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Broadly Neutralizing Antibodies for HIV Prevention: Mechanisms, Clinical Trials, and Implementation Challenges

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ABSTRACT

Broadly neutralizing antibodies (bNAbs) against HIV-1 Env have redefined prospects for biomedical prevention, offering long-acting, mechanism-based protection complementary to antiretroviral pre-exposure prophylaxis (PrEP). This review synthesized recent mechanistic, translational, and clinical evidence on bNAbs for HIV prevention and appraises barriers to implementation. The purpose was to provide clinicians, translational scientists, and policymakers a critical, up-to-date assessment of where bNAb-based prevention stands and what is needed for impact at population scale. Literature was identified by searching PubMed/MEDLINE, Embase, and Web of Science (January 2010–September 2025) using terms related to "HIV," "broadly neutralizing antibody," "PrEP," "clinical trial," "Fc engineering," and "vectored immunoprophylaxis," prioritizing randomized trials, large cohort analyses, systematic reviews, and seminal mechanistic studies. The AMP efficacy trials showed overall null efficacy of VRC01 but strong efficacy (~75%) against viruses with in-vitro sensitivity (IC80 <1 μg/mL), validating neutralization sensitivity as a correlate of protection and motivating more potent/longer-acting antibodies and combinations. Next-generation CD4bs, V3-glycan, V2-apex, and MPER bNAbs with LS or related FcRn-enhancing substitutions achieved prolonged half-life, enabling quarterly to semiannual dosing; dual/triple regimens broaden coverage and curb escape, and trispecifics and AAV-vectored delivery are advancing. Remaining gaps included scalable sensitivity assays or genotypic predictors to guide selection, manufacturing cost and cold-chain constraints, and comparative effectiveness versus long-acting small-molecule PrEP. In conclusion, bNAb prevention was biologically validated with promising pharmacologic refinements; clinical implementation will hinge on rational antibody selection, simplified diagnostics, and cost-efficient delivery systems aligned with global PrEP programs.

Keywords: HIV prevention, Broadly neutralizing antibodies, PrEP; Fc engineering, Implementation

INTRODUCTION

HIV remains a major global health challenge: in 2021 an estimated 1.5 million people acquired HIV and 38 million were living with the virus, with the African Region disproportionately affected [1, 2]. Despite declining incidence since 2010, current trajectories fall short of 2025 and 2030 targets, underscoring the need for additional prevention modalities beyond oral tenofovir–emtricitabine and long-acting cabotegravir [3].

Broadly neutralizing antibodies (bNAbs) isolated from individuals with chronic infection recognize conserved Env epitopes (e.g., CD4-binding site [CD4bs], V3 glycan, V2 apex, membrane-proximal external region [MPER]) and neutralize diverse clades at low concentrations. Advances in B-cell cloning, structural vaccinology, and Fc engineering (e.g., LS mutation to enhance FcRn binding) have yielded antibodies with improved potency and extended half-life, enabling infrequent parenteral dosing suitable for prevention [4].

The pivotal AMP trials tested VRC01 prophylaxis in 4,600+ participants across two continents. Although overall efficacy was not significant, protection was substantial against VRC01-sensitive viruses, establishing neutralization sensitivity (in vitro IC80 threshold) and serum concentration as correlates thereby charting a route for next-generation candidates and combinations [5]. In parallel, dual/triple bnAb regimens (e.g., 3BNC117 plus 10-1074, and cocktails including VRC07-523LS, PGDM1400, PGT121) have demonstrated safety, pharmacokinetics (PK), and antiviral activity in phase 1 studies; trispecific constructs and AAV-vectored immunoprophylaxis are entering

or progressing through clinical testing [6]. This review critically synthesizes current evidence on: (i) molecular and biochemical mechanisms of bNAbs; (ii) translational data linking neutralization to protection; (iii) diagnostic/biomarker needs to guide selection; (iv) therapeutic strategies, dosing, and formulations; and (v) future directions, including genotypic prediction, manufacturing, and programmatic integration alongside long-acting small-molecule PrEP. Appraisal of the readiness of bNAb-based prevention for clinical and public-health implementation and outline research and policy priorities for impact is the objective of the study.

