AVAC

Global Advocacy for HIV Prevention

HIV Vaccines: The Basics

May 2018

Presentation Overview

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

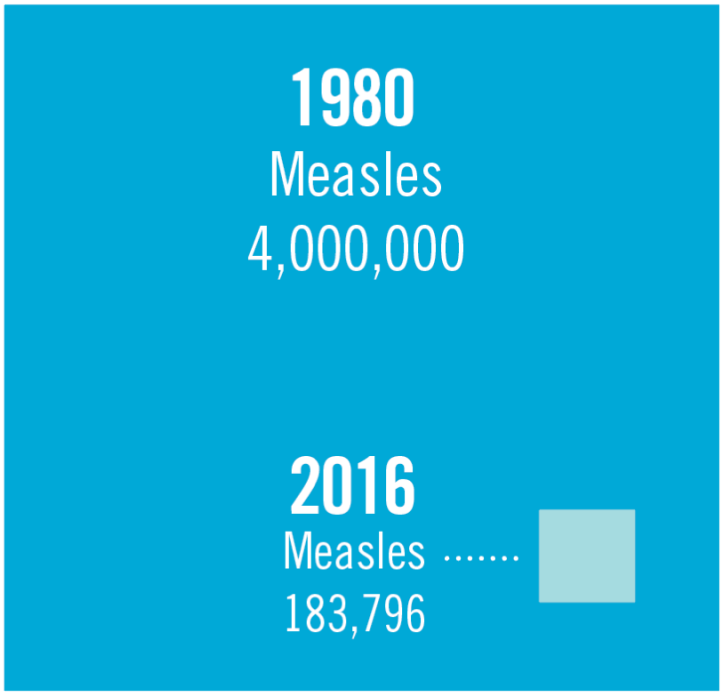
What is a Vaccine?

- 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

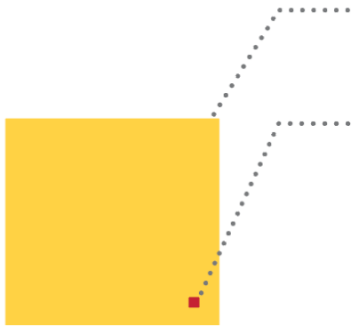
Why a Vaccine Cannot Cause HIV

- 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?

