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Mini Review

Recent Clinical Advances in HIV Vaccine Research: Focus on Germline Targeting, mRNA Platforms, and Broadly Neutralizing Antibodies

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Abstract

Background: Despite four decades of research, an effective preventive HIV vaccine remains elusive. The virus's extraordinary genetic diversity, glycosylation shield, and conformational masking have thwarted traditional vaccine approaches. Recent advances in structural biology, mRNA technology, and B cell immunology have catalyzed a paradigm shift toward rational vaccine design.

Objectives: This systematic review evaluates recent clinical advances (2024–2026) in three strategic domains: germline-targeting immunogens designed to initiate Broadly Neutralizing Antibody (bnAb) precursors, mRNA platform applications for HIV vaccine delivery, and passive immunization with bnAbs.

Methods: A systematic search of PubMed, ClinicalTrials.gov, and major HIV conference proceedings identified 50 recent primary research articles, clinical trial reports, and high-quality reviews. Studies were included if they reported phase 1-2 clinical trial data on germline-targeting vaccines, mRNA-based HIV vaccines, or bnAb passive immunization.

Results: Four landmark clinical trials published in 2025 provide proof-of-concept for germline targeting in humans. The IAVI G002/G003 trials demonstrated that mRNA-encoded nanoparticles can prime bnAb precursors and drive early somatic hypermutation. The IAVI C101 trial showed that an engineered envelope trimer (GT1.1) expanded VRC01-class B cells with bnAb-like structural characteristics. A phase 1 mRNA trimer trial achieved autologous tier 2 neutralization in 80% of recipients with membrane-anchored immunogens. A phase 2 bnAb combination trial (HVTN 206/HPTN 114) is evaluating passive immunization for prevention.

Conclusion: Sequential immunization strategies that shepherd B cells through defined maturation stages have achieved clinical proof-of-concept. The convergence of germline targeting, mRNA platforms, and bnAbs represents a transformative advance, though efficacy trials remain necessary.

Introduction

The development of a preventive HIV vaccine ranks among the most formidable challenges in modern medicine. Unlike acute viral infections where natural immunity confers protection, HIV infection fails to elicit broadly neutralizing antibodies (bnAbs) in most individuals, and the virus establishes latent reservoirs within weeks of exposure. Four decades of research have yielded only one vaccine regimen the RV144 trial in Thailand, demonstrating modest (31%) efficacy, insufficient for licensure but sufficient to prove that vaccine-induced protection is possible. The fundamental obstacle is HIV's unparalleled genetic diversity. Circulating strains differ by up to 35% in envelope sequences, and within a single infected individual, the virus exists as a quasispecies of related but antigenically distinct variants. Traditional vaccine strategies that succeed against relatively stable pathogens inactivated virus, protein subunits, or viral vectors expressing native antigens have uniformly failed against HIV because immune responses focus on variable epitopes that readily mutate [1]. Against this backdrop, a new paradigm has emerged: rational vaccine design based on reverse engineering of bnAbs. Rare HIV-infected individuals (approximately 1-2% of those infected) develop bnAbs capable of neutralizing diverse viral isolates after years of infection. These antibodies target conserved regions of the envelope glycoprotein, including the CD4 binding site, the V2-apex, the V3-glycan patch, the gp120-gp41 interface, and the membrane-proximal external region. If a vaccine could elicit such antibodies before exposure, protection might be achievable. This review focuses on three interconnected strategies that have advanced to clinical testing:

1. **Germline targeting**: Priming naive B cells that carry precursor forms of bnAb genes, then guiding their maturation through sequential immunogens
2. **mRNA platforms**: Leveraging the speed, flexibility, and immunogenicity of mRNA-LNP technology, validated during COVID-19, for HIV vaccine delivery
3. **Broadly neutralizing antibodies**: Passive administration of bnAbs to provide immediate protection, serving as a bridge to active vaccination

The past 18 months have witnessed unprecedented clinical progress, with four major trials reporting positive results in 2025. This systematic review synthesizes these advances, evaluates their significance, and identifies remaining challenges [2].

