HIV Vaccine Development: Current Approaches

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Biomedical Advanced Research and Development Authority (BARDA) | Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | Broadway Cares/Equity Fights AIDS | Cancer Research UK | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada)

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As of July 2023
Outline

The Burden of Disease

Challenges in HIV Vaccine Development

Strategies for Vaccine Development
HIV; Burden of Disease
HIV remains a major health issue globally
As much as ever, the world needs an efficacious HIV vaccine

**Global number of people living with HIV in 2022**
39.0 million

**Number of people newly infected worldwide - 2022**
1.3 million

**Number of AIDS-related deaths in 2022**
680 000

**African Region remains most severely affected**
60% of global new infections
Women and girls accounted for 46% of all new infections in 2022.
130 000 new infections in children in 2022.

Unrelenting HIV incidence and unmet goals reinforce the need for new prevention tools

We did not come close to meeting the 2020 target of 500,000 new HIV infections

The development of new prevention tools that provide longer lasting protection, including efficacious vaccines, and long-acting ARVs and broadly neutralizing antibodies for PrEP, will be essential

Risks to future progress in decreasing incident infection rates:

- Demographic changes ("youth bulge")
- Increasing number of people in need of treatment
- Risk of drug resistance
- Donor fatigue and competing global priorities

An effective HIV vaccine would be transformative

An HIV vaccine could:

• Provide long-lasting protection with a limited number of doses within a discrete timeframe before window of HIV infection risk.

• Be distributed widely and confidentially (and not apparent to partners, parents and peers).

• Overcome challenges of behavior change and adherence.

• Protect all people at risk of HIV infection, including those most vulnerable to HIV who may be difficult to reach with other prevention interventions.
Challenges in HIV Vaccine Development
Traditional vaccine approaches have failed for HIV

- HIV is hyper variable (the result of active, ongoing replication and “error-prone” replication processes).
- Once HIV infects, it maintains persistent infection for life. There are no examples of natural clearance of infection and no “natural immunity”.
- HIV evades, avoids or escapes from antiviral antibodies and T cell responses
- HIV attacks and directly infects key immune effector cells (CD4 T cells and some “antigen presenting” cells).
- Common animal models have uncertain value in reliably predicting efficacy of vaccine candidates in humans.
HIV Vaccine Strategies - Picture of Success?
Nine Phase II/III clinical trials have been completed since the discovery of HIV/AIDS. These vaccine candidates were designed using an empirical approach where different parts of the virus were formulated to stimulate either B- or T-cell response following vaccination.
An effective HIV Vaccine will likely need to stimulate **Neutralizing Antibodies** and **Cell Mediated Immunity**
IAVI is prioritizing a rational approach to HIV vaccine design

**EMPIRICAL APPROACH**

Test different vaccine candidates; if one demonstrates protection efficacy, then identify correlates of protection.

**RATIONAL DESIGN APPROACH**

Identify a correlate of protection, then create a strategy to elicit that correlate of protection by rational design.
Vaccines to Induce bnAbs against HIV
Major approaches to bnAb-based HIV vaccine design to be tested in humans in the coming years

**Lineage-based vaccine design** – sequence of immunogens derives from sequence of Env variants in a longitudinal case study of bnAb development from natural infection. Priming immunogen selected to bind UCA for one lineage.

*Trials: prime/boost for CH103, CH235, DH270 lineages from Haynes and colleagues*

**Germline-targeting vaccine design** – priming immunogen engineered to broadly activate diverse precursors within a bnAb class (spanning many lineages); boost immunogens are successively more native-like.

*Trials: priming VRC01-class responses, three different immunogens from Schief, Sanders, Stamatatos and their colleagues; priming BG18-class responses by Schief and colleagues*

**Immunofocusing vaccine design** – immunogen sequence designed to focus responses to one or more particular epitopes, but “germline agnostic”.

*Trials: Fusion peptide vaccine by Kwong, Mascola and colleagues*
We’ve learned from PLWH.

- bnAbs neutralize diverse isolates, some up to 99% of all isolates
- bnAbs can provide sterilizing immunity in animal models
- bnAbs can protect in humans
- If a vaccine can elicit bnAbs, it could prevent HIV infection
A sequence of different vaccines may be needed.
Vaccines to Induce Cell Mediated Responses
Cell-Mediated Immunity (CMI) in HIV Infection

Viral load in natural infection

Hypothetical viral load after vaccination

Transmission “threshold”
CMI Approaches for Coping with viral diversity

The mosaic vaccines: computational design of small sets of artificial viral proteins to provide optimal coverage of the diverse forms of HIV.

Conserved region vaccines: focuses on conserved regions with minimal diversity across all forms of HIV.

Networked epitope vaccines: focus on highly networked mutation-constrained regions in the HIV proteome.
Six highly functionally conserved regions of the HIV-1 proteome

Computed bi-valent mosaic

Mosaic 1
1 2 3 4 5 6
Mosaic 2
1 2 3 4 5 6

Reshuffled regions for synthetic immunogen genes

tHIVconsv1
1 2 3 4 5 6

tHIVconsv2
2 6 1 3 5

tHIVconsv3
3 6 2 5 1 4

tHIVconsv4
4 1 5 2 6 3

tHIVconsv5
5 3 1 1 6 2

tHIVconsv62
6 5 1 3 2 1

Courtesy of Tom Hanke – University of Oxford
HIV continues to cause a high burden of disease around the world.

Demographic changes coupled with high incidence in specific groups could reverse gains in epidemic control.

A vaccine used together with other available interventions could end the pandemic.

Traditional vaccine development strategies have failed for HIV.

A successful strategy will likely require eliciting bnAb and CMI responses and there are several promising strategies currently in development.
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