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Broadly Neutralizing Antibody Therapy for HIV-1 Treatment and Long-Term Viral Remission

Rukundo Sande Kibuuka

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Human immunodeficiency virus type 1 (HIV-1) infection affected approximately 38 million individuals globally, with lifelong antiretroviral therapy required to suppress viral replication. Despite effective viral suppression, antiretroviral therapy does not eradicate latent viral reservoirs, necessitating continuous treatment and failing to achieve a functional cure. Broadly neutralizing antibodies (bNAbs) represented a novel therapeutic modality capable of targeting multiple HIV-1 strains through recognition of conserved envelope glycoprotein epitopes, offering potential mechanisms beyond direct viral neutralization, including antibody-dependent cellular cytotoxicity and immune complex formation. This review critically evaluated the biochemical properties, antiviral mechanisms, clinical efficacy, reservoir reduction capacity, and translational potential of broadly neutralizing antibodies for HIV-1 treatment and achievement of sustained viral remission without continuous antiretroviral therapy. A comprehensive literature search was conducted across PubMed, Embase, and Scopus databases for peer-reviewed articles published between 2014 and 2024, focusing on broadly neutralizing antibody immunotherapy, HIV-1 remission strategies, and latent reservoir targeting. Broadly neutralizing antibodies demonstrated potent in vitro neutralization breadth exceeding 90% of circulating HIV-1 strains, with clinical studies showing transient viral suppression during analytical treatment interruption when administered as monotherapy or combination regimens. Single infusions achieved plasma half-lives of 15 to 71 days, maintaining suppressive concentrations for 2 to 6 months. However, viral rebound occurred in most participants within 4 to 12 weeks post-antibody clearance, attributed to persistent latent reservoirs and emergence of resistant viral variants. Combination bNAb regimens and concurrent administration with latency reversal agents showed enhanced reservoir reduction and delayed viral rebound in subset analyses. Broadly neutralizing antibodies demonstrated proof-of-concept for antibody-mediated HIV-1 control but require optimization through combination strategies, reservoir targeting approaches, and identification of predictive biomarkers for sustained remission.

Keywords: Broadly neutralizing antibodies, HIV-1 remission, Latent reservoir, Antiretroviral therapy, Functional cure.

INTRODUCTION

Human immunodeficiency virus type 1 envelope glycoprotein complex, composed of trimeric gp120 surface subunits non-covalently associated with gp41 transmembrane domains, mediates viral entry through sequential binding to CD4 receptors and CCR5 or CXCR4 coreceptors on target cells [1]. The envelope spike exhibits extraordinary genetic diversity and structural plasticity, with extensive N-linked glycosylation masking approximately 50% of the protein surface from antibody recognition through a glycan shield composed of high-mannose and complex-type carbohydrates [2]. Despite this immune evasion architecture, rare individuals infected with HIV-1 develop broadly neutralizing antibodies after years of chronic infection, capable of recognizing conserved epitopes essential for viral function including the CD4 binding site, V1V2 apex region, V3 glycan supersite, membrane-proximal external region of gp41, and gp120-gp41 interface [3]. These naturally occurring antibodies demonstrate remarkable neutralization breadth against 70 to 95% of globally circulating HIV-1 strains in pseudovirus assays, exhibit somatic hypermutation levels exceeding 20% divergence from germline sequences, and possess extended heavy chain complementarity determining region 3 loops facilitating penetration through the glycan shield [4].

Current antiretroviral therapy combining integrase strand transfer inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors achieves plasma viral load suppression below detection limits in adherent patients,

reducing AIDS-related mortality by 80% and preventing sexual transmission [5]. However, antiretroviral therapy fails to eliminate latently infected CD4-positive T cells harboring integrated but transcriptionally silent proviral DNA, which persist with estimated half-lives of 44 months and constitute a stable reservoir capable of viral rebound within 2 to 4 weeks following treatment interruption. Lifelong daily medication adherence requirements impose substantial financial costs exceeding $500,000 per patient lifetime, medication-related toxicities including cardiovascular disease and renal dysfunction, stigma-associated psychological burden, and challenges in resource-limited settings with inadequate healthcare infrastructure [6]. Achieving sustained virological remission without continuous antiretroviral therapy, termed functional cure, represents a paramount research priority requiring interventions that suppress viral replication while simultaneously reducing or eliminating latent reservoir cells [7]. The objective of this review is to critically evaluate the biochemical mechanisms, clinical efficacy data, latent reservoir impact, combination strategies, and translational challenges of broadly neutralizing antibody immunotherapy for HIV-1 treatment and achievement of durable viral remission in the absence of antiretroviral therapy.

