Webinar series: HIV vaccine innovation: Industry perspectives & partnership opportunities

Organized by the CPP HIV Vaccine Industry Partnership Group and the HIV Vaccine Research Network of IAS

Webinar 1: Scientific updates on HIV vaccine advancements

This session provides high-value scientific updates from leading researchers and organizations working at the frontier of immunogen design, bnAb discovery, and vaccine platform innovation. Organized by the Global HIV Vaccine Enterprise and CPP Vaccine Industry Group

1. Opening & Framing Remarks

The session opened by framing the HIV vaccine field as entering a new phase of accelerated scientific progress, driven by advances in structure-based immunogen design, bnAb discovery, and novel vaccine platforms. Speakers emphasized the importance of closer alignment between scientific innovation and product development realities, particularly in a changing prevention landscape shaped by long-acting interventions.

Key message:
Scientific momentum is strong, but translation into viable, scalable vaccine products is now the central challenge.

Presenter 1: NIH HIV vaccine portfolio overview

Summary:
The presentation outlined clinical progress across a coordinated NIH portfolio of 28 trials, with Duke's consortium having produced materials for nearly half. Germline-targeting immunogen strategies, using both protein nanoparticles and mRNA platforms, are successfully activating rare bnAb precursor B cells in human trials, with structural studies confirming on-target binding mechanisms. The program is now advancing toward therapeutic immunization in people living with HIV.

Key points:

- Precursor B-cell activation confirmed in up to 12/14 vaccinees in the V3 glycan prime-boost trial, with clone re-engagement verified after boosting
- Structural validation shows vaccine-induced antibodies bind HIV in the same way as known broadly neutralizing antibodies

- Both autologous and heterologous neutralization achieved in the CD4 binding site program
- Serum heterologous neutralizing antibodies induced with mRNAs to V2 apex in non-human primates and a human trial now ongoing.
- Two new therapeutic trials (HVTN 808/809) launching soon that utilize mRNAs that induce V2 apex and V3 glycan supersite neutralizing antibodies and incorporating analytical treatment interruption as a readout
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Takeaway:
Germline-targeting immunogens have now demonstrated, in early human trials, that they can activate the specific rare B-cell precursors they were designed to engage. The field is now focused on maturing those responses into broadly neutralizing activity. Additionally, therapeutic HIV vaccine trials will assess whether vaccination of people living with HIV can lead to viral control.

Presenter 2: Protective antibody thresholds and viral resistance

Summary:
This presentation drew on findings from the AMP trial (VRC01 antibody-mediated prevention) to address two practical questions for vaccine development: how much antibody is needed in serum to prevent infection, and whether HIV is evolving resistance fast enough to undermine vaccine-mediated protection.

Key points:

- VRC01 passive infusion achieved 75% efficacy against highly sensitive viruses, but near-zero efficacy against resistant strains
- The PT80 metric (combining viral sensitivity and serum antibody concentration) was validated as a correlate of protection
- HIV-1 is measurably evolving toward reduced neutralization sensitivity, particularly at the CD4 binding site and V2 glycan epitopes, raising the question of whether virus panels used in trials need continual updating
- Deeper sequencing in the AMP trial revealed that multi-variant transmission occurs in ~40% of infections and that discordant neutralization phenotypes within a single participant create selective pressure that allows resistant lineages to outcompete sensitive ones

Takeaway:
The AMP trial has shifted vaccine design thinking in two concrete ways: PT80 provides a quantitative benchmark for the antibody levels a vaccine will need to induce, and the higher-than-expected prevalence of resistant and multi-variant transmissions means vaccines will need to cover a broader range of transmitted founder virus phenotypes than previously assumed.

Presenter 3: Sequential immunization - proof of concept

Summary:
This presentation described a sequential immunization strategy designed to induce broadly

neutralizing antibodies (bnAbs) through stepwise B-cell maturation, beginning with a germline-targeting prime and followed by a boosting immunogen. Two clinical trials are presented, demonstrating that this approach can elicit VRC01-class B cells and, after boosting, produce bona fide bnAbs in human.

Key points:

- GT1.1 prime expanded VRC01-class B cells from zero detectable precursors to ~1 in 2,500, with induced antibodies structurally homologous to VRC01 and capable of accommodating the N276 glycan
- VRC01-class memory B cells persisted for up to two years without restimulation; ~40% of lineages were reactivated by a subsequent BG505 SOSIP boost
- Multiple boost-trial monoclonal antibodies achieved heterologous neutralization, with some qualifying as bona fide bnAbs by neutralizing >50% of strains on a 119-virus panel
- BRILLIANT-02, a purpose-designed sequential mRNA trial with optimized shaping and polishing immunogens, is now underway in South Africa

Takeaway:
This study provides the first clinical proof of concept that sequential vaccination can guide B-cell maturation to produce genuine broadly neutralizing antibodies in humans. The response remains at the memory B-cell level rather than in serum, which is the next barrier to clear. The field is now moving from opportunity-driven trials toward rationally designed sequential regimens with purpose-built immunogens at each stage..

Presenter 4: Prime-boost optimisation and safety

Summary:
This presentation reported immunological results from heterologous prime-boost trials (IAVI G002/G003) using an eOD-GT8 prime followed by a core immunogen boost, demonstrating that this regimen can drive VRC01-class B-cell maturation to high frequencies and with highly polyclonal responses. A safety signal observed in one trial is being addressed in an ongoing follow-on study, with the goal of proceeding to a full bnAb-inducing sequential regimen.

