

The End?



REPORT 2011

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In Memoriam: Winstone Zulu (1964-2011)

This year's *AVAC Report* is dedicated to **Winstone Zulu**, a pioneering AIDS and TB activist who passed away in October 2011.

Diagnosed with HIV in 1990, Winstone Zulu was the first person in Zambia to publicly disclose his HIV status. Recognized as one of the leading African activists involved in the global health movement on AIDS from its earliest stages, he worked on HIV/AIDS and TB prevention, treatment and care for over two decades. His activism embodied a deep commitment to friends and family affected by HIV and TB. He was a tireless advocate for the rights of sex workers, gay men and women, and disabled people. From his early days at Kara Counseling in Zambia to his leadership in the international movement, his energy and determination

were indefatigable. He lobbied G8 leaders; spoke to mass rallies on five continents; and inspired audiences at schools, churches and parliaments.

In 2004, Zulu wrote:

Yes, I have lived positively with HIV for a dozen years.

Yes, I have given hope, I hope, to some people.

Yes, I try not to be weepy most of the time.

And yes, I am glad to be here.

This report lays out many objectives that Zulu embraced and would have put his considerable energy behind as part of a leading activist seeking to end the epidemic in our lifetime. Our own efforts are energized and sustained by his memory.

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Achieving the End

A science-based agenda to end the epidemic

For the first time, the end of the global AIDS epidemic is within reach. Recent breakthroughs in HIV prevention research (see box at right) have created unprecedented opportunities to curb new HIV infections, save lives and set the world on a path toward eliminating HIV transmission in our lifetime.

But ending the global pandemic won't be simple or quick, and our success is far from assured.

To capitalize on today's opportunities, the global AIDS response urgently needs a coherent, long-term plan. This plan needs to be:

- *Comprehensive*—Smart combinations of the potent tools at our disposal will be essential.
- *Science-based*—Implementation of new tools needs to be as rigorous as the science that created them.
- *Actionable*—Clear priorities, roles and timelines are essential to keep us on track for the long haul.
- *Optimistic, but realistic*—We have a long road ahead, and will need to allow for setbacks along the way.

A Three-Part Agenda for Impact

This *AVAC Report* presents a three-part agenda for ending the AIDS epidemic. It is intended as a vision and a challenge to the field, and a first step in holding all of us—civil society, researchers, governments, and funders—accountable for progress.

Each of the major priorities that follow demands action now—but the dividends will come in the short, medium and long terms.

Game Changers: Recent breakthroughs in HIV prevention research

- **Voluntary Medical Male Circumcision:** Trials in 2006 showed that this procedure reduces a man's risk of infection from a female partner by about 60 percent.
- **Topical Microbicides:** In 2010, an ARV-containing gel reduced women's risk of becoming infected by 39 percent in one trial. (In November 2011, the same gel showed no effect in a different trial. Clarifying the role of this tool is a must.)
- **Pre-Exposure Prophylaxis (PrEP):** Study data from 2010 and 2011 showed that daily use of certain antiretroviral medicines reduced the risk of infection among gay men and transgender women (by 42 percent) and serodiscordant couples (by up to 73 percent).
- **HIV Treatment as Prevention:** In 2011, a trial found that starting ART at CD4 cell count 350-500 reduced HIV-infected individuals' risk of transmission by 96 percent.
- **AIDS Vaccines:** In 2011, scientists found strong clues about why a protective vaccine changed HIV risk in the RV144 trial.

1. DELIVER today's proven strategies at scale for immediate impact

- *Model* combination prevention programs to identify the parameters that have the greatest impact on reducing infection in different settings.
- *Mobilize demand* for new tools among people who could benefit the most and their health providers, through social marketing and other efforts.

- *Reprogram* existing resources when evidence shows they could be used to greater effect.
- *Fund* evidence-based scale-up today—and save money in the future—through substantial increases in commitments from European and developing country funders.

2. DEMONSTRATE and roll out newly available HIV prevention tools, including PrEP and microbicides, for even greater impact in five to ten years

- *Plan* for the introduction of PrEP and microbicides in the next several years and/or follow-on research to address outstanding questions.
- *Pilot* these interventions through demonstration projects that help define their optimal use and real-world impact.
- *Prioritize* the use of these interventions in populations, and in combinations, where the potential benefits are greatest.

3. DEVELOP long-term solutions—including an effective vaccine and a cure—that will enable us to close the door on AIDS

Combination Prevention: Priority approaches

Today

- **Test:** Scale up innovative, ethical HIV testing programs that link directly to prevention and treatment interventions.
- **Treat:** Expand access to early HIV treatment to preserve health and prevent transmission.
- **Circumcise:** Roll out VMMC, an effective and underutilized solution.

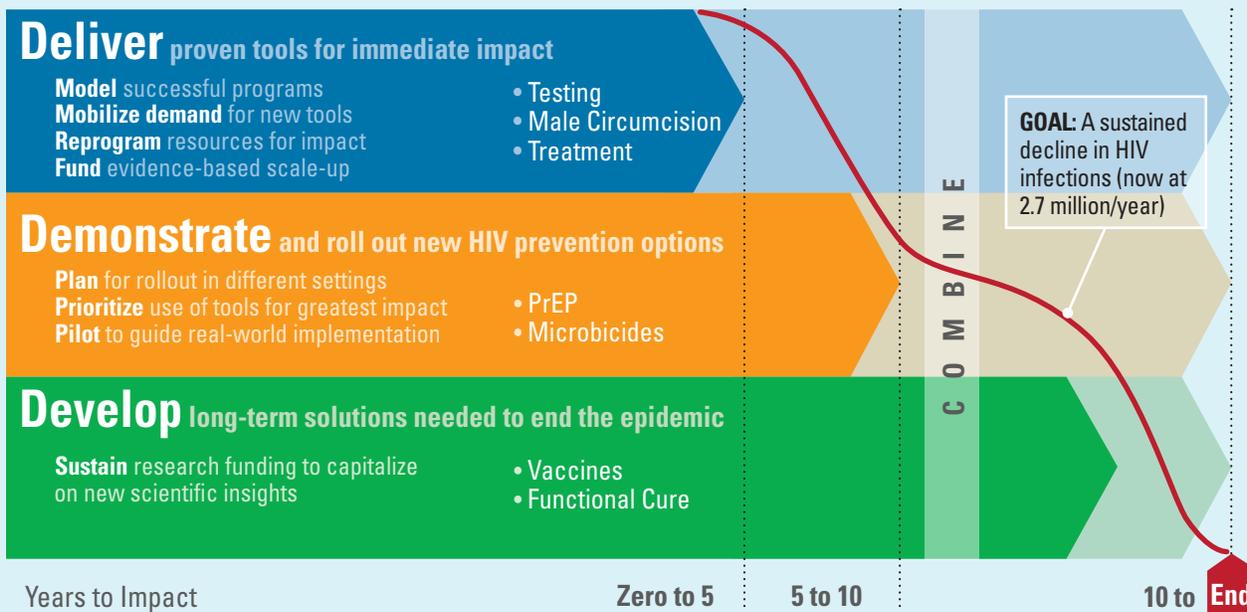
Integrate with **other proven tools**—from condoms to prevention of pediatric infection—for greatest impact.

The Future

- **PrEP and microbicides** (near- to mid-term): Evaluate in pilot projects, carry out confirmatory research of tenofovir-based products and accelerate development of pipeline for long-acting, second-generation candidates.
- **AIDS vaccines and a cure** (mid- to long-term): Identify through sustained, well-funded and innovative research that follows the most promising leads.

- *Sustain* funding for research to capitalize on recent scientific insights that have energized the search for an AIDS vaccine and a cure.

A Three-Part Agenda for Ending AIDS



Not If, But How

The essential business of ending AIDS in our lifetime

A letter from the Executive Director

We can end the AIDS epidemic in our lifetime. That's the view from AVAC and, in an exciting movement, from civil society groups, scientists and top political leaders around the world.

By “ending the AIDS epidemic”, we mean drastically reducing the number of new infections and preserving the health of people living with HIV, so that they do not progress to AIDS. To us, the phrase “in our lifetime” means “in the foreseeable future”: at a point on the horizon that is within sight for many of us, provided that critical steps are taken in the immediate future.

To be sure, global health inequities, including persistent gaps in access to basic health services, clean water and facilities for safe childbirth, as well as lack of access to treatment for HIV and TB for many, mean that there will have been many preventable deaths before even finishing this page. Pediatric HIV deserves special mention here. Babies should not have to contract HIV infection, and we have a way to prevent that from happening at this very moment—if implementation science and logistics can be addressed.

Still, everyone alive today does have the opportunity to take part in the movement that is setting its sights on ending the AIDS epidemic. The hope fueling this movement stems from scientific breakthroughs that have validated new prevention strategies (see timeline, p. 5) as well as from economic and epidemiological models and analyses that clearly show the power of combination prevention. We now have tools that, if used strategically and synergistically, can control the epidemic and eventually bring it to an end.¹ This is the power of combination prevention and the reason it is such an exciting and important time to be an HIV prevention research advocate.

The end of the AIDS epidemic won't come overnight. It will not be simple.

Science

“...We now have an unprecedented opportunity, based on solid scientific data, to control and ultimately end the AIDS pandemic.”

— Anthony Fauci

AIDS: Let Science Inform Policy, *Science*, July 1, 2011

¹ *How to Get to Zero: Faster. Smarter. Better*, UNAIDS (Nov 2011), <http://www.unaids.org/en/resources/unaidspublications/2011/>.