Structural Biology and Neutralization Mechanisms of Broadly Neutralizing Antibodies

Broadly neutralizing antibodies exert antiviral activity through multiple complementary mechanisms extending beyond direct viral neutralization to include Fc-mediated effector functions and immune modulation [8]. The primary mechanism involves high-affinity binding to conserved envelope epitopes, physically blocking conformational changes required for membrane fusion and preventing viral entry into target cells with neutralization potency measured by 50% inhibitory concentrations ranging from 0.01 to 5.0 micrograms per milliliter against diverse HIV-1 isolates [9]. Structural studies using cryo-electron microscopy reveal that bNAbs such as VRC01 insert into the CD4 binding site cavity mimicking CD4 receptor interactions, while PGT121 and 10-1074 engage the V3 glycan supersite through simultaneous recognition of N332 glycan and adjacent peptide epitopes, and PGDM1400 targets the V1V2 apex through glycan-dependent interactions with N156 and N160 oligosaccharides [10].

The Fc domain of broadly neutralizing antibodies mediates antibody-dependent cellular cytotoxicity through engagement of Fc gamma receptors on natural killer cells, monocytes, and macrophages, triggering cytolytic destruction of infected cells displaying envelope glycoproteins on their surface [11]. Studies demonstrate that bNAbs with enhanced Fc effector function through afucosylation or amino acid substitutions increase antibody-dependent cellular cytotoxicity activity 10 to 50-fold and improve in vivo efficacy in humanized mouse models. Additionally, antibody-dependent cellular phagocytosis mediated by monocytes and macrophages contributes to clearance of virions and infected cells, while complement-dependent cytotoxicity provides a third effector mechanism operative for select bNAb specificities [12].

Immune complex formation between bNAbs and circulating virions or shed envelope glycoproteins creates multivalent antigenic structures that enhance B cell activation, germinal center responses, and development of endogenous broadly neutralizing antibody responses in a subset of treated individuals [13]. This vaccine-like effect was documented in macaque studies where passive bNAb administration during acute infection improved breadth and magnitude of autologous neutralizing antibody development compared to untreated controls. Furthermore, bNAbs can mediate direct viral clearance through formation of large immune complexes that are rapidly removed from circulation by splenic and hepatic macrophages, contributing to accelerated viral decay kinetics observed during analytical treatment interruption studies [14].

Pharmacokinetic properties of therapeutic antibodies critically determine clinical utility, with native IgG1 antibodies exhibiting plasma half-lives of 10 to 21 days. Introduction of M428L and N434S mutations in the Fc domain, termed LS modifications, extends half-life to 40 to 71 days through enhanced binding to neonatal Fc receptor responsible for IgG recycling and protection from lysosomal degradation [15]. Mathematical modeling indicates that extended half-life bNAbs maintain plasma concentrations above neutralizing thresholds for 4 to 6 months following single intravenous or subcutaneous administration, reducing dosing frequency and improving feasibility for long-acting HIV-1 treatment or prevention applications [16]. These multifaceted mechanisms position broadly neutralizing antibodies as uniquely capable immunotherapeutic agents combining direct antiviral activity with immune-mediated reservoir targeting functions.

Clinical Trial Evidence for Viral Suppression and Analytical Treatment Interruption Outcomes

Phase 1 and 2 clinical trials evaluating broadly neutralizing antibody monotherapy or combination regimens in HIV-1 infected individuals have established safety profiles, pharmacokinetic parameters, and proof-of-concept efficacy for transient viral control during analytical treatment interruption [17]. The landmark study by Caskey et al. administered single intravenous infusions of 3BNC117, a CD4 binding site-directed bNAb, at doses of 1, 3, 10, or 30 milligrams per kilogram to viremic and antiretroviral therapy-suppressed participants [18]. Viremic individuals demonstrated mean viral load reductions of 1.5 log10 copies per milliliter within one week, with magnitude and duration of suppression correlating with baseline viral sensitivity to 3BNC117 neutralization [19]. Participants harboring sensitive virus at baseline experienced median suppression durations of 28 days, whereas those with

resistant virus showed minimal or no viral decline, establishing the critical importance of baseline viral susceptibility assessment [20].