Methods

Search Strategy

A systematic literature search was conducted in PubMed, ClinicalTrials.gov, and conference proceedings of the Conference on Retroviruses and Opportunistic Infections (CROI) and the International AIDS Society (IAS) for the period January 2024 through December 2025. Search terms included combinations of: "HIV vaccine," "clinical trial," "broadly neutralizing antibody," "germline targeting," "mRNA vaccine," "phase 1," "prevention," "bnAb," "VRC01-class," "germinal center," and "sequential immunization"[2].

Inclusion and Exclusion Criteria

Studies were included if they: (1) reported primary data from human clinical trials (phases 1-2); (2) evaluated HIV vaccines or bnAb passive immunization for prevention; (3) focused on germline-targeting strategies, mRNA platforms, or bnAb induction/administration; (4) were published in peer-reviewed journals or presented at major conferences between January 2024 and December 2025; and (5) included safety and immunogenicity endpoints.

Exclusion criteria included: animal studies (unless providing critical mechanistic insights), therapeutic vaccine studies (prevention only), studies of vaccines for HIV-infected individuals (e.g., for co-infections), and studies without original data (narrative reviews, commentaries) [2, 3].

Data Extraction and Synthesis

Data were extracted on trial design, participant characteristics, vaccine platforms, immunogen design, adjuvant use, immunization schedules, safety outcomes, and immunogenicity endpoints (B cell responses, neutralizing antibodies, T cell responses). Given heterogeneity in study designs and endpoints, results were synthesized narratively, organized by strategic approach (germline targeting, mRNA platforms, bnAbs) [3].

Results

1. Germline-Targeting Vaccines: Clinical Proof-of-Concept

Germline targeting represents a fundamental departure from empiric vaccine design. Rather than immunizing with native HIV envelope proteins (which fail to engage bnAb precursors), this strategy employs engineered immunogens optimized to bind and activate the unmutated common ancestors of known bnAbs [2, 3].

1.1. IAVI G002 and G003: mRNA-Encoded Nanoparticles

The most significant advance emerged from the IAVI G002 (United States) and IAVI G003 (Rwanda and South Africa) trials, published in *Science* in July 2025. These phase 1 trials enrolled nearly 80 healthy HIV-negative adults to evaluate a sequential immunization strategy targeting VRC01-class bnAbs, antibodies that mimic CD4 binding to the conserved CD4 binding site on gp120 [3].

Design: The strategy employed a heterologous prime-boost regimen. The priming immunogen (eOD-GT8 60-mer) was an engineered nanoparticle displaying 60 copies of a germline-targeting epitope designed to bind unmutated common ancestor VRC01-class B cell receptors. The boosting immunogen (Core-g28v2 60-mer) was designed to engage intermediate forms of these B cells as they acquired somatic mutations. Both immunogens were delivered as mRNA-encoded nanoparticles using the same lipid nanoparticle technology deployed in COVID-19 vaccines[3].

Key Findings: All participants who received both priming and boosting doses developed VRC01-class antibody responses, a striking result given that these B cell precursors are extremely rare (estimated frequency <1 in 100,000 naive B cells). More than 80% achieved "elite" immune features associated with bnAb development, including specific heavy chain usage (IGHV1-2*02) and CDRL3 motifs characteristic of VRC01-class antibodies.

Critically, the boosting immunogen drove somatic hypermutation, the process by which B cells refine their antibody genes through mutation and selection. VRC01-class B cells displayed median mutation frequencies of approximately 5% after boosting, with some clones exceeding 10% mutations. Structural analysis confirmed that elicited antibodies mimicked true bnAbs in their mode of envelope recognition, including accommodation of the N276 glycan, a key obstacle that normally prevents non-bnAbs from accessing the CD4 binding site. The G003 trial, conducted in African populations where HIV burden is highest, demonstrated that immune responses were remarkably similar to those in North American participants. This finding is essential for global vaccine applicability and suggests that genetic background does not pose an insurmountable barrier to germline-targeting approaches [1-3].

Safety: The mRNA-nanoparticle platform was generally well tolerated. However, 18% of G002 participants experienced skin reactions predominantly urticaria, a higher rate than seen with COVID-19 mRNA vaccines. Grade 3 adverse events were uncommon, and no vaccine-related serious adverse events occurred [4].

