Lessons Learned from HIV Vaccine Efficacy Trials

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Research reported in this publication was supported by the National Institute of Allergy And Infectious Diseases of the National Institutes of Health under Award Number UM1A1068614. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
What immune responses are required for an effective HIV vaccine?

Potent NAb responses

Broadly reactive NAbs

Immune responses that prevent viral escape

Memory T cells responses that suppress viral replication

Persistent immune response

The rapid integration of HIV after acquisition and the inability for early therapy to interrupt this integration means the goal of an HIV vaccine must be to prevent acquisition or eradicate recent infection.

It takes 50 to 100 times more neutralizing antibody to inhibit HIV than it does SARS-CoV-2.
Have we partially answered two critically important questions that informs HIV vaccine design?

• The role of non-neutralizing antibodies in protection against HIV, in particular the role of non-neutralizing anti-Env V2 Antibodies

versus

• The role of neutralizing antibodies in protection against HIV
HIV Vaccine Efficacy Studies: 1984-2023

1984-2000
Optimism that recombinant monomeric envelope protein vaccines might work

2000-2010
T-cell based vaccines/recombinant proteins: STEP, Phambili HVTN 505; RV144, partial success: correlated to non neutralizing antibodies to V1V2 loop

2010-2015
HIV bNAb isolated and shown to protect in NHP; Ad26 Mosaic vaccine similar protection in NHP

2015-2023
Non-neutralizing antibody approach did not lead to VE, but some COP identified
Passive infusion of a BNAB provides evidence of protection in vaccine sensitive viruses
Prime-Boost Vector based vaccine approaches

- **RV144/Thai Trial**  
  (ALVAC+AIDSVAX B/E)

- **HVTN 505**  
  (VRC DNA/rAd5)

- **HVTN 702/Uhambo**  
  (ALVAC + bivalent subtype C gp120/ MF59 boost)

- **HVTN 705/Imbokodo**  
  (4 Mosaic Ad26 Constructs + gp140 Clade C Boost)

- **HVTN 706/Mosaico**  
  (4 Mosaic Ad26 Constructs + bivalent gp140 (Clade C + Mosaic)
What did these trials demonstrate in the COP analyses?

• Several functional antibody assays such as antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC) have been correlated with reduced acquisition of infection in RV144.

• In addition to humoral immune responses, certain cellular immune responses like Env-specific polyfunctional CD4 T cell signatures identified in the RV144 study and in sub-analyses in HVTN 702 were correlated with decreased HIV risk.

• HVTN 505 identified a strong correlation between HIV-1 acquisition and Env-specific CD8+ T cell responses and IgG3 Env breadth
Take home message for non-neutralizing HIV Vaccine studies

- Results from 4 different vaccine efficacy trials in different populations with different regimens are consistent with a role for V1V2 antibodies. A role for V1V2 IgG and/or V1V2 IgG3 in partially protecting against HIV-1 acquisition is consistent with results from RV144, HVTN 505, Uhambo (HVTN 702), and Imbokodo (HVTN 705).

- Three vaccine efficacy trials with evidence of an HIV-1 IgG3 immune correlate of decreased risk. (RV144, HVTN 505, Imbokodo/HVTN 705.)

- Two vaccine efficacy trials with evidence of serum/plasma Env IgA negatively modulated antibody Fc effector function (RV144, HVTN 505) (not fully evaluated in Uhambo/HVTN 702; ongoing analysis for serum IgA Env and pilot testing for mucosal IgA in Imbokodo/HVTN 705 ongoing).
Will neutralizing antibodies be the game-changer?

• Is immuno-prophylaxis with mono-clonal antibodies the vaccine world’s long-acting PrEP?

• Can we actively vaccinate to induce broadly neutralizing antibodies?