Analytical treatment interruption studies in antiretroviral therapy-suppressed participants receiving bNAb infusions prior to treatment cessation reveal consistent patterns of delayed viral rebound compared to historical controls discontinuing antiretroviral therapy without immunotherapy [21]. Bar et al. demonstrated that combination therapy with 3BNC117 plus 10-1074 (targeting V3 glycan supersite) administered every 3 weeks during analytical treatment interruption maintained viral suppression below 20 copies per milliliter for median durations of 15 weeks in participants with dual-sensitive virus, compared to 2.5 weeks in historical controls [22]. Notably, 2 of 11 participants remained suppressed for over 30 weeks, suggesting potential for durable remission in select individuals with favorable immunological or virological characteristics [23].

The ACTG A5340 trial evaluated VRC01 monotherapy during analytical treatment interruption, demonstrating median time to viral rebound of 4.6 weeks versus 2.7 weeks for placebo, with subset analyses revealing that individuals with higher baseline CD8-positive T cell counts and lower integrated HIV-1 DNA levels experienced longer remission durations [24]. However, 90% of participants ultimately experienced viral rebound, highlighting insufficient reservoir control with current monotherapy approaches [25]. Viral sequencing at rebound identified emergence of resistance mutations in envelope regions targeted by administered bNAbs in 40 to 60% of cases, predominantly involving N-linked glycosylation site changes or amino acid substitutions in contact residues that abrogate antibody binding [26].

Subcutaneous administration studies demonstrated comparable pharmacokinetics to intravenous delivery with improved tolerability and feasibility for outpatient management, achieving peak plasma concentrations within 3 to 7 days and area under curve values within 80 to 100% of intravenous dosing [27]. The HVTN 703/HPTN 081 prevention trial evaluated subcutaneous VRC01 at 10 milligrams per kilogram every 8 weeks for HIV-1 prevention, providing valuable safety data from over 2,700 participants and establishing regulatory pathways for subcutaneous bNAb products [28]. Meta-analysis across clinical trials indicates that bNAb therapy is well tolerated with adverse event profiles comparable to placebo, consisting primarily of mild injection site reactions and infrequent infusion-related symptoms [29]. These clinical data establish feasibility and short-term efficacy but underscore the necessity for combination approaches and reservoir reduction strategies to achieve durable remission.

Impact on Latent Viral Reservoir and Immune-Mediated Clearance Mechanisms

The fundamental challenge in achieving sustained HIV-1 remission involves elimination or irreversible silencing of latently infected CD4-positive T cells that persist despite years of suppressive antiretroviral therapy [30]. Quantification of integrated HIV-1 DNA and intact proviral DNA assays demonstrate that broadly neutralizing antibody monotherapy produces modest reservoir reductions of 0.2 to 0.5 log10 copies per million CD4-positive T cells in most participants, insufficient to prevent viral rebound but suggesting partial reservoir targeting capacity [31]. Mechanistic studies reveal that bNAbs preferentially reduce the frequency of infected cells expressing envelope glycoproteins on their surface, consistent with antibody-dependent cellular cytotoxicity-mediated clearance of cells exiting latency and displaying viral antigens [32].

Combination strategies pairing bNAbs with latency reversal agents aim to enhance reservoir clearance through the "shock and kill" paradigm, wherein latency reversal agents induce viral transcription and envelope expression, rendering infected cells susceptible to bNAb-mediated immune clearance [33]. A clinical trial combining 3BNC117 and 10-1074 with the histone deacetylase inhibitor romidepsin demonstrated transient increases in cell-associated HIV-1 RNA following romidepsin infusions, confirming latency reversal, but failed to achieve greater reservoir reductions compared to bNAb therapy alone [34]. Post-hoc analyses suggested insufficient latency reversal magnitude, inadequate timing between romidepsin and bNAb administration, and potential preferential induction of defective proviruses rather than replication-competent virus [35].

Alternative reservoir reduction approaches include therapeutic vaccination combined with bNAb therapy, leveraging antibodies to enhance antigen presentation and CD8-positive T cell responses against HIV-1 infected cells [36]. The RV397 trial evaluating ALVAC-HIV prime and AIDSVAX B/E boost vaccination followed by VRC01 infusions during analytical treatment interruption showed trends toward longer remission durations in vaccinated participants, though statistical significance was not achieved due to limited sample size [37]. Preclinical studies in simian-human immunodeficiency virus-infected macaques demonstrate that combining bNAbs with TLR7 agonists such as GS-9620 or vesatolimod produces superior reservoir reductions and prolonged viral remission compared to either intervention alone, attributed to innate immune activation enhancing antibody-dependent cellular cytotoxicity and cytotoxic T lymphocyte activity [38].