Significance: These trials provide the first clinical demonstration that sequential immunization can guide bnAb precursor B cells through defined maturation stages in humans. As the authors noted, they establish "clinical proof of concept that heterologous boosting can advance bnAb precursor maturation" [3, 4]..

1.2. IAVI C101: First-in-Human Germline-Targeting Env Trimer

A complementary approach using a protein trimer immunogen was reported in *Science* in October 2025. The IAVI C101 trial tested GT1.1, an engineered gp140 trimer designed to target VRC01-class precursors, adjuvanted with AS01B (the same adjuvant used in the shingles vaccine).

Design: Forty-eight healthy HIV-negative adults received either low-dose (30 μg) or high-dose (300 μg) GT1.1 at weeks 0, 8, and 24, randomized 5:1 vaccine-to-placebo.

Key Findings: The vaccine expanded VRC01-class memory B cells in a dose-dependent manner. In the high-dose group, VRC01-class cells comprised 33% of CD4 binding site-specific memory B cells (median) and reached a frequency of 1 in 2,500 of all IgG memory B cells, a striking expansion given that no such cells were detectable pre-vaccination.

Somatic hypermutation accumulation was robust. By week 26, VRC01-class B cells displayed median mutation levels of 4.9%, significantly higher than B cells targeting other epitopes ($p < 0.01$). In some individuals, mutations exceeded 10%. Cryo-electron microscopy of monoclonal antibodies isolated from vaccinated participants revealed structural mimicry of true VRC01-class bnAbs, including the characteristic CDRL1 deletions or flexibility that allow glycan accommodation. Although neutralization was not a primary endpoint, a subset of elicited antibodies neutralized heterologous pseudoviruses lacking the N276 glycan or homologous BG505 pseudoviruses. Approximately one-third of week 26 antibodies bound fully glycosylated Env trimers with nanomolar affinity, indicating meaningful advancement along the bnAb maturation pathway [1-4].

Significance: The C101 trial demonstrates that a conventional protein-adjuvant vaccine can successfully prime bnAb precursors, complementing the mRNA approach. High-dose recipients were offered enrollment in follow-up trials testing sequential boosters with BG505

SOSIP trimers, positioning this regimen for continued evaluation [1].

2. mRNA Platform Advances for HIV Vaccines

The COVID-19 pandemic validated mRNA-LNP technology for rapid vaccine development. Several properties make this platform attractive for HIV: (1) speed of antigen design and manufacture, (2) intrinsic adjuvanticity through innate immune activation, (3) ability to encode membrane-anchored antigens in native conformation, and (4) suitability for complex sequential immunization regimens [5].

2.1. Phase 1 Trial of mRNA-Encoded Envelope Trimers

Parks and colleagues reported a randomized, open-label phase 1 trial evaluating three mRNA-encoded envelope trimers in *Science Translational Medicine* in July 2025. The study compared soluble versus membrane-anchored forms of BG505-derived trimers [6].

Rationale: Native HIV envelope trimers are membrane-anchored. Soluble trimers, while easier to produce, expose immunodominant epitopes at the trimer base that elicit non-neutralizing antibodies, a potential distraction from bnAb development. Membrane anchoring might obscure these undesirable epitopes [6].

Design: One hundred eight participants received two doses of soluble or membrane-anchored trimers, with a subset receiving a third dose. The study was conducted at multiple US sites.

Key Findings: Membrane-anchored trimers reduced the frequency of base-binding serum antibodies compared with soluble trimers, confirming the design hypothesis. More impressively, three immunizations with membrane-anchored trimers elicited autologous tier 2 neutralizing antibodies in 80% of recipients, versus only 4% receiving soluble trimers. Tier 2 neutralization refers to the ability to neutralize "hard-to-neutralize" primary isolates, a stringent benchmark in the field.

Safety: Vaccines were generally well tolerated, but 6.5% of participants developed urticaria again, higher than seen with COVID-19 mRNA vaccines but comparable to the G002 experience. No anaphylaxis or vaccine-related serious adverse events occurred.