Key points:

- Two immunizations (a prime followed by a boost) induced the desired VRC01-class immune cells in the majority of participants (over 94% by week 24) at consistently high frequencies
- Responses were highly polyclonal, reducing the risk of viral escape from the VRC01-class repertoire
- Structural analysis confirmed vaccine-induced antibodies bind the HIV envelope in the same mode as VRC01
- A higher-than-expected rate of urticaria in G002, not seen in G003, likely linked to the HIV antigens carried by the mRNA, is under active investigation
- G004, currently ongoing in South Africa, is testing a lower dose of the same regimen alongside a second vaccine targeting a different part of the virus (the V3 glycan site), with a full multi-step broadly neutralizing antibody regimen planned if safety and immune responses are acceptable

Takeaway:
Heterologous prime-boost immunization has now demonstrated consistent, high-frequency induction of mature VRC01-class B-cell precursors in humans, with polyclonal responses and confirmed on-target binding, representing a meaningful step beyond simply detecting rare precursors. The immediate priority is resolving the urticaria safety signal observed with mRNA-expressed HIV antigens, which IAVI G004 is designed to address before advancing to a full bnAb-inducing regimen.

Presenter 5: Africa-led clinical trial pipeline

Summary:
This presentation provided a progress update on the BRILLIANT program, an Africa-led clinical trial initiative testing germline-targeting HIV vaccine strategies. Two trials are either completing enrolment or in protocol development, and a third (IAVI G004) is actively enrolling in South Africa, together forming a coordinated pipeline designed to establish the safety and immunogenicity data needed to advance to a full bnAb-inducing regimen.

Key points:

- BRILLIANT-011 is on track to complete enrolment by end of March 2026, with final vaccinations in September 2026 and B-cell sequencing and immune analysis to follow; no serious adverse events or HIV acquisitions have occurred to date
- BRILLIANT-002, in protocol development and awaiting regulatory approval in South Africa, will test an mRNA version of the GT1.1 germline-targeting immunogen (GR2) across multiple dosing levels and schedules, with sequential boosting immunogens, in 60 HIV-negative adults across Cape Town, Johannesburg and Durban
- IAVI G004, a dose-escalation safety and immunogenicity trial of mRNA-delivered HIV immunogens, is currently enrolling Part B in South Africa across six sites; it is specifically designed to address the lower-dose safety question raised by earlier trials and to generate data to support the next generation of studies
- All three trials prioritise the African population, reflecting both the burden of HIV on the continent and the need to establish safety and immunogenicity data in the populations where a vaccine would have the greatest impact

Takeaway:
The BRILLIANT program represents a deliberate, stepwise approach to building the clinical evidence base for bnAb induction in Africa. The immediate focus is on confirming that germline-targeting mRNA immunogens are safe and immunogenic at appropriate doses in African populations, with the results from these trials intended to open the door to a full sequential bnAb vaccine regimen on the continent.

Panel Discussion Summary

Summary

The panel discussion addressed two broad themes: how the arrival of highly effective long-acting PrEP agents (such as lenacapavir) reshapes the strategic landscape for HIV vaccine development, and how findings from monoclonal antibody trials, particularly the PT80 correlate from the AMP trial, can inform what we should expect and demand from vaccine-induced immune responses.

Key discussion areas:

- The availability of highly effective PrEP modalities was welcomed, but raised practical questions about target product profiles, trial site selection, and how vaccines and PrEP fit together in combination prevention strategies
- Therapeutic vaccination in people living with HIV introduces significant complexity: background immunity varies widely between individuals with different viral strains and carrying different pre-existing antibody and T-cell responses, making it difficult to predict how any given immunogen will interact with that landscape
- One potentially attractive feature of germline-targeting immunogens in people living with HIV is that the virus itself, through low-level replication or viral blips during treatment interruption, could act as a natural shaping or polishing immunogen, complementing the sequential vaccination strategy
- On correlates of protection, the panel acknowledged that PT80 is VRC01-specific and therefore of limited direct transferability to vaccine-induced polyclonal responses, but agreed it remains the best available benchmark. Critically, VRC01 is not among the most potent bnAbs, so the protective threshold derived from AMP should be treated as a floor, not a target

Panel takeaway:
The field has useful but imperfect tools for defining success: PT80 provides a quantitative starting point for protective thresholds, but was derived from a moderately potent monoclonal antibody and cannot be straightforwardly applied to the polyclonal, multi-specificity responses a vaccine would ideally induce. The goal should be to exceed that benchmark, not to accept it. Meanwhile, the advent of highly effective PrEP and the push toward therapeutic vaccination are together forcing the field to think more carefully about who a vaccine is for, what it needs to do, and where trials can realistically be conducted.

Brief recap:
The first session highlighted significant scientific progress in HIV vaccine research, particularly in germline-targeting immunogen design, bnAb-informed strategies, and emerging platform technologies such as mRNA and nanoparticles. Early clinical data are beginning to validate key concepts, marking an important transition from discovery to proof-of-concept in humans.

At the same time, discussions emphasized that increasing scientific sophistication brings greater complexity in vaccine design and delivery, raising important questions around feasibility, scalability, and real-world implementation.

The panel underscored that the broader landscape is evolving rapidly, with long-acting prevention tools setting a higher bar for vaccines, and with growing interest in integrating vaccine approaches into cure strategies.

Overall message:
While the scientific foundation for HIV vaccines is stronger than ever, future success will depend on aligning innovation with practical development pathways, strengthening collaboration across sectors, and ensuring that promising approaches can be translated into viable, accessible products.