corresponding increase in genetic diversity after one year [26]. After three years, the viral sequences obtained from both partners gave rise to distinct phylogenetic clusters in the phylogenetic tree [26]. Therefore, autologous neutralizing antibody responses are generally not associated with control of viremia in most HIV-1 infected individuals and lag behind viral escape variants [27].

While almost all infected individuals develop strain-specific neutralizing antibodies, specifically against autologous viruses, large clinical cohort studies revealed that approximately 10–30% of HIV-1 infections result in some level of serum neutralization breadth after several years of infection [28]. In rare cases, around 1-2% of HIV-1-infected individuals, termed elite neutralizers, develop broadly neutralizing antibodies (bnAbs) [29, 30]. The neutralization breadth of an antibody refers to its ability to recognize and neutralize different clades and strains of HIV-1 by targeting conserved sites on the functional envelope trimer [31]. BnAbs can recognize and inactivate many different heterologous HIV-1 variants, while

low-breadth autologous antibodies are more specific to the initially transmitted founder strains [31]. The neutralization breadth of most bnAbs increases with the time of infection as they go through several rounds of somatic hypermutation [32]. Nevertheless, the pathway to neutralization breadth also differs depending on the epitope being targeted [33].

BINDING EPITOPES OF HIV-1 bnAbs

Recent advances in stabilizing and expressing a nearly complete form of the HIV-1 trimer vastly refined our understanding of the metastability of the trimer and its structures allowing for the detailed characterization of bnAb epitopes [34, 35]. Sites of vulnerability (**Figure 2**) to bnAbs include the CD4 binding site (CD4bs), the V1/V2 loops at the trimer apex, the V3 glycan high mannose supersite, the silent face of gp120, the gp120-gp41 interface, the gp41 fusion peptide, and the membrane-proximal external region (MPER) [35–38]. Examples of bnAbs and their respective targets are shown in **Table 1**. Epitopes on the high-mannose patch are of particular interest for vaccine design considering they are frequently targeted by various classes of bnAbs, which do not require multiple rounds of maturation [39]. A recent study that investigated an HIV-1 V2 loop-directed bnAb lineage reported that extensive antibody somatic hypermutation does not necessarily result in increased breadth and that many mutations do not impact or negatively affect breadth [40]. While the majority of bnAbs can interact with both trimeric and monomeric envelope spikes, some bnAbs require intact quaternary structures that are believed to form only on the functional trimer [41, 42]. In contrast, non-neutralizing antibodies typically bind to monomeric envelope subunits [43].

EFFECTOR FUNCTIONS OF HIV-1 bnAbs

Recent data indicates that the principal mode of protection conferred by bnAbs involves the direct neutralization of virions [73, 74]. However, bnAbs also elicit innate effector mechanisms via Fc-mediated interactions with FcγRs present on diverse immune cell types including natural killer (NK) cells, macrophages, and neutrophils [75, 76]. This engagement triggers processes such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), both of which may substantially augment the overall protective efficacy [77, 78]. Additionally, Fc-mediated complement-dependent effector functions, including complement-dependent cytotoxicity (CDC) or complement-dependent cellular phagocytosis (CDCP), have also been associated with the elimination of HIV-1 [79]. Both effector functions are usually initiated upon binding many molecules of IgG to a multivalent antigen or by high local antigen densities, which in turn allow the multimerization (i.e., hexamerization) of neighboring IgG-Fc domains [3, 79, 80]. The hexameric structure forms an ideal platform for complement component 1q attachment and activation of the complement cascade that results in CDC or CDCP [81].

Clinical evidence of a protective role for Fc-mediated effector functions in HIV-1-infected individuals has been demonstrated in several studies [82–87]. For example, elevated levels of virus-specific ADCC in the patient serum/plasma have been correlated with slower disease progression [82–84]. Fc-mediated effector functions also played an important role in controlling HIV-1 infection in elite controllers [85]. Furthermore, ADCC was identified as an immune correlate of the modest protection observed in the RV144 vaccine trial [86, 87]. Studies using passive immunization with bnAbs, and non-neutralizing antibodies in animal models, have provided valuable insights into the contribution of Fc-mediated effector functions to protective efficacy [88–90]. While some experiments suggest a significant role for these functions, others report conflicting results. For instance, in non-human primate models, the protective effect of certain bnAbs was partially abrogated when Fc-receptor binding was eliminated, suggesting the involvement of Fc-mediated effector functions [91, 92]. However, in other studies [73, 93, 94], the absence of evidence for a contribution of Fc-mediated effector function challenges this notion, raising questions about the variability in bnAb efficacy across different viral infection models.

Recent advances in mathematical modeling and HIV-1 dynamics have enabled quantification of the relative contribution of Fc-mediated effector functions to the antiviral activity of bnAbs, particularly in contexts where established infections need to be treated [84, 93]. These models suggest that Fc-mediated effector functions can account for a substantial portion (around 20-45%) of bnAb activity. On the other hand, investigations into engineered bnAb variants with enhanced FcγR binding aimed at boosting ADCC activity have brought about mixed results [93, 95], calling attention to the complex role of effector functions in modulating therapeutic outcomes.

Therefore, having an understanding of the interplay between Fab-mediated neutralization and Fc-mediated effector functions, as well as the factors influencing their effectiveness, is crucial for optimizing antibody-based strategies for HIV-1 prevention and therapeutic intervention. One of the ways by which Fc-mediated effector functions confer protection against viral infections, thereby contributing to overall efficacy is by targeting infected cells for elimination as seen in a recent clinical trial [96]. Cells infected with HIV-1 exhibit increased vulnerability to elimination compared to cell-free HIV-1 virions through ADCC and ADCP, owing to the diminished abundance of envelope spikes on the surface of these virions [97]. The presence of fewer spikes makes cell-free HIV-1 virions less favorable targets for immune-mediated clearance, even in the presence of complement [98]. Further research into the differential abilities of bnAbs to recruit effector functions *in vivo* will be essential for advancing antibody-based HIV-1 therapies.

CHALLENGES OF ELICITING bnAbs

HIV-1-specific bnAbs have been evaluated in various populations and clinical scenarios [99]. Evidence that bnAbs play a key role in controlling new and pre-existing HIV-1 infections supports the idea that a vaccine capable of eliciting bnAbs could provide the immune system with the head start necessary to prevent HIV-1 infection [22]. Despite recent advances in vaccine design, such as soluble envelope trimer engineering, eliciting bnAbs against HIV-1 remains particularly challenging [34] given that most targets displayed on the viral envelope spike require prolonged antibody maturation pathways to be generated and effective [100]. Besides extensive somatic hypermutation, bnAbs feature other unusual characteristics such as long complementary determining

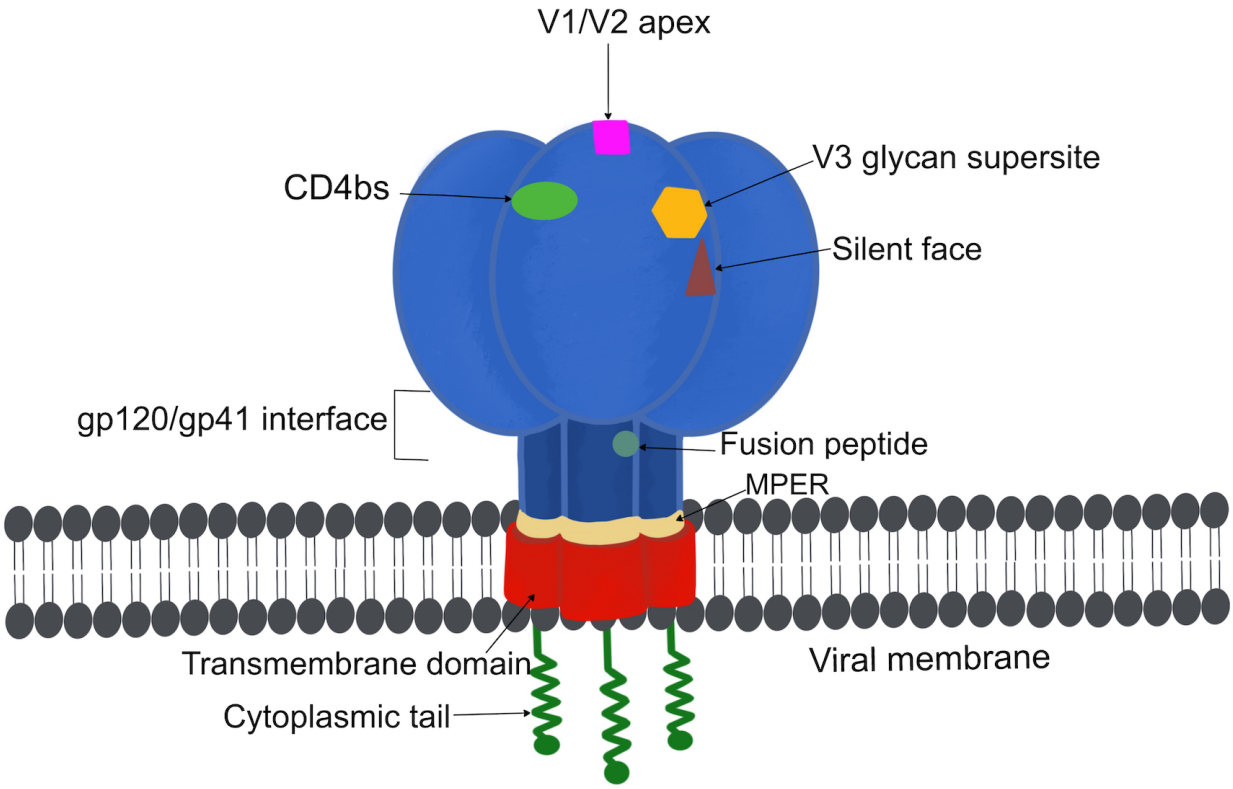

FIGURE 2 ● **Sites of vulnerability on an HIV-1 envelope spike.** BnAbs can be directed against several epitopes on gp120 including the CD4bs, the V1/V2 apex, the V3 glycan supersite site, and the silent face as well as epitopes on gp41 such as the gp41-gp120 interface region, the fusion peptide and the MPER. Examples of bnAbs targeting these sites are shown in **Table 1**.

TABLE 1 ● Examples of broadly neutralizing HIV-1 envelope-specific antibodies and their respective binding sites.

Envelope Subunit	Epitope	Specific antibodies
gp120	V1/V2 apex	PG9 [44]; PG16 [45]; PGT141-145 [46]; CH01-04 [47]; PGDM1400 [48]; CAP256-VRC26.01-33 [49]; VRC38.01 [50]; PCT64 [51]
	V3 glycan supersite	2G12 [52]; PGT121 [46]; PGT128 [46]; PGT135 [46];10-1074 [53]; PCDN-33A [54]; BG18 [55]; DH270.6 [56]
	CD4bs	B12 [57]; VRC01 [58]; 3BNC117 [59]; 8ANC131 [60]; CH235.N6 [61]; PGV04 [62]; N49-P7 [63]; ACS101-103 [64]
	Silent face	VRC-PG05 [65]; SF12 [66]
	gp120/gp41 interface	8ANC195 [67] ; 35022 [68]
gp41	Fusion peptide	VRC34.01 [69]; ACS202 [70]; PGT151 [46]
	MPER	4E10 [71]; 2F5 [71]; 10E8 [72]; DH511 [72]

CD4bs = CD4 binding site, MPER = membrane proximal external region.

regions (CDRs), polyreactivity, and a high prevalence of rare precursor genes [101]. To address these challenges, novel strategies such as targeting germline precursors of bnAbs have been implemented for HIV-1 vaccine design [102, 103]. A recent phase 1 clinical trial with a germline-targeting priming vaccine candidate (IAVI G001) reported the presence of VRC01-class bnAb precursors in 97% of the vaccine recipients [104]. The key to the apparent success appears to be the targeting of germinal B-cells with a nanoparticle carrying 60 copies of an engineered antigen (eOD-GT8 60mer) resembling the inferred immunogenic precursor target of VRC01 recognized by immature B cells, and a subsequent inoculation with a more refined version of the antigen of interest. This guided immune response resulted in the production both VRC01-class B-cells precursors and memory B cells [104]. These encouraging results establish a clinical proof of concept for germline-targeting vaccine priming and support the development of boosting regimens to further enhance bnAb maturation. Currently, two clinical trials (NCT05001373 and NCT05414786) are being conducted to assess the safety and immunogenicity of mRNA-based vaccines based on the eOD-GT8 60mer [105].