Methods (narrative review approach)

Searches were conducted in PubMed/MEDLINE, Embase, and Web of Science for English-language records (January 2010–September 30, 2025) using combinations of: "HIV," "broadly neutralizing antibody," "bNAb," "preexposure prophylaxis," "PrEP," "clinical trial," "AMP," "VRC01," "VRC07-523LS," "3BNC117," "10-1074," "N6LS," "CAP256V2LS," "trispecific," "Fc engineering," and "vectored immunoprophylaxis." Inclusion prioritized randomized trials, prospective cohorts, systematic reviews/meta-analyses, and mechanistic papers with standardized neutralization analyses; meeting abstracts and authoritative program reports were considered for the most recent developments. Reference lists and trial registries (ClinicalTrials.gov) were hand-searched for additional studies. Evidence was synthesized qualitatively with emphasis on mechanistic coherence, risk of bias, generalizability, and clinical relevance.

1. MOLECULAR AND BIOCHEMICAL BASIS

1.1. Env targets and paratopic solutions

bNAbs engage conserved Env epitopes that resist mutational escape due to functional constraints: the CD4-binding site (e.g., VRC01-class, VRC07-523LS, N6LS), glycan-dependent V3 base (e.g., PGT121, 10-1074), V2 apex (e.g., PGDM1400, CAP256-V2), and the MPER (e.g., 10E8 variants). These antibodies exploit germline-encoded frameworks, long HCDR3 loops, and glycan accommodations to access recessed, glycan-shielded surfaces. Fc-domain engineering (LS or analogous substitutions) increases FcRn-mediated recycling, prolonging serum persistence without altering Fab specificity [7].

1.2. Fc engineering and pharmacokinetics

The LS (M428L/N434S) or YTE (M252Y/S254T/T256E) substitutions enhance pH-dependent FcRn binding, typically extending half-life 2–4-fold in humans; among HIV bNAbs, VRC01LS, VRC07-523LS, and N6LS exemplify this strategy, enabling quarterly–semiannual dosing. Comparative analyses suggest LS often achieves favorable PK relative to YTE in human studies, though platform effects and antibody context matter [8].

1.3. Neutralization potency/breadth and coverage modeling

Protection requires sufficient serum concentrations relative to the virus's neutralization sensitivity profile. In silico coverage studies and empirical datasets (e.g., CATNAP) show that combinations targeting non-overlapping epitopes increase breadth at stringent IC80 cutoffs (≤1 μg/mL), a threshold aligned with AMP correlates. Rational selection of dual/triple regimens is therefore guided by additive/synergistic coverage and resistance barriers [9].

2. PATHOPHYSIOLOGY AND TRANSLATIONAL EVIDENCE

2.1. Proof-of-concept from AMP

The harmonized AMP trials (HVTN 704/HPTN 085; HVTN 703/HPTN 081) infused VRC01 every eight weeks. Overall prevention efficacy was not significant; however, secondary sieve/phenotype analyses demonstrated ~75% efficacy against viruses with IC80 < 1 μg/mL, establishing neutralization sensitivity as a mechanistic correlate of protection. Serum bNAb concentration is also associated with risk reduction, supporting PK-informed dosing [10].

2.2. Sensitivity landscape and escape

Viruses isolated from AMP seroconverters provided a contemporary panel across clades. These analyses confirmed that many circulating isolates exhibit intermediate or low sensitivity to single bNAbs, explaining AMP's null overall efficacy and justifying more potent antibodies or cocktails. Genotypic predictors using Env sequence features can estimate bNAb susceptibility and may enable point-of-care decision support once validated [11].

2.3. Translational lessons from therapeutic studies

Although focused on treatment rather than prevention, dual bNAb therapy (e.g., 3BNC117+10-1074) achieved transient suppression and delayed rebound during analytical treatment interruption, highlighting complementary coverage and the need to pre-empt pre-existing resistance. These data inform prevention by quantifying serum targets and escape pathways relevant to incident infections [12].

3. DIAGNOSTIC AND BIOMARKER IMPLICATIONS

3.1. Phenotypic neutralization assays

Standardized TZM-bl pseudovirus assays (GCLP-validated) remain the reference method to quantify serum neutralizing titers and virus susceptibility (IC50/IC80) and were used throughout AMP and early-phase trials. While robust and reproducible, these assays require specialized labs and turnaround times inconsistent with routine PrEP clinics [13].