As *AVAC Report* went to press, there was the disappointing news that the 1% tenofovir gel arm of the ongoing VOICE trial would be discontinued due to lack of efficacy. This finding came in the same week that the Global Fund to Fight AIDS, Tuberculosis and Malaria announced that it had insufficient funds for the planned Round 11 grant cycle. Ensuring that the Fund is replenished and continues to support countries worldwide is a top priority for ending AIDS.

But disappointing as these developments are, they do not refute the fundamental premise of this exciting time. As stated in recent publications and speeches from key political leaders like US Secretary of State Hillary Clinton: It can be done. If we spend more today, and make wiser decisions, we will save money and lives over the long term.

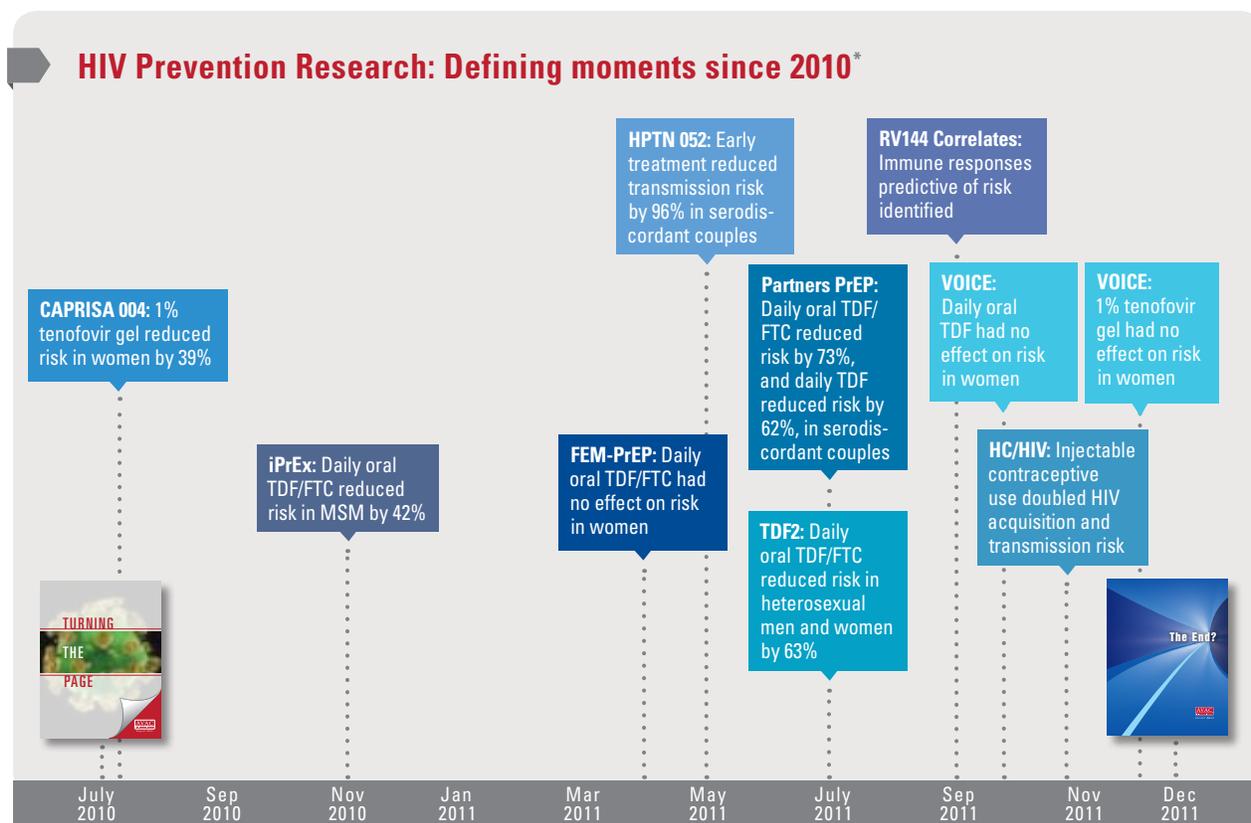
To get where we need to go, the global AIDS response needs to align itself with some of the principles of business management. That's why

If AIDS prevention were a business, there is no question that now would be the time to invest.

this letter is subtitled, "The essential business of ending AIDS in our lifetime". To save money and lives, the AIDS response needs to be guided by some business principles.

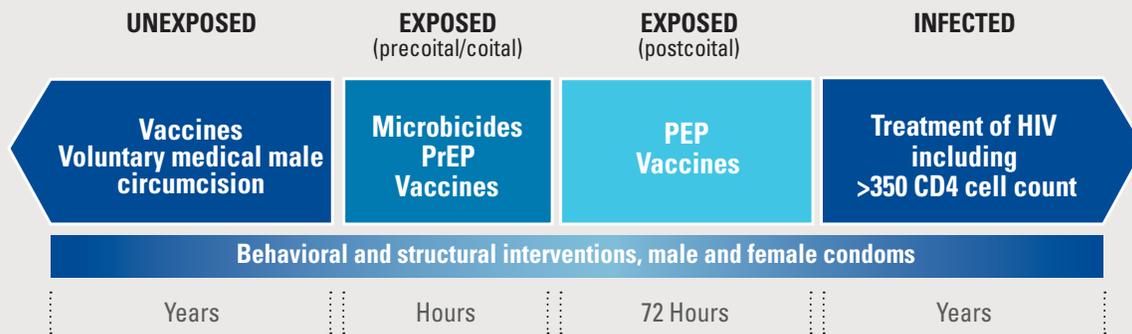
To start with: invest in success.

If AIDS prevention were a business, there is no question that now would be the time to invest. We've had major breakthroughs, surprising proofs of concept of new prevention tools and an exhilarating accumulation of evidence from clinical trials, epidemiological modeling and real-world practice, all of which would be foolish to ignore.



* This figure lists only the point estimate of efficacy from each trial. For the full picture of data on each finding, please visit www.avac.org/trials.

Many Opportunities for HIV Prevention



To end AIDS, we need HIV prevention options that are highly effective before, during and after exposure or infection. We have some of the tools listed above, and we must continue the search for the others.

Smart businesses also know when to pull the plug on approaches that haven't panned out. In the 30 years of the epidemic, there has been a significant increase in global funding and awareness. And many victories have been won. But funds have also been spent on redundant and poorly coordinated research. On the implementation side, there's a hefty price tag associated with self-perpetuating projects and methodologies, both large and small, that fund salaries, per diems, meetings and workshops, but do not, at the end of the day, have a demonstrable impact on the trends of the epidemic. This type of "business as usual" has to change.

Another tenet of good business is to have a clear, milestone-driven plan for bringing a product to market. This hasn't been the norm for HIV biomedical prevention research. There has been no "3 by 5"-style initiative focused on voluntary medical male circumcision. The microbicide field has struggled to develop a milestone-driven product development plan for 1% tenofovir gel. Recent disappointment from the VOICE trial (see Part Two) shouldn't detract from the need for more coordination around vaginal and rectal microbicide product development. There is also uncertainty about how to proceed with tenofovir-based oral PrEP for gay men and transgender women.

Future clinical trials need to be plan-driven, too. For example, there may be a point where we have the PrEP products we need, and that may be the time to stop or dramatically scale back investment in the pipeline. PrEP, microbicide and vaccine developers and funders need to be honest and transparent about which trials are on the critical path and where there is redundancy.

Every organization, including AVAC, needs to make certain that the precious resources available for ending AIDS are put where they are needed most. On page eight you'll find an introduction to *AVAC Playbook 2012*, which reflects our strategic priorities for 2012. These priorities are introduced and explored throughout the Report. They reflect input from our partners around the world (see p. 34) and are being put into action in context-specific strategies every day. Yes, there will still be meetings, per diems and workshops. But there will also be the question—at every turn—is the money being spent as effectively as possible? Does our work and the work of our partners align with the goal of controlling and ultimately ending the epidemic?

Some of the *Playbook* contents will change in 12—or even 2—months' time. The only guarantee in biomedical prevention research is that there are no guarantees. We will revise the

priorities accordingly, tracking progress and adjusting tactics in order to get ever closer to the ultimate goal.

As optimistic as we are here at AVAC, we haven't lost our propensity for realism. The AIDS epidemic will not come to an end in our lifetime without substantial changes in government and civil society commitments to comprehensive AIDS programs; innovative, integrated programs providing ARV-based prevention in its current and emerging forms; voluntary medical male circumcision taken to scale in countries where it has the greatest impact; an end to criminalization of sex work, homosexuality and HIV transmission—and many other factors.

But as the global advocacy and activist community said in 2000, regarding whether antiretrovirals could be delivered to HIV-positive people in developing countries, the question is: not “if”, but “how”?

Determining how to end AIDS is surely hard, but it is doable.

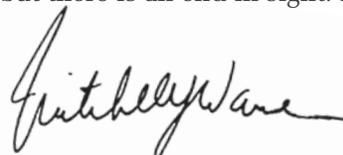
We need to act on the promise of combination prevention—and debate less about the relative merits of one strategy versus another one. We must gather evidence about what effective

combination prevention programs look like in different settings through impact evaluations and innovative clinical trials. Communities, researchers and advocates need to shift from advocacy for one specific intervention to working for well-defined combination packages.

We need to spend the money we do have more wisely—and not retreat from global commitments to the additional financial support required to see this effort through.

