

HIV Vaccines in 2026 and Beyond: Promise and Persistence



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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Bar reported serving as a consultant for Viiv Healthcare,
Merck & Co, Inc, and AbbVie, Inc. (Updated November 11,
2025)

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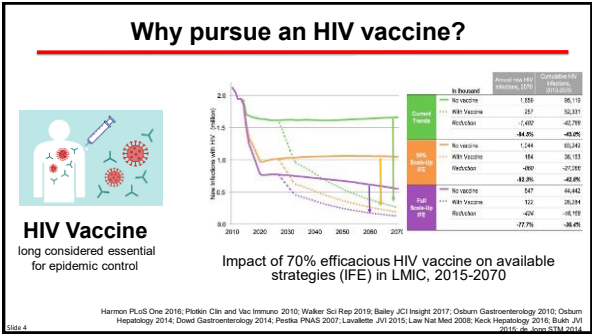
Learning Objectives

After attending this presentation, learners will be able to:

- Describe the rationale for pursuing preventative and therapeutic HIV vaccines
- Characterize the germline targeting approach that is currently being developed to induce broadly neutralizing antibodies by vaccination
- Describe the strategy of conserved T-cell epitope vaccines

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Modern biomedical HIV prevention toolkit

ART - TasP

ART - PrEP

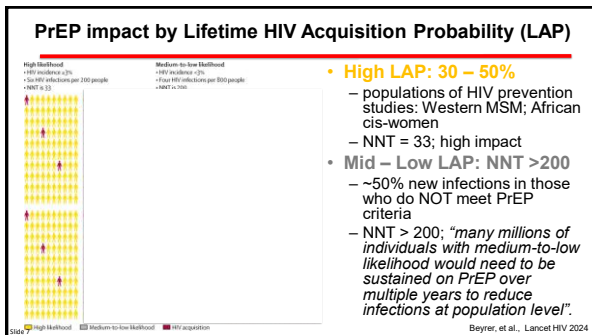
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Evidence for PrEP in population-level prevention

- PrEP associated with decline in population-level HIV incidence in 4 high-resource settings: MSM in UK, Netherlands, Australia, US.
 - 95% viral suppression in PWH,
 - **66% of PrEP-indicated people with PrEP coverage**
- Intervention programs in LMIC have not shown community-wide incidence changes
 - S African cis-women: **sustained** PrEP from sexual debut through childbearing years
 - Oral PrEP uptake currently insufficient
 - High requirements for implementation of LEN as PrEP in high incidence settings
- **50% HIV diagnoses in those who do not meet PrEP criteria**

Beyrer et al., J Law Med Ethics, 2022; Beyrer, et al., Lancet HIV 2024

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Why pursue HIV cure?

- ART is a modern miracle...with early diagnosis and continued treatment, PWH live long, healthy lives.
- But,
 - Stigma, Cost, Insecure access, Toxicity, Required adherence
 - Community of PWH strongly support
- Cure is scientific priority**
 - Therapeutic vaccine is key component of HIV cure

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Preventive HIV Vaccine & HIV Cure

- Goal: “One-shot” vaccine or cure intervention that does not require continued access to PrEP or ART
 - Lessons dependence on uncertain HIV infrastructure, healthcare systems, political will.

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Vaccine Strategies – new approaches

Now:

- AMP: Proof-of-concept for bnAb
- Phase 1: Germline-targeting immunogens can prime B cell lineages

Past: Strain-specific neutralizing or non-neutralizing Antibodies

- RV144 – 33% efficacy in low-incidence population
- All others – no efficacy

Antibody vaccine

Now:

- In trials: networked or mosaic epitopes to focus responses
- Combination immunotherapy

