

The field of HIV vaccine is flourishing. Here are five developments to watch!

1 The first efficacy trial in seven years is a “go!”

HVTN 702 advances the field

In a matter of months, the first vaccine efficacy trial in seven years will launch in South Africa. The trial, known as HVTN 702, will evaluate a vaccine strategy known as ALVAC-protein, a modification of the prime-boost combo that showed modest protection in the RV144 study in Thailand in 2009. This program, which is being conducted solely in South Africa under the name “Uhambo”, was developed by a global partnership of research groups, developers and funders known as the P5 (Pox-Protein Public-Private Partnership).

The decision to move forward with HVTN 702 was based on data from HVTN 100, a smaller trial in South Africa that evaluated immune responses and safety of the vaccine. Responses compared favorably to those seen in the Thai trial, indicating to the P5 that moving forward with HVTN 702 was justified.

HVTN 702 is expected to begin enrolling volunteers by late-2016 and will measure safety and efficacy in 5,400 participants. The study will run for five years. Because it’s being carried out only in South Africa, questions remain about what the results will mean for other countries, regions and globally.

2 Industry engagement expands in an African trial

One step closer to the hope of a global vaccine

Janssen is continuing research on a regimen using an Ad26 vector, MVA vector and a gp140 protein boost with plans for initiation of a multi-site efficacy trial in late-2017. Three Phase I/II trials are underway globally. This research program is a partnership between the US NIH, HVTN, MHRP, IAVI and the Beth Israel Deaconess Medical Center.

An antigen is the vaccine component that prompts a pathogen-specific response. A “mosaic” immunogen consists of small pieces of synthetic protein from many HIV types. The hope for a mosaic immunogen is that it would teach the immune system to block many viral strains. This would reduce the chance that HIV would “escape” from vaccine-induced protection.








The pharmaceutical industry is a center of expertise, money and momentum in research. However, its investment in HIV vaccines is somewhat limited—the science is difficult and potential profits are a gamble. Janssen should be applauded for its drive behind both development and clinical testing of this product. Furthermore, MHRP, which coordinates and implements trial site activities, has committed to robust participatory practices to ensure meaningful input from advocates and communities.