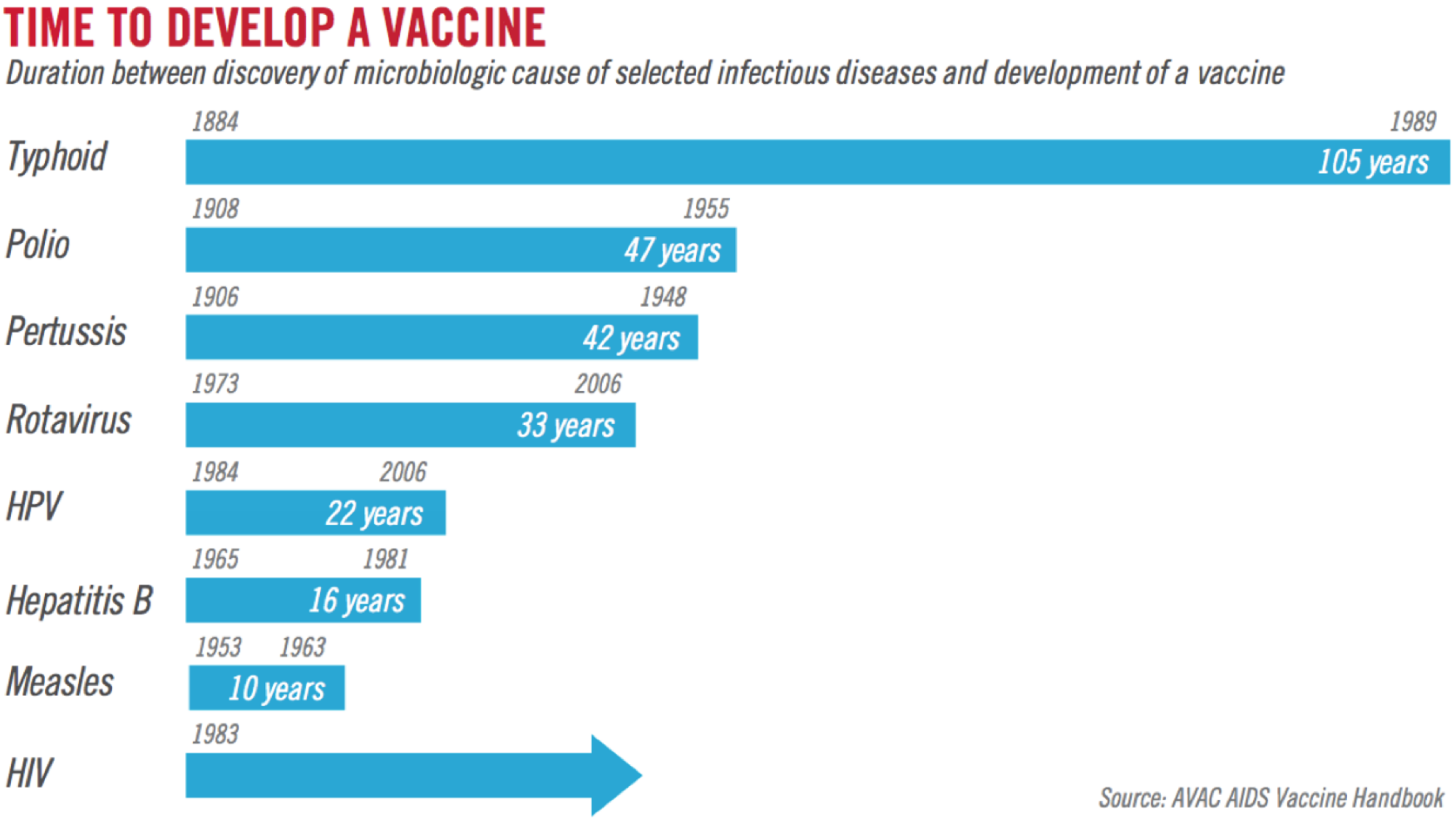


EPIDEMICS SUCCESSFULLY COMBATED WITH VACCINES (CASES 1980 – 2016)



Data from the World Health Organization, estimated cases

Vaccine Research in History



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

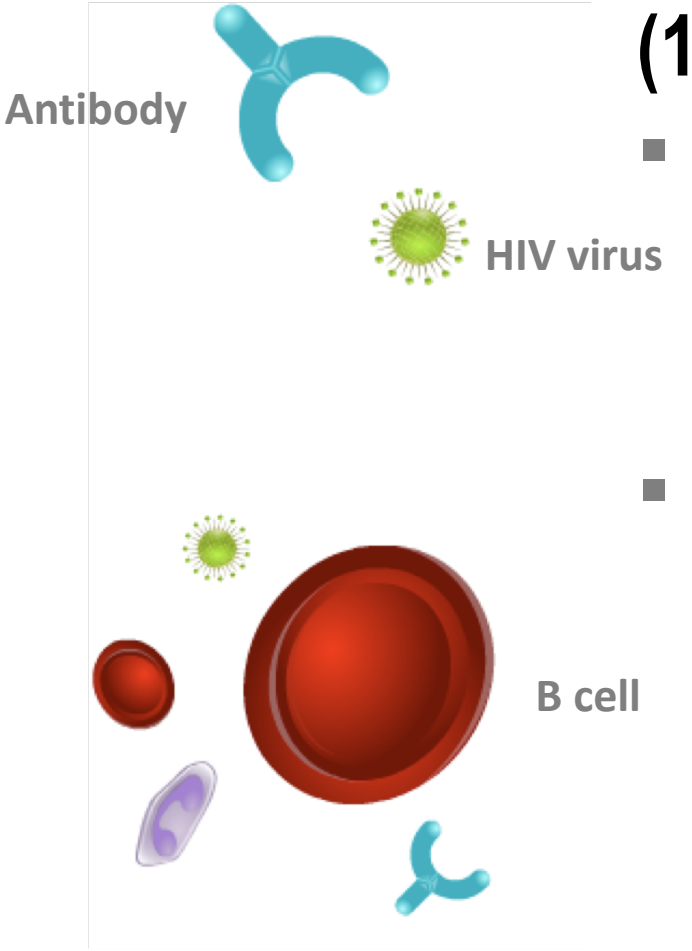
How Might an HIV Vaccine Work?