Significance: This trial provides the first evidence that mRNA-encoded, membrane-anchored HIV trimers can elicit tier 2 autologous neutralizing antibodies in humans, a critical milestone. However, these antibodies are not yet broadly neutralizing; they recognize the autologous (vaccine-matched) virus but not heterologous strains. Nevertheless, the 80% response rate compares favorably to historical protein vaccines, which rarely induce tier 2 responses [6].

2.2. Integration with Germline Targeting

The G002/G003 trials utilized mRNA-encoded nanoparticles, demonstrating platform feasibility for complex, multivalent immunogens. The mRNA platform enabled rapid iteration from preclinical testing to clinical trials, a timeline that would be impossible with traditional protein manufacturing. Ongoing trials are evaluating additional mRNA-encoded immunogens targeting other bnAb lineages, including those targeting the V2-apex (PGDM1400-class) and V3-glycan (PGT121-class) . The platform's flexibility allows mixing of multiple immunogens in a single formulation, potentially enabling simultaneous priming of multiple bnAb lineages [1,2].

3. Broadly Neutralizing Antibodies for Prevention

The bnAb field has advanced along two parallel tracks: active vaccination (described above) and passive administration of bnAbs for immediate protection. Passive immunization offers several advantages: (1) immediate, high-titer protection without requiring an immune response, (2) defined product with predictable pharmacokinetics, (3) potential for long-acting formulations, and (4) use as a bridge to active vaccination in populations at highest risk [7].

3.1. Phase 2 bnAb Combination Trial: HVTN 206/HPTN 114

The most advanced bnAb prevention trial is HVTN 206/HPTN 114, a phase 2 study evaluating a combination of three engineered bnAbs with extended half-lives . The trial, sponsored by the National Institute of Allergy and Infectious Diseases, builds on promising phase 1 data showing safety and tolerability [6].

Product Composition: The three bnAbs target distinct conserved epitopes:

- **VRC07-523LS:** Targets the CD4 binding site; engineered with LS mutations (M428L/N434S) to extend half-life to approximately 4-6 weeks
- **PGT121.414.LS:** Targets the V3-glycan patch centered on N332; similarly engineered for extended half-life
- **PGDM1400LS:** Targets the V2-apex centered on N160; the most potent bnAb in the combination

Design: The trial aims to enroll up to 200 HIV-negative adults who will receive intravenous infusions of the three bnAbs in combination. The primary objective is safety and tolerability; secondary objectives include pharmacokinetics, neutralization breadth and durability, and anti-drug antibody development. The combination approach is designed to prevent escape, HIV would need to mutate three independent epitopes simultaneously to evade all three antibodies.

Status and Significance: As of the 2025 trial protocol, the study is actively enrolling. If safety and neutralization profiles are favorable, this regimen could advance to efficacy trials, potentially providing the first licensed biomedical prevention product requiring only quarterly or semi-annual administration [6].

3.2. The Antibody-Mediated Prevention (AMP) Legacy

The current trial follows the AMP trials (HVTN 703/HPTN 081 and HVTN 704/HPTN 085), which tested VRC01 alone in over 4,600 participants. Those trials showed that VRC01 provided 75% protection against highly sensitive viruses but no protection against resistant viruses. The lesson: single bnAbs are insufficient due to viral diversity, but combinations or more potent individual bnAbs might achieve meaningful protection. The HVTN 206/HPTN 114 combination addresses this by targeting three distinct epitopes with enhanced potency. PGDM1400, in particular, is among the most potent bnAbs ever isolated, with neutralization breadth exceeding 80% of diverse isolates at sub-microgram concentrations [7].

4. T Cell Vaccines: The Conserved Element Approach

While bnAb induction remains the primary goal for preventive vaccines, T cell responses may provide secondary protection, particularly for viral containment if breakthrough infection occurs. The conserved element approach focuses T cell responses on regions of HIV that cannot mutate without crippling viral fitness. The HVTN 119 trial evaluated a DNA vaccine encoding seven highly conserved elements of p24Gag, the viral capsid protein . The rationale is that CD8+ T cell responses targeting conserved epitopes are associated with viral control in infected individuals; a vaccine that pre-arms such responses might limit viral replication after acquisition, potentially reducing clinical progression and transmission risk [8, 9].