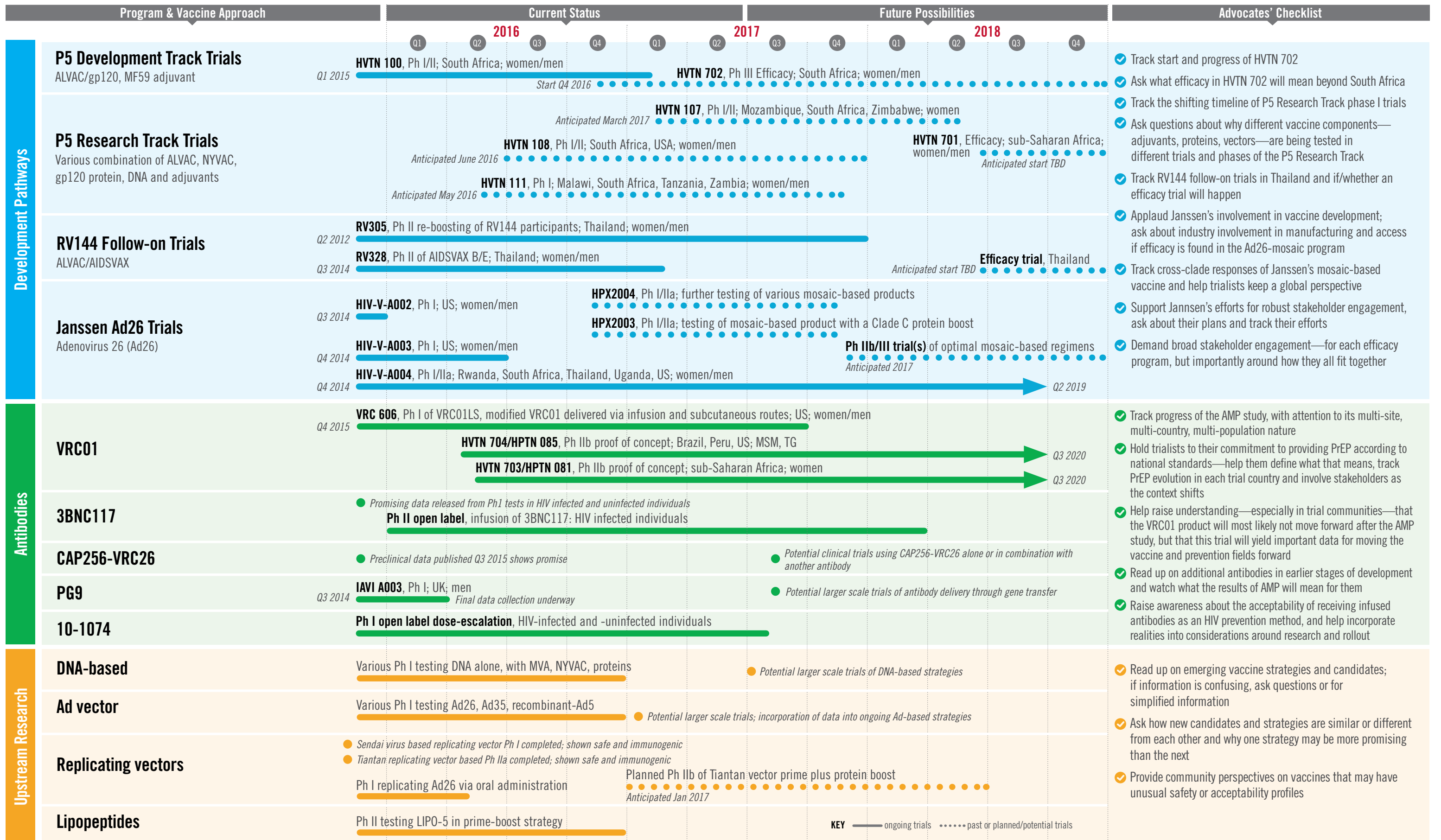
3 Probing the pipeline

New ideas are on the way—but they need to be clearly different from what’s available today

Plans for oil pipelines may be getting scrapped as part of the bid to save the planet, but the bid to effectively and sustainably control HIV rests in part on the vaccine pipeline—a range of trials of different vaccine approaches. Beyond the efficacy trials described above there are a range of other concepts in small, earlier-stage clinical trials. It’s hard to predict which of the concepts will hold promise and why. For advocates, a key role is to ask developers, including those proposing trials and describing candidates: Where does this approach fit in the broader pipeline? What makes it similar or different from other approaches and how are decisions about moving forward made? If you don’t understand the answers—keep asking! It’s a balance between quality and quantity that communities and researchers need to strike together.

Vaccine Strategies in the Pipeline

Vaccine Component				Delivery Mechanism		
 <p>DNA DNA + MVA DNA + AIDSVAX</p>	 <p>Adenovirus vectors</p>	 <p>Lipopeptides</p>	 <p>Proteins</p>	 <p>Electroporation</p>	 <p>Oral</p>	 <p>Intradermal</p>
Variations on the only strategy to show efficacy to date	Carry synthetic fragments of HIV that help prompt strong T-cell responses	A molecular hybrid (amino acid plus lipid); used to generate T-cell responses	Molecular compounds made by a virus that can prompt an immune response	Delivery method using an electrical field to increase the permeability of cells to the vaccine	Delivery strategy that could prompt strong mucosal responses	Delivery into the skin rather than the muscle; uses a much smaller needle



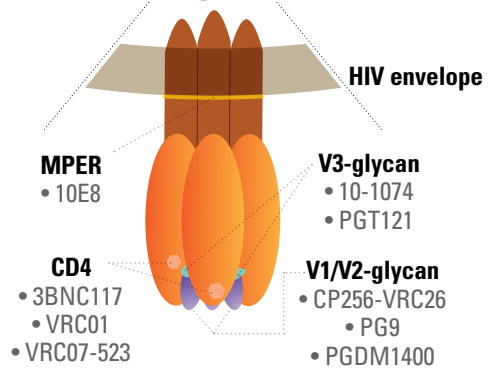
4 Bringing bNAb to block HIV

Out of the shadow of the vaccine syringe, into the spotlight

Antibodies are potent immune responses that the body makes to fight all sorts of invaders. For HIV vaccine advocates they're familiar as the proverbial "holy grail" of vaccine-induced responses. Antibodies that block the activity of a wide range of HIV strains, a.k.a. broadly neutralizing antibodies (bNAb), are thought to be the single most important defense that a vaccine could teach the body to make.

