HIV Vaccines: The Basics

May 2018
What is a vaccine?
How would an HIV vaccine work?
Where are we in the search?
What is needed now?
What is a Vaccine?

- A substance that teaches the body how to recognize and protect itself against a disease-causing agent, e.g. a virus or bacterium.
- No effective HIV vaccine available today.
- HIV vaccines cannot cause HIV.
- Most licensed vaccines against other diseases are 70–99% effective.
Why a Vaccine Cannot Cause HIV

- The whole virus – killed or weakened – is not used in experimental HIV vaccines
- Vaccine components resemble the virus and cause immune responses, but they are NOT the actual virus
- Only safe, *synthetic* pieces of the HIV virus are used in vaccine research
Why the Interest in Vaccines?

**EPIDEMICS SUCCESSFULLY COMBATED WITH VACCINES (CASES 1980 – 2016)**

- **1980**
  - Measles: 4,000,000

- **2016**
  - Measles: 183,796

- **1980**
  - Polio: 400,000

- **2016**
  - Polio: 37

*Data from the World Health Organization, estimated cases*
**TIME TO DEVELOP A VACCINE**

Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine

<table>
<thead>
<tr>
<th>Disease</th>
<th>Year of Discovery</th>
<th>Year of Development</th>
<th>Time to Develop in Years</th>
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<tr>
<td>Typhoid</td>
<td>1884</td>
<td>1989</td>
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<td>Polio</td>
<td>1908</td>
<td>1955</td>
<td>47</td>
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<tr>
<td>Pertussis</td>
<td>1906</td>
<td>1948</td>
<td>42</td>
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<td>Rotavirus</td>
<td>1973</td>
<td>2006</td>
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<td>HPV</td>
<td>1984</td>
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<td>Measles</td>
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<tr>
<td>HIV</td>
<td>1983</td>
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Source: AVAC AIDS Vaccine Handbook
Vaccines are Essential

- To end the epidemic, an HIV vaccine is needed
- Proven prevention options have slowed HIV’s spread – but thousands of people continue to get infected daily
- There is a need for a range of HIV prevention methods; there is no silver bullet
- Vaccines are one of the world’s most effective public health tools
- Cost-effective - single or several doses can provide protection for years
Types of HIV Vaccines

- **Preventive vaccines**
  - Designed for people who are **NOT** infected with HIV
  - If effective, would reduce risk of infection
  - May also reduce viral load set point after infection

- **Therapeutic vaccines**
  - Designed for people who **ARE** living with HIV
  - If effective, would train the body’s immune system to help control HIV in the body
How Do Preventive Vaccines Work?

By teaching the body to recognize and fight a pathogen

- Vaccine carries something that ‘looks and feels’ like the pathogen
- The body reacts by activating the immune system and creating antibodies or killer cells and a memory response
- Upon exposure to the actual pathogen, antibodies and killer cells are waiting to respond and attack

Note: This is general definition, not specific to HIV vaccines
A preventive vaccine would teach the body to recognize and fight HIV, should it be exposed

- Vaccine would carry a component that ‘looks and feels’ like HIV, but is **not HIV and cannot cause HIV infection**
- Vaccine components are copied pieces of the virus known to generate an immune response
- Body would react by creating antibodies and/or killer cells and a memory response
- Upon exposure to HIV, antibodies and killer cells would be waiting to prevent and/or control infection
Preventive HIV vaccines are designed to elicit two arms of the immune system – **humoral** and cellular

(1) **Humoral immunity**

- Primary action of humoral arm is creating antibodies: Y-shaped proteins produced by B cells in response to a pathogen to prevent infection.
- Antibodies have multiple functions: attaching to and helping destroy pathogens, keeping the pathogens from entering host cells (neutralization), and calling other cells into action (sensitization).
Preventive HIV vaccines are designed to elicit two arms of the immune system – humoral and **cellular**

(2) **Cellular immunity**

- Two types of T cells:
  - Cytotoxic T lymphocytes (CTL) and T-helper cells
- T cells recognize HIV-infected cells, coordinate the immune response (helper cells) and kill the infected cells (CTLs)
Preventing vs. Controlling Infection

HIV PREVENT ESTABLISHED INFECTION?

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A. Lower Initial Peak of Viremia
B. Lower Set Point
C. Stop Progression

Solid line – viral load in natural HIV infection
Dotted line – potential changes due to vaccination

Courtesy of HIV Vaccine Trials Network
How Are Vaccines Typically Made?

- **Live attenuated vaccines** (examples: Sabin polio vaccine, measles, mumps, and rubella)
- **Whole killed virus vaccines** (example: influenza, rabies and Salk polio vaccine)

*Note: This is general vaccine development, not specific to HIV vaccines.*
Developing an HIV Vaccine is Difficult

- Numerous modes of transmission
- HIV kills the very immune cells the body uses to defend against disease
- HIV makes many copies of itself and mutates, making itself unrecognizable to the immune system
- Mutation leads to different subtypes of the virus throughout the world
- Nobody has ever eliminated HIV with their own immune system
Examples of recombinant vaccines:
- DNA vaccines
- Vector vaccines (viral and bacterial)
- Subunit vaccines