We need to prepare for disappointments—and not let bumps in the road detract from the critical goals, which range from an AIDS vaccine that prevents enough infections to be used on a wide scale, to the vision of a world in which innovative community-led models for treatment adherence are the norm.

Finally, we must talk less and do more. This year's *AVAC Report* is shorter than in years past. The issues are clear. The road ahead is still long, but there is an end in sight. Let's get going!



Mitchell Warren
AVAC Executive Director

Priority Tools and Actions

Deliver

- ▶ Test
- ▶ Circumcise
- ▶ Treat
- ▶ Model
- ▶ Reprogram
- ▶ Fund

Demonstrate

- ▶ PrEP
- ▶ Microbicides
- ▶ Plan
- ▶ Prioritize
- ▶ Pilot

Develop

- ▶ Vaccine
- ▶ Cure
- ▶ Sustain the science
- ▶ Control the epidemic

To end the AIDS epidemic we need to define, evaluate and implement combination prevention in every community affected by HIV. In the boxes above, we identify some of the key strategies and actions needed to make this a reality.

AVAC PLAYBOOK 2012

AVAC’s goal is to work with partners worldwide to ensure that the answer to the question “Will we end the epidemic?” is a resounding “Yes.”

If this is the goal, then we all need to examine our priorities. We need to do more of some things and less of others. And we need to be sure that we’re keeping track of what should happen in the next 12 months, the next few years and the next few decades.

AVAC Playbook 2012 focuses specifically on the next 12 months. It includes our analysis of what the top strategic goals should be on a global level, and particularly in hard-hit countries, over the coming year. It also includes our own organizational priorities for contributing to these goals.

You can download a copy of an updated version of *AVAC Playbook 2012* at www.avac.org.

| AVAC PLAYBOOK 2012: GLOBAL GOALS | | | | |
|----------------------------------|--|--|---|-------------------------------|
| DELIVER | Testing/Diagnostics | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| | <ul style="list-style-type: none"> › Scaled-up and efficient testing programs with high levels of linkage to evidence-based prevention, treatment and care. › Swift execution of a research agenda on testing modalities and affordable diagnostics that meets emerging needs. | <ul style="list-style-type: none"> › Roll out VMMC with strategic, long-term plans in countries that meet WHO-recommended criteria, with goal of 80 percent circumcision. | <ul style="list-style-type: none"> › Universal access to ARVs at CD4 count 350 or below for all people with HIV. › Acceleration of treatment provision to specific groups at CD4 between 350 and 550, with phased implementation plans in majority of countries by end of 2012. | |
| DEMONSTRATE | PrEP | Microbicides | | Partnerships |
| | <ul style="list-style-type: none"> › Swift implementation of pilots and phased implementation in countries and communities where oral TDF/FTC-based PrEP is relevant; clear action on evaluating PrEP and developing policies in countries where it might be introduced over the long-term. | <ul style="list-style-type: none"> › A clear and accelerated product development pathway to clarifying the effectiveness of 1% tenofovir gel. › Donor decisions and actions about future trials and overall pipeline are accessible to, and shaped by, civil society and other stakeholders. | | |
| DEVELOP | Vaccines | Ethics and Trial Conduct | | Partnerships |
| | <ul style="list-style-type: none"> › Maintain funding to build on recent breakthroughs. › Connect the vaccine agenda to combination prevention. › Identify and close funding gaps for RV144 follow-on trials. | <ul style="list-style-type: none"> › Increase uptake and utilization of GPP. › Guide new consensus on decision making about when to add emerging strategies to the standard of prevention. › Guide and advocate for post-trial access plans. | | |

| AVAC PLAYBOOK 2012: AVAC PRIORITIES | | | | |
|-------------------------------------|---|---|--|-------------------------------|
| DELIVER | Testing/Diagnostics | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| | <ul style="list-style-type: none"> › Evaluate, inform and accelerate the testing research agenda. | <ul style="list-style-type: none"> › Catalyze civil society advocacy for ambitious scale-up of VMMC in slow-implementing countries. | <ul style="list-style-type: none"> › Support civil society-led action on the policies, guidance and funding streams to optimize the benefit of treatment as part of combination prevention. | |
| DEMONSTRATE | PrEP | Microbicides | | Partnerships |
| | <ul style="list-style-type: none"> › Ensure that PrEP demonstration projects are launched for relevant populations. | <ul style="list-style-type: none"> › Amplify civil society demand for a firm and cohesive plan for 1% tenofovir gel and future products. | | |
| DEVELOP | Vaccines | Ethics and Trial Conduct | | Partnerships |
| | <ul style="list-style-type: none"> › Make the case for sustained funding, including resources to engage community in discussing future trials. | <ul style="list-style-type: none"> › Publish a new consensus statement on standard of prevention in biomedical prevention trials. | | |

The End

Develop

- ▶ Vaccine
- ▶ Cure
- ▶ Sustain the science
- ▶ Control the epidemic

Demonstrate

- ▶ PrEP
- ▶ Microbicides
- ▶ Plan
- ▶ Prioritize
- ▶ Pilot

Deliver

- ▶ Test
- ▶ Circumcise
- ▶ Treat
- ▶ Model
- ▶ Reprogram
- ▶ Fund

DELIVER

DELIVER

Test. Circumcise. Treat.

These are three key steps to getting on track to end the AIDS epidemic in our lifetime. In this section, we describe the agendas specific to testing, voluntary medical male circumcision (VMMC) and treatment, and discuss these interventions one by one.

But the reality is that no intervention can be viewed in isolation. Testing, VMMC and treatment are the core elements of combination prevention packages that must also include condoms, syringe exchange and harm-reduction programs, prevention of pediatric infection, and smart, strategic behavior change communication. Male and female condoms and harm-reduction programs are highly effective, relatively inexpensive and still imperfectly deployed.

| AVAC "PLAYBOOK" 2012 | | | | |
|------------------------|--|-------------------|---|------------------------|
| DELIVER | Testing/Diagnostic | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| DEMONSTRATE | PrEP | Mircumcision | | |
| Comprehensive Approach | GLOBAL GOALS | | AVAC PRIORITY | |
| | <ul style="list-style-type: none"> Deliver evidence-based strategies in combinations that will have maximum impact on the epidemic. Support research that generates answers about synergistic use of multiple new prevention strategies. | | <ul style="list-style-type: none"> Advocate for the reallocation of prevention funds to align with evidence and be spent by policy makers who have access to well-designed decision-making tools at a country level. | |

While we haven't devoted a specific section to these strategies, the resources and know-how invested in scaling up combination prevention must improve the logistics, communication and delivery of these strategies too.

Model. Reprogram. Fund. If the world is serious about implementing HIV testing, VMMC and scaled-up antiretroviral treatment, then these three actions are of the utmost importance.

Test

HIV testing is the first and most important step toward ending AIDS. There is a growing array of treatment and prevention strategies tailored to an individual's HIV status. For example, earlier treatment initiation (above 350 CD4 cells) to preserve health and minimize infectiousness for HIV-positive people, or, daily oral PrEP using TDF/FTC for HIV-negative gay men and

transgender women. In the future, oral PrEP could be offered to HIV-negative heterosexual men and women.

Broad counseling messages that apply to everyone, regardless of their status, still have a place. The core messages and tools—use condoms, be faithful and minimize concurrent partnerships, delay sexual debut and employ harm-reduction techniques during drug use—are still essential in every community.

| AVAC "PLAYBOOK" 2012 | | | | |
|--------------------------|--|---------------------------|--|------------------------|
| DELIVER | Testing/Diagnostic | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| DEMONSTRATE | PEP | Mircumcision | | |
| Testing / Diagnostics | GLOBAL GOALS | | AVAC PRIORITY | |
| | Vaccines | Prisons and Social Unrest | Partnerships | |
| | <ul style="list-style-type: none"> › Scaled-up and efficient testing programs with high levels of linkage to evidence-based prevention, treatment and care. › Swift execution of a research agenda on testing modalities and affordable diagnostics that meets emerging needs. | | <ul style="list-style-type: none"> › Evaluate, inform and accelerate the testing research agenda. | |

HIV transmission, homosexuality, sex work and injection drug use are themselves drivers of the epidemic and should not be tolerated by any government or donor.

- **Make plans for scaling up HIV testing a priority component of national AIDS strategies**, with a strong emphasis on testing

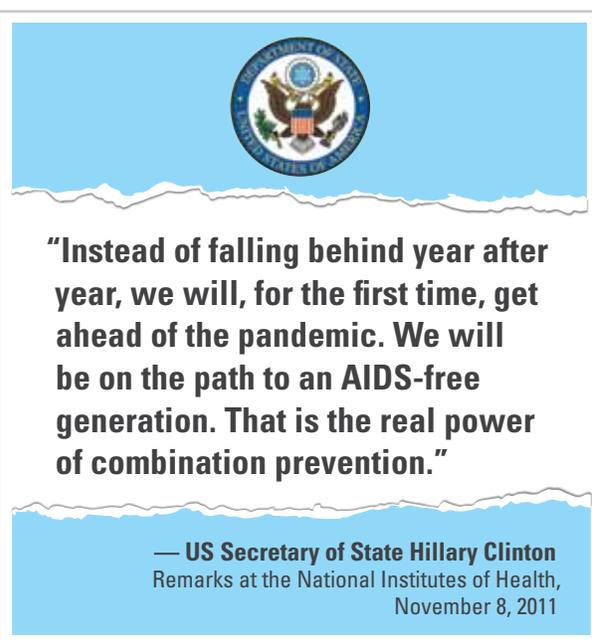
programs that are integrated with or linked to prevention, treatment and care services. These plans and resultant programs should be evaluated in terms of both the number of people tested who learn their results and the number of those people who are then referred to evidence-based services tailored to their diagnosis, relationship status and, for women of childbearing age, pregnancy status.