Bonsignori et al, Immun Rev 2017
AMP Studies

Phase 2b Proof-of-Concept Trials (Harmonized Protocols) Designed to Test the Efficacy of VRC01 Antibody (targeting CD4 binding site) to Prevent HIV Acquisition

AMP = Antibody Mediated Prevention

HVTN 704/HPTN 085
(MSM and TG in the Americas & Europe)

HVTN 703/HPTN 081
(Women in sub-Saharan Africa)
In Vitro Sensitivity to VRC01 Predicts Efficacy

- Consistent evidence that VRC01 conferred prevention efficacy

  Against viruses measured to be neutralization sensitive

  Not against viruses measured to be neutralization resistant

- Monotone pattern with VRC01 protection wearing off with IC50, IC80, reciprocal of instantaneous inhibitory potential (IIP)

- Thus, the TZM-bl target cell assay discriminates prevention efficacy
Estimated PE Over Time by IC80* (Pooled Trials)

- Estimated PE against the most sensitive viruses (IC80 < 1 μg/ml) is 60-80% after two doses and constant thereafter.
- Estimated PE against more resistant viruses is near zero by 80 weeks.

*IC80 of the most resistant variant in a case’s set of virus isolates with IC80 measured.
Take home message role of neutralizing in HIV protection

- AMP demonstrated that broadly neutralizing antibodies are capable of preventing HIV acquisition and provide the future roadmap for vaccine development.
- The target neutralization titer (>1 to 200) in the TZM-bl assay maybe a useful correlate in future trials.
- AMP also demonstrated that we need to make bNAbs to more than one site
- Vaccine approaches need to shift to eliciting antibodies to known conformational structures that elicit such antibodies.
Epitope Specificity: Broadly Neutralizing mAbs in Development

Viral membrane

CD4 Supersite

V1V2 Glycan

N332 Glycan-V3 Supersite

Membrane-proximal external region (MPER)

35022
PGT151
8ANC195

PG9, PG16
PGT141-145
CAP256-VRC26
PGDM1400
CH01-04

PGT121
PGT128
10-1074
DH270

Image by Stewart-Jones, Doria-Rose & Stuckey
Adapted from Stewart-Jones et al, Cell 2016 & Pancera et al, Nature 2014

Thanks to the NIAID Vaccine Research Center

Blue circles = mAb in Network Program
Multiple bnAbs Targeting Different Sites on HIV-1 Trimer Are Needed for Achieving High Prevention Efficacy

**Figure Source:** VRC
Pathway to an HIV-1 Vaccine

- Reproducible evidence from HIV-1 efficacy trials that cellular and humoral responses work together for decreasing HIV-1 risk.
- Difference from COVID-19: Neutralizing antibodies to key targets on the virus easily elicited by COVID infection and vaccination. However, bnAb less commonly elicited in infection and not yet elicited by vaccination.
Larry will outline the HVTN approach toward a HIV vaccine regimen that elicits Broadly Neutralizing Antibodies

- Experimental medicine will set the pace to evaluate the concept of bNAb-vaccine design
- the use new technology such as mRNA may allow us to rapidly iterate
- The need for speed is needed to advance concepts
Funding Acknowledgements

Funders & Other Collaborators

• Bill & Melinda Gates Foundation (BMGF)
• Janssen Vaccines & Prevention, B.V.
• NIAID/DAIDS
• Ragon Institute of MIT, MGH and Harvard
• US Army Medical Materiel Development Activity (USAMMDA)
• SAMRC & INSERM
• EDTCP
Acknowledgements

HVTN Executive Management Team:

- Larry Corey
- Georgia Tomaras
- Dan Barouch
- Julie McElrath
- Peter Gilbert
- Susan Buchbinder
- Hyman Scott
- Jorge Sanchez
- Scott Hammer (in memoriam)
- Jim Kublin
- Troy Martin
- Yunda Huang
- Holly Janes

Everyone involved in the HVTN, our colleagues at DAIDS, all the site staff, our Global CABs, and all the participants in our clinical trials programs.