Do not contain HIV – only synthetic copies of fragments of HIV that will create an immune response but cannot cause HIV infection
<table>
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<tr>
<th>YEAR</th>
<th>TRIAL NAME/PRODUCT/CLADE</th>
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<td>VAX003 AIDSVAX B/B</td>
<td>Canada, Netherlands, Puerto Rico, US</td>
<td>5,417</td>
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<td>2003</td>
<td>VAX004 AIDSVAX B/E</td>
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<td>2007</td>
<td>STEP MRK-Ad5 B</td>
<td>Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US</td>
<td>3,000</td>
<td>Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men.</td>
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<td>Phambili MRK-Ad5 B</td>
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<td>Immunizations halted based on STEP trial result.</td>
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<td>2009</td>
<td>Thai Prime-Boost/RV 144 ALVAC-HIV (vCP1521) and AIDSVAX B/E</td>
<td>Thailand</td>
<td>16,402</td>
<td>Modest efficacy (31.2%)</td>
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<td>2013</td>
<td>HVTN 505 DNA and Ad5 A/B/C</td>
<td>US</td>
<td>2,500</td>
<td>Immunizations halted early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load among vaccine recipients who became infected with HIV; follow-up continues.</td>
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Efficacy Trials Pipeline

Available to download at www.avac.org/infographics.
In 2009 a trial in Thailand (‘RV144’) showed that a vaccine can reduce HIV risk
- Moderately effective – 31% protection
- Not good enough to license – what’s next?

The Pox-Protein Public Private Partnership (P5) formed to determine and implement next steps

Next steps include:
- Several small-scale clinical trials in southern Africa, started January 2015 and ongoing
- A large-scale trial (HVTN 702, or the Uhambo Study) launched in October 2016, using a similar regimen to RV144, but made for South Africa; the trial is ongoing
A mosaic vaccine is designed to help the body recognize many clades or strains of HIV

Several mosaic candidates have been developed

Phase I/II clinical trials are ongoing

HPX2008/HVTN 705 (The Imbokodo Study): Phase IIb proof of concept efficacy trial testing a mosaic candidate, delivered using an adenovirus type 26 vector, began in November 2017
Direct transfer of antibodies (passive immunization) being tested for prevention, treatment, and as part of cure

- Multiple bNAb tested in early clinical trials: www.bnaber.org
- Many show safety, tolerability, viral reduction among HIV-positive participants
- First proof-of-concept studies of bNAb VRC01 for prevention, the AMP studies, initiated in 2016: www.ampstudy.org & www.ampstudy.org.za
- Researchers identifying and developing more powerful antibodies, and easier ways of delivering them

Early phase studies are also testing combination bNAb approaches
Antibody Research

- Numerous broadly neutralizing antibodies (bNAb) discovered since 2009
- Five main targets of bNAb on the virus envelope
- Studies have shown bNAb can neutralize many different types of HIV
- bNAb research may provide insights into vaccine development and/or could be the basis for a prevention strategy on its own
### HIV-SPECIFIC NEUTRALIZING ANTIBODIES: Targets and research status

#### Structure of HIV

<table>
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<tr>
<th>HIV envelope target</th>
<th>Antibody</th>
<th>Pre-clinical</th>
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Advocates’ Checklist

- Emphasize that sustained control and the eventual end of the HIV epidemic will depend on methods that provide long-lasting protection, including a vaccine
- Promote continued investment to sustain momentum in HIV vaccine research
- Ensure vaccine trials are well-conducted, conform to Good Participatory Practices, and react quickly to the changing realities of the HIV response
- Demand that stakeholders have a role in planning with researchers for outcomes and next steps from ongoing vaccine trials
- Support global partnerships to ensure researchers work together to manage the pipeline of vaccine and antibody candidates
Key Resources

- AVAC: [www.avac.org/vaccines](http://www.avac.org/vaccines)
- Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID)
  - At Duke: [www.chavi-id-duke.org](http://www.chavi-id-duke.org)
  - At Scripps: [www.cavi-id.org](http://www.cavi-id.org)
- Collaboration for AIDS Vaccine Discovery: [www.cavd.org](http://www.cavd.org)
- Global HIV Vaccine Enterprise: [www.vaccineenterprise.org](http://www.vaccineenterprise.org)
- HIV Px R&D Database (PxRD): [www.data.avac.org](http://www.data.avac.org)
- HIV Vaccine Trials Network (HVTN): [www.hvtn.org](http://www.hvtn.org)
- International AIDS Vaccine Initiative (IAVI): [www.iavi.org](http://www.iavi.org)
- NIAID: [www.niaid.nih.gov/topics/hivaid/research/vaccines/Pages/default.aspx](http://www.niaid.nih.gov/topics/hivaid/research/vaccines/Pages/default.aspx)
- Pox-Protein Public-Private Partnership (P5): [www.hivresearch.org/media/pnc/9/media.749.pdf](http://www.hivresearch.org/media/pnc/9/media.749.pdf)
Questions, comments and requests for materials should be sent to avac@avac.org

Information about HIV prevention generally at www.avac.org and vaccines specifically at www.avac.org/prevention-option/hiv-vaccine

For the latest news and updates, sign up for our Advocates’ Network mailing list at www.avac.org/signup or follow us on Facebook at www.facebook.com/hivpxxresearch and on Twitter at www.twitter.com/hivpxxresearch