- **Invest in research to identify optimal testing strategies.** How do home-based testing campaigns compare to community mobilization models, which seek to bring massive numbers of people out to fixed or mobile sites for testing? Many planned evaluations of combination prevention (see p. 32) are looking at different approaches to

But there's also a critical unmet need for prevention programs that start with HIV testing and then move to messages about and linkages to combinations of services tailored to whether an individual is HIV-positive or –negative, in a relationship with a person of known or unknown HIV-serostatus, pregnant or using contraception, and so on. Why is HIV testing so important? Because impact depends on uptake. If people don't use a service, it doesn't matter how effective it is. The impact of earlier antiretroviral (ARV) treatment (ART) and ARV-based prevention for HIV-negative people depends to an enormous degree on uptake of testing and linkages to relevant services.

Sadly, rates of testing in many countries are abysmally low. There are many reasons for this, including issues with stock outs of test kits and other commodities, lack of available services (including ART), stigma and individual unwillingness to be tested. Unless the testing bottleneck is overcome, the potential of so many promising strategies will not be realized in terms of lives saved and infections averted. Action is needed and should include the following steps:

- **Safeguard human rights, and invest in an enabling environment.** Testing works in environments where people feel confident that they will receive non-judgmental support and high-quality services from their providers, regardless of the result. The human rights context must be considered as the foundation for scaled-up testing. Laws that criminalize



scaled-up testing and linkage to care. These and other investigations can provide valuable information on testing strategies that yield the greatest uptake and efficiency in identifying people with HIV, including those in early stages of infection. It will be key to track these data, act on new findings, and fill gaps with well-designed research and impact evaluation.

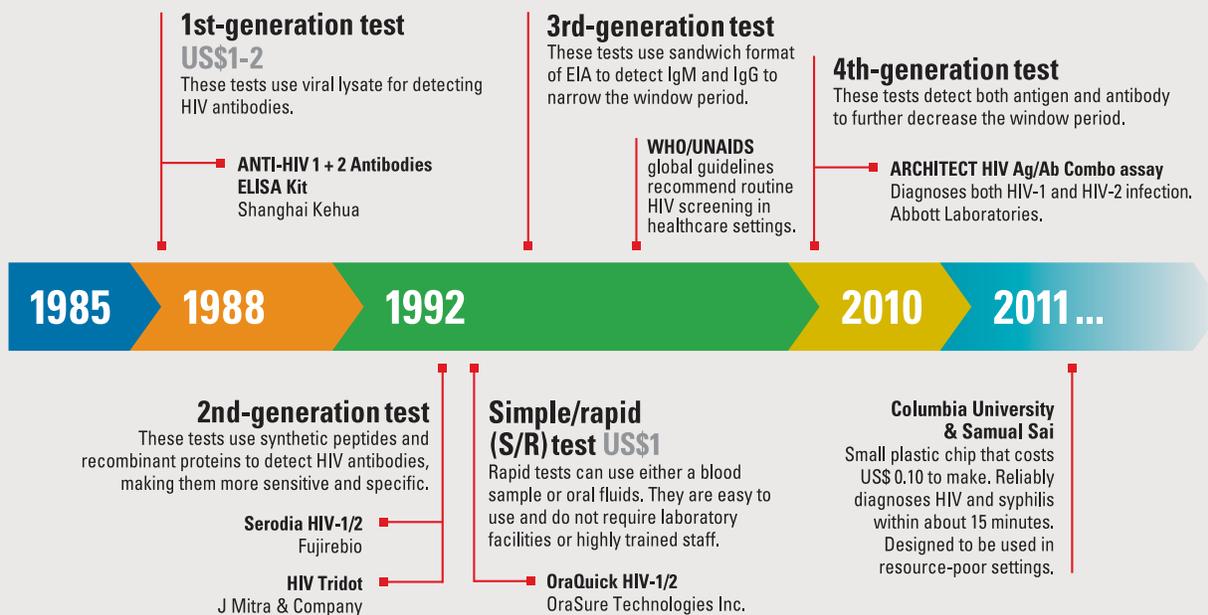
- **Conduct a critical review of stand-alone testing.** There must be a move away from, or more evidence-based justification of, stand-alone testing initiatives in which individuals learn their status and receive referrals but little follow-up or direct linkage to on-site services. Testing without linkage to prevention, treatment and care services is by and large a less efficient use of resources than testing that immediately connects people, both

HIV-positive and HIV-negative, to prevention and treatment offerings.

- **Invest in new diagnostics.** Work on testing should include out-of-the-box thinking. Is self-testing feasible using rapid, accurate diagnostics that a person might pick up for pennies at a bar, a pharmacy or a general store? The rapid tests that are currently available have varying degrees of accuracy. Investment into more accurate, affordable home-based and point-of-care diagnostics must be a priority. National quality control programs for diagnostics need to be strengthened.

All of the steps identified above are imminently doable, provided countries and donors agree on innovative, ambitious approaches that link the first step—an HIV test—to the last one: an end to the AIDS epidemic in our lifetime.

Advances in HIV Testing: A timeline



- HIV Assays: Operational Characteristics (Phase 1): Report 14: Simple/Rapid Tests, WHO (2004), http://www.who.int/diagnostics_laboratory/publications/hiv_assays_rep_14.pdf.
- "Diagnostics," AIDS Medicines and Diagnostics Services (AMDS), WHO, <http://www.who.int/hiv/amds/diagnostics/en/index.html>.
- Emily Singer. "Technology Review's Annual List of 35 Innovators Under 35," *Technology Review* (Sept/Oct 2011), <http://www.technologyreview.com/tr35/profile.aspx?TRID=962>.

Circumcise

In March 2012, it will be five years since UNAIDS and the World Health Organization issued guidance identifying voluntary medical male circumcision (VMMC) as a key prevention tool for countries with high HIV/AIDS prevalence and low levels of VMMC. The guidance is based on dramatic findings: a simple surgical procedure reduces an HIV-negative man's risk of acquiring HIV from a female sexual partner by approximately 60 percent.

The news was big; the reaction, less so. Slow implementation of VMMC has caused one of the biggest missed HIV prevention opportunities of the past five years. Had there been swifter, more ambitious implementation of large-scale VMMC campaigns, then many countries would be significantly closer to realizing the benefit of this intervention.

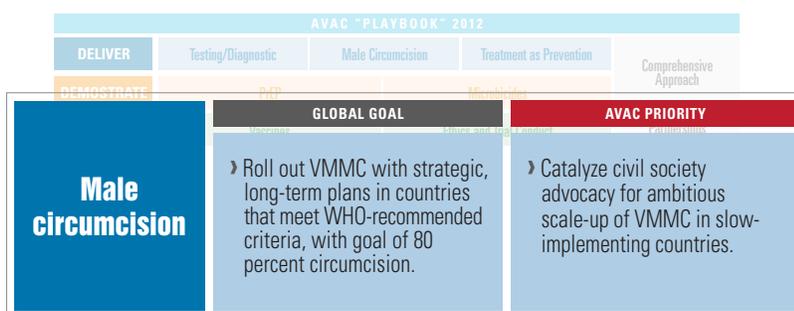
Orange Farm, South Africa, is one place where the potential benefits of VMMC have started to be realized. Home to the first randomized controlled VMMC trial, Orange Farm has seen massive expansion of VMMC services in recent years. Earlier this year, researchers from the French ANRS, which helped conduct the initial clinical research and subsequent implementation, released long-term prevalence and incidence calculations. They calculated that there had been a 55 percent reduction in incidence among men in Orange Farm who'd been circumcised during the trial or during the implementation, compared to those who'd remained uncircumcised.²

Many countries have moved slowly on VMMC implementation. In Zimbabwe, which has one of the lowest rates of VMMC in southern Africa, roughly 42,000 circumcisions have been

performed since the country launched its VMMC strategy in 2009—even though approximately 1.9 million circumcisions are needed to optimize the prevention benefits at a population level.³

In South Africa, where Orange Farm has been a notable exception to slow rates of rollout, there is now a national male circumcision policy in place. This document outlining the new policy was launched in 2011 with strong political and cultural leadership including endorsements from the country's president, Jacob Zuma, and the Zulu King Goodwill Zwelithini.

It's hoped that the South African plan will catalyze action on the ambitious goal of



circumcising 80 percent of 15- to 49-year-old men by 2015. But the country has yet to launch a mass national campaign. It has no national communications or monitoring and evaluation strategy and there are reports of

The Kindest Cut: The potential impact of VMMC as an ending AIDS strategy

Achieving 80 percent VMMC coverage by 2015, and maintaining it thereafter would avert more than 20 percent of projected new HIV infections in Botswana, Lesotho, Malawi, Namibia, Rwanda, Swaziland, Uganda, Zambia and Zimbabwe.

C Hankins et al. "Voluntary Medical Male Circumcision: An Introduction to the Cost, Impact, and Challenges of Accelerated Scaling Up," *PLoS Medicine* (Nov 29, 2011) 8(11):e1001127. doi:10.1371/journal.pmed.1001127.

² P Lissouba et al. "Adult Male Circumcision as an Intervention Against HIV: An Operational Study of Uptake in a South African Community (ANRS 12126)," *BMC Infectious Diseases* (Sept 26, 2011) 11:253. doi:10.1186/1471-2334-11-253.