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

Immune Responses

Preventive HIV vaccines are designed to elicit two arms of the immune system – **humoral** and cellular



(1) Humoral immunity

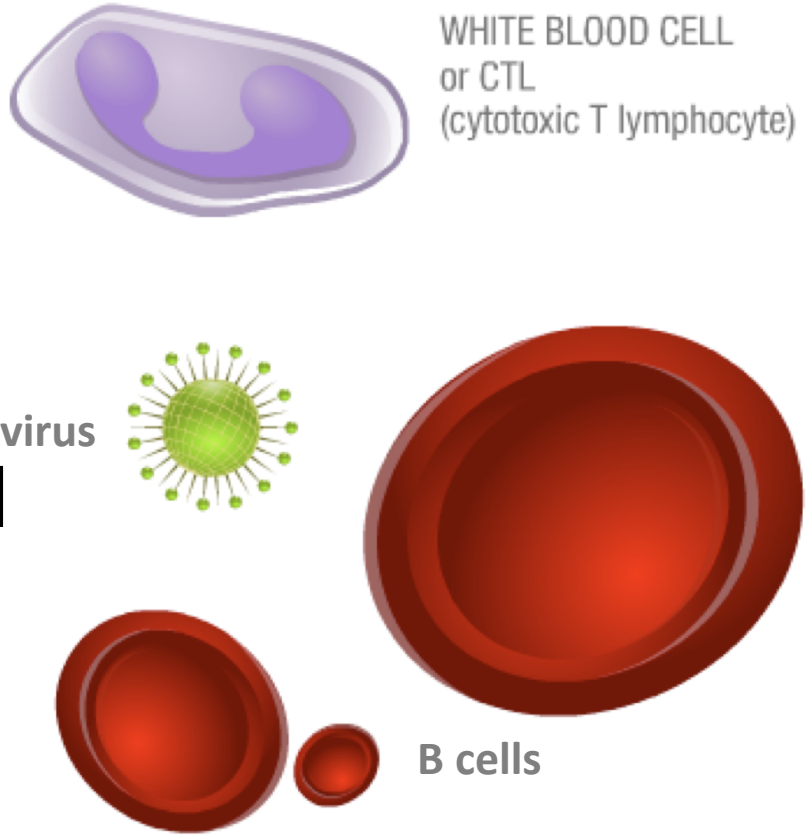
- Primary action of humoral arm is creating antibodies: Y-shaped proteins produced by B cells in response to a pathogen to prevent infection
- Antibodies have multiple functions: attaching to and helping destroy pathogens, keeping the pathogens from entering host cells (neutralization), and calling other cells into action (sensitization).