3.2. Correlates and candidate surrogates

Two measurable correlates have emerged: (i) in-vitro virus sensitivity to the specific bNAb/cocktail (e.g., IC80 < 1 µg/mL for VRC01 in AMP) and (ii) achieved serum antibody concentration at exposure (PK), both associated with prevention efficacy. These could underpin exposure-response modeling and regulatory endpoints if prospectively validated for newer bNAbs.

3.3. Genotypic prediction and rapid triage

Sequence-based models trained on CATNAP and clinical isolates can predict susceptibility to single or combination bNAbs, offering a pragmatic path to "precision PrEP" without onsite phenotyping. Further validation against incident viruses in ongoing studies is needed before clinical deployment [14].

3.4. Immunogenicity monitoring

Anti-drug antibodies (ADA) can reduce effective concentrations, especially with gene-delivered bNAbs. Functional ADA assays adapted from TZM-bl are available for clinical monitoring in trials and may be necessary if vectored approaches advance to practice [15].

4. THERAPEUTIC STRATEGIES AND BIOCHEMICAL TARGETS

4.1. Single bNAbs with half-life extension

Phase 1 studies across routes (IV, SC, IM) showed favorable safety/PK; mean half-life ≈42 days—substantially longer than VRC01—and higher neutralization titers than VRC01 at comparable doses. Dose-route relationships inform quarterly/biannual regimens [16]. First-in-human and subsequent studies support prolonged half-life and broad potency versus VRC01-class peers, positioning N6LS for inclusion in prevention cocktails [17]. V2-apex antibody with potent activity against clade C; phase 1 trials reported acceptable safety/PK and subcutaneous administration feasibility (with rHuPH20), supporting combination regimens [18].

4.2. Dual and triple combinations

Randomized phase 1 in healthy adults confirmed safety and immunogenicity; therapeutic studies in PWH documented antiviral activity and resistance constraints when deployed as a pair. Fc-extended LS variants maintain serum levels for months, compatible with quarterly dosing [19]. A platform trial tested combinations of VRC07-523LS with PGT121, PGDM1400, and 10-1074 (dual and triple), characterizing safety, PK, and immunologic activity to de-risk future efficacy trials [20]. A phase 1 trial combining VRC07-523LS with additional specificities demonstrated safety and antiviral activity, with modeling predicting extended breadth and higher resistance barriers than any monotherapy [21].

4.3. Multispecifics and bispecifics

First-in-human evaluation of a trispecific molecule targeting multiple Env sites reflects a strategy to consolidate breadth and dosing convenience; early data show acceptable safety and pharmacology, though efficacy remains to be proven [22]. Combining MPER neutralization with CD4 receptor blockade aims to increase potency and limit escape; a recent clinical study is designed to inform prophylactic development paths [23].

4.4. Vectored immunoprophylaxis (VIP)

AAV-mediated in vivo expression of bNAbs (e.g., AAV8-VRC07; earlier rAAV1-PG9DP) achieved detectable serum antibody levels and acceptable safety, though ADA responses blunted expression in some participants. VIP could eliminate repeated infusions, but vector immunogenicity, control over dose/expression, and reversibility remain key hurdles before prevention applications [24].

4.5. Comparators: long-acting small-molecule PrEP

Cabotegravir LA demonstrated superiority to daily TDF/FTC in HPTN 083/084 and sustained high effectiveness in open-label follow-up, establishing the current benchmark for long-acting prevention. Emerging twice-yearly lenacapavir (capsid inhibitor) shows near-complete protection in phase 3 and is the subject of global access initiatives, setting a demanding bar for bNAb strategies on efficacy, dosing simplicity, and cost.

5. FUTURE DIRECTIONS AND RESEARCH GAPS

5.1. Precision selection and simplified diagnostics

Translating AMP's correlate into practice requires rapid, scalable methods to estimate susceptibility to a proposed bnAb cocktail. Two plausible pathways are (i) validated sequence-based predictors integrated into clinic workflows and (ii) regional surveillance panels updating coverage maps to guide standardized regimens without per-patient testing. Prospective validation against incident viruses is a priority [25].

5.2. Dosing, routes, and adherence

Half-life extension supports quarterly to semiannual dosing via IV, SC, or IM routes. SC/IM formulations (with or without hyaluronidase) would enable task-sharing in primary care. Real-world trials should test clinic-based vs community delivery and co-administration with vaccines or contraceptives to leverage attendance synergies [26].