HIV-1 bnAbs FOR TREATMENT

Antiretroviral therapy (ART) has effectively lowered HIV-1-associated morbidity and mortality rates by suppressing viral replication [106] and demonstrated remarkable efficacy in prevention [107]. However, ART does not eradicate established HIV-1 infections, thus highlighting the need for a life-long treatment to prevent HIV-1 reactivation from long-lived viral reservoirs [108–110]. Most HIV-1-infected individuals who discontinue ART typically exhibit a viral rebound within weeks even including those who initiated ART early during acute infection with long-term suppression of plasma viremia [111]. Due to barriers to universal ART uptake including stigma, adverse effects, emerging drug resistance and reluctant to adhere to lifelong ART medication, novel preventive and therapeutic interventions are highly desirable [112, 113]. At a minimum, alternative intervention characteristics should include durable viral suppression below viral transmission levels, prevention of disease progression, low susceptibility to drug resistance, and being generally safe and reasonably tolerated [111].

To date, HIV-1-specific bnAbs are being thoroughly investigated as potential ART alternatives because they directly target specific viral epitopes and potentially harness host immune responses [114]. While first-generation bnAbs were generally safe when administered in the context of ongoing viremia or during ART interruption, they had limited potency and limited antiviral activity after multiple high-dose infusions [115, 116]. In contrast, second-generation bnAbs revealed enhanced potency requiring less frequent administrations to maintain serum concentrations at acceptable target levels [117]. Multiple potent second-generation bnAbs against HIV-1 have been and are currently being assessed in clinical trials for HIV-1 treatment (**Table 2**). As of now, single, combination, and repeated administrations of these second-generation bnAbs have been generally well tolerated with rare adverse events [111].

Clinical data from prevention trials (**Table 2**) consistently demonstrate that bnAbs extend viral suppression, regardless of ART. However, their effectiveness depends on virus sensitivity and therapeutic antibody levels. In recent trials, a single infusion of bnAb 3BNC117 (NCT02018510) reduced HIV-1 viremia for up to 28 days, but with the emergence of resistant strains [59]. BnAb VRC01 (NCT01950325) showed reduced viremia, though some participants had minimal response due to resistant virus [118]. Single doses of bnAb 10-1074 (NCT02511990) and PGT121 (NCT02960581) led to the rapid emergence of resistant viruses, despite their potency [119] [120]. In contrast, multiple bnAb doses, as shown in a phase 2a trial (NCT02446847), may prolong suppression, with notable delays in viral rebound compared to historical controls [121]. These findings underscore the potential limitations of single-dose bnAb regimens and highlight the importance of exploring multiple dosing strategies to achieve sustained viral suppression in HIV-1-infected individuals.

Combining bnAbs targeting various HIV-1 neutralizing epitopes has been trialed to combat resistance. Recent phase 1 trials showed that pairing 3BNC117 and 10-1074 increased viral suppression with fewer escape mutants. One trial (NCT02825797) reported 15 weeks of suppression without mutants after three doses at weeks 0, 3, and 6 [122]. Another trial with an eight-dose regimen over 28 weeks achieved complete viral suppression for 43 weeks post-ART interruption or 15 weeks post-infusion, without escape mutants [123]. However, due to HIV-1 diversity, this combination may only benefit approximately 50% of clade B-infected individuals sensitive to both antibodies [122]. Testing a triple bnAb formulation (NCT03205917) consisting of PGDM1400, PGT121, and VRC07-523LS showed promising coverage; however, viral rebound occurred within a median of 20 days post-infusion for two (i.e., PGDM1400 and PGT121) out of the three antibodies [124], indicating the need for further refinement in antibody selection for sustained effectiveness.

Potential improvements in antibody selection may involve conducting genotypic and phenotypic analysis of plasma virus samples [125], akin to the Zurich Primary HIV Infection Study [126], to identify candidates responsive to specific bnAbs. Additionally, implementing computational studies capable of predicting viral rebound and delineating HIV-1 escape pathways from other bnAbs, for which therapy trials are lacking, could inform the design of optimal treatments [127, 128].

Furthermore, antibody Fc domain engineering methods to significantly improve the half-life of existing bnAbs have been successfully implemented in recent clinical trials [122, 129, 130]. The half-life of circulating IgGs is regulated through Fc binding to the neonatal Fc receptors protecting them from lysosomal degradation [131, 132]. To increase the half-life of an IgG molecule, a serine and leucine double mutation can be introduced at positions M428L and N434S in the Fc domain. The double mutation not only increases the serum half-life and the persistence in genital tissues but also retains neutralizing antibody levels for longer time [133, 134]. Such changes in LS-antibodies are expected to be translated into administering bnAbs treatments at 3–6-month intervals, which could be a promising alternative to ART regimens, especially in geographically isolated locations. In summary, although the clinical trials utilizing bnAbs discussed above have shown promise, further fine-tuning in the selection of bnAbs and their treatment schedules is necessary to optimize prevention

TABLE 2 ● Examples of completed and active clinical trials using second-generation HIV-1bnAbs for the treatment of HIV-1.

CLINICAL TRIAL IDENTIFIER	BROADLY NEUTRALIZING ANTIBODIES	ENVELOPE BINDING SITE
COMPLETED		
NCT02960581	PGT121	V3 glycan
NCT03205917	PGDM1400	V1/V2 loop
	PGT121	V3 glycan
	VRC07-523LS	CD4bs
NCT02018510	3BNC117	CD4bs
NCT02446847	3BNC117	CD4bs
NCT02588586	3BNC117	CD4bs
NCT02825797	3BNC117	CD4bs
	10-1074	V3 glycan supersite
NCT03526848	3BNC117	CD4bs
	10-1074	V3 glycan supersite
NCT02511990	10-1074	V3 loop
NCT03707977	VRC01LS	CD4bs
	10-1074	V3 glycan supersite
NCT02664415	VRC01	CD4bs
NCT01950325	VRC01	CD4bs
NCT02840474	VRC01LS	CD4bs
	VRC07-523LS	CD4bs
NCT03254277	3BNC117-LS	CD4bs
NCT04250636	3BNC117-LS	CD4bs
	10-1074-LS	V3 glycan supersite
NCT03875209	10E8.4	MPER
NCT02579083	VRC01-N	CD4bs
NCT03015181	VRC01-523LS	CD4bs
NCT03837756	3BNC117	CD4bs
	10-1074-LS	V3 glycan supersite
NCT03041012	3BNC117	CD4bs
ACTIVE		
NCT04871113	GSK3810109A	CD4bs
NCT04319367	10-1074-LS	V3 glycan supersite
NCT05300035	10-1074-LS	V3 glycan supersite
NCT03374202	AAV-VRC07	CD4bs
NCT04357821	VRC07-523LS	CD4bs
	10-1074	V3 glycan supersite
NCT04173819	3BNC117-LS-J	CD4bs
	10-1074-LS-J	V3 glycan supersite
NCT04983030	PGDM1400	V1/V2 loop
	PGT121	V3 glycan
	VRC07-523LS	CD4bs
NCT05281510	VRC07-523LS	CD4
	CAP256V2LS	V1/V2 loop
NCT05719441	VRC07-523LS	CD4bs
	PGT121.414.LS	V3 glycan

effectiveness in both ART-treated and untreated individuals.

HIV-1 bnAbs AND VIRAL RESERVOIRS

The HIV-1 viral reservoir consists of latently infected cells such as resting CD4+ T cells and other long-lived cells that harbor integrated HIV-1 DNA within their genome, allowing the virus to persist in the body for extended periods [135]. The presence of these reservoirs is a critical obstacle to viral eradication. The reservoirs are usually established within the first few days of infection and enable viral rebound after ART interruption despite generally efficient suppression of viral replication by ART [136]. However, early ART initiation during acute infection may limit the size and diversity of HIV-1 reservoirs compared to late ART initiation during chronic infection [112, 136, 137].

In the search for an eradication strategy, various approaches for reducing and eliminating viral reservoirs have been investigated, including, but not limited, to the "shock and kill" strategy, which aims to reactivate dormant infected cells for immune clearance [138, 139]; gene editing techniques like CRISPR/Cas9 to directly target and disrupt viral

DNA [140, 141]; immune-based therapies such as therapeutic vaccines and immunomodulatory agents to enhance immune response [142–144]; development of novel antiretroviral drugs with enhanced potency [145, 146]; and exploration of combination approaches integrating multiple strategies for more effective reservoir targeting [147, 148]. An antibody-based strategy for eliminating viral reservoirs, employing bnAbs to target and eradicate HIV-infected cells, has also been explored [149]. While earlier stage 1 clinical trials showed limited success [118, 150], [151] recent preclinical studies and early clinical trials have demonstrated the potential to diminish viral reservoir and delay viral rebound [96, 152, 153] . For example, a recent phase 1b/2a study (NCT03041012) assessed whether early intervention with bnAb 3BNC117 followed by a histone deacetylase inhibitor (romidepsin) shortly after ART initiation could alter the course of HIV-1 infection. The authors found that early intervention with 3BNC117 at ART initiation enhanced elimination of plasma viruses and infected cells, boosted HIV-1-specific CD8+ immunity, and was associated with sustained ART-free virologic control among individuals with 3BNC117-sensitive virus [152]. These findings lend evidence to interventions administered at the time of ART initiation as a strategy to limit HIV-1 persistence. Another recent phase 1b study examined the impact of multiple infusions of 3BNC117 and 10-1074 in individuals chronically infected with HIV on sustained viral suppression without ART and reservoir size when administered independently [96]. Analysis of the reservoir after six months of therapy indicated alterations in the size and makeup of the intact proviral reservoir with no observed reduction in the defective reservoir.

Understanding the differences in viral reservoirs and susceptibility to bnAbs between individuals starting ART early versus those with chronic infection is essential for designing clinical trials and implementing HIV-1 cure strategies focused on reducing viral reservoirs [136]. For example, children living with HIV-1 and receiving ART from birth are particularly suitable for bnAb treatment due to their limited viral resistance and smaller viral reservoir size [154] . Moreover, they offer an opportunity for ART-sparing strategies, avoiding long-term toxicities and adherence issues. A bnAb treatment study in Botswana (NCT03707977) achieved sustained HIV-1 suppression in children with favorable reservoir characteristics, including a smaller initial proviral reservoir and sensitivity to bnAb neutralization [129] . Despite these promising results, challenges remain, such as understanding the long-term effects of antibody infusions in children, the establishment of long-lived viral reservoirs, and their susceptibility to bnAbs. To tackle the latter, various combinations of bnAbs with potent latency-reversing agents or other immunomodulatory approaches, such as toll-like receptor agonists, cytokines, checkpoint blockade inhibitors, or therapeutic vaccines, are currently under investigation [99].

Although promising, there are lingering questions about the effectiveness and accessibility of bnAbs in tissues compared to the bloodstream, as well as concerns about viral escape mutations and the selection pressures influencing viral rebound in the presence of non-suppressive bnAb therapy. Nonetheless, therapies based on bnAbs offer a promising avenue for researching an HIV-1 cure, and are central to further exploration in current studies.

ROLE OF bnAbs FOR PREVENTION

Whether bnAbs can be used to prevent HIV-1 acquisition has been recently assessed in two randomized phase 2b efficacy clinical trials conducted in the Americas and Europe (HVTN 704/HPTN 085; NCT02716675) as well as in sub-Saharan Africa (HVTN 703/HPTN 081, NCT02568215) [155]. Both proof of concept studies used the CD4bs-specific antibody VRC01 administered either at a low dose of 10 mg/kg or at a high dose of 30 mg/kg. Both trials showed that VRC01 was not able to prevent HIV-1 acquisition more efficiently than placebo. Out of 2699 participants in HVTN 704/HPTN 085, 32 infections occurred in the low dose group, 28 infections in the high dose group, and 38 infections in the placebo group. The estimated prevention efficacy of the pooled groups versus placebo was 26.5%.