Past: CD8 T cells to whole proteins

- STEP – possible enhancement of acquisition
- All others – no efficacy

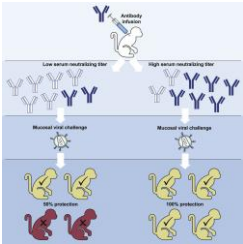
Cellular vaccine

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Antibody vaccine

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HIV Prevention: NHP data



- NHP challenge studies consistently show bnAbs confer protection vs. SHIV challenge
- Meta-analysis of single bnAbs vs. mucosal SHIV challenge in 274 RM, 16 bnAbs, 18 studies
- Serum-Neutralizing Antibody Titer (ID50) correlates with protection
 - Higher titers required for efficacious protection

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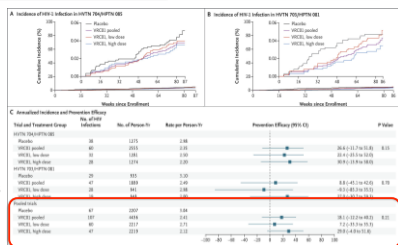
The IAS–USA Annual Virtual Course Update: Emerging Challenges in HIV Medicine, December 4, 2025

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HIV Prevention: AMP Trial

- 4623 participants
 - MSM/TGW in Americas; Women in Africa
- VRC01 at 10 & 30 mg/kg, vs. placebo; monthly X 20 doses

- No significant overall protection:
 - 2.35 (VRC01) vs. 2.98 (placebo) annual incidence
 - Prevention efficacy: 26.6 (95% CI: -11.7 to 51.8), $p=0.15$

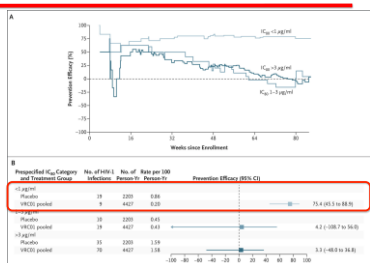


Corey et al. NEJM 2021

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HIV Prevention: AMP Trial

- Prespecified secondary analyses of inferred sensitive viruses ($IC_{50} < 1 \mu\text{g/mL}$):
 - 0.2 (VRC01) vs. 0.86 (placebo) annual incidence
 - 75.4% estimated prevention efficacy, (95% CI, 45.5 to 88.9)
- Provides optimism that more broad, potent bnAbs could provide strong protective efficacy vs. "sensitive" viruses



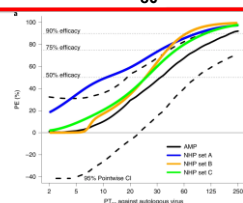
Corey et al. NEJM 2021

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Correlates of protection: PT_{80}

Calculation of predicted serum IC_{50} titer (PT_{80}) for a bnAb against a reference virus:

$$\text{Serum bnAb concentration} \times \left(\frac{\text{Clinical lot bnAb potency against a reference virus}}{\text{Clinical lot bnAb } IC_{50} \text{ against a reference virus}} \right) = PT_{80}$$

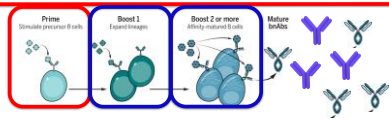


- PT_{80} : predicted serum ID80 titer
- 90% Preventive Efficacy required $PT_{80} \sim 200$ (AMP); ~ 100 (NHP)
- Goalpost for passive or active bnAb induction

Gilbert Nat Med 2022

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bnAb vaccines: germline-targeting immunogens



B cell lineage - germline targeting immunogen design

- **Priming immunogens:** Env trimers or engineered proteins to bind naïve B cell lineages
- **Boosting/Shepherding immunogens:** coax B cell lineages towards producing mature bnAbs
- **Multiple epitopes in development:** CD4bs, V2, V3, MPER, Fusion, Interface
- **Goal:** Induction of multiple, polyclonal bnAb lineages

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CH505: Virus - Ab co-evolution → CH103 bnAb



- Acute HIV cohort participant CH505: broadly neutralizing plasma developed over years of viremia
- Monoclonal bnAbs (CH103) identified, characterized
- Virus and antibody repertoire co-evolution characterized: TF Env bound to bnAb UCA B cell
- **Provides roadmap for vaccination**

Liao et al., Nature 2013

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Paired Prevention & Therapy: CH505 Trimer Vaccine HVTN300 & A5422



- **CH505 Trimer Immunogen:** binds UCA of bnAb lineages and induces nAb responses preclinically
- Parallel prevention & therapy studies
 - Same schedule, overlapping objectives and endpoint assessments
 - Can we prime B-cell precursors?
 - And, can we expand anAb responses?