Scientists have mapped the shape and structure of bNAb and identified points of contact and binding with the envelope trimer, shown at right. Understanding the shape of the binding sites for bNAb is key to vaccine development. They have also made strides in understanding how bNAb mature in the body and in mapping the complex array of immune responses that lead to their natural occurrence. Scientists are encouraged that many bNAb attach to

bNAb Targets on HIV



a relatively small, conserved portion of the virus. This narrows the target area for vaccine development.

The graphic shows key bNAb—as of 2016—and their targets on the HIV envelope. All of this work is being used to guide vaccine development and to inform passive immunization trials (see below).

5 AMP – Fast-tracked into global trials

There is great excitement about the launch of the first passive immunization efficacy trial; but what will come next?

Ideally a vaccine would teach the body to make bNAb as part of durable protection against HIV. But it's also possible to make bNAb in the lab and deliver them directly to a person. This is known as passive immunization. Scientists have modified bNAb to increase their effectiveness and certain antibodies have moved into clinical testing of safety and efficacy against HIV.

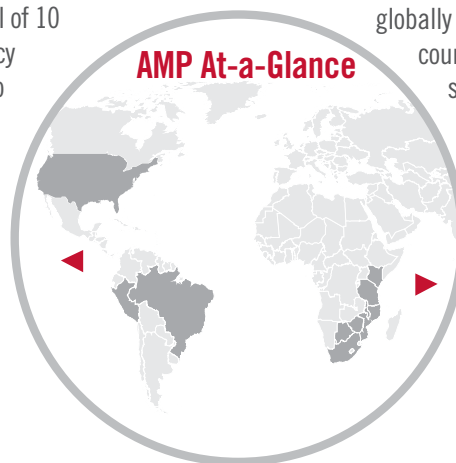
Farthest along is VRC01, the bNAb tested in the trial known as the Antibody Mediated Prevention—or AMP—Study. AMP consists of two separate protocols—one for men who have sex with men and transgender individuals in Brazil, Peru and the US (HVTN 704/HPTN 085); the other for women in sub-Saharan Africa (HVTN 703/HPTN 081). Participants receive the antibody through a 30-60 minute intravenous infusion, every 8 weeks, for a total of 10 infusions. AMP will evaluate safety and efficacy of VRC01 for HIV prevention and is expected to finish in 2020.

Sound complex? It is. Many experts say the point of current bNAb trials isn't to

identify a new strategy for widespread use. Instead, a positive result could lead to more focused vaccine development efforts. Other researchers say that more potent antibodies that could protect in smaller, more easily-administered doses could perhaps make it to market one day. For this to happen, the dosage (amount delivered to a person) would need to come down from the current AMP dosage, and the half-life (time that protective levels of antibody stay in the blood) would need to go up. While the field has learned that it can never predict the outcome of an efficacy trial, it is commonly understood that VRC01 is not potent enough to be delivered in amounts small enough to be marketable. Other bNAb, such as CAP256-VRC26 and 3BNC117, have shown promise in animal and early clinical testing and would be prioritized for further research, either separately or in bNAb combinations.

As bNAb trials are being rolled out in the research world, daily oral PrEP is arriving in the real world. Same world? Indeed. AMP teams have committed to following national standards for PrEP rollout—which, as prevention advocates are well aware, is rapidly evolving globally and at country levels. The map pictured highlights countries where AMP will be conducted against the current status of PrEP rollout.

AMP in the Americas
 ● Brazil
 ▲ Peru**
 ▲ ● ● United States



AMP in Africa

- Botswana ●
- Kenya ▲ ● ● ●
- Malawi** ●
- Mozambique** ●
- South Africa ▲ ● ● ●
- Tanzania ● ● ●
- Zimbabwe* ● ● ●

* Application for PrEP approval expected in 2016
 ** PrEP demo projects planned

KEY	▲ PrEP approved	● PrEP demo projects ongoing
	● Regulatory application for PrEP approval filed as of August 2016	■ PrEP being offered as part of DREAMS
		● PrEP guidelines issued (national or clinical)

ACRONYMS	MHRP: US Military HIV Research Program
AMP: Antibody Mediated Prevention	NIH: National Institutes of Health
HVTN: HIV Vaccine Trials Network	IAVI: International AIDS Vaccine Initiative