³ K Dickson et al. "Voluntary Medical Male Circumcision: A Framework Analysis of Policy and Program Implementation in Eastern and Southern Africa," *PLoS Medicine* (Nov 29, 2011) 8(11):e1001133. doi:10.1371/journal.pmed.1001133.

lagging implementation at the provincial level—even in cases where money has flowed from national coffers to support provincial VMMC programming. The promise of the plan won't be realized without equally ambitious and well-thought-out programming.

As the title of a recent report from Ugandan civil society advocates states, in too many countries VMMC implementation can be characterized as “Too Little, Too Slow”⁴. In Uganda it took four years to develop VMMC guidelines—and while guidelines are now available, they remain inadequate as they are still not paired with a country-authored strategy setting targets and guiding district-level planning.

On a positive note, some countries, like Tanzania, have increased the number of circumcisions performed over the past year. To stay on track to end AIDS in our lifetime, 2012 should be the

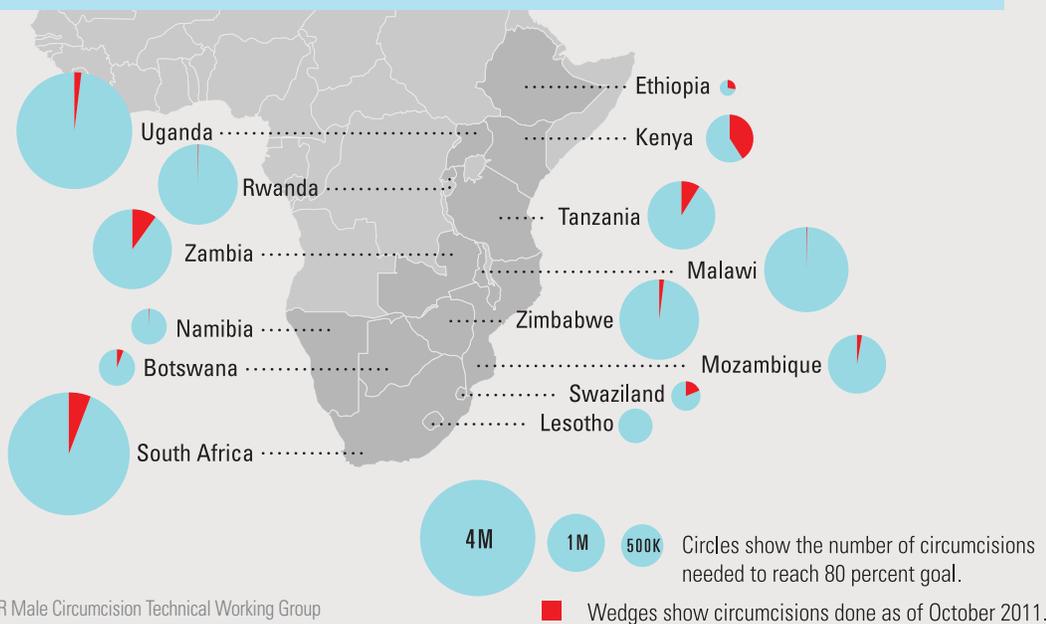
year that male circumcision truly takes off. In Zimbabwe, as few as four male circumcisions would avert one new HIV infection by 2025. The latest modeling data suggest that a US\$1.5 billion investment in rapid VMMC scale-up (circumcision of 80 percent of adult men in 13 priority countries by 2015) would yield US\$16.6 billion in savings on treatment and care services for HIV-positive individuals over 15 years⁵—and that doesn't include the economic and social benefits of reduced HIV incidence in families and communities.

Four steps stand out for maximizing the prevention benefit of VMMC:

- **Galvanize global and national leadership.** VMMC lacks the passionate advocates and international champions that transformed AIDS treatment access in poor countries from a lofty goal to an achievable reality. With recent

Progress in VMMC Scale-up in Priority Countries

Experts hope to circumcise more than 20 million men in 14 African countries by 2015, to reduce their risk of HIV infection



⁴ “Male Circumcision: Too Little, Too Slow,” Results from a community survey of Uganda’s policy and programs focused on safe male circumcision for HIV prevention (2010-2011) Health Resources Action Group, Uganda; Mama’s Club, Uganda (2011), <http://www.avac.org/toolittletooslow>.
⁵ C Hankins et al. “Voluntary Medical Male Circumcision: An Introduction to the Cost, Impact, and Challenges of Accelerated Scaling Up,” *PLoS Medicine* (Nov 29, 2011) 8(11):e1001127. doi:10.1371/journal.pmed.1001127.

remarks from US Secretary of State Hillary Clinton, identifying VMMC as one of three pillars of an effective prevention response, there is hope that this can start to change.⁶ Champions at a country level are also absolutely essential. Top political, religious and cultural leaders can be essential to mobilizing demand.

- **Close the funding gap.** PEPFAR funding for VMMC has paid for roughly 75 percent of surgeries performed to date,⁷ yet the dollars committed are a surprisingly low percentage of overall PEPFAR prevention spending, according to US advocates tracking allocations. There are places where funds need to be invested in demand mobilization and others where the demand is high and the funds simply aren't there to provide the services. These are glaring missed opportunities. Developing countries should be investing their own resources in VMMC programs. PEPFAR should increase its investment in VMMC, shifting money from less effective prevention efforts. Existing Global Fund grants should be reviewed for possible prevention reprogramming, and in the future, any new proposals from countries with high HIV prevalence and low levels of VMMC should be ranked based on whether they include VMMC as a cornerstone of combination HIV prevention.
- **Keep up the research.** Clinical research on adult VMMC devices, including PrePex and the ShangRing, is underway in several countries, and these devices have the potential to greatly simplify the VMMC procedure, which would be very beneficial in countries with shortages of health workers.
- **Put VMMC in the context of combination prevention.** No strategy—regardless of its effectiveness—should stand on its own. Some of the most innovative VMMC programs today are microcosms of combination prevention.

Slow implementation of VMMC has caused one of the biggest missed HIV prevention opportunities of the past five years.

They offer couples counseling, HIV testing, referrals and linkage to care—as well as the surgery. Nor is it an intervention for men alone. VMMC has myriad implications for women. Some are positive, like the significant secondary prevention benefit and the reduction in risk of acquiring human papillomavirus and therefore cervical cancer. It also is critical to monitor, analyze and act on data on shifts in condom use, prevalence of coerced sex and the blaming of female partners if HIV infection occurs post-circumcision.

VMMC is a test case for the task of implementing evidence-based prevention at a scale that brings the epidemic under control. To be sure, there are many differences between VMMC, a surgical procedure, and use of coitally-dependent gel or daily pill. There may be reasons that a gel or a pill for HIV prevention is more acceptable to users and providers. On the other hand, VMMC is a one-off procedure, which sets it apart from user-dependent methods.

The point is not to parse the differences between each emerging strategy but to emphasize that VMMC is one of the most powerful biomedical HIV prevention tools at hand and that success in ending the epidemic depends on how well it is implemented. This holds true for any new emerging strategy. Therefore, the ability to follow through on VMMC rollout is an indicator of readiness for work on PrEP, microbicides and more complex combination prevention.

⁶ Hillary Rodham Clinton "Remarks on 'Creating an AIDS-Free Generation,'" delivered at the National Institutes of Health, Bethesda, MD, Nov 8, 2011, <http://www.state.gov/secretary/rm/2011/11/176810.htm>.

⁷ Ibid.

Treat

Antiretroviral treatment for HIV-positive people is prevention. And not just any prevention—it’s one of the most effective prevention interventions available to countries, communities and individuals living with HIV.

In a world that would have been almost unimaginable even a year ago, US Secretary of State Hillary Clinton, UNAIDS head Michel Sidibé, and South African Archbishop Desmond Tutu are just a few of the global leaders who are talking about an end to the AIDS epidemic. And each individual has singled out antiretroviral treatment for HIV-positive people as a pillar of this goal.

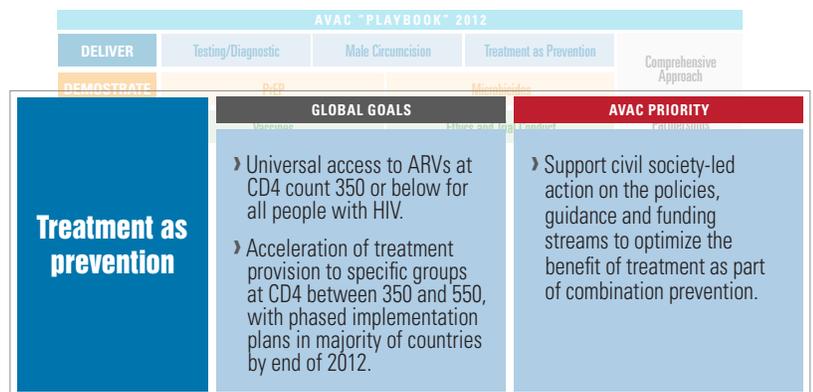
As Harlem Hospital clinician Wafaa el-Sadr said in a November debate on treatment as a prevention tool, after years of noteworthy successes that have failed to turn the tide of the epidemic, we now have powerful tools for treating and preventing HIV, “And lo and behold, they are the same thing.”⁸

The chief data behind this statement come from the HPTN 052 trial. This trial halted randomization in mid-2011 (four years ahead of its scheduled completion in 2015) following a recommendation from its independent data and safety monitoring board. HPTN 052 is examining the impact of earlier initiation of antiretroviral therapy (between CD4 350 and 550) versus initiation according to prevailing guidelines, on risk of transmission within HIV-serodiscordant couples. The trial found that earlier initiation reduced transmission within the partnership by at least 96 percent.⁹ It also found a significant reduction in cases of extrapulmonary TB in individuals who initiated ART early. The combination benefit of improved health, reduced

TB and reduced infectiousness is a triple benefit that is truly remarkable.