Key Findings: The conserved element vaccine induced CD4+ and CD8+ T cell responses to five of seven conserved elements, compared with only two elements induced by full-length Gag vaccination. The responses targeted regions critical for viral capsid integrity, mutations that escape these T cells likely impair viral fitness.

Significance: This T cell approach is not intended as a stand-alone preventive vaccine but as a component of a comprehensive strategy combining bnAb-inducing and T cell-inducing components. The conserved element design is platform-agnostic and could be incorporated into mRNA or viral vector regimens.

Discussion

1. Synthesis of Key Findings

This systematic review identifies three major advances in HIV vaccine research from 2024-2026:

First, germline targeting has achieved clinical proof-of-concept. The IAVI G002/G003 and C101 trials demonstrate that engineered immunogens can successfully prime rare bnAb precursor B cells in humans and guide their initial maturation [3, 5]. These findings validate two decades of structural biology and mouse model work, showing that the "reverse vaccinology" approach, designing immunogens based on bnAb epitope knowledge—is feasible in humans. The demonstration of somatic hypermutation accumulation (4-5% median, >10% in some clones) is particularly important. Somatic hypermutation is the engine of affinity maturation; bnAbs typically carry 30-40% mutations relative to germline. While 5% represents only the first step, the fact that boosting drove additional mutations suggests that continued sequential immunization might eventually achieve full bnAb maturation. Ongoing trials testing third and fourth boosters will determine whether this trajectory continues [1, 2, 5].

Second, mRNA platforms have been successfully deployed for HIV vaccines. The G002/G003 trials used mRNA-encoded nanoparticles; the Parks trial used mRNA-encoded membrane-anchored trimers. Both showed robust immunogenicity, and the membrane-anchored trimer trial achieved 80% autologous tier 2 neutralization, a benchmark not previously reached with protein vaccines. The urticaria signal (6.5-18% incidence) bears monitoring . COVID-19 mRNA vaccines have urticaria rates of approximately 1-2%, suggesting either HIV antigens are more reactogenic or the higher multivalency of nanoparticle immunogens increases mast cell activation. Nevertheless, the reactions were self-limited and not dose-limiting.

Third, bnAb passive immunization is advancing to phase 2 combination trials. The HVTN 206/HPTN 114 study will determine whether a cocktail of three engineered bnAbs can provide safe, durable protection. If successful, this approach could provide near-term prevention options while active vaccines continue development.

2. Comparison with Historical HIV Vaccine Trials

The current data contrast sharply with previous HIV vaccine trials. The Vax003/Vax004 protein subunit trials (2003) showed no efficacy. The STEP trial (2007) of adenovirus-5 vectored Gag/Pol/Nef not only failed but suggested increased infection risk in vaccinees with pre-existing Ad5 immunity. The HVTN 505 DNA/recombinant adenovirus-5 trial (2013) was halted for futility. RV144 (2009) provided the only efficacy signal (31%) but was insufficient for licensure and not reproducible in the subsequent HVTN 702 trial (2020). The current trials differ fundamentally in their rational design. Rather than presenting native antigens and hoping for protective responses, germline targeting engineers immunogens based on known bnAb development pathways. This approach is theoretically grounded and testable; the G002/G003 and C101 results provide the predicted immunologic outcomes.

3. Remaining Challenges and Unanswered Questions

Will sequential immunization eventually elicit true bnAbs? The current trials demonstrate priming and early maturation, not bnAb induction. Whether 3, 4, or 5 immunizations can drive VRC01-class B cells to the 30-40% mutation levels required for broad neutralization remains unknown. Mathematical modeling suggests 3-5 years of sequential immunization might be required, a challenging timeline for clinical trials but potentially acceptable for eventual licensure.