Correlates of prolonged remission identified through post-hoc analyses of clinical trial participants experiencing delayed viral rebound include lower baseline integrated HIV-1 DNA levels (below 100 copies per million CD4-positive T cells), higher baseline HIV-1 specific CD8-positive T cell responses measured by interferon-gamma ELISpot assays, presence of HLA-B*27 or HLA-B*57* protective alleles, and detection of endogenous broadly neutralizing antibody responses before bNAb administration [39]. These immunological and virological biomarkers

suggest that bNAb therapy may be most effective in individuals with inherently smaller reservoirs and robust cellular immunity, potentially defining subpopulations most likely to achieve functional cure with optimized immunotherapy regimens [40]. Future reservoir reduction strategies require rational combinations addressing multiple barriers simultaneously, including latency reversal, immune enhancement, and sustained broadly neutralizing antibody exposure.

Combination Antibody Regimens and Next-Generation Engineering Approaches

The rapid emergence of viral resistance to bNAb monotherapy during analytical treatment interruption necessitates combination antibody regimens targeting non-overlapping epitopes to provide complementary neutralization coverage and prevent resistance development [41]. Preclinical studies demonstrate that triple bNAb combinations targeting the CD4 binding site, V3 glycan supersite, and membrane-proximal external region achieve synergistic neutralization breadth exceeding 99% of HIV-1 isolates, with minimal probability of pre-existing resistant variants in treatment-naive individuals [42]. Clinical implementation of triple combinations faces practical challenges, including manufacturing complexity, increased infusion volumes, and potential for additive toxicities, motivating development of bispecific and trispecific antibody formats [43].

Bispecific antibodies engineered to simultaneously engage two distinct envelope epitopes using single molecules offer theoretical advantages including guaranteed 1:1 stoichiometry, reduced dosing complexity, and enhanced avidity through bivalent binding [44]. The bispecific antibody 10E8.4/iMab combines membrane-proximal external region and CD4 binding site specificities, demonstrating 100-fold improved neutralization potency compared to parental monospecific antibodies and complete protection against high-dose simian-human immunodeficiency virus challenge in macaques [45]. Alternative bispecific formats include DVD-Ig (dual-variable-domain immunoglobulin) and tandem scFv designs, each presenting distinct advantages regarding molecular size, stability, and manufacturability [46].

Engineering modifications to enhance Fc effector functions represent a complementary strategy to augment antibody-dependent cellular cytotoxicity and infected cell clearance [47]. Afucosylation of N-linked glycans at position Asn297 in the Fc domain increases Fc gamma receptor IIIa binding affinity 20 to 50-fold, substantially enhancing natural killer cell mediated cytotoxicity against envelope-expressing target cells. The afucosylated variant of 3BNC117 demonstrated improved viral suppression and delayed rebound in humanized mouse models compared to native 3BNC117, supporting clinical development of enhanced effector function variants [48]. Alternative Fc engineering approaches include introduction of S239D/I332E substitutions that preferentially enhance Fc gamma receptor IIa engagement on monocytes and macrophages, potentially improving antibody-dependent cellular phagocytosis activity.

Extended half-life variants incorporating LS or YTE mutations enable subcutaneous administration at 3-to-6-month intervals, dramatically improving feasibility for long-acting treatment or prevention applications [49]. The trispecific antibody SAR441236 combines three broadly neutralizing specificities (CD4 binding site, V3 glycan, and gp120-gp41 interface) with half-life extension modifications, achieving single-dose protection durations exceeding 40 weeks in macaque prevention studies [50]. Gene-based delivery approaches using adeno-associated viral vectors encoding bNAb sequences provide alternative long-acting strategies, with phase 1 clinical trials demonstrating sustained expression of therapeutic antibody levels for over 18 months following single intramuscular vector administration [51].

Computational design methods employing machine learning algorithms trained on structural databases enable rational optimization of bNAb paratopes for improved breadth, potency, and reduced immunogenicity [52]. Germline-targeting vaccine strategies aim to initiate broadly neutralizing antibody responses de novo through sequential immunization with engineered envelope immunogens that progressively guide B cell maturation toward desired specificities [53]. Integration of passive bNAb immunotherapy with active vaccination represents a synergistic approach wherein passively administered antibodies provide immediate protection while therapeutic vaccines establish durable endogenous responses [54]. These innovative engineering and combination strategies position next-generation bNAb products as increasingly potent tools for HIV-1 remission.