In the weeks and months that followed the initial data release from 052, we heard two things: First, advocates were not surprised. They assumed that such data already existed. Second, many thought that early treatment *à la* HPTN 052 would be too expensive to implement as a large-scale prevention strategy.

These two reactions came with two questions: Why is HPTN 052 news? And why, given



treatment shortages and funding crises, is it realistic to think about using the HPTN 052 results as the basis for new prevention strategies? These two questions are fundamental. Answering the first is easier than the second. HPTN 052 confirms observational data linking decreased viral load with decreased rates of transmission. It is a randomized controlled trial so it meets a higher standard of scientific evidence than previous related observational studies.

Another way to ask the second question is, “Can the HPTN 052 results be translated to HIV prevention programs that have a public health benefit in terms of reduced incidence at the community level?” The broad answer to this question is “Yes”. In all of the debates and discussions that have ensued post-HPTN 052,

⁸ “Treatment as Prevention,” Emerging Issues in Today’s HIV Response Debate, USAID, 6th in series (Nov 10, 2011), [mms://wbmswebcast1.worldbank.org/HDN/2011-11-16/HDN_USAID_Debate.wmv](https://www.wbmswebcast1.worldbank.org/HDN/2011-11-16/HDN_USAID_Debate.wmv).

⁹ MS Cohen et al. “Prevention of HIV-1 Infection with Early Antiretroviral Therapy,” *New England Journal of Medicine* (Aug 11, 2011) 365(6):493-505.

there's virtual consensus that treatment can be used as prevention, that the prevention effect observed in HPTN 052 is real and that there is an imperative to act on this powerful new evidence.

There is disagreement about whether the results warrant an immediate shift in resources from existing prevention programs to treatment scale-up. Some say, "Yes, of course." Others say, "We should wait and learn about resistance, the durability of the effect, and so on." The stakes are far too high for there to be a stalemate on this issue. The US PEPFAR Scientific Advisory Board (SAB) recently released its recommendations on HPTN 052 for PEPFAR programs (see box, p. 18). They represent key steps for all countries, not only those funded by PEPFAR. Of note, the first three recommendations are currently supported by WHO guidance documents.¹⁰ The fourth recommendation, urging prioritization of specific groups with CD4 cell counts greater than 350, is not part of WHO guidance, and it is of the utmost importance that WHO address this gap in guidance as soon as possible.

We echo the PEPFAR SAB recommendations in the list of imperatives below:

- **Be ambitious.** Now is the time for global public health leaders to champion the movement to end AIDS. This should start—but not end—with US President Obama setting a target of treating six million people by 2013, using current PEPFAR funds. Other countries, both in the developing and developed world, should follow suit by setting targets and contributing their own funds. There's every reason to believe that expanded treatment targets can be reached with the resources already available at hand. Ambition can be defined by a change in vision, even if the budget remains the same.
- **Start by meeting the needs of HIV-positive people in care.** At the recent debate on

We now have powerful tools
for treating and preventing HIV,
“And lo and behold, they are the
same thing.”

spending more on treatment as prevention, Sten Vermund of Vanderbilt University said, “Millions of people are currently in care and we do not have policy in place nor drug available to treat them. Those people are infectious every single day of their lives, and we have the opportunity to immediately transfer funds to treat them from less-effective, self-delusionary strategies.” We couldn't say it better, so we won't. (For more on what to spend less on, see “Reprogram”, on p. 21.)

- **Put prevention of pediatric infection on the treatment continuum, and prioritize treatment of pregnant women.** Prevention of pediatric infection through treatment of pregnant and breastfeeding mothers and their newborns is the original form of ARV-based prevention. WHO recognizes a range of options for this strategy. From “Option A”, which consists of short-course, single-drug therapy for mother and infant, to “Option B”, which involves limited-duration combination therapy for mother and infant, to “Option B-plus” which provides the mother with combination therapy for life. Expanding to option B-plus in all countries is a critical step to realizing the dual goals of eliminating pediatric HIV infections and ending the AIDS epidemic by keeping HIV-positive mothers alive, healthy and disease-free.
- **Implement and research in parallel—not sequentially.** There are still critical questions to be answered about treatment as prevention. As the box on page 32 summarizes, there are a

¹⁰ “HIV/AIDS: Guidelines,” WHO, <http://www.who.int/hiv/pub/guidelines/en/>.

PEPFAR Scientific Advisory Board Treatment as Prevention Recommendations

- Accelerate the support of the scale-up of antiretroviral therapy (ART) to all HIV-infected individuals with CD4+ cell count <350 cells/mm³, irrespective of World Health Organization (WHO) disease stage for treatment and prevention (Goal: 90% coverage).
- Offer ART to all patients with HIV-related tuberculosis (TB), irrespective of CD4+ cell count and integrated during TB treatment.
- Endorse WHO guidelines for prevention of mother-to-child transmission (PMTCT) in pregnant and breastfeeding women with a CD4+ cell count >350 cells/mm³, with a preference for Option B (ART throughout pregnancy and breastfeeding) where locally appropriate.
- Support the use of ART in specific populations with CD4+ cell counts >350 cells/mm³ in order to prevent transmission to others based on the results of HPTN 052. The benefit of this intervention has been demonstrated for heterosexual discordant couples. Careful evaluations, including assessment of benefit/risk/impact/feasibility and modeling exercises are urgently needed to identify populations that should be prioritized for this intervention, given local conditions.
- Intensify efforts to establish effective programs for engaging key affected populations in HIV prevention, care and treatment programs. Particular efforts should be undertaken to ensure key affected populations eligible for treatment receive ART in an enabling environment that supports their human rights.
- Seek and secure sufficient resources to implement the recommendations, given the scientific basis for, and potential impact of, their implementation.

PEPFAR Scientific Advisory Board Recommendations for the Office of the US Global AIDS Coordinator: Implications of HPTN 052 for PEPFAR's Treatment Programs, PEPFAR (Sept 2011), <http://www.pepfar.gov/documents/organization/177126.pdf>.

number of ongoing initiatives that will inform implementation of combination prevention. But we should not wait for these study data to begin implementation. Throughout the AIDS epidemic, the response has been based on the best available information and then fine-tuned as research provided new information. This is what needs to happen now.

- **Provide decision-making tools to policymakers and program implementers in developing countries.** We cannot pay for everything that has been done in the past. Nor should we, as some programs, like abstinence-based prevention, have not had a demonstrable impact on incidence. Yet there are also difficult choices to be made. Modeling and feedback from ongoing impact evaluations need to be responsive to the priority questions from leaders on the frontlines.
- **Get the normative guidance in place so that countries have the “green light” to act.** Normative guidance from UNAIDS and WHO is often a pre-requisite for the development of national plans on specific strategies. WHO is planning normative guidance for all ARV-based prevention. This should be developed with all due speed. Even before that, a separate guidance on HIV-serodiscordant couples should be released.
- **Include treatment in combination prevention initiatives.** Impact evaluation of combination prevention packages that include male circumcision, prevention of pediatric HIV infections and comprehensive prevention is the best way to understand how to optimize the prevention benefits of treatment. In different settings, different approaches will be needed to reach people with effective therapy and adherence support so that those who are highly likely to transmit are likely to remain virologically suppressed. These approaches need to be tested, analyzed and

used to improve the predictions and questions generated by models (see next section).

- **Plan for PrEP as an additional tool in specific situations.** Oral PrEP using tenofovir-based drugs has demonstrated effectiveness in gay men and transgender women, as well as in HIV-serodiscordant couples. Topical PrEP using 1% tenofovir gel has worked in one trial in women. This evidence isn't enough to inform large-scale rollout, but it is the basis for a call to action on demonstration projects, follow-up research, and inclusion in models of future combination prevention packages (for more on topical and oral PrEP, see Part Two).
- **Stay clear on the terms.** Behind the excitement and even hype around HPTN 052, there are real areas of uncertainty—including some ambiguity about what “treatment as prevention” means (see box at right). Is it achieving universal access to ARVs for people with a CD4 cell count of 350? Is it programs that start individuals regardless of CD4 cell count? Or programs that target key populations, such as HIV-serodiscordant couples and pregnant women? The answer to all of these questions is yes. But what constitutes treatment as prevention will vary by country. It is critical to define what treatment as prevention means in a given context and to fill in the knowledge gaps so that these definitions get clearer over time.
- **Be prepared for, but not deterred by, disappointment.** HPTN 052 is exciting for the possibilities it has raised and the momentum it has generated. But there are still many unknowns about the durability of the effect, feasibility of implementation and so on. The task at hand is to acknowledge the limitations of what we know, and yet remain optimistic enough to pursue the dream.