5.3. Manufacturing, cost, and supply chain

Cost-of-goods for mAbs typically exceeds US$50/g, with affordability for LMICs likely requiring <US$10/g and continuous or intensified manufacturing. Cold-chain (2–8 °C) integrity and global supply resilience are additional

barriers. Public-private initiatives and platform manufacturing could reduce costs and improve sustainability, but rigorous cost-effectiveness analyses versus cabotegravir/lenacapavir are needed [27].

5.4. Regulatory science and endpoints

If robust exposure–response relationships are reproduced for newer bNAbs, serum concentration and modeled coverage against regional panels could serve as surrogate endpoints for accelerated decisions, with post-marketing effectiveness studies. A harmonized framework akin to influenza mAb susceptibility surveillance would speed iteration [28].

5.5. Equity and program integration

bNAb prevention must be positioned within combination prevention, not as a stand-alone solution. Programs should plan for choice architecture (daily oral, CAB-LA, lenacapavir-LA, bnAbs), address legal/structural barriers, and ensure equitable access where incidence remains highest. Global epidemiology emphasizes sustained investment to meet 2030 targets [29].

Table 1. Selected clinical investigations of HIV bNAbs relevant to prevention

Study / Setting	Antibody(ies) & Design	Key Findings	Implications	References
HVTN 704/HPTN 085 & HVTN 703/HPTN 081 (AMP)	VRC01 IV q8w; randomized, placebo-controlled efficacy trials	No overall efficacy; ~75% efficacy vs viruses with IC80 < 1 µg/mL; serum concentration correlated with protection.	Validates neutralization sensitivity and exposure as correlates; motivates more potent/longer-acting combos.	[30]
Phase 1 VRC07-523LS	Multiple routes/doses in HIV-negative adults	Safe; mean t½ ≈42 days; improved breadth/potency vs VRC01.	Candidate for quarterly/biannual dosing; backbone for combos.	[31]
HVTN 130/HPTN 089	Dual/triple regimens (VRC07-523LS with PGT121, PGDM1400, 10-1074)	Acceptable safety/PK; immunologic activity characterized.	Enables rational selection of prophylactic cocktails.	[32]
3BNC117 + 10-1074	Phase 1 in healthy adults; therapeutic studies in PWH	Safe; antiviral activity; LS variants sustain months-long levels.	Feasible quarterly prevention strategy; high barrier to escape when paired.	[33]
N6LS	First-in-human/early studies	Extended half-life with broad CD4bs neutralization.	Potential single-agent with higher intrinsic coverage.	[34]
CAP256V2LS	Phase 1; SC with rHuPH20	Acceptable safety/PK; clade-C potency.	Regionalized combinations; SC delivery feasible.	[35]
Trispecific SAR441236	First-in-human	Acceptable safety; trispecific strategy advancing.	Single-molecule breadth; simplified dosing possible.	[36]
AAV8-VRC07 (VIP)	Phase 1 in PWH	Safe; variable expression; ADA limited levels in some.	Long-term expression feasible; immunogenicity hurdles to solve.	[37]

CONCLUSION

The bNAb prevention field has advanced from theoretical promise to biologic validation. AMP clarified that neutralization sensitivity and adequate serum exposure are necessary for protection, directing development toward potent, extended-half-life molecules and rational combinations that cover circulating diversity at protective IC80 thresholds. Next-generation CD4bs antibodies (VRC07-523LS, N6LS), V3-glycan/V2-apex partners (10-1074, PGT121, PGDM1400, CAP256V2LS), and multispecific constructs can plausibly deliver quarterly–semiannual injectable prophylaxis. Early clinical data establish safety and favorable PK, and therapeutic studies reinforce

complementarity and resistance considerations. Yet, implementation will hinge on three enablers: (1) scalable susceptibility assessment (phenotypic or validated genotypic) to match cocktails to epidemiology or individuals; (2) manufacturability and affordability—addressing cost-of-goods and cold-chain—to compete with highly effective long-acting small-molecule PrEP; and (3) program design that offers choice and integrates bNAbs within combination prevention, prioritizing high-incidence settings. If these gaps are addressed through coordinated clinical, manufacturing, and policy innovation, bNAb-based prevention could become a durable, acceptable, and equitable tool, complementing antiretroviral PrEP and accelerating progress toward incidence reduction targets. Advance phase 2/3 efficacy trials of optimized dual/triple bNAb regimens with embedded genotypic/phenotypic triage and costed manufacturing/supply strategies benchmarked against cabotegravir and lenacapavir.

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