Immune Responses

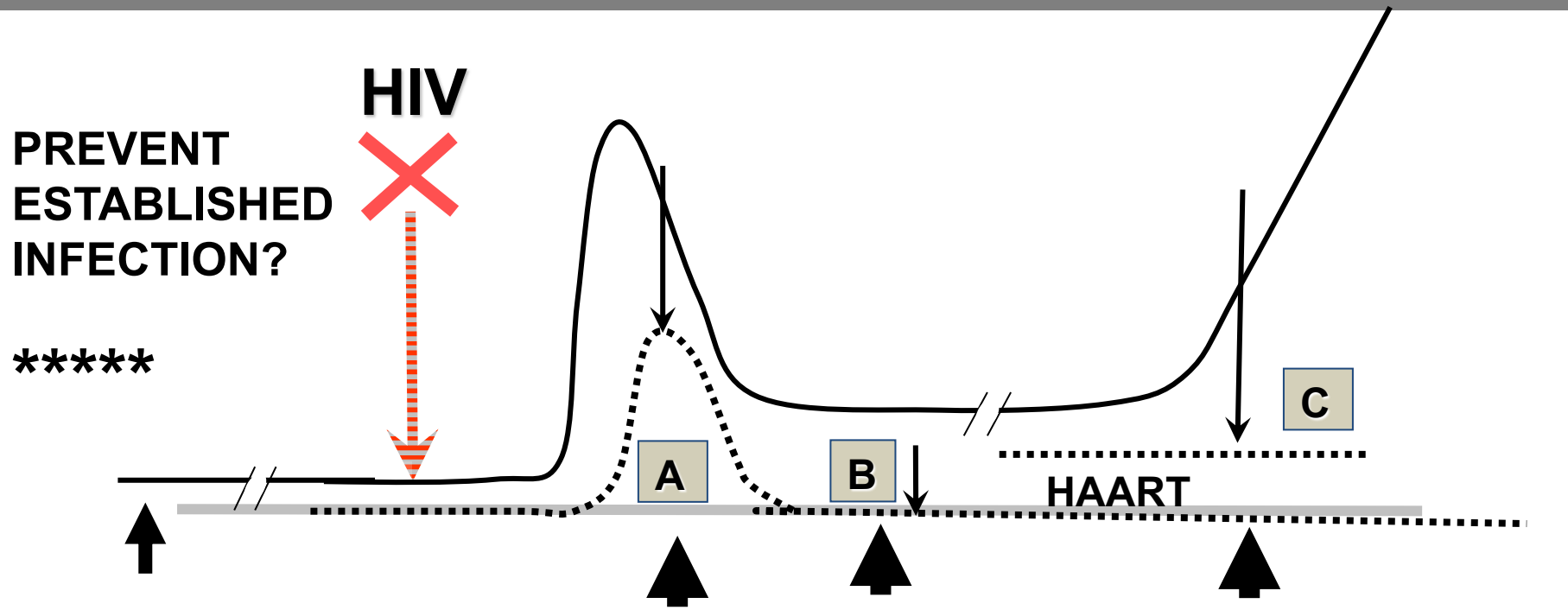
Preventive HIV vaccines are designed to elicit two arms of the immune system – humoral and **cellular**

(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