Among the 1924 participants in HVTN 703/HPTN 081, 28 HIV-1 infections occurred in the low-dose group, 19 in the high-dose group, and 29 in the placebo group. Similarly, the estimated prevention efficacy was non-significant at 8.8%. Although VRC01 did not prevent overall HIV-1 acquisition more effectively than placebo a pooled data analysis looking at the incidence of infection with VRC01-sensitive isolates revealed an estimated prevention efficacy of over 75% suggesting that bnAb prophylaxis could be effective. Recently, a more potent and half-life enhanced bnAb (VRC07-523LS) was also tested in a phase 1 study (NCT03015181) and deemed safe for clinical use [130]. It will be of interest to see whether this antibody reveals a better prevention efficacy compared to the previous trials.

More clinical studies are beginning to focus on bnAb combination regimens as an alternative to single regimens like VRC01 (**Table 3**). Currently, a double regimen including the two bnAbs CAP256V2LS and VRC07-523LS was tested for safety and pharmacokinetics. The phase 1 clinical trial conducted in South Africa with 42 HIV-negative participants (CAPRISA 012B) reported no serious adverse events or dose-limiting toxicities [117]. Another phase 1 clinical trial is looking at the safety and pharmacokinetics of the bnAb combination 3BNC117 and 10-1074 in 25 HIV-1 negative participants for prophylactic use against HIV-1 (NCT02824536) [156].

Aside from infusions, a recent phase 1 clinical study (NCT02579083) described the use of MB66, a multipurpose prevention technology vaginal film product, in combination with bnAb VRC01-N against HIV-1 and HSV8-N against HSV-1 and 2 [157] . MB66 was well tolerated when administered over seven consecutive days. The study observed peak antibody levels in vaginal secretions one-hour post-film administration, which remained significantly elevated through 24 hours. Vaginal samples collected after 24 hours significantly neutralized both HIV-1 and HSV-2 *ex vivo*.

CONCLUSION

The administration of HIV-1 envelope-specific bnAbs in humans has shown both safety and efficacy in reducing viremia. Moreover, bnAbs maintain short-term viral suppression of antibody-sensitive HIV-1 variants in the absence of ART. While both single-dose and multi-dose regimens are viable, multi-dose regimens have demonstrated prolonged HIV-1 suppression. Notably, individuals infected with HIV-1 who exhibit high sensitivity to specific bnAbs experience superior

TABLE 3 ● Examples of completed and active clinical trials using second-generation HIV-1bnAbs for the prevention of HIV-1.

CLINICAL TRIAL IDENTIFIER	BROADLY NEUTRALIZING ANTIBODIES	ENVELOPE BINDING SITE
COMPLETED		
NCT02568215	VRC01	CD4bs
NCT02716675	VRC01	CD4bs
NCT02824536	3BNC117 10-1074	CD4bs, V3 glycan supersite
ACTIVE		
NCT04408963	CAP256V2LS	V1/V2 Loops

and longer-lasting viral suppression compared to those with lower sensitivity. Although combinatorial therapy with multiple bnAbs has partially addressed sensitivity issues, genotyping and phenotyping of locally circulating viruses will be essential for optimizing therapy outcomes. Enhanced bnAb combination therapies with extended intervals between treatments could offer patients greater flexibility without the need for daily oral medications like ART.

In the context of passive HIV-1 vaccination, HIV-1 envelope-specific bnAbs have been tested in high-risk uninfected populations, yielding limited protection. Initial clinical trials using a single bnAb regimen, such as VRC01, failed to achieve statistically significant protection compared to unvaccinated controls. Therefore, further studies employing combinatorial antibody regimens and improved antibody candidates, particularly those with extended half-lives, are necessary to explore the prophylactic potential of HIV-1-specific bnAbs, especially in high-risk groups such as men and transgender individuals who have sex with men.

The persistence of viral reservoirs poses a challenge to HIV eradication efforts despite effective ART. Various strategies are being explored, including antibody-based approaches using bnAbs to target and eliminate HIV-infected cells with recent studies showing promise in reducing the viral reservoir and delaying viral rebound. However, challenges remain in understanding differences in viral reservoirs and bnAb susceptibility, tissue accessibility, viral escape mutations, and rebound under non-suppressive bnAb therapy. Despite these challenges, bnAb-based therapies offer hope for significant advances towards eliminating HIV-1 infections.

ACKNOWLEDGEMENTS

The authors thank Valerie Gach for crafting Figure 1 and Figure 2 with Procreate (Version 5.3.6).

CONFLICT OF INTEREST

The authors declare that no competing interest exists.

Please cite this article as: Juan C Becerra, Lauren Hitchcock, Khoa Vu, Johannes S Gach (2024). **Neutralizing the threat: harnessing broadly neutralizing antibodies against HIV-1 for treatment and prevention**. **Microbial Cell** 11: 207-220. doi: 10.15698/mic2024.07.826

References

1. Twigg HL (**2005**). Humoral immune defense (antibodies): recent advances. **Proc Am Thorac Soc** 2 (5): 417–421. doi:10.1513/pats.200508-089JS

2. Burton DR (**2002**). Antibodies, viruses and vaccines. **Nat Rev Immunol** 2 (9): 706–713. doi:10.1038/nri891

3. De Taeye SW, Rispens T, Vidarsson G (**2019**). The Ligands for Human IgG and Their Effector Functions. **Antibodies (Basel)** 8 (2): 30. doi:10.3390/antib8020030

4. Walsh SR, Seaman MS (**2021**). Broadly Neutralizing Antibodies for HIV-1 Prevention. **Front Immunol** 12: 712,122. doi:10.3389/fimmu.2021.712122

5. Prete GQD, Lifson JD, Keele BF (**2016**). Nonhuman primate models for the evaluation of HIV-1 preventive vaccine strategies: model parameter considerations and consequences. **Curr Opin HIV AIDS** 11 (6): 546–554. doi:10.1097/COH.0000000000000311

6. Gach JS, Gorlani A, Dotsey EY, Becerra JC, Anderson CT, Berzins B, Felgner PL, Forthal DN, Deeks SG, Wilkin TJ, Casazza JP, Koup RA, Katlama C, Autran B, Murphy RL, Achenbach CJ (**2016**). HIV-1-Specific Antibody Response and Function after DNA Prime and Recombinant Adenovirus 5 Boost HIV Vaccine in HIV-Infected Subjects. **PLoS One** 11 (8): 160,341–160,341. doi:10.1371/journal.pone.0160341

7. Beltran-Pavez C, Ferreira CB, Merino-Mansilla A, Fabra-Garcia A, Casadella M, Noguera-Julian M, Paredes R, Olvera A, Haro I, Brander C, Garcia F, Gatell JM, Yuste E, Sanchez-Merino V (**2018**). Guiding the humoral response against HIV-1 toward a MPER adjacent region by immunization with a VLP-formulated antibody-selected envelope variant. **PLoS One** 13 (12): 208,345–208,345. doi:10.1371/journal.pone.0208345

8. Galimidi RP, Klein JS, Politzer MS, Bai S, Seaman MS, Nussenzweig MC, West AP, Bjorkman PJ (**2015**). Intra-spike crosslinking overcomes antibody evasion by HIV-1. **Cell** 160 (3): 433–446. doi:10.1016/j.cell.2015.01.016

9. Moyo T, Ferreira RC, Davids R, Sonday Z, Moore PL, Travers SA, Wood NT, Dorfman JR (**2017**). Chinks in the armor of the HIV-1 Envelope glycan shield: Implications for immune escape from anti-glycan broadly neutralizing antibodies. **Virology** 501: 12–24. doi:10.1016/j.virol.2016.10.026

10. Crispin M, Doores KJ (**2015**). Targeting host-derived glycans on enveloped viruses for antibody-based vaccine design. **Curr Opin Virol** 11: 63–69. doi:10.1016/j.coviro.2015.02.002

11. Amitai A, Chakraborty AK, Kardar M (**2018**). The low spike density of HIV may have evolved because of the effects of T helper cell depletion on affinity maturation. **PLoS Comput Biol** 14 (8): 1006,408–1006,408. doi:10.1371/journal.pcbi.1006408

12. Zhu P, Liu J, Bess J, Chertova E, Lifson JD, Grisé H, Ofek GA, Taylor KA, Roux KH (**2006**). Distribution and three-dimensional structure of AIDS virus envelope spikes. **Nature** 441 (7095): 847–852. doi:10.1038/nature04817

13. Stano A, Leaman DP, Kim AS, Zhang L, Autin L, Ingale J, Gift SK, Truong J, Wyatt RT, Olson AJ, Zwick MB (**2017**). Dense Array of Spikes on HIV-1 Virion Particles. **J Virol** 91 (14): 415–432. doi:10.1128/JVI.00415-17

14. Schiller J, Chackerian B (**2014**). Why HIV virions have low numbers of envelope spikes: implications for vaccine development. **PLoS Pathog** 10 (8): 1004,254–1004,254. doi:10.1371/journal.ppat.1004254

15. Ota T, Doyle-Cooper C, Cooper AB, Huber M, Falkowska E, Doores KJ, Hangartner L, Le K, Sok D, Jardine J, Lifson J, Wu X, Mascola JR, Poignard P, Binley JM, Chakrabarti BK, Schief WR, Wyatt RT, Burton DR, Nemazee D (**2012**). Anti-HIV B Cell lines as candidate vaccine biosensors. **J Immunol** 189 (10): 4816–4824. doi:10.4049/jimmunol.1202165

16. Klein JS, Bjorkman PJ (**2010**). Few and far between: how HIV may be evading antibody avidity. **PLoS Pathog** 6 (5): 1000,908–1000,908. doi:10.1371/journal.ppat.1000908

17. Burton DR (**2023**). Antiviral neutralizing antibodies: from in vitro to in vivo activity. **Nat Rev Immunol** 23 (11): 720–734. doi:10.1038/s41577-023-00858-w

18. Burton DR, Hangartner L (**2016**). Broadly Neutralizing Antibodies to HIV and Their Role in Vaccine Design. **Annu Rev Immunol** 34: 635–659. doi:10.1146/annurev-immunol-041015-055515

19. Moore PL, Crooks ET, Porter L, Zhu P, Cayanan CS, Grise H, Corcoran P, Zwick MB, Franti M, Morris L, Roux KH, Burton DR, Binley JM (**2006**). Nature of nonfunctional envelope proteins on the surface of human immunodeficiency virus type 1. **J Virol** 80 (5): 2515–2528. doi:10.1128/JVI.80.5.2515-2528.2006

20. Cook JD, Khondker A, Lee JE (**2022**). Conformational plasticity of the HIV-1 gp41 immunodominant region is recognized by multiple non-neutralizing antibodies. **Commun Biol** 5 (1): 291–291. doi:10.1128/JVI.80.5.2515-2528.2006

21. Moore PL, Gray ES, Morris L (**2009**). Specificity of the autologous neutralizing antibody response. **Curr Opin HIV AIDS** 4 (5): 358–363. doi:10.1128/JVI.80.5.2515-2528.2006

22. Griffith SA, Mccoy LE (**2021**). To bnAb or Not to bnAb: Defining Broadly Neutralising Antibodies Against HIV-1. **Front Immunol** 12: 708,227–708,227. doi:10.3389/fimmu.2021.708227

23. Gao F, Chen Y, Levy DN, Conway JA, Kepler TB, Hui H (**2004**). Unselected mutations in the human immunodeficiency virus type 1 genome are mostly nonsynonymous and often deleterious. **J Virol** 78 (5): 2426–2433. doi:10.1128/jvi.78.5.2426-2433.2004

24. Bar KJ, Tsao CY, Iyer SS, Decker JM, Yang Y, Bonsignori M, Chen X, Hwang KK, Montefiori DC, Liao HX, Hraber P, Fischer W, Li H, Wang S, Sterrett S, Keele BF, Ganusov VV, Perelson AS, Korber BT, Georgiev I, Mclellan JS, Pavlicek JW, Gao F, Haynes BF, Hahn BH, Kwong PD, Shaw GM (**2012**). Early low-titer neutralizing antibodies impede HIV-1 replication and select for virus escape. **PLoS Pathog** 8 (5): 1002,721–1002,721. doi:10.1371/journal.ppat.1002721