Model

In this brave new world of ending the epidemic, epidemiological modelers can sometimes seem like our most intrepid guides. To be sure, they can conjure projections that seem to map what will happen if *this* is done or *that* is not. But, as modelers hasten to explain, they cannot predict the future. One need only look at the multiplicity of conclusions regarding the potential impact of treatment as prevention. Reuben Granich and his colleagues from the World Health Organization have made the case that universal access to testing and treatment could end the epidemic by 2050.¹¹ John Blandford and his team at the CDC have produced a model that, without being quite as optimistic, is also firm in its finding that

A Guide to the Language of ARV-based Prevention

ART

Antiretroviral therapy; a combination of medications leading to viral suppression in people living with HIV

ARV

Antiretrovirals; treatment drugs that are individually or co-formulated

Long-acting methods

Strategies, such as a periodic shot of ARVs or a vaginal ring (inserted monthly that could potentially provide continuous protection against HIV

Microbicides

Substances that can block HIV in the vagina or rectum; refers to a range of products including topical PrEP, non-ARV-based compounds and/or “multipurpose” technologies

Multipurpose technologies

The emerging term for combination HIV prevention, STI prevention and/or contraceptive products

PrEP

Pre-exposure prophylaxis using ARVs

Topical PrEP

ARV-based microbicides

Treatment as prevention

Systematic use of ART to reduce sexual transmission risk in HIV-positive people; also known as TasP, T4P, TisP and TLC+ (testing and linkage to care, plus treatment)

¹¹ RM Granich et al. “Universal Voluntary HIV Testing with Immediate Antiretroviral Therapy as a Strategy for Elimination of HIV Transmission: A Mathematical Model,” *Lancet* (Jan 3, 2009) 3:373(9657):48-57.

scaling up earlier treatment will help “bend the curves” of new infections, morbidity, mortality and, eventually, costs associated with the epidemic in Kenya.¹² And Timothy Hallett of Imperial College London and the HIV Modeling Consortium has led work that shows just how easily a treatment-as-prevention benefit can be lost in a setting where there’s poor retention in ART programs.¹³

Each of these models can generate nearly endless conversations and questions. None represents “the truth”. As the world seeks to build momentum for the movement to end the AIDS epidemic, it is critical to engage with modeling as a powerful advocacy tool. The most useful modeling is often the modeling that surprises, and that raises questions or urges further exploration via well-framed research projects.

Models are needed to define questions like:

- What levels of uptake of testing and treatment, and of treatment adherence, are needed to optimize treatment as prevention?
- What are the prevention gains from incremental expansion of ART coverage for specific populations above CD4 cell count 350.
- How does rapid and successful scale-up of voluntary medical male circumcision (VMMC) change the treatment as prevention needs of a given country?
- What are the synergies between combinations of different interventions?

Models are on shakier ground when they are interpreted as being solid predictors of what will happen in the future. With this in mind, the following steps are key:

- **Model combination prevention.** Combination prevention is at the heart of the movement to end AIDS. The most helpful models are, increasingly, those that look at multiple

interventions and their effects on one another, rather than comparing one intervention to another. Such models would show the prevention benefit of different interventions, the synergies between interventions, and the paths to greatest impact.

- **Model success.** What will it take to realize the benefits of combination prevention? How high will retention or adherence in ART programs need to be to sustain a prevention benefit? And what rate of uptake of VMMC will reduce the impact on treatment programs—in terms of newly infected individuals needing treatment—over five or ten years? These are the kinds of questions that models can help address.
- **Incorporate advocates as allies as models are being developed and debated.** The HIV Modeling Consortium, an initiative funded by the Bill & Melinda Gates Foundation and housed at Imperial College London is one key convener that can ensure that civil society voices are shaping the modeling agenda. The consortium is coordinating a wide range of research activities in mathematical modeling of the HIV epidemic. It should ensure that there are advocates present at each of its think tank meetings. It should also develop a civil society-oriented request for applications that includes guidance as to how groups can work with their national governments effectively and/or make direct requests for modeling assistance, which will bolster their advocacy work in specific contexts.

The best way to develop better models is to work with expert epidemiologists, social scientists and clinicians to gather the types of real-world data needed to shape updated projections. Put another way, models can be immensely helpful in making decisions, but it is the implementation of the decisions that will make the real difference.

¹² AVAC Advocate’s Network Update, Sept 16, 2011, <http://www.avac.org/ht/d/sp/i/38498/TPL/AN/pid/38498/displaytype/iframe>.

¹³ J Eaton and T Hallett, forthcoming.

Reprogram

One cornerstone of the movement to end AIDS is the conviction that many goals can be achieved through better use of the resources that are currently at hand. As the authors of “Towards an improved investment framework for an effective response to HIV/AIDS” wrote in the *Lancet* earlier this year: AIDS funding will have a far greater impact if investments are made and evaluated on the basis of their impact on relevant parameters, such as greater reductions in incidence and greater gains in the health and longevity of people living with HIV. Counting

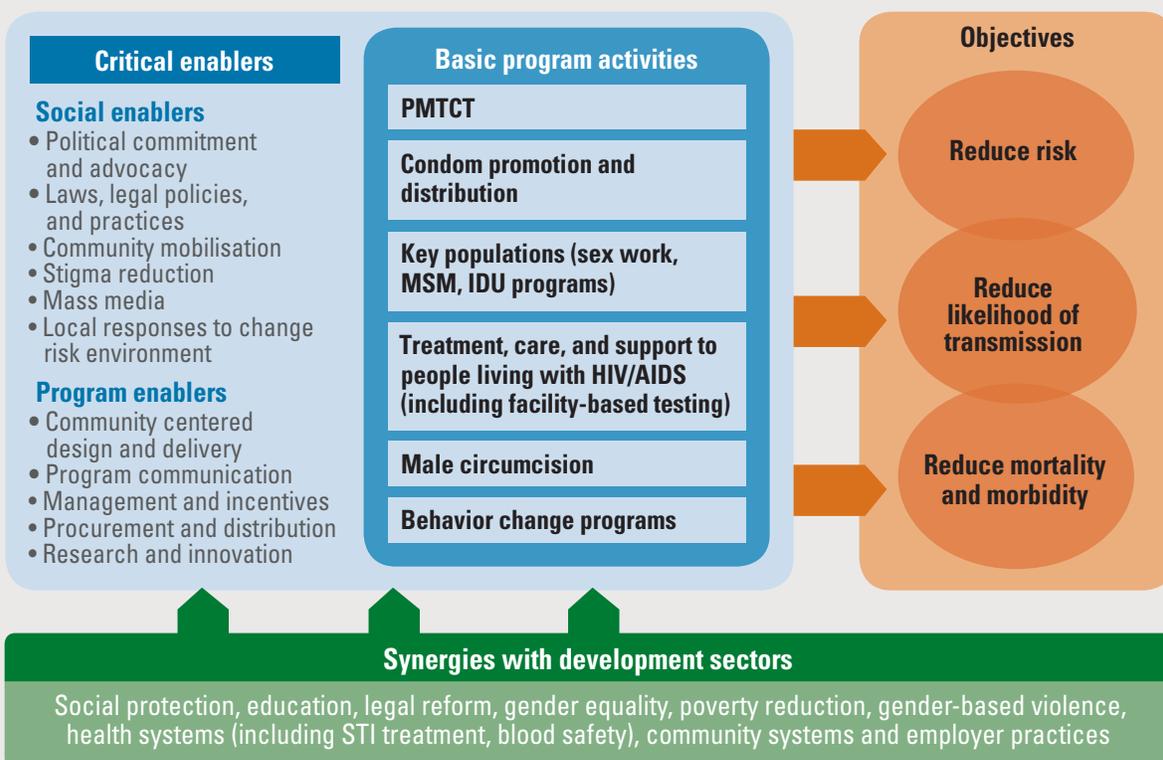
the number of condoms purchased or HIV tests administered isn't enough to measure success.¹⁴

To act on this, the following changes should be adopted:

- **Shift from a silo approach** to prevention interventions to a smart use of combination strategies.
- **Shift from the WHO-defined Option A** for prevention of pediatric infection (short-course or single-dose ARV treatment for mother and infant) to Option B-plus (lifelong treatment for pregnant and lactating HIV-positive women, regardless of CD4 cell count; such programs

Core Activities for an Effective AIDS Response

| | |
|------------------|---|
| For whom? | Explicitly identify and promise populations on the basis of the epidemic profile. |
| How? | Use the human rights approach to achieve dignity and security. |



B Schwartländer et al. “Towards an Improved Investment Approach for an Effective Response to HIV/AIDS,” *Lancet* (June 11, 2011) 377(9782):2031-41.

¹⁴ B Schwartländer et al. “Towards an Improved Investment Approach for an Effective Response to HIV/AIDS,” *Lancet* (June 11, 2011) 377(9782):2031-41.

