Much of HIV prevention research is organized by intervention. There are separate leadership structures, funding streams and scientific agendas for PrEP, microbicides, vaccines and so on. In the real world, the borders blur. The same issues arise in different fields, although joint discussion and problem solving is unusual. It’s essential to merge some of these dialogues and dismantle the siloes that separate different realms, like family planning and HIV prevention. These distinctions hinder progress. To address this, we have identified four priority actions focused on overlapping areas.

AIDS vaccines: Proceed—with deliberate speed

There is a lot happening in the AIDS vaccine field—in many different areas. The past year has brought increased clarity about the design and sequence of trials to build on the result of the RV144 trial, which enrolled over 16,000 volunteers in Thailand and found evidence of modest protection in 2009. There also continue to be exciting breakthroughs in antibody-based research with progress in understanding how potent, broadly neutralizing antibodies (BNAbs) mature in the body, and an increasingly clear picture of virus-antibody binding sites. Efforts to evaluate passive
immunization strategies that infuse BNAbs directly—rather than teaching the body to make them via a vaccine—are also moving ahead.

But if the RV144 follow-on trials (see box, left) are the next—albeit delayed—big thing, and broadly neutralizing antibodies are touted as the hope on the long-term horizon, what happens in between?

As the graphic on page 23 shows, the candidates that could move into clinical trials in the midterm (e.g., the next five to seven years) use various vectors including adenoviruses found only in chimpanzees, “alternative” human adenoviruses, such as Ad26 and Ad35 and, possibly, replicating vectors that use attenuated, non-disease causing versions of viruses to stimulate the immune system.

Decisions about moving these vectors forward will need to weigh scientific promise against the imperative to protect trial participants. All prevention research weighs these concerns. But they will be intensified for AIDS vaccines given the data from a meta-analysis of the Step and Phambili studies, which shows that recipients of a particular Ad5-vectored vaccine strategy may have been at increased risk of acquiring HIV compared to placebo recipients (see box, page 24 for a full description of the meta-analysis.) There will also be safety concerns with replicating vectors, whose potency derives in part from the fact that the disabled virus still retains some of its functions—and so stimulates the immune system on an ongoing basis. Introducing a disabled version of any virus in a vaccine is a risk that has to be balanced against the potential protective benefits of the strategy.

The guiding principle for the field is always to err on the side of caution. The question now is how much caution—and how should the field proceed.

Looking at the questions related to adenoviruses, there is consensus that “Ad5 is dead” for AIDS vaccines. While Ad5 is still being used as a vector in TB vaccine research, there won’t be any more AIDS vaccine clinical trials based on that vector. But what about alternative Ads—and about other vectored candidates? It is hard to say without knowing what caused the apparent enhancement of risk.

One possible explanation is that the vaccine-induced immune cells that migrated to the sites of HIV infection—e.g., the vaginal or rectal mucosa—which is what these vaccine strategies were designed to do. But if the cellular immunity wasn’t part of a potent response that blocked or controlled the virus then the immune cells would have become targets HIV. A vaccine that results in more target cells at the site of exposure could theoretically increase a person’s risk of acquiring HIV.

**RV144 Follow-on Trials: Lagging timelines**

The next scheduled efficacy trials in the AIDS vaccine field are meant to build on the results of the Thai RV144 trial that showed modest efficacy in 2009. As one next step, a consortium known as the Pox-Protein Public-Private Partnership (P5) was formed to move an RV144-like vaccine strategy into additional trials in Southern Africa and Thailand.

While there is now clarity, particularly about the regimens that will be evaluated in Southern Africa, the timelines for trial launch continue to be pushed back. It has taken longer than expected to select and manufacture the protein boost that will be used in the trials. Novartis, the P5 partner developing the boost, has finally begun manufacture of the clade C boost for the South African licensure trial, which is scheduled to begin in 2016.

A proposed Southern African “correlates” clinical study will gather information on other RV144-like vaccines, but is not designed to lead to licensure. There are still questions about when the Thai trial might begin, since the clade B/E boost that would be used in that trial hasn’t been finalized.

As the Thai trial timeline slips, there is discussion about whether an additional industry partner should step in to work on a different protein boost.

Regarding these delays, some stakeholders say that the science of developing and manufacturing a new candidate can’t be rushed; others argue that industry hasn’t treated the project with sufficient urgency. The truth almost certainly lies somewhere in between.

AVAC thinks it is useful to look at the current coordinating structures and make sure that they are still adding efficiency. Is there a different approach to coordination that could allow the Southern African and Thai trials to proceed more quickly? We also look for the current timelines to hold.