Can multiple bnAb lineages be induced simultaneously? The current trials focus on VRC01-class (CD4 binding site) antibodies. However, protection likely requires bnAbs targeting multiple epitopes, as no single bnAb neutralizes all isolates. Simultaneous priming of VRC01-class, PGDM1400-class (V2-apex), and PGT121-class (V3-glycan) lineages might be necessary. The mRNA platform could potentially co-encode multiple immunogens, but competition between B cell lineages remains a concern.

Will germline targeting work in diverse genetic backgrounds? The G003 trial showed similar responses in African and North American participants, but this represents only two populations. HLA polymorphism, germline immunoglobulin gene variation, and prior pathogen exposure differ globally. The conserved nature of bnAb germline genes (e.g., IGHV1-2*02 for VRC01-class) is reassuring, but confirmation in larger, more diverse populations is needed.

What explains the urticaria signal? The consistently higher rate of urticaria with HIV mRNA vaccines versus COVID-19 mRNA vaccines requires investigation. Possibilities include nanoparticle multivalency, HIV envelope glycosylation patterns, or adjuvant effects of mRNA encoding different antigen classes. Phase 2 trials with larger sample sizes will better define safety profiles.

Can passive bnAbs provide durable protection? The LS mutations extend half-life to 4-6 weeks, potentially enabling quarterly administration. However, phase 2 data on duration of protective neutralization titers are pending. Anti-drug antibody development could shorten effective half-life; the HVTN 206/HPTN 114 trial includes ADA monitoring to address this [9, 10].

4. Implications for the HIV Prevention Pipeline

The current trials have reshaped the HIV vaccine pipeline . Major efficacy trials (e.g., the Mosaico study, which tested a mosaic Ad26-based regimen) have ended without success, and the field has pivoted to discovery-stage research. The termination of the ADVANCE and BRILLIANT programs, USAID-funded vaccine development investments has reduced resources, but the scientific momentum from the 2025 results has attracted continued funding from NIH and philanthropic sources.

The path forward involves:

- **Iterative optimization**: Testing modified immunogens to improve bnAb precursor engagement and reduce off-target responses
- **Extended sequential regimens**: Third and fourth boosters in ongoing rollover studies
- **Combination approaches**: Co-delivery of germline-targeting immunogens for multiple bnAb lineages
- **Integration of T cell components**: Conserved element vaccines to provide cellular immunity

5. Limitations of This Review

Several limitations merit acknowledgment. First, the reviewed trials are phase 1, with small sample sizes (generally 50-200 participants); safety signals and immunogenicity estimates require confirmation in larger trials. Second, the primary endpoints are immunologic rather than clinical; whether the induced responses prevent HIV acquisition remains unknown. Third, the field is evolving rapidly; new data from ongoing trials may modify conclusions. Fourth, publication bias may favor positive results; negative or null findings from industry-sponsored trials may be underrepresented.

Conclusion

The years 2024-2026 have witnessed transformative advances in HIV vaccine research. The convergence of three strategic approaches germline targeting, mRNA platforms, and broadly neutralizing antibodies has produced clinical proof-of-concept for rational vaccine design. The IAVI G002/G003 and C101 trials demonstrate that sequential immunization can prime and guide bnAb precursor B cells in humans, achieving somatic hypermutation accumulation and structural mimicry of true bnAbs. mRNA-encoded membrane-anchored trimers have elicited autologous tier 2 neutralizing antibodies at unprecedented frequencies (80%). Phase 2 bnAb combination trials are evaluating passive immunization as a potential prevention modality [1, 3, 5, 8, 11]. These advances do not yet constitute a licensed vaccine. True bnAb induction remains to be demonstrated; efficacy trials are years away. However, the field has emerged from decades of empiric iteration into an era of rational, structure-guided design. For the first time, the scientific community has a clear roadmap: sequential immunization to shepherd B cells through defined maturation stages, leveraging mRNA platforms for rapid iteration and multivalent presentation, and bnAbs as both a prevention bridge and a template for vaccine design [1, 2, 5, 11]. The remaining challenges, driving full bnAb maturation, targeting multiple epitopes simultaneously, ensuring global applicability are substantial but no longer insurmountable. After 40 years of frustration, a preventive HIV vaccine is finally within plausible reach [3, 4, 6].

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