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)

Courtesy of HIV Vaccine Trials Network

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

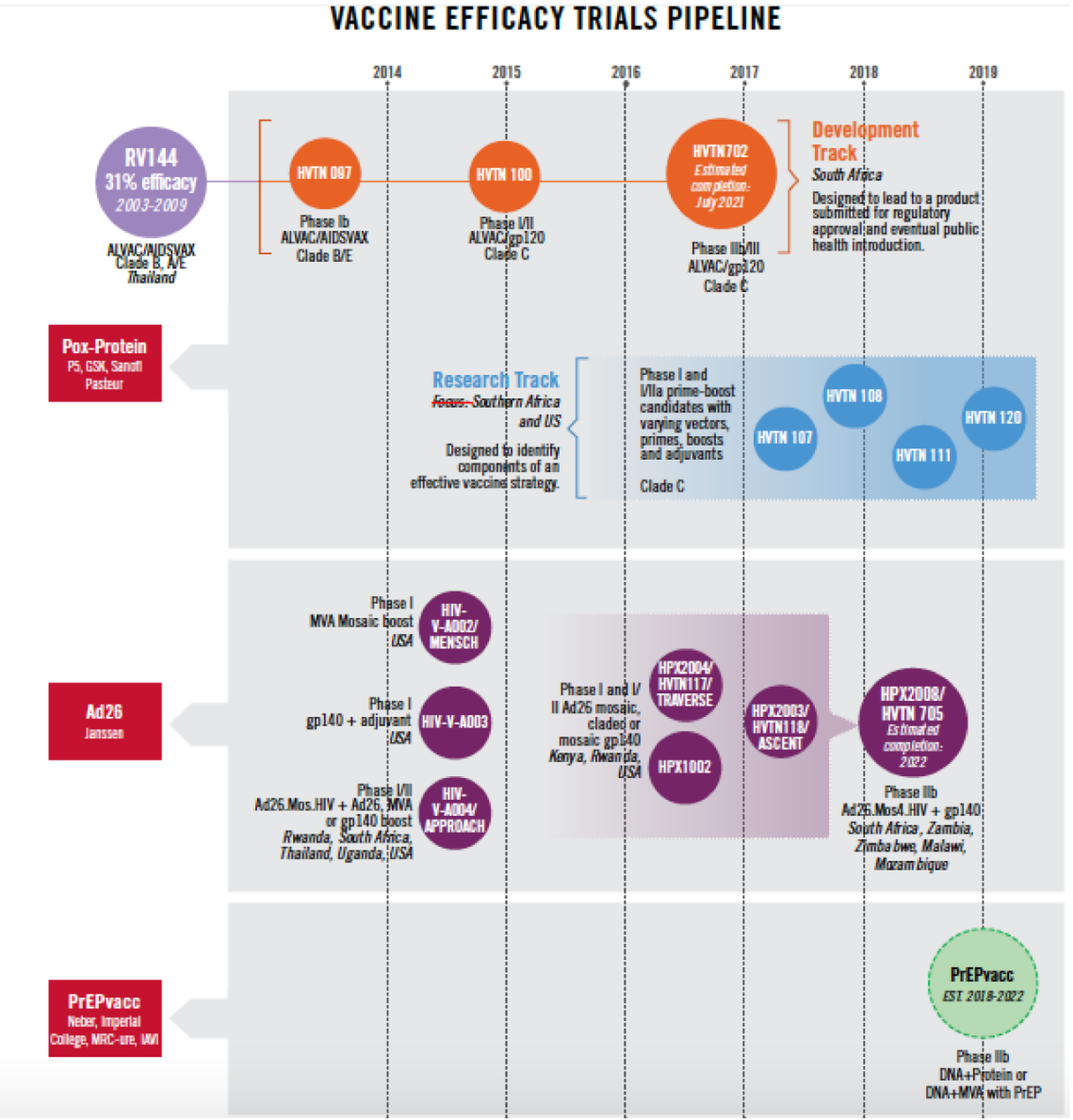
How Are HIV Vaccines Made?