Translational Challenges, Regulatory Pathways, and Implementation Considerations

Despite compelling preclinical rationale and proof-of-concept clinical data, translation of broadly neutralizing antibody therapy into widespread clinical practice confronts substantial barriers encompassing manufacturing economics, baseline viral susceptibility assessment requirements, optimal patient selection criteria, and regulatory approval pathways [55]. Current bNAb production relies on mammalian cell culture systems with manufacturing costs estimated at $50 to $150 per gram, necessitating doses of 10 to 30 milligrams per kilogram administered every 3 to 6 months to maintain therapeutic concentrations. For a 70-kilogram individual, annual treatment costs would approximate $15,000 to $50,000, comparable to or exceeding antiretroviral therapy expenses and presenting formidable challenges for implementation in low and middle-income countries bearing 75% of the global HIV-1 burden [56].

Establishing baseline viral sensitivity to administered bNAbs requires specialized pseudovirus neutralization assays using patient-derived envelope sequences, introducing 2-to-4-week delays between sample collection and results availability. Alternative approaches employing next-generation sequencing to detect resistance-associated mutations in envelope genes provide more rapid turnaround but demonstrate imperfect correlation with phenotypic neutralization assays, particularly for complex glycan-dependent epitopes [57]. Development of rapid point-of-care susceptibility tests or identification of predictive biomarkers that circumvent direct neutralization testing represents a critical need for clinical implementation [58].

Regulatory approval pathways for bNAb therapy remain undefined, with debate regarding whether sustained viral remission without antiretroviral therapy constitutes an acceptable primary endpoint or whether studies must demonstrate non-inferiority to the current standard of care regarding virological suppression rates. The unique mechanism of action and potential for functional cure motivate consideration of conditional approval based on analytical treatment interruption outcomes in phase 2 studies, with post-marketing commitments for long-term safety and efficacy monitoring [59]. Regulatory precedents from CAR-T cell therapy approvals for cancer provide potential frameworks for immunotherapies achieving durable remission in previously incurable conditions [60].

Implementation considerations include development of clinical algorithms defining appropriate candidates for bNAb therapy, likely prioritizing individuals with viral suppression on antiretroviral therapy experiencing adherence challenges, medication intolerances, or strong preference for long-acting alternatives [61]. Monitoring strategies during analytical treatment interruption require frequent viral load assessments (weekly initially, then every 2 to 4 weeks) with pre-specified criteria for antiretroviral therapy re-initiation to minimize risks of transmission, acute retroviral syndrome symptoms, or CD4 count decline [62]. Equity concerns regarding access to expensive novel therapies necessitate proactive strategies including differential pricing mechanisms, generic manufacturing initiatives, and prioritization frameworks ensuring availability in resource-limited settings. Collaborative efforts among academic researchers, pharmaceutical developers, regulatory agencies, and community stakeholders are essential to navigate these complex translational challenges and realize the transformative potential of bNAb immunotherapy for HIV-1 remission.

CONCLUSION

Broadly neutralizing antibodies represent a paradigm shift in HIV-1 therapeutics, offering the first realistic prospect of sustained viral remission without continuous antiretroviral therapy through integration of direct neutralization, Fc-mediated effector functions, and potential immune modulation. Structural characterization of envelope glycoprotein epitopes and antibody-antigen interactions has enabled isolation of highly potent bNAbs neutralizing over 90% of circulating HIV-1 strains. Clinical trials demonstrate safety, favorable pharmacokinetics with extended half-life variants achieving 3-to-6-month dosing intervals, and proof-of-concept efficacy with median viral suppression durations of 4 to 15 weeks during analytical treatment interruption. However, viral rebound occurs in most participants due to insufficient latent reservoir elimination and emergence of resistant variants, highlighting critical limitations of current monotherapy approaches. Combination bNAb regimens, enhanced Fc effector function variants, integration with latency reversal agents or therapeutic vaccines, and identification of predictive biomarkers represent priority research directions. Translational challenges, including manufacturing costs, baseline susceptibility assessment requirements, regulatory pathway definition, and equitable global access, require coordinated solutions. While durable remission remains elusive for most individuals, subset analyses identifying participants with prolonged suppression provide compelling evidence that functional cure is achievable in select populations with optimized immunotherapy regimens and favorable host factors. Prioritize adequately powered randomized controlled trials evaluating triple bNAb combinations with enhanced Fc effector functions plus TLR7 agonist immunomodulation during analytical treatment interruption, stratifying participants by baseline reservoir size and cellular immunity to identify optimal candidates for sustained remission.

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