25. Charpentier C, Nora T, Tenaillon O, Clavel F, Hance AJ (**2006**). Extensive recombination among human immunodeficiency virus type 1 quasispecies makes an important contribution to viral diversity in individual patients. **J Virol** 80 (5): 2472–2482. doi:10.1128/JVI.80.5.2472-2482.2006

26. Yu F, Wen Y, Wang J, Gong Y, Feng K, Ye R, Jiang Y, Zhao Q, Pan P, Wu H, Duan S, Su B, Qiu M (**2018**). The Transmission and Evolution of HIV-1 Quasispecies within One Couple: a Follow-up Study based on Next-Generation Sequencing. **Sci Rep** 8 (1): 1404–1404. doi:10.1038/s41598-018-19783-3

27. Alter G, Moody MA (**2010**). The humoral response to HIV-1: new insights, renewed focus. **J Infect Dis** 202 (2): 315–322. doi:10.1086/655654

28. Mccoy LE, Mcknight A (**2017**). Lessons learned from humoral responses of HIV patients. **Curr Opin HIV AIDS** 12 (3): 195–202. doi:10.1097/COH.0000000000000361

29. Walker LM, Simek MD, Priddy F, Gach JS, Wagner D, Zwick MB, Phogat SK, Poignard P, Burton DR (**2010**). A limited number of antibody specificities mediate broad and potent serum neutralization in selected HIV-1 infected individuals. **PLoS Pathog** 6 (8): 1001,028–1001,028. doi:10.1371/journal.ppat.1001028

30. Landais E, Moore PL (**2018**). Development of broadly neutralizing antibodies in HIV-1 infected elite neutralizers. **Retrovirology** 15 (1): 61–61. doi:10.1186/s12977-018-0443-0

31. Conti S, Karplus M (**2019**). Estimation of the breadth of CD4bs targeting HIV antibodies by molecular modeling and machine learning. **PLoS Comput Biol** 15 (4): 1006,954–1006,954. doi:10.1371/journal.pcbi.1006954

32. Scheid JF, Mouquet H, Feldhahn N, Seaman MS, Velinzon K, Pietzsch J, Ott RG, Anthony RM, Zebroski H, Hurley A, Phogat A, Chakrabarti B, Li Y, Connors M, Pereyra F, Walker BD, Wardemann H, Ho D, Wyatt RT, Mascola JR, Ravetch JV, Nussenzweig MC (**2009**). Broad diversity of neutralizing antibodies isolated from memory B cells in HIV-infected individuals. **Nature** 458 (7238): 636–640. doi:10.1038/nature07930

33. Derdeyn CA, Moore PL, Morris L (**2014**). Development of broadly neutralizing antibodies from autologous neutralizing antibody responses in HIV infection. **Curr Opin HIV AIDS** 9 (3): 210–216. doi:10.1097/COH.0000000000000057

34. De Taeye SW, Moore JP, Sanders RW (**2016**). HIV-1 Envelope Trimer Design and Immunization Strategies To Induce Broadly Neutralizing Antibodies. **Trends Immunol** 37 (3): 221–232. doi:10.1016/j.it.2016.01.007

35. Reiss E, Van Haaren MM, Van Schooten J, Claireaux MAF, Maisonnasse P, Antanasijevic A, Allen JD, Bontjer I, Torres JL, Lee WH, Ozorowski G, Bernat NV, Kaduk M, Aldon Y, Burger JA, Chawla H, Aartse A, Tolazzi M, Gao H, Mundsperger P, Crispin M, Montefiori DC, Hedestam CGK, Scarlatti G, Ward AB, Grand RL, Shattock R, Dereuddre-Bosquet N, Sanders RW, Van Gils MJ (**2022**). Fine-mapping the immunodominant antibody epitopes on consensus sequence-based HIV-1 envelope trimer vaccine candidates. **NPJ Vaccines** 7 (1): 152–152. doi:10.1038/s41541-022-00576-9

36. Miller EP, Finkelstein MT, Erdman MC, Seth PC, Fera D (**2021**). A Structural Update of Neutralizing Epitopes on the HIV Envelope, a Moving Target. **Viruses** 13 (9): 1774–1774. doi:10.3390/v13091774

37. Ding C, Patel D, Ma Y, Mann J, Wu J, Gao Y (**2021**). Employing Broadly Neutralizing Antibodies as a Human Immunodeficiency Virus Prophylactic & Therapeutic Application. **Front Immunol** 12: 697,683–697,683. doi:10.3389/fimmu.2021.697683

38. Gach JS, Leaman DP, Zwick MB (**2011**). Targeting HIV-1 gp41 in close proximity to the membrane using antibody and other molecules. **Curr Top Med Chem** 11 (24): 2997–3021. doi:10.2174/156802611798808505

39. Lorin V, Fernández I, Masse-Ranson G, Bouvin-Pley M, Molinos-Albert LM, Planchais C, Hieu T, Péhau-Arnaudet G, Hrebík D, Girelli-Zubani G, Fiquet O, Guivel-Benhassine F, Sanders RW, Walker BD, Schwartz O, Scheid JF, Dimitrov JD, Plevka P, Braibant M, Seaman MS, Bontems F, Santo JPD, Rey FA, Mouquet H (**2022**). Epitope convergence of broadly HIV-1 neutralizing IgA and IgG antibody lineages in a viremic controller. **J Exp Med** 219 (3): 20212,045–20212,045. doi:10.1084/jem.20212045

40. Sacks D, Bhiman JN, Wiehe K, Gorman J, Kwong PD, Morris L, Moore PL (**2019**). Somatic hypermutation to counter a globally rare viral immunotype drove off-track antibodies in the CAP256-VRC26 HIV-1 V2-directed bNAb lineage. **PLoS Pathog** 15 (9): 1008,005–1008,005. doi:10.1371/journal.ppat.1008005

41. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, Wrin T, Simek MD, Fling S, Mitcham JL, Lehrman JK, Priddy FH, Olsen OA, Frey SM, Hammond PW, Kaminsky S, Zamb T, Moyle M, Koff WC, Poignard P, Burton DR (**2009**). Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. **Investigators PGP** 326 (5950): 285–289. doi:10.1126/science.1178746

42. Gorny MK, Stamatatos L, Volsky B, Revesz K, Williams C, Wang XH, Cohen S, Staudinger R, Zolla-Pazner S (**2005**). Identification of a new quaternary neutralizing epitope on human immunodeficiency virus type 1 virus particles. **J Virol** 79 (8): 5232–5237. doi:10.1128/JVI.79.8.5232-5237.2005

43. Sanders RW, Derking R, Cupo A, Julien JP, Yasmeen A, De Val N, Kim HJ, Blattner C, Peña ATDL, Korzun J, Golabek M, Reyes KDL, Ketas TJ, Van Gils MJ, King CR, Wilson IA, Ward AB, Klasse PJ, Moore JP (**2013**). A next-generation cleaved, soluble HIV-1 Env trimer, BG505 SOSIP.664 gp140, expresses multiple epitopes for broadly neutralizing but not non-neutralizing antibodies. **PLoS Pathog** 9 (9). doi:10.1371/journal.ppat.1003618

44. Mclellan JS, Pancera M, Carrico C, Gorman J, Julien JP, Khayat R, Louder R, Pejchal R, Sastry M, Dai K, Dell O, Patel S, Shahzad-Ul-Hussan N, Yang S, Zhang Y, Zhou B, Zhu T, Boyington J, Chuang JC, Diwanji GY, Georgiev D, Kwon I, Lee YD, Louder D, Moquin MK, Schmidt S, Yang SD, Bonsignori ZY, Crump M, Kapiga JA, H S, et al (**2011**). **Structure of HIV-1 gp120 V1/V2 domain with broadly neutralizing antibody PG9** 480: 336–343. doi:10.1056/NEJMoa2031738

45. Pejchal R, Walker LM, Stanfield RL, Phogat SK, Koff WC, Poignard P, Burton DR, Wilson IA (**2010**). Structure and function of broadly reactive antibody PG16 reveal an H3 subdomain that mediates potent neutralization of HIV-1. **Proc Natl Acad Sci U S A** 107 (25): 11,483–11,488. doi:10.1073/pnas.1004600107

46. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien JP, Wang SK, Ramos A, Chan-Hui PY, Moyle M, Mitcham JL, Hammond PW, Olsen OA, Phung P, Fling S, Wong CH, Phogat S, Wrin T, Simek MD, Koff WC, Wilson IA, Burton DR, Poignard P, Investigators PGP (**2011**). Broad neutralization coverage of HIV by multiple highly potent antibodies. **Nature** 477 (7365): 466–470. doi:10.1038/nature10373

47. Bonsignori M, Hwang KK, Chen X, Tsao CY, Morris L, Gray E, Marshall DJ, Crump JA, Kapiga SH, Sam NE, Sinangil F, Pancera M, Yongping Y, Zhang B, Zhu J, Kwong PD, Dell SO, Mascola JR, Wu L, Nabel GJ, Phogat S, Seaman MS, Whitesides JF, Moody MA, Kelsoe G, Yang X, Sodroski J, Shaw GM, Montefiori DC, Kepler TB, et al (**2011**). Analysis of a clonal lineage of HIV-1 envelope V2/V3 conformational epitope-specific broadly neutralizing antibodies and their inferred unmutated common ancestors. **J Virol** 85: 9998–10,009. doi:10.1128/JVI.05045-11

48. Sok D, Van Gils MJ, Pauthner M, Julien JP, Saye-Francisco KL, Hsueh J, Briney B, Lee JH, Le KM, Lee PS, Hua Y, Seaman MS, Moore JP, Ward AB, Wilson IA, Sanders RW, Burton DR (**2014**). Recombinant HIV envelope trimer selects for quaternary-dependent antibodies targeting the trimer apex. **Proc Natl Acad Sci U S A** 111 (49): 17,624–17,629. doi:10.1073/pnas.1415789111

49. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, Dekosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, Mckee K, Nonyane M, Dell SO, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, et al (**2014**). Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. **Nature** 509 (7498): 55–62. doi:10.1038/nature13036

50. Cale EM, Gorman J, Radakovich NA, Crooks ET, Osawa K, Tong T, Li J, Nagarajan R, Ozorowski G, Ambrozak DR, Asokan M, Bailer RT, Bennici AK, Chen X, Doria-Rose NA, Druz A, Feng Y, Joyce MG, Louder MK, Dell SO, Oliver C, Pancera M, Connors M, Hope TJ, Kepler TB, Wyatt RT, Ward AB, Georgiev IS, Kwong PD, Mascola JR, et al (**2017**). Virus-like Particles Identify an HIV V1V2 Apex-Binding Neutralizing Antibody that Lacks a Protruding Loop. **Immunity** 46 (5): 777–791. doi:10.1016/j.immuni.2017.04.011

51. Landais E, Murrell B, Briney B, Murrell S, Rantalainen K, Berndsen ZT, Ramos A, Wickramasinghe L, Smith ML, Eren K, De Val N, Wu M, Cappelletti A, Umotoy J, Lie Y, Wrin T, Algate P, Chan-Hui PY, Karita E, Ward AB, Wilson IA, Burton DR, Smith D, Pond S, Poignard P, Investigators IPC, Network I (**2017**). HIV Envelope Glycoform Heterogeneity and Localized Diversity Govern the Initiation and Maturation of a V2 Apex Broadly Neutralizing Antibody Lineage. **Immunity** 47 (5): 990–1003. doi:10.1016/j.immuni.2017.11.002

52. Gach JS, Furtmüller PG, Quendler H, Messner P, Wagner R, Katinger H, Kunert R (**2010**). Proline is not uniquely capable of providing the pivot point for domain swapping in 2G12, a broadly neutralizing antibody against HIV-1. **J Biol Chem** 285 (2): 1122–1127. doi:10.1074/jbc.M109.058792

53. Mouquet H, Scharf L, Euler Z, Liu Y, Eden C, Scheid JF, Halper-Stromberg A, Gnanapragasam PN, Spencer DI, Seaman MS, Schuitemaker H, Feizi T, Nussenzweig MC, Bjorkman PJ (**2012**). Complex-type N-glycan recognition by potent broadly neutralizing HIV antibodies. **Proc Natl Acad Sci U S A** 109 (47): 3268–3277. doi:10.1073/pnas.1217207109