- **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**

HIV Vaccine Efficacy Results to Date

YEAR	TRIAL NAME/ PRODUCT/CLADE	LOCATION	#	RESULT
2003	**VAX003** AIDSVAX B/B	Canada, Netherlands, Puerto Rico, US	5,417	No effect
2003	**VAX004** AIDSVAX B/E	Thailand	2,546	No effect
2007	**STEP** MRK-Ad5 B	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US	3,000	Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men.
2007	**Phambili** MRK-Ad5 B	South Africa	801	Immunizations halted based on STEP trial result.
2009	**Thai Prime-Boost/RV 144** ALVAC-HIV (vCP1521) and AIDSVAX B/E	Thailand	16,402	Modest efficacy (31.2%)
2013	**HVTN 505** DNA and Ad5 A/B/C	US	2,500	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.

Efficacy Trials Pipeline



Available to download at www.avac.org/infographics.

Pox-Protein Strategies

- 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

Mosaic Vaccine Strategies

- 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

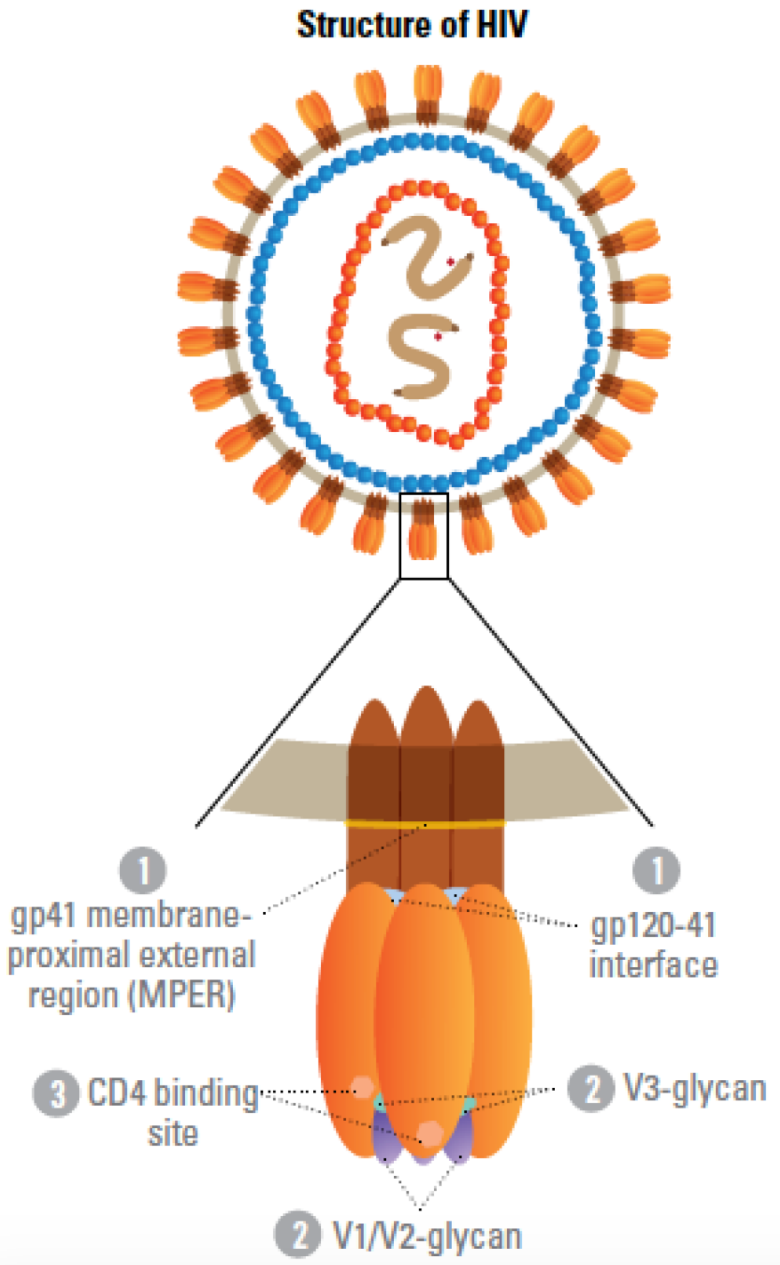
Antibody Research

- Direct transfer of antibodies (passive immunization) being tested for prevention, treatment, and as part of cure
  - Multiple bNAbs 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 (bNAbs) discovered since 2009
- Five main targets of bNAbs on the virus envelope
- Studies have shown bNAbs 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



HIV envelope target	Antibody	Status			
		Pre-clinical	Phase I	Phase II	Phase IIb/III
CD4 binding site	3BNC117		●		
	VRC01		●		●
	VRC07-523		●		
	N6		●		
gp41 membrane proximal external region (MPER)	10e8		●		
	4e10	●			
gp120-41 interface	8ANC195	●			
	PGT151	●			
V1/V2-glycan	CAP256-VRC26		●		
	PGDM1400		●		
	PG9		●		
	CH01	●			
V3-glycan	PGT121		●		
	PGT128	●			
	PGT135	●			
	10-1074		●		
CD4 binding / V3-glycan	3BNC117+ 10-1074		●		
	CAP256-VRC26 +PGT121			●	
	CAP256-VRC26 + VRC07		●		

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
- Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID)
  - At Duke: www.chavi-id-duke.org
  - At Scripps: www.cavi-id.org
- Collaboration for AIDS Vaccine Discovery: www.cavd.org
- European AIDS Vaccine Initiative (EAVI 2020): www.eavi2020.eu
- European HIV Vaccine Alliance (EHVA): www.ehv-a.eu
- Global HIV Vaccine Enterprise: www.vaccineenterprise.org
- HIV Px R&D Database (PxRD): www.data.avac.org
- HIV Vaccines & Microbicides Resource Tracking Working Group: www.hivresourcetracking.org
- HIV Vaccine Trials Network (HVTN): www.hvtn.org
- International AIDS Vaccine Initiative (IAVI): www.iavi.org
- NIAID: www.niaid.nih.gov/topics/hivaids/research/vaccines/Pages/default.aspx
- NIH Vaccine Research Center (VRC): www.vrc.nih.gov
- Pox-Protein Public-Private Partnership (P5): www.hivresearch.org/media/pnc/9/media.749.pdf
- US Military HIV Research Program (MHRP): www.hivresearch.org
- Vaccine Advocacy Resource Group (VARG): http://www.avac.org/blog/introducing-varg

Connect with AVAC

- 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/hivpxresearch* and on Twitter at *www.twitter.com/hivpxresearch*