RV144 provided the proof of concept that an HIV vaccine is, in fact, possible. However, the continued delays in launching trials designed to build on this result make it harder to maintain the optimism.
At an Ad5 “mini-summit” convened by the US National Institutes of Health in September 2013, Tony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID), laid out the four key questions facing the field:

- Is there a problem with some or all adenovirus 5 vectors?
- Is this a problem with Ad5 only or all adenovirus vectors?
- Is it a problem with any vaccine that causes activated cells to migrate to mucosal surfaces [as was perhaps the case with the Step study]?
- Is this a universal problem that is only seen when the vaccine is not efficacious in preventing acquisition of infection?
A complementary perspective on the issue came at the AIDS Vaccine 2013 conference in Barcelona from Glenda Gray, Director of the Office of AIDS Research at the South African Medical Research Council and of the University of the Witwatersrand in South Africa. In a succinct summary of the state of the field, she said:

- It is possible to develop a vaccine regimen that will prevent acquisition of HIV.
- It is possible to develop a vaccine regimen that may increase the risk of HIV acquisition.
- It is possible that many HIV vaccine regimens will need to “balance” these factors associated with increased acquisition (e.g., a strong but only partially effective mucosal T-cell response) with the factors associated with protection from acquisition (a partially effective antibody response).

There are no definitive answers to Fauci’s questions—and there’s a world of complexity in Gray’s bullet points. Proceeding with caution is difficult, since it isn’t clear how to predict, measure or mitigate risk. There aren’t obvious correlates of risk linked to the Ad5-vectored candidates, and there is debate about what types of markers might be predictive. There isn’t likely to be agreement in this area anytime soon, and there may never be a filter for screening out candidates that induce cell-mediated immunity and are more likely to increase risk of infection. (Candidates that induce broadly neutralizing antibodies wouldn’t be expected to have this problem since BNAbs aren’t cells and can’t be infected.)

Could trials be designed to manage risk? Yes—but there are uncertainties here, too. One proposal at the mini-summit was to offer participants PrEP, a monoclonal antibody or a microbicide for a finite period to provide additional protection. But the fact that the apparent enhancement emerged early in the Step trial and late in the Phambili trial complicates even this reasonable suggestion.

### Up Close: The meta-analysis of Ad5 candidates

In 2013 the vaccine field grappled with the results of a meta-analysis of data from trials evaluating vaccine strategies that included a vector based on adenovirus serotype 5 (Ad5). In scientific terms, a meta-analysis pools together data from multiple clinical trials of the same treatment or intervention—or of multiple similar treatments or interventions. This approach is used to systematically and quantitatively review the data on a given topic. By combining data, meta-analyses may sometimes allow for a more definitive conclusion about a topic, since larger data sets can allow for more precision, as well as exploration across sub-groups.

The analysis, conducted by Peter Gilbert and colleagues at the HIV Vaccine Trials Network, looked at infections in the vaccine and placebo arms of the Step, Phambili and HVTN 505 trials. Pooling data from these trials, there were 200 infections among participants who received at least one injection of the vaccine; there were 147 infections in the comparable placebo group. Overall, this translated into a 33 percent elevated risk in vaccine recipients compared with placebo recipients. No trend to higher risk of HIV infection was seen in HVTN 505. When the data from this trial were excluded, the vaccine-associated risk in Step and Phambili rose to 41 percent.

The Ad5 strategy tested in HVTN 505 contained synthetic fragments of HIV envelope (the outer coating of the virus). The vaccines in Step and Phambili did not. It is possible that immune responses targeting env elicited by the HVTN 505 vaccine may have mitigated the risk seen in the other two Ad5 trials. There is discussion now about whether env should be consistently used as a vaccine insert based on these data.

Like all meta-analyses, this one has limitations. By definition it was conducted post-hoc (it wasn’t planned before the trials were launched), and it isn’t as statistically conclusive as it might be if there were larger data sets. Step and Phambili data are not directly comparable. Step participants were in the trial for much longer than Phambili participants—and much of the data from Phambili was collected after participants learned whether they had received the vaccine or the placebo. Overall, 80 percent of infections were in men—primarily men who were uncircumcised and had pre-existing antibodies to Ad5. The available data suggest that there was more enhancement in men than women—and one proposal for mitigating risk is to move other Ad candidates forward in women first. But the numbers are small. Even with these limitations, the meta-analysis is being taken seriously as an indication that the Ad5 candidate in Step and Phambili affected risk of HIV infection.

This development is an absolute worst-case scenario for the field. Upcoming vaccine trials, like the RV144 follow-on trials, will vigilantly monitor for both harm and efficacy.
So where does this leave the field? One option is to hold off on alternative Ad candidates and focus on broadly neutralizing antibodies and the RV144 follow-on trials since there is no evidence of enhancement from that strategy. This would be an extremely risk-averse approach—and in AVAC’s view, it is an excess of caution for a field that needs to evaluate a diversity of approaches.