54. Macleod DT, Choi NM, Briney B, Garces F, Ver LS, Landais E, Murrell B, Wrin T, Kilembe W, Liang CH, Ramos A, Bian CB, Wickramasinghe L, Kong L, Eren K, Wu CY, Wong CH, Pond SLK, Wilson IA, Burton DR, Poignard P, Network I (**2016**). Early Antibody Lineage Diversification and Independent Limb Maturation Lead to Broad HIV-1 Neutralization Targeting the Env High-Mannose Patch. **Immunity** 44 (5): 1215–1226. doi:10.1016/j.immuni.2016.04.016

55. Freund NT, Wang H, Scharf L, Nogueira L, Horwitz JA, Bar-On Y, Golijanin J, Sievers SA, Sok D, Cai H, Lorenzi JCC, Halper-Stromberg A, Toth I, Piechocka-Trocha A, Gristick HB, Van Gils MJ, Sanders RW, Wang LX, Seaman MS, Burton DR, Gazumyan A, Walker BD, West AP, Bjorkman PJ, Nussenzweig MC (**2017**). Coexistence of potent HIV-1 broadly neutralizing antibodies and antibody-sensitive viruses in a viremic controller. **Sci Transl Med** 9 (373): 2144–2144. doi:10.1126/scitranslmed.aal2144

56. Bonsignori M, Kreider EF, Fera D, Meyerhoff RR, Bradley T, Wiehe K, Alam SM, Aussedat B, Walkowicz WE, Hwang KK, Saunders KO, Zhang R, Gladden MA, Monroe A, Kumar A, Xia SM, Cooper M, Louder MK, Mckee K, Bailer RT, Pier BW, Jette CA, Kelsoe G, Williams WB, Morris L, Kappes J, Wagh K, Kamanga G, Cohen MS, Hraber PT, et al (**2017**). Staged induction of HIV-1 glycan-dependent broadly neutralizing antibodies. **Sci Transl Med** 9 (381): 7514–7514. doi:10.1126/scitranslmed.aai7514

57. Zwick MB, Parren PW, Saphire EO, Church S, Wang M, Scott JK, Dawson PE, Wilson IA, Burton DR (**2003**). Molecular features of the broadly neutralizing immunoglobulin G1 b12 required for recognition of human immunodeficiency virus type 1 gp120. **J Virol** 77 (10): 5863–5876. doi:10.1128/jvi.77.10.5863-5876.2003

58. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, Zhou T, Schmidt SD, Wu L, Xu L, Longo NS, Mckee K, Dell SO, Louder MK, Wycuff DL, Feng Y, Nason M, Doria-Rose N, Connors M, Kwong PD, Roederer M, Wyatt RT, Nabel GJ, Mascola JR (**2010**). Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. **Science** 329 (5993): 856–861. doi:10.1126/science.1187659

59. Caskey M, Klein F, Lorenzi JC, Seaman MS, West AP, Buckley N, Kremer G, Nogueira L, Braunschweig M, Scheid JF, Horwitz JA, Shimeliovich I, Ben-Avraham S, Witmer-Pack M, Platten M, Lehmann C, Burke LA, Hawthorne T, Gorelick RJ, Walker BD, Keler T, Gulick RM, Fatkenheuer G, Schlesinger SJ, Nussenzweig MC (**2016**). Corrigendum: Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. **Nature** 535 (7613): 580–580. doi:10.1126/science.1187659

60. Zhou T, Lynch RM, Chen L, Acharya P, Wu X, Doria-Rose NA, Joyce MG, Lingwood D, Soto C, Bailer RT, Ernandes MJ, Kong R, Longo NS, Louder MK, Mckee K, Dell SO, Schmidt SD, Tran L, Yang Z, Druz A, Luongo TS, Moquin S, Srivatsan S, Yang Y, Zhang B, Zheng A, Pancera M, Kirys T, Georgiev IS, Gindin T, , et al (**2015**). Structural Repertoire of HIV-1-Neutralizing Antibodies Targeting the CD4 Supersite in 14 Donors. **Cell** 161 (6): 1280–1292. doi:10.1016/j.cell.2015.05.007

61. Bonsignori M, Zhou T, Sheng Z, Chen L, Gao F, Joyce MG, Ozorowski G, Chuang GY, Schramm CA, Wiehe K, Alam SM, Bradley T, Gladden MA, Hwang KK, Iyengar S, Kumar A, Lu X, Luo K, Mangiapani MC, Parks RJ, Song H, Acharya P, Bailer RT, Cao A, Druz A, Georgiev IS, Kwon YD, Louder MK, Zhang B, Zheng A, et al (**2016**). Maturation Pathway from Germline to Broad HIV-1 Neutralizer of a CD4-Mimic Antibody. **Cell** 165 (2): 449–463. doi:10.1016/j.cell.2016.02.022

62. Falkowska E, Ramos A, Feng Y, Zhou T, Moquin S, Walker LM, Wu X, Seaman MS, Wrin T, Kwong PD, Wyatt RT, Mascola JR, Poignard P, Burton DR (**2012**). PGV04, an HIV-1 gp120 CD4 binding site antibody, is broad and potent in neutralization but does not induce conformational changes characteristic of CD4. **J Virol** 86 (8): 4394–4403. doi:10.1128/JVI.06973-11

63. Sajadi MM, Dashti A, Tehrani ZR, Tolbert WD, Seaman MS, Ouyang X, Gohain N, Pazgier M, Kim D, Cavet G, Yared J, Redfield RR, Lewis GK, Devico AL (**2018**). Identification of Near-Pan-neutralizing Antibodies against HIV-1 by Deconvolution of Plasma Humoral Responses. **Cell** 173 (7): 1783–1795. doi:10.1016/j.cell.2018.03.061

64. Van Schooten J, Farokhi E, Schorcht A, Van Den Kerkhof T, Gao H, Van Der Woude P, Burger JA, Meesters T, Bijl T, Ghalaiyini R, Turner HL, Dorning J, Van Schaik B, Van Kampen A, Labranche CC, Stanfield RL, Sok D, Montefiori DC, Burton DR, Seaman MS, Ozorowski G, Wilson IA, Sanders RW, Ward AB, Van Gils MJ (**2022**). Identification of IOMA-class neutralizing antibodies targeting the CD4-binding site on the HIV-1 envelope glycoprotein. **Nat Commun** 13 (1): 4515–4515. doi:10.1038/s41467-022-32208-0

65. Zhou T, Zheng A, Baxa U, Chuang GY, Georgiev IS, Kong R, Dell SO, Shahzad-Ul-Hussan S, Shen CH, Tsybovsky Y, Bailer RT, Gift SK, Louder MK, Mckee K, Rawi R, Stevenson CH, Stewart-Jones GBE, Taft JD, Waltari E, Yang Y, Zhang B, Shivatare SS, Shivatare VS, Lee CD, Wu CY, Mullikin JC, Bewley CA, Burton DR, Polonis VR, Shapiro L, et al (**2018**). A Neutralizing Antibody Recognizing Primarily N-Linked Glycan Targets the Silent Face of the HIV Envelope. **Immunity** 48 (3): 500–513. doi:10.1016/j.immuni.2018.02.013

66. Schoofs T, Barnes CO, Suh-Toma N, Golijanin J, Schommers P, Gruell H, West AP, Bach F, Lee YE, Nogueira L, Georgiev IS, Bailer RT, Czartoski J, Mascola JR, Seaman MS, Mcelrath MJ, Doria-Rose NA, Klein F, Nussenzweig MC, Bjorkman PJ (**2019**). Broad and Potent Neutralizing Antibodies Recognize the Silent Face of the HIV Envelope. **Immunity** 50 (6): 1513–1529. doi:10.1016/j.immuni.2019.04.014

67. Scharf L, Wang H, Gao H, Chen S, Mcdowall AW, Bjorkman PJ (**2015**). Broadly Neutralizing Antibody 8ANC195 Recognizes Closed and Open States of HIV-1 Env. **Cell** 162 (6): 1379–1390. doi:10.1016/j.cell.2015.08.035

68. Huang J, Kang BH, Pancera M, Lee JH, Tong T, Feng Y, Imamichi H, Georgiev IS, Chuang GY, Druz A, Doria-Rose NA, Laub L, Sliepen K, Van Gils MJ, Peña ATDL, Derking R, Klasse PJ, Migueles SA, Bailer RT, Alam M, Pugach P, Haynes BF, Wyatt RT, Sanders RW, Binley JM, Ward AB, Mascola JR, Kwong PD, Connors M (**2014**). Broad and potent HIV-1 neutralization by a human antibody that binds the gp41-gp120 interface. **Nature** 515 (7525): 138–142. doi:10.1038/nature13601

69. Kong R, Xu K, Zhou T, Acharya P, Lemmin T, Liu K, Ozorowski G, Soto C, Taft JD, Bailer RT, Cale EM, Chen L, Choi CW, Chuang GY, Doria-Rose NA, Druz A, Georgiev IS, Gorman J, Huang J, Joyce MG, Louder MK, Ma X, Mckee K, Dell SO, Pancera M, Yang Y, Blanchard SC, Mothes W, Burton DR, Koff WC, C W (**2016**). Fusion peptide of HIV-1 as a site of vulnerability to neutralizing antibody. **Science** 352 (6287): 828–833. doi:10.1126/science.aae0474

70. Van Gils MJ, Van Den Kerkhof TL, Ozorowski G, Cottrell CA, Sok D, Pauthner M, Pallesen J, De Val N, Yasmeen A, De Taeye SW, Schorcht A, Gumbs S, Johanna I, Saye-Francisco K, Liang CH, Landais E, Nie X, Pritchard LK, Crispin M, Kelsoe G, Wilson IA, Schuitemaker H, Klasse PJ, Moore JP, Burton DR, Ward AB, Sanders RW (**2016**). An HIV-1 antibody from an elite neutralizer implicates the fusion peptide as a site of vulnerability. **Nat Microbiol** 2: 16,199–16,199. doi:10.1038/nmicrobiol.2016.199

71. Binley JM, Wrin T, Korber B, Zwick MB, Wang M, Chappey C, Stiegler G, Kunert R, Zolla-Pazner S, Katinger H, Petropoulos CJ, Burton DR (**2004**). Comprehensive cross-clade neutralization analysis of a panel of anti-human immunodeficiency virus type 1 monoclonal antibodies. **J Virol** 78 (23): 13,232–13,252. doi:10.1128/JVI.78.23.13232-13252.2004

72. Williams LD, Ofek G, Schätzle S, Mcdaniel JR, Lu X, Nicely NI, Wu L, Lougheed CS, Bradley T, Louder MK, Mckee K, Bailer RT, Dell SO, Georgiev IS, Seaman MS, Parks RJ, Marshall DJ, Anasti K, Yang G, Nie X, Tumba NL, Wiehe K, Wagh K, Korber B, Kepler TB, Alam SM, Morris L, Kamanga G, Cohen MS, Bonsignori M, et al (**2017**). Potent and broad HIV-neutralizing antibodies in memory B cells and plasma. **Sci Immunol** 2 (7): 2200–2200. doi:10.1126/sciimmunol.aal2200

73. Hangartner L, Beauparlant D, Rakasz E, Nedellec R, Hozé N, Mckenney K, Martins MA, Seabright GE, Allen JD, Weiler AM, Friedrich TC, Regoes RR, Crispin M, Burton DR (**2021**). Effector function does not contribute to protection from virus challenge by a highly potent HIV broadly neutralizing antibody in nonhuman primates. **Sci Transl Med** 13 (585): 3349–3349. doi:10.1126/scitranslmed.abe3349

74. Stab V, Stahl-Hennig C, Ensser A, Richel E, Fraedrich K, Sauermann U, Tippler B, Klein F, Burton DR, Tenbusch M, Überla K (**2023**). HIV-1 neutralizing antibodies provide sterilizing immunity by blocking infection of the first cells. **Cell Rep Med** 4 (10): 101,201–101,201. doi:10.1016/j.xcrm.2023.101201

75. Lewis GK, Pazgier M, Evans DT, Ferrari G, Bournazos S, Parsons MS, Bernard NF, Finzi A (**2017**). Beyond Viral Neutralization. **AIDS Res Hum Retroviruses** 33 (8): 760–764. doi:10.1089/AID.2016.0299