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HVTN300: induction of bnAb-lineage nAbs



Vaccine- induced, CD4bs, CDRH3-
binder bnAb precursor bound to Env

Desired mAbs found in 7/11 of vaccinees post-immunization.

I) Priming of targeted lineages
II) Induction of precursor nAb responses



Rob Parks, Barton Haynes, Elize Domin, Amanda Eaton, David Montefiori, Ruth Parsons, Priyamvada Acharya

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GT1.1 – induction of VRC01-class bnAbs



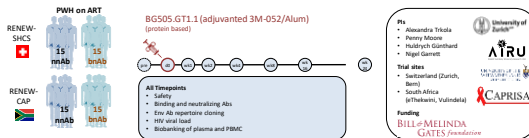
- **GT1.1 - immunogen engineered from BG505 to prime CD4bs & V2 bnAb lineages**
- Phase 1 trial safe.
- B cell receptor sequencing and mAb analyses
 - CD4bs-specific memory B cells were of the VRC01-class.
 - mAbs were similar to VRC01-class bnAbs

Caniels, et al., Science 2025

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RENEW-SHCS and RENEW-CAP: Vaccinating PWH



- Two linked phase 1 studies of BG505.GT1.1 + adjuvants
 - PWH in Europe & S Africa who did or did not make bnAbs prior to ART
 - Test capacity to **prime new responses**, **restimulate prior Ab responses**
 - **Pre-clinical work to enhance nAb responses w individualized vaccines**

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Cellular vaccines

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Cellular Vaccines

More than two decades of largely failed approaches

Trial	Regimen	Comment	Author/Paper
ACTG 5088	ALVAC (vCP1452)	Intermittent interruptions but not associated with reduced VL	Kilmon, JID 2008
ACTG 5024	ALVAC (vCP1452) + S-1	0.5 log VL reduction during ATI	Jobson, JID 2006
ACTG 5087	AIS	0.24 log10	Schackel, JID 2010
MANDON-42	ALVAC-HIV	No VL effect; activated CD4 cells may have induced early failure	Papagno, AIDS 2011
Bimor	p24 peptide ribosome (Viro-42)	ATI: no VL effect at primary endpoint, mild benefit at later time points	Potter, Lancet HIV 2014
IRAMING-02	DNA prime/MVA boost	No effect (HIV DNA)	Achilles, Lancet HIV 2015
GeneCore	Replication-defective HIV with RV29 fusion protein (RV40)	Reduced VL, set-point (compared to historical data)	Tang, Vaccine 2016
GeneCore	DNA prime/MVA boost (vira-like particle)	No apparent effect during ATI (unpublished)	Thompson, PLoS One 2016
ACTG 5281	GraphPR, gp120/RTA55env and IL-12 peptide (ProTeVac)	Mildest CD4 effects, no CD8 effects, low dose IL-12 better than high dose IL-12	Jacobson, AIDS 2016

Cure: ChAdA63 prime and MVA boost encoding conserved HIV regions:

- Aelx 002, Aelx 003: no impact on time-to-rebound, rise in virus load, peak virus load or set-point
- River: no impact on time-to-rebound, rise in virus load, peak virus load, set-point or reservoir size

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Conserved Multi-Epitope Vaccines