Replicating vectors also raise complex questions about balancing risks and benefits. Some of the most promising animal data seen to date has come from these vaccines, but it may be difficult to move them into humans. At Oregon Health Sciences University, Louis Picker and colleagues are working with an attenuated cytomegalovirus vector. In one study, half of the animals vaccinated and subsequently infected with SIV were able to clear infection. In animal studies, promising results have also been seen with vaccines using attenuated versions of varicella-zoster virus (VZV) and HHV-8 (a herpes virus tied to the AIDS-related cancer Kaposi’s sarcoma). For all of the excitement about these data, it’s still not clear if and how replicating vectors based on these viruses can be evaluated in humans, given safety concerns. The promise is there—and should be pursued. But as with the Ad-vector candidates, the next steps must balance urgency and caution. Specifically, the field should:

- **Develop clear and actionable recommendations based on discussions at the Ad5 mini-summit.** Work is already underway to do this. Given that there were strong, sometimes conflicting opinions, it may be a challenge to put forward recommendations that steer the field in one direction or another. But this is what’s needed, not just a summary of the issues. These need not be set in stone; they can build in opportunities for course correction, too.

- **Map the pathway for clinical trials of replicating vectors.** The Ad5 mini-summit was a frank, productive discussion and an excellent model for generating an agenda for action. The Global HIV Vaccine Enterprise has established itself as a key convener on “timely topics”. This approach should be turned to replicating vectors, engaging civil society throughout. One key issue is the possibility that regulatory authorities might view these candidates differently depending on the severity of the epidemic. Discussion is needed as to whether it would be acceptable to move ahead outside of the US, if the US FDA advised against a replicating vector.

- **Apply rigorous standards for immunogenicity.** Alternative Ads and replicating vectors that move into clinical trials should be held to a rigorous standard in terms of the immune responses that they induce, the immunogenicity. It’s not known what types of immune responses will be protective, but the field can use the best available information to choose stringent criteria for immunogenicity.

- **Be prepared to discard candidates.** A candidate shouldn’t move into larger trials just because it is the next in line. The field has to be selective in its investments, looking at factors like inserts and adjuvants as well as immunogenicity to select candidates that are qualitatively or quantitatively different from what has been tested before.
**Maintain investment in community engagement.** Clinical trials are invaluable to advancing the search for an AIDS vaccine. And clinical trials of the complexity anticipated in the future cannot happen without robust, well-funded stakeholder engagement. Yet various aspects of stakeholder engagement are being scaled back. The US NIAID has cut funding for its engagement on prevention research with US community-based organizations—a decision that is penny-wise (no new trials are planned in the US) but pound foolish (stakeholder engagement cannot be switched on and off—it depends on sustained investment).

**Hormonal contraceptives and HIV risk: Invest in a complex trial**

Over the past year, AVAC has intensified its work in the area of hormonal contraception and HIV risk. We see this issue as fundamental to effective HIV prevention for women. It is one where action must be taken, even in the midst of uncertainty. As the figure on page 29 shows, there are mixed data concerning the relationship between injectable progestogen-only hormonal contraceptives like Depo-Provera and HIV risk. Some studies suggest that this method increases women's risk of acquiring HIV, others do not.

The two main issues in this arena are: how to proceed in the context of uncertainty and whether to attempt to conduct a randomized controlled trial that might eliminate some of this uncertainty. In terms of what to do next, there are immediate steps, such as moving to increase method mix—the range of family planning options that women can choose from. At present, roughly 60 percent of women in sub-Saharan Africa use injectable contraceptives. This option is discrete and long-acting. It is selected and, given available options, preferred by many women. Many family planning programs in sub-Saharan Africa offer women few other choices—perhaps the contraceptive pill, which requires daily use, and condoms. In the context of limited choices, it is hard to know which options women actually prefer.

Another next step must be providing practical information to policy makers and service providers about how to operationalize the 2012 WHO technical guidance note on hormonal contraceptives, which included new language on progestogen-only contraceptives specifying that women who are at high risk of HIV should be strongly urged to use condoms when using this method. Nearly two years after the guidance note was issued, there has been less-than-satisfying progress in this area. WHO had initially committed to developing a communications strategy; the work is being finalized in partnership with Johns Hopkins University, and a strategy is expected in 2014. Unfortunately, there has been scant involvement of civil society in this latest process even though many women's groups involved in a 2012 consultation on the topic had clear recommendations and expertise that should have been incorporated.

These steps won't address the underlying question about whether specific hormonal contraceptives increase HIV risk. Here, the major question is whether to attempt a randomized controlled trial that would seek to answer the question of how various methods, including Depo-Provera, impact HIV risk. WHO, FHI 360, Wits

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