76. Su B, Dispinseri S, Iannone V, Zhang T, Wu H, Carapito R, Bahram S, Scarlatti G, Moog C (**2019**). **Update on Fc-Mediated Antibody Functions Against HIV-1 Beyond Neutralization Front Immunol** 10: 2968–2968. doi:10.3389/fimmu.2019.02968

77. Danesh A, Ren Y, Jones RB (**2020**). Roles of fragment crystallizable-mediated effector functions in broadly neutralizing antibody activity against HIV. **Curr Opin HIV AIDS** 15 (5): 316–323. doi:10.1097/COH.0000000000000644

78. Lu LL, Suscovich TJ, Fortune SM, Alter G (**2018**). Beyond binding: antibody effector functions in infectious diseases. **Nat Rev Immunol** 18 (1): 46–61. doi:10.1038/nri.2017.106

79. Dufloo J, Guivel-Benhassine F, Buchrieser J, Lorin V, Grzelak L, Dupouy E, Mestrallet G, Bourdic K, Lambotte O, Mouquet H, Bruel T, Schwartz O (**2020**). Anti-HIV-1 antibodies trigger non-lytic complement deposition on infected cells. **EMBO Rep** 21 (2): 49,351–49,351. doi:10.15252/embr.201949351

80. Ugurlar D, Howes SC, De Kreuk BJ, Koning RI, De Jong RN, Beurskens FJ, Schuurman J, Koster AJ, Sharp TH, Parren P, Gros P (**2018**). Structures of C1-IgG1 provide insights into how danger pattern recognition activates complement. **Science** 359 (6377): 794–797. doi:10.1126/science.aao4988

81. Diebolder CA, Beurskens FJ, De Jong RN, Koning RI, Strumane K, Lindorfer MA, Voorhorst M, Ugurlar D, Rosati S, Heck AJ, Van De Winkel JG, Wilson IA, Koster AJ, Taylor RP, Saphire EO, Burton DR, Schuurman J, Gros P, Parren PW (**2014**). Complement is activated by IgG hexamers assembled at the cell surface. **Science** 343 (6176): 1260–1263. doi:10.1126/science.1248943

82. Wren LH, Chung AW, Isitman G, Kelleher AD, Parsons MS, Amin J, Cooper DA, Stratov I, Navis M, Kent SJ, Investigators ASC (**2013**). Specific antibody-dependent cellular cytotoxicity responses associated with slow progression of HIV infection. **Immunology** 138 (2): 116–123. doi:10.1111/imm.12016

83. Chung AW, Navis M, Isitman G, Wren L, Silvers J, Amin J, Kent SJ, Stratov I (**2011**). Activation of NK cells by ADCC antibodies and HIV disease progression. **J Acquir Immune Defic Syndr** 58 (2): 127–131. doi:10.1097/QAI.0b013e31822c62b9

84. Wang P, Gajjar MR, Yu J, Padte NN, Gettie A, Blanchard JL, Russell-Lodrigue K, Liao LE, Perelson AS, Huang Y, Ho DD (**2020**). Quantifying the contribution of Fc-mediated effector functions to the antiviral activity of anti-HIV-1 IgG1 antibodies in vivo. **Proc Natl Acad Sci U S A** 117 (30): 18,002–18,009. doi:10.1073/pnas.2008190117

85. Lambotte O, Ferrari G, Moog C, Yates NL, Liao HX, Parks RJ, Hicks CB, Owzar K, Tomaras GD, Montefiori DC, Haynes BF, Delfraissy JF (**2009**). Heterogeneous neutralizing antibody and antibody-dependent cell cytotoxicity responses in HIV-1 elite controllers. **Aids** 23 (8): 897–906. doi:10.1073/pnas.2008190117

86. Haynes BF, Gilbert PB, Mcelrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM, Evans DT, Montefiori DC, Karnasuta C, Sutthent R, Liao HX, Devico AL, Lewis GK, Williams C, Pinter A, Fong Y, Janes H, Decamp A, Huang Y, Rao M, Billings E, Karasavvas N, Robb ML, Ngauy V, De Souza MS, Paris R, Ferrari G, Bailer RT, Soderberg KA, Andrews C, et al (**2012**). Immune-correlates analysis of an HIV-1 vaccine efficacy trial. **N Engl J Med** 366 (14): 1275–1286. doi:10.1056/NEJMoa1113425

87. Gray GE, Huang Y, Grunenberg N, Laher F, Roux S, Andersen-Nissen E, De Rosa SC, Flach B, Randhawa AK, Jensen R, Swann EM, Bekker LG, Innes C, Lazarus E, Morris L, Mkhize NN, Ferrari G, Montefiori DC, Shen X, Sawant S, Yates N, Hural J, Isaacs A, Phogat S, Diazgranados CA, Lee C, Sinangil F, Michael NL, Robb ML, Kublin JG, et al (**2019**). Immune correlates of the Thai RV144 HIV vaccine regimen in South Africa. **Sci Transl Med** 11 (510): 1880–1880. doi:10.1126/scitranslmed.aax1880

88. Horwitz JA, Bar-On Y, Lu CL, Fera D, Lockhart A, Lorenzi J, Nogueira L, Golijanin J, Scheid JF, Seaman MS, Gazumyan A, Zolla-Pazner S, Nussenzweig MC (**2017**). Non-neutralizing Antibodies Alter the Course of HIV-1 Infection In Vivo. **Cell** 170 (4): 637–648. doi:10.1126/scitranslmed.aax1880

89. Bournazos S, Klein F, Pietzsch J, Seaman MS, Nussenzweig MC, Ravetch JV (**2014**). Broadly neutralizing anti-HIV-1 antibodies require Fc effector functions for in vivo activity. **Cell** 158 (6): 1243–1253. doi:10.1016/j.cell.2014.08.023

90. Halper-Stromberg A, Lu CL, Klein F, Horwitz JA, Bournazos S, Nogueira L, Eisenreich TR, Liu C, Gazumyan A, Schaefer U, Furze RC, Seaman MS, Prinjha R, Tarakhovsky A, Ravetch JV, Nussenzweig MC (**2014**). Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice. **Cell** 158 (5): 989–999. doi:10.1016/j.cell.2014.07.043

91. Hessell AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR (**2007**). Fc receptor but not complement binding is important in antibody protection against HIV. **Nature** 449 (7158): 101–104. doi:10.1038/nature06106

92. Hessell AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, Parren PW, Marx PA, Burton DR (**2009**). Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. **Nat Med** 15 (8): 951–954. doi:10.1038/nm.1974

93. Asokan M, Dias J, Liu C, Maximova A, Ernste K, Pegu A, Mckee K, Shi W, Chen X, Almasri C, Promsote W, Ambrozak DR, Gama L, Hu J, Douek DC, Todd JP, Lifson JD, Fourati S, Sekaly RP, Crowley AR, Ackerman ME, Ko SH, Kilam D, Boritz EA, Liao LE, Best K, Perelson AS, Mascola JR, Koup RA (**2020**). Fc-mediated effector function contributes to the in vivo antiviral effect of an HIV neutralizing antibody. **Proc Natl Acad Sci U S A** 117 (31): 18,754–18,763. doi:10.1073/pnas.2008236117

94. Parsons MS, Lee WS, Kristensen AB, Amarasena T, Khoury G, Wheatley AK, Reynaldi A, Wines BD, Hogarth PM, Davenport MP, Kent SJ (**2019**). Fc-dependent functions are redundant to efficacy of anti-HIV antibody PGT121 in macaques. **J Clin Invest** 129 (1): 182–191. doi:10.1172/JCI122466

95. Moldt B, Shibata-Koyama M, Rakasz EG, Schultz N, Kanda Y, Dunlop DC, Finstad SL, Jin C, Landucci G, Alpert MD, Dugast AS, Parren PW, Nimmerjahn F, Evans DT, Alter G, Forthal DN, Schmitz JE, Iida S, Poignard P, Watkins DI, Hessell AJ, Burton DR (**2012**). A nonfucosylated variant of the anti-HIV-1 monoclonal antibody b12 has enhanced FcγRIIIa-mediated antiviral activity in vitro but does not improve protection against mucosal SHIV challenge in macaques. **J Virol** 86 (11): 6189–6196. doi:10.1128/JVI.00491-12

96. Gaebler C, Nogueira L, Stoffel E, Oliveira TY, Breton G, Millard KG, Turroja M, Butler A, Ramos V, Seaman MS, Reeves JD, Petroupoulos CJ, Shimeliovich I, Gazumyan A, Jiang CS, Jilg N, Scheid JF, Gandhi R, Walker BD, Sneller MC, Fauci A, Chun TW, Caskey M, Nussenzweig MC (**2022**). Prolonged viral suppression with anti-HIV-1 antibody therapy. **Nature** 606 (7913): 368–374. doi:10.1038/s41586-022-04597-1

97. Gach JS, Bouzin M, Wong MP, Chromikova V, Gorlani A, Yu KT, Sharma B, Gratton E, Forthal DN (**2017**). Human immunodeficiency virus type-1 (HIV-1) evades antibody-dependent phagocytosis. **PLoS Pathog** 13 (12): 1006,793–1006,793. doi:10.1371/journal.ppat.1006793

98. Gach JS, Matsuno SY, Mercado M, Hangartner L, Forthal DN (**2022**). Internalization of HIV-1 by Phagocytes Is Increased When Virions Are Opsonized with Multimeric Antibody in the Presence of Complement. **J Virol** 96 (2): 168,921–168,921. doi:10.1128/JVI.01689-21

99. Caskey M (**2020**). Broadly neutralizing antibodies for the treatment and prevention of HIV infection. **Curr Opin HIV AIDS** 15 (1): 49–55. doi:10.1097/COH.0000000000000600

100. Doria-Rose NA, Joyce MG (**2015**). Strategies to guide the antibody affinity maturation process. **Curr Opin Virol** 11: 137–147. doi:10.1016/j.coviro.2015.04.002

101. Roskin KM, Jackson K, Lee JY, Hoh RA, Joshi SA, Hwang KK, Bonsignori M, Pedroza-Pacheco I, Liao HX, Moody MA, Fire AZ, Borrow P, Haynes BF, Boyd SD (**2020**). Aberrant B cell repertoire selection associated with HIV neutralizing antibody breadth. **Nat Immunol** 21 (2): 199–209. doi:10.1038/s41590-019-0581-0

102. Caniels TG, Medina-Ramírez M, Zhang J, Sarkar A, Kumar S, Labranche A, Derking R, Allen JD, Snitselaar JL, Capella-Pujol J, Sánchez IDM, Yasmeen A, Diaz M, Aldon Y, Bijl TPL, Venkatayogi S, Beem JSM, Newman A, Jiang C, Lee WH, Pater M, Burger JA, Van Breemen MJ, De Taeye SW, Rantalainen K, Labranche C, Saunders KO, Montefiori D, Ozorowski G, Ward AB, et al (**2023**). Germline-targeting HIV-1 Env vaccination induces VRC01-class antibodies with rare insertions. **Cell Rep Med** 4 (4): 101,003–101,003. doi:10.1016/j.xcrm.2023.101003

103. Steichen JM, Lin YC, Havenar-Daughton C, Pecetta S, Ozorowski G, Willis JR, Toy L, Sok D, Liguori A, Kratochvil S, Torres JL, Kalyuzhniy O, Melzi E, Kulp DW, Raemisch S, Hu X, Bernard SM, Georgeson E, Phelps N, Adachi Y, Kubitz M, Landais E, Umotoy J, Robinson A, Briney B, Wilson IA, Burton DR, Ward AB, Crotty S, Batista FD (**2019**). A generalized HIV vaccine design strategy for priming of broadly neutralizing antibody responses. **Science** 366 (6470). doi:10.1126/science.aax4380

104. Leggat DJ, Cohen KW, Willis JR, Fulp WJ, Decamp AC, Kalyuzhniy O, Cottrell CA, Menis S, Finak G, Ballweber-Fleming L, Srikanth A, Plyler JR, Schiffner T, Liguori A, Rahaman F, Lombardo A, Philiponis V, Whaley RE, Seese A, Brand J, Ruppel AM, Hoyland W, Yates NL, Williams LD, Greene K, Gao H, Mahoney CR, Corcoran MM, Cagigi A, Taylor A, et al (**2022**). Vaccination induces HIV broadly neutralizing antibody precursors in humans. **Science** 378 (6623): 6502–6502. doi:10.1126/science.aax4380