- Immunogens based on **conserved regions** containing a wide range of **critical T cell epitopes**
- focuses immune response on protective epitopes
- broad coverage of global diversity in HIV strains and HLA alleles

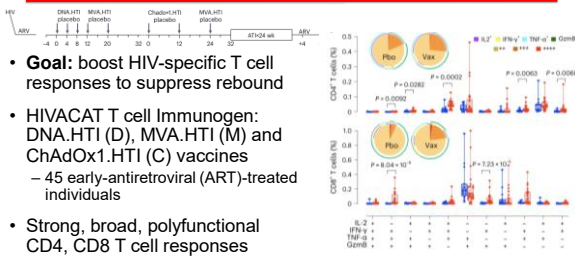
The diagram illustrates the concept of conserved multi-epitope vaccines for HIV. It shows the HIV-1 genome with conserved regions (Gag, Pol, Tat, Rev, Env) and the resulting proteins. A vaccine construct is shown containing conserved regions and T cell epitopes. The vaccine is administered to a human, leading to the activation of CD4+ T cells and CD8+ T cells. The CD4+ T cells produce cytokines (IL-2, IL-4, IL-5, IL-6, IL-10, IL-13) and proliferate. The CD8+ T cells produce cytokines (IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13) and kill target cells. The diagram also shows the HIV-1 infection cycle and the role of the vaccine in preventing infection.

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Akbari, et al., B J Inf Dis, 2023

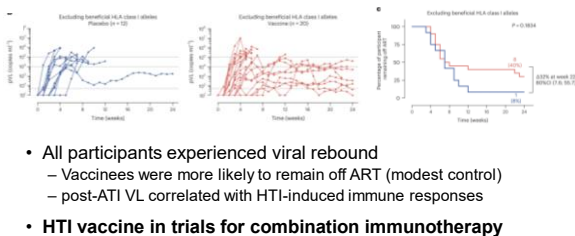
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AELIX-002: HTI vaccine trial



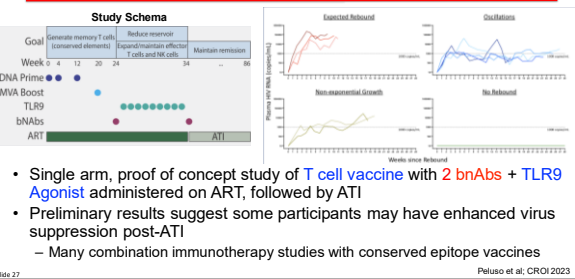
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AELIX-002: HTI vaccine trial



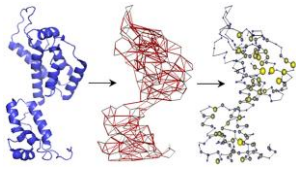
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UCSF/amfAR study — preliminary results



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Networked Epitope Vaccines



- IAVI C114 - phase 1 trial in prevention and therapy:
 - Gorilla Adenovirus Vectored HIV Networked Epitopes Vaccine (GRAdHIVNE1)

Protein structure constraint revealed conserved epitopes

- Networked epitopes (those with greater connectivity) were least able to tolerate mutations
- HIV control associated with CD8 T cell responses against highly networked epitopes

Slide 28 Gaiha et al., Science 2019

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Summary – promise, but persistence required

- **Ending the HIV epidemic may require efficacious vaccine**
 - Goal: limited-dosed, 70% efficacious vaccine for general population
 - PrEP implementation is promising but challenging
 - unable to address ~50% acquisitions outside PrEP-indicated, dependent on ongoing support
- **Antibody vaccines**
 - Proof-of-concept from NHP and AMP trials; nAb correlate for control
 - Germline targeting immunogens demonstrate priming for multiple epitopes, early nAb responses. Searching for boost.
 - Trials in PWH/PWoH
- **Cellular vaccines**
 - Cellular correlates for control
 - Conserved/networked epitopes are in trials for PWH/PWoH, combination immunotherapy

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Q and A Session



IAS-USA

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