105. Matarazzo L, Bettencourt PJG (**2023**). mRNA vaccines: a new opportunity for malaria. **tuberculosis and HIV Front Immunol** 14: 1172,691–1172,691. doi:10.3389/fimmu.2023.1172691

106. Zhao Y, Wu Z, Mcgoogan JM, Shi CX, Li A, Dou Z, Ma Y, Qin Q, Brookmeyer R, Detels R, Montaner JSG (**2018**). Immediate Antiretroviral Therapy Decreases Mortality Among Patients With High CD4 Counts in China: A Nationwide, Retrospective Cohort Study. **Clin Infect Dis** 66 (5): 727–734. doi:10.1093/cid/cix878

107. Gandhi RT, Bedimo R, Hoy JF, Landovitz RJ, Smith DM, Eaton EF, Lehmann C, Springer SA, Sax PE, Thompson MA, Benson CA, Buchbinder SP, Rio CD, Eron JJ, Günthard HF, Molina JM, Jacobsen DM, Saag MS (**2023**). Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society-USA Panel. **JAMA** 329 (1): 63–84. doi:10.1001/jama.2022.22246

108. Denton PW, Søgaard OS, Tolstrup M (**1956**). Impacts of HIV Cure Interventions on Viral Reservoirs in Tissues. **Front Microbiol** 10. doi:10.3389/fmicb.2019.01956

109. Chun TW, Stuyver L, Mizell SB, Ehler LA, Mican JA, Baseler M, Lloyd AL, Nowak MA, Fauci AS (**1997**). Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. **Proc Natl Acad Sci U S A** 94 (24): 13,193–13,197. doi:10.1073/pnas.94.24.13193

110. Petitjean G, Tabaa YA, Tuaillon E, Mettling C, Baillat V, Reynes J, Segondy M, Vendrell JP (**2007**). Unintegrated HIV-1 provides an inducible and functional reservoir in untreated and highly active antiretroviral therapy-treated patients. **Retrovirology** 4: 60–60. doi:10.1186/1742-4690-4-60

111. Hsu DC, Mellors JW, Vasan S (**2021**). Can Broadly Neutralizing HIV-1 Antibodies Help Achieve an ART-Free Remission. **Front Immunol** 12: 710,044–710,044. doi:10.3389/fimmu.2021.710044

112. Li JZ, Aga E, Bosch RJ, Pilkinton M, Kroon E, Maclaren L, Keefer M, Fox L, Barr L, Acosta E, Ananworanich J, Coombs R, Mellors JW, Landay AL, Macatangay B, Deeks S, Gandhi RT, Smith DM (**2022**). Time to Viral Rebound After Interruption of Modern Antiretroviral Therapies. **Clin Infect Dis** 74 (5): 865–870. doi:10.1093/cid/ciab541

113. Iacob SA, Iacob DG, Jugulete G (**2017**). Improving the Adherence to Antiretroviral Therapy, a Difficult but Essential Task for a Successful HIV Treatment-Clinical Points of View and Practical Considerations. **Front Pharmacol** 8: 831–831. doi:10.3389/fphar.2017.00831

114. Phelps M, Balazs AB (**2021**). Contribution to HIV Prevention and Treatment by Antibody-Mediated Effector Function and Advances in Broadly Neutralizing Antibody Delivery by Vectored Immunoprophylaxis. **Front Immunol** 12: 734,304–734,304. doi:10.3389/fimmu.2021.734304

115. Trkola A, Kuster H, Rusert P, Joos B, Fischer M, Leemann C, Manrique A, Huber M, Rehr M, Oxenius A, Weber R, Stiegler G, Vcelar B, Katinger H, Aceto L, Gunthard HF (**2005**). Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies. **Nature Med** 11 (6): 615–622. doi:10.1038/nm1244

116. Stiegler G, Armbruster C, Vcelar B, Stoiber H, Kunert R, Michael NL, Jagodzinski LL, Ammann C, Jäger W, Jacobson J, Vetter N, Katinger H (**2002**). Antiviral activity of the neutralizing antibodies 2F5 and 2G12 in asymptomatic HIV-1-infected humans: a phase I evaluation. **AIDS** 16 (15): 2019–2025. doi:10.1038/nm1244

117. Mahomed S, Garrett N, Capparelli EV, Osman F, Mkhize NN, Harkoo I, Gengiah TN, Mansoor LE, Baxter C, Archary D, Yende-Zuma N, Samsunder N, Carlton K, Narpala S, Mcdermott AB, Doria-Rose NA, Moore PL, Morris L, Karim QA, Mascola JR (**2023**). Safety and pharmacokinetics of escalating doses of neutralising monoclonal antibody CAP256V2LS administered with and without VRC07-523LS in HIV-negative women in South Africa (CAPRISA 012B): a phase 1, dose-escalation, randomised controlled trial. **Abdool Karim SS** 10 (4): 3–6. doi:10.1016/S2352-3018(23)00003-6

118. Lynch RM, Boritz E, Coates EE, Dezure A, Madden P, Costner P, Enama ME, Plummer S, Holman L, Hendel CS, Gordon I, Casazza J, Conan-Cibotti M, Migueles SA, Tressler R, Bailer RT, Mcdermott A, Narpala S, Dell SO, Wolf G, Lifson JD, Freemire BA, Gorelick RJ, Pandey JP, Mohan S, Chomont N, Fromentin R, Chun TW, Fauci AS, Schwartz RM (**2015**). Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. **Sci Transl Med** 7 (319): 319–206. doi:10.1126/scitranslmed.aad5752

119. Caskey M, Schoofs T, Gruell H, Settler A, Karagounis T, Kreider EF, Murrell B, Pfeifer N, Nogueira L, Oliveira TY, Learn GH, Cohen YZ, Lehmann C, Gillor D, Shimeliovich I, Unson-O'brien C, Weiland D, Robles A, Kümmerle T, Wyen C, Levin R, Witmer-Pack M, Eren K, Ignacio C, Kiss S, West AP, Mouquet H, Zingman BS, Gulick RM, Keler T, et al (**2017**). Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. **Nat Med** 23 (2): 185–191. doi:10.1038/nm.4268

120. Stephenson KE, Julg B, Tan CS, Zash R, Walsh SR, Rolle CP, Monczor AN, Lupo S, Gelderblom HC, Ansel JL, Kanjilal DG, Maxfield LF, Nkolola J, Borducchi EN, Abbink P, Liu J, Peter L, Chandrashekar A, Nityanandam R, Lin Z, Setaro A, Sapiente J, Chen Z, Sunner L, Cassidy T, Bennett C, Sato A, Mayer B, Perelson AS, Decamp A, et al (**2021**). Safety, pharmacokinetics and antiviral activity of PGT121, a broadly neutralizing monoclonal antibody against HIV-1: a randomized, placebo-controlled, phase 1 clinical trial. **Nat Med** 27 (10): 1718–1724. doi:10.1038/s41591-021-01509-0

121. Scheid JF, Horwitz JA, Bar-On Y, Kreider EF, Lu CL, Lorenzi JC, Feldmann A, Braunschweig M, Nogueira L, Oliveira T, Shimeliovich I, Patel R, Burke L, Cohen YZ, Hadrigan S, Settler A, Witmer-Pack M, West AP, Juelg B, Keler T, Hawthorne T, Zingman B, Gulick RM, Pfeifer N, Learn GH, Seaman MS, Bjorkman PJ, Klein F, Schlesinger SJ, Walker BD, et al (**2016**). HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. **Nature** 535 (7613): 556–560. doi:10.1038/nature18929

122. Mendoza P, Gruell H, Nogueira L, Pai JA, Butler AL, Millard K, Lehmann C, Suárez I, Oliveira TY, Lorenzi J, Cohen YZ, Wyen C, Kümmerle T, Karagounis T, Lu CL, Handl L, Unson-O'brien C, Patel R, Ruping C, Schlotz M, Witmer-Pack M, Shimeliovich I, Kremer G, Thomas E, Seaton KE, Horowitz J, West AP, Bjorkman PJ, Tomaras GD, Gulick RM, et al (**2018**). Combination therapy with anti-HIV-1 antibodies maintains viral suppression. **Nature** 561 (7724): 479–484. doi:10.1038/s41586-018-0531-2

123. Sneller MC, Blazkova J, Justement JS, Shi V, Kennedy BD, Gittens K, Tolstenko J, Mccormack G, Whitehead EJ, Schneck RF, Proschan MA, Benko E, Kovacs C, Oguz C, Seaman MS, Caskey M, Nussenzweig MC, Fauci AS, Moir S, Chun TW (**2022**). Combination anti-HIV antibodies provide sustained virological suppression. **Nature** 606 (7913): 375–381. doi:10.1038/s41586-018-0531-2

124. Julg B, Stephenson KE, Wagh K, Tan SC, Zash R, Walsh S, Ansel J, Kanjilal D, Nkolola J, Walker-Sperling VEK, Ophel J, Yanosick K, Borducchi EN, Maxfield L, Abbink P, Peter L, Yates NL, Wesley MS, Hassell T, Gelderblom HC, Decamp A, Mayer BT, Sato A, Gerber MW, Giorgi EE, Gama L, Koup RA, Mascola JR, Monczor A, Lupo S, et al (**2022**). Safety and antiviral activity of triple combination broadly neutralizing monoclonal antibody therapy against HIV-1: a phase 1 clinical trial. **Nat Med** 28 (6): 1288–1296. doi:10.1038/s41591-022-01815-1

125. Moldt B, Parvangada A, Martin R, Pace C, Balakrishnan M, Thomsen ND, Collins S, Kuster H, Braun DL, Günthard HF, Geleziunas R, Callebaut C (**2021**). Evaluation of Broadly Neutralizing Antibody Sensitivity by Genotyping and Phenotyping for Qualifying Participants to HIV Clinical Trials. **J Acquir Immune Defic Syndr** 88 (1): 61–69. doi:10.1097/QAI.0000000000002722

126. Freind MC, De Lara CT, Kouyos RD, Wimmersberger D, Kuster H, Aceto L, Kovari H, Flepp M, Schibli A, Hampel B, Grube C, Braun DL, Günthard HF (**2024**). Cohort Profile: The Zurich Primary HIV. **Infection Study Microorganisms** 12 (2): 302–302. doi:10.3390/microorganisms12020302

127. Lamont C, Otwinowski J, Vanshylla K, Gruell H, Klein F, Nourmohammad A (**2022**). Design of an optimal combination therapy with broadly neutralizing antibodies to suppress HIV-1. **Elife** 11: 76,004–76,004. doi:10.7554/eLife.76004

128. Moraka NO, Choga WT, Pema MN, Chawawa MK, Gobe I, Mokomane M, Bareng OT, Bhebhe L, Kelentse N, Mulenga G, Holme MP, Mohammed T, Koofhethile CK, Makhema JM, Shapiro R, Lockman S, Moyo S, Gaseitsiwe S (**2023**). Predicted resistance to broadly neutralizing antibodies (bnAbs) and associated HIV-1 envelope characteristics among seroconverting adults in Botswana. **Sci Rep** 13 (1): 18,134–18,134. doi:10.1038/s41598-023-44722-2

129. Shapiro RL, Ajibola G, Maswabi K, Hughes M, Nelson BS, Niesar A, Holme MP, Powis KM, Sakoi M, Batlang O, Moyo S, Mohammed T, Maphorisa C, Bennett K, Hu Z, Giguel F, Reeves JD, Reeves MA, Gao C, Yu X, Ackerman ME, Mcdermott A, Cooper M, Caskey M, Gama L, Jean-Philippe P, Yin DE, Capparelli EV, Lockman S, Makhema J, et al (**2023**). Broadly neutralizing antibody treatment maintained HIV suppression in children with favorable reservoir characteristics in Botswana. **Sci Transl Med** 15 (703): 4–4. doi:10.1128/JVI.00491-12

130. Gaudinski MR, Houser KV, Doria-Rose NA, Chen GL, Rothwell RSS, Berkowitz N, Costner P, Holman LA, Gordon IJ, Hendel CS, Kaltovich F, Conan-Cibotti M, Lorenzo MG, Carter C, Sitar S, Carlton K, Gall J, Laurencot C, Lin BC, Bailer RT, Mcdermott AB, Ko SY, Pegu A, Kwon YD, Kwong PD, Namboodiri AM, Pandey JP, Schwartz R, Arnold F, Hu Z, et al (**2019**). Safety and pharmacokinetics of broadly neutralising human monoclonal antibody VRC07-523LS in healthy adults: a phase 1 dose-escalation clinical trial. **Lancet HIV** 6 (10): 667–679. doi:10.1016/S2352-3018(19)30181-X

131. Akilesh S, Christianson GJ, Roopenian DC, Shaw AS (**2007**). Neonatal FcR expression in bone marrow-derived cells functions to protect serum IgG from catabolism. **J Immunol** 179 (7): 4580–4588. doi:10.4049/jimmunol.179.7.4580

132. Roopenian DC, Akilesh S (**2007**). FcRn: the neonatal Fc receptor comes of age. **Nat Rev Immunol** 7 (9): 715–725. doi:10.1038/nri2155

133. Zalevsky J, Chamberlain AK, Horton HM, Karki S, Leung IW, Sproule TJ, Lazar GA, Roopenian DC, Desjarlais JR (**2010**). Enhanced antibody half-life improves in vivo activity. **Nat Biotechnol** 28 (2): 157–159. doi:10.1038/nbt.1601

134. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, Wang K, Bao S, Kraemer TD, Rath T, Zeng M, Schmidt SD, Todd JP, Penzak SR, Saunders KO, Nason MC, Haase AT, Rao SS, Blumberg RS, Mascola JR, Nabel GJ (**2014**). Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. **Nature** 514 (7524): 642–645. doi:10.1038/nature13612

135. Chen J, Zhou T, Zhang Y, Luo S, Chen H, Chen D, Li C, Li W (**2022**). The reservoir of latent HIV. **Front Cell Infect Microbiol** 12: 945,956–945,956. doi:10.3389/fcimb.2022.945956

136. Moldt B, Günthard HF, Workowski KA, Little SJ, Eron JJ, Overton ET, Lehmann C, Rokx C, Kozal MJ, Gandhi RT, Braun DL, Parvangada A, Li J, Martin R, Selzer L, Cox S, Margot N, Liu H, Slamowitz D, Makadzange T, Collins SE, Geleziunas R, Callebaut C (**2022**). Evaluation of HIV-1 reservoir size and broadly neutralizing antibody susceptibility in acute antiretroviral therapy-treated individuals. **AIDS** 36 (2): 205–214. doi:10.1097/QAD.0000000000003088

137. Leyre L, Kroon E, Vandergeeten C, Sacdalan C, Colby DJ, Buranapraditkun S, Schuetz A, Chomchey N, De Souza M, Bakeman W, Fromentin R, Pinyakorn S, Akapirat S, Trichavaroj R, Chottanapund S, Manasnayakorn S, Rerknimitr R, Wattanaboonyoungcharoen P, Kim JH, Tovanabutra S, Schacker TW, O'connell R, Valcour VG, Phanuphak P, Robb ML, Michael N, Trautmann L, Phanuphak N, Ananworanich J, Chomont N, et al (**2020**). Abundant HIV-infected cells in blood and tissues are rapidly cleared upon ART initiation during acute HIV infection. **Sci Transl Med** 12 (533): 3491–3491. doi:10.1126/scitranslmed.aav3491

138. Kula-Pacurar A, Rodari A, Darcis G, Van Lint C (**2021**). Shocking HIV-1 with immunomodulatory latency reversing agents. **Semin Immunol** 51: 101,478–101,478. doi:10.1016/j.smim.2021.101478

139. Abner E, Jordan A (**2019**). HIV "shock and kill" therapy: In need of revision. **Antiviral Res** 166: 19–34. doi:10.1016/j.antiviral.2019.03.008

140. Dash PK, Chen C, Kaminski R, Su H, Mancuso P, Sillman B, Zhang C, Liao S, Sravanam S, Liu H, Waight E, Guo L, Mathews S, Sariyer R, Mosley RL, Poluektova LY, Caocci M, Amini S, Gorantla S, Burdo TH, Edagwa B, Gendelman HE, Khalili K (**2019**). CRISPR editing of CCR5 and HIV-1 facilitates viral elimination in antiretroviral drug-suppressed virus-infected humanized mice. **Proc Natl Acad Sci U S A** 120: 2217887,120–2217887,120. doi:10.1073/pnas.2217887120

141. Liu Y, Binda CS, Berkhout B, Das AT (**2023**). CRISPR-Cas attack of HIV-1 proviral DNA can cause unintended deletion of surrounding cellular DNA. **J Virol** 97 (12): 133,423–133,423. doi:10.1128/jvi.01334-23

142. Seddiki N, Picard F, Dupaty L, Lévy Y, Godot V (**2020**). The Potential of Immune Modulation in Therapeutic HIV-1 Vaccination. **Vaccines** 8 (3): 419–419. doi:10.3390/vaccines8030419

143. Richel E, Wagner JT, Klessing S, Vincenzo RD, Temchura V, Überla K (**2023**). Antigen-dependent modulation of immune responses to antigen-Fc fusion proteins by Fc-effector functions. **Front Immunol** 14: 1275,193–1275,193. doi:10.3389/fimmu.2023.1275193

144. Martinsen JT, Gunst JD, Højen JF, Tolstrup M, Søgaard OS (**2020**). The Use of Toll-Like Receptor Agonists in HIV-1 Cure Strategies. **Front Immunol** 11: 1112–1112. doi:10.3389/fimmu.2020.01112

145. Prener L, Baszczyński O, Kaiser MM, Dračínský M, Stepan G, Lee YJ, Brumshtein B, Yu H, Jansa P, Lansdon EB, Janeba Z (**2023**). Design and Synthesis of Novel HIV-1 NNRTIs with Bicyclic Cores and with Improved Physicochemical Properties. **J Med Chem** 66 (3): 1761–1777. doi:10.1021/acs.jmedchem.2c01574

146. Cambou MC, Landovitz RJ (**2020**). Novel Antiretroviral Agents. **Curr HIV/AIDS Rep** 17 (2): 118–124. doi:10.1007/s11904-020-00486-2

147. Jean MJ, Fiches G, Hayashi T, Zhu J (**2019**). Current Strategies for Elimination of HIV-1 Latent Reservoirs Using Chemical Compounds Targeting Host and Viral Factors. **AIDS Res Hum Retroviruses** 35 (1): 1–24. doi:10.1089/AID.2018.0153

148. Ngo MH, Pankrac J, Ho RCY, Ndashimye E, Pawa R, Ceccacci R, Biru T, Olabode AS, Klein K, Li Y, Kovacs C, Assad R, Jacobson JM, Canaday DH, Tomusange S, Jamiru S, Anok A, Kityamuweesi T, Buule P, Galiwango RM, Reynolds SJ, Quinn TC, Redd AD, Prodger JL, Mann JFS (**2024**). Effective and targeted latency reversal in CD4. **Emerg Microbes Infect** 13 (1): 2327,371–2327,371. doi:10.1080/22221751.2024.2327371

149. Frattari GS, Caskey M, Søgaard OS (**2023**). Broadly neutralizing antibodies for HIV treatment and cure approaches. **Curr Opin HIV AIDS** 18 (4): 157–163. doi:10.1097/COH.0000000000000802

150. Cohen YZ, Lorenzi JCC, Krassnig L, Barton JP, Burke L, Pai J, Lu CL, Mendoza P, Oliveira TY, Sleckman C, Millard K, Butler AL, Dizon JP, Belblidia SA, Witmer-Pack M, Shimeliovich I, Gulick RM, Seaman MS, Jankovic M, Caskey M, Nussenzweig MC (**2018**). Relationship between latent and rebound viruses in a clinical trial of anti-HIV-1 antibody 3BNC117. **J Exp Med** 215 (9): 2311–2324. doi:10.1084/jem.20180936

151. Gruell H, Gunst JD, Cohen YZ, Pahus MH, Malin JJ, Platten M, Millard KG, Tolstrup M, Jones RB, Alberto WDC, Lorenzi JCC, Oliveira TY, Kümmerle T, Suárez I, Unson-O'brien C, Nogueira L, Olesen R, Østergaard L, Nielsen H, Lehmann C, Nussenzweig MC, Fätkenheuer G, Klein F, Caskey M, Søgaard OS (**2022**). Effect of 3BNC117 and romidepsin on the HIV-1 reservoir in people taking suppressive antiretroviral therapy (ROADMAP): a randomised, open-label, phase 2A trial. **Lancet Microbe** 3 (3): 203–214. doi:10.1016/S2666-5247(21)00239-1

152. Gunst JD, Pahus MH, Rosás-Umbert M, Lu IN, Benfield T, Nielsen H, Johansen IS, Mohey R, Østergaard L, Klastrup V, Khan M, Schleimann MH, Olesen R, Støvring H, Denton PW, Kinloch NN, Copertino DC, Ward AR, Alberto W, Nielsen SD, Puertas MC, Ramos V, Reeves JD, Petropoulos CJ, Martinez-Picado J, Brumme ZL, Jones RB, Fox J, Tolstrup M, Nussenzweig MC, et al (**2022**). Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial. **Nat Med** 28 (11): 2424–2435. doi:10.1038/s41591-022-02023-7

153. Rosás-Umbert M, Gunst JD, Pahus MH, Olesen R, Schleimann M, Denton PW, Ramos V, Ward A, Kinloch NN, Copertino DC, Escribà T, Llano A, Brumme ZL, Jones RB, Mothe B, Brander C, Fox J, Nussenzweig MC, Fidler S, Caskey M, Tolstrup M, Søgaard OS (**2022**). Administration of broadly neutralizing anti-HIV-1 antibodies at ART initiation maintains long-term CD8. **Nat Commun** 13 (1): 6473–6473. doi:10.1038/s41467-022-34171-2

154. Mavigner M, Chahroudi A (**2023**). The next thing" to treat children with HIV? **Sci Transl Med** 15 (703): 293–293. doi:10.1126/scitranslmed.adi0293

155. Corey L, Gilbert PB, Juraska M, Montefiori DC, Morris L, Karuna ST, Edupuganti S, Mgodi NM, Decamp AC, Rudnicki E, Huang Y, Gonzales P, Cabello R, Orrell C, Lama JR, Laher F, Lazarus EM, Sanchez J, Frank I, Hinojosa J, Sobieszczyk ME, Marshall KE, Mukwekwerere PG, Makhema J, Baden LR, Mullins JI, Williamson C, Hural J, Mcelrath MJ, Bentley C, et al (**2021**). Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition. **N Engl J Med** 384 (11): 1003–1014. doi:10.1056/NEJMoa2031738

156. Cohen YZ, Butler AL, Millard K, Witmer-Pack M, Levin R, Unson-O'Brien C, Patel R, Shimeliovich I, Lorenzi JCC, Horowitz J, Walsh SR, Lin S, Weiner JA, Tse A, Sato A, Bennett C, Mayer B, Seaton KE, Yates NL, Baden LR, deCamp AC, Ackerman ME, Seaman MS, Tomaras GD, Nussenzweig MC, Caskey M (**2019**). Safety, pharmacokinetics, and immunogenicity of the combination of the broadly neutralizing anti-HIV-1 antibodies 3BNC117 and 10-1074 in healthy adults: A randomized, phase 1 study. **PLoS One** 14 (8): e0219,142. doi:10.1371/journal.pone.0219142

157. Politsch JA, Cu-Uvin S, Moench TR, Tashima KT, Marathe JG, Guthrie KM, Cabral H, Nyhuis T, Brennan M, Zeitlin L, Spiegel HML, Mayer KH, Whaley KJ, Anderson DJ (**2021**). Safety, acceptability, and pharmacokinetics of a monoclonal antibody-based vaginal multipurpose prevention film (MB66): A Phase I randomized trial. . **PLoS Med** 18 (2): e1003,495. doi:10.1371/journal.pmed.1003495