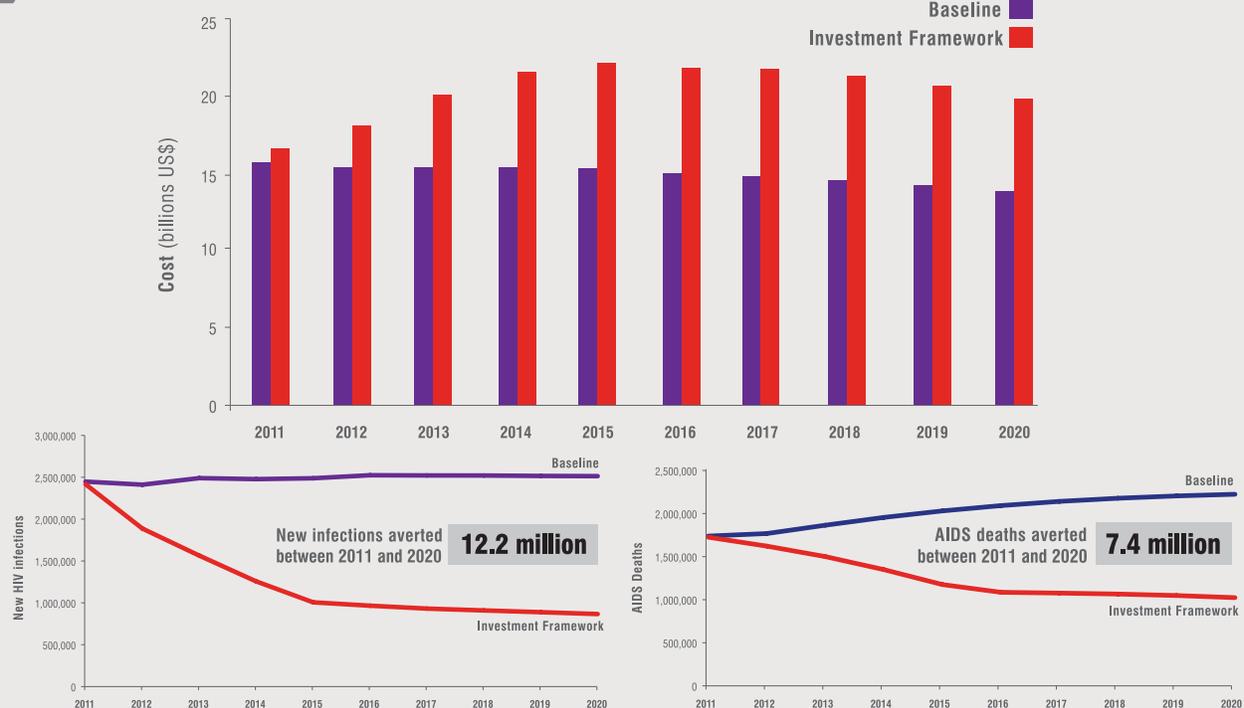
should, ideally, make a concerted effort to reach the woman’s partner as well).

- **Shift from stand-alone testing centers** to testing centers that link individuals to prevention and care services.
- **Shift increased civil society funding** to initiatives that synergize with and/or take on service provision—and scaling back or re-examining civil society funding that is not linked to measurable outcomes aligned with ending AIDS.
- **Shift and/or expand from individual counseling and testing** to couples-oriented interventions in countries and contexts where interventions targeted at HIV-serodiscordant couples will have an impact on new infections.
- **Shift from a “broad and shallow” approach** to a “targeted and deep” approach¹⁵ to prevention programming that prioritizes focused, evidence-informed combination interventions for specific communities and contexts.

Fund

The three figures below project what will happen if the world increases its investment in evidence-based AIDS programs—and what will happen if it doesn’t. As the top figure shows, increasing spending between now and 2015 will result in diminishing funding requirements by 2015. Yes, the price tag is higher than the current baseline of approximately US\$15 billion per year. But look at the bottom two graphics, and it becomes clear why the increased funding is essential. Maintaining spending at baseline levels results in no change in HIV incidence or deaths between 2011 and 2020. Spend US\$15 billion per year for the next nine years and have no impact on current trends. Or: spend more money on smarter programs and start to turn the tide of the epidemic once and for all. The right choice should be clear to us all. Failure to act will waste money and—more importantly—precious lives. ■

Invest Now to Save Lives and Funds



B Schwartländer et al. “Towards an Improved Investment Approach for an Effective Response to HIV/AIDS,” *Lancet* (June 11, 2011) 377(9782):2031-41.

¹⁵ Ibid.

The End

Develop

- ▀ Vaccine
- ▀ Cure
- ▀ Sustain the science
- ▀ Control the epidemic

Demonstrate

- ▀ PrEP
- ▀ Microbicides
- ▀ Plan
- ▀ Prioritize
- ▀ Pilot

Deliver

- ▀ Test
- ▀ Circumcise
- ▀ Treat
- ▀ Model
- ▀ Reprogram
- ▀ Fund

DEMONSTRATE

DEMONSTRATE

PART

2

Plan. Prioritize. Pilot. For the effort to end AIDS to remain on track over the next 10 to 15 years, today's emerging prevention tools—i.e., PrEP, microbicides and an AIDS vaccine—need to remain on track for introduction and delivery.

If the “test, circumcise, treat” agenda detailed in the previous section is fully implemented, rates of new HIV infections could drop significantly in the next decade, as could the number of people living with HIV who progress to and die from full-blown AIDS. As the epidemic comes under control, it will become even more apparent where new tools can be added to combination prevention packages to have the greatest impact and synergy. The need to persevere holds for AIDS vaccines and the search for a cure (see Part Three).

We can't know for certain where new tools might be needed if today's powerful options are fully deployed. But we cannot afford to assume that the strategies described in Part One will be enough. HIV-negative women still do not have a tool that they can use themselves to reduce

risk. For HIV-negative women in serodiscordant couples, the prevention benefits of earlier ART initiation depend on male involvement. Neither VMMC nor earlier treatment have been evaluated in randomized trials in gay men, other MSM or transgender women. The need for a rectal microbicide for gay men and transgender women is seldom acknowledged, and this should change.

Oral and topical PrEP have shown proof of effectiveness with tenofovir-based compounds in key trials. Other trials of the same or similar strategies have found no effect. New interventions are studied in multiple effectiveness trials precisely because the outcomes may vary. Contradictory results such as the CAPRISA 004 and VOICE data on 1% tenofovir gel are not a reason to halt development. Instead, conflicting data make it even more important that there is a swift and transparent process for using additional clinical trials and other analyses to clarify the potential of emerging tools.

The Washington Post

“AIDS remains the leading cause of orphanhood and of death among women of reproductive age ... Barack Obama has achieved great things thus far in his presidency ... He is in a position to make a game-changing impact on the war against AIDS.”

— Archbishop Desmond Tutu
“The End of AIDS is Within Our Reach”
The Washington Post, September 21, 2011

Plan

In the past two years the biomedical prevention research field has learned much about defining and managing success, and the challenges have been ones that advocates have longed for.

Each trial that has had a positive result prepared in a different way, and executed specific steps once the good news was released. For example:

- The RV144 vaccine trial team had a road map that specified next steps for three different tiers of efficacy and used that to shape the messages around the evidence of modest protection.
- The iPrEx PrEP trial team had submitted the follow-on protocol for iPrEx OLE, the open-label extension trial, before the results of iPrEx were known.
- The CAPRISA 004 microbicide trial team had no immediate plan or protocol when its trial data became available but has since developed, adapted and obtained funding for a follow-on protocol that seeks to understand how women view a range of prevention strategies. (When *AVAC Report 2011* went to press, the South African Medicines Control Council had not yet approved the protocol.)
- The Partners PrEP trial team had a plan but changed it when the placebo arm of the study stopped early. It's now rolling placebo-arm participants who remained HIV-negative into the active arms. The study will run to its scheduled completion date and expand on the initial data.

Now is the time for the biomedical prevention field to move from a trial-by-trial approach to define product delivery pathways to a far more comprehensive, forward-looking planning

HIV-negative women still do not have a tool that they can use themselves to reduce risk.

process that anticipates the needs of potential first-generation products, like tenofovir-based oral and topical PrEP, and maps a clear path to second-generation products.

Plan for Success: First-generation PrEP

- **Define the terms.** Broad plans and modeling exercises that center on “PrEP” and don't tease out the real differences between the oral and topical products add needless confusion.

| AVAC "PLAYBOOK" 2012 | | | | |
|----------------------|---|-------------------|---|------------------------|
| DELIVER | Testing/Diagnostic | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| Oral PrEP | GLOBAL GOAL <ul style="list-style-type: none"> › Swift implementation of pilot programs and/or phased implementation in countries and communities where oral TDF/FTC-based PrEP is relevant › Clear action on evaluating PrEP and developing policies in countries where it might be introduced over the long-term | | AVAC PRIORITY <ul style="list-style-type: none"> › Ensure that PrEP demonstration projects are launched for relevant populations. | |

There are two formulations of 1% tenofovir gel—one adapted specifically for rectal use. There are two dosing strategies for 1% tenofovir gel that have been evaluated in effectiveness trials (see box, p. 26). Effective planning depends on precise definitions: Who is being planned for, and with, and what is the exact intervention in question?

- **Ensure that PrEP implementation and modeling exercises are relevant to today's context.** If combination prevention is the

Similar Data, Different Next Steps: The case of iPrEx, CAPRISA 004 and VOICE

In 2010, the iPrEx trial of oral TDF/FTC in gay men and other men who have sex with men (MSM) and transgender women showed evidence of benefit. So did the CAPRISA 004 trial of 1% tenofovir gel. In November 2011, the 1% tenofovir gel arm of the VOICE trial halted due to futility. Even before this development, iPrEx and CAPRISA 004 had triggered different steps. Why is this?

The data on oral TDF/FTC for gay men, other MSM, and transgender women came from a larger trial with greater statistical power that focused on a product that had already been brought to market as an approved treatment for HIV-positive people. Along with the slightly stronger data from iPrEx, oral PrEP using TDF/FTC involves a vastly simpler product development pathway than 1% tenofovir gel. TDF/FTC is licensed for use as treatment, and commercial manufacturing capacity exists today. Subsequent steps include the follow-on open label trial, iPrEx OLE, as well as planned demonstration projects in MSM in Miami and San Francisco. There is also action on the part of Gilead, the developer and manufacturer of TDF/FTC, to submit data to the FDA in an effort to get a label change indicating that TDF/FTC can be used for prevention in the iPrEx populations.

In contrast, CAPRISA 004 involved a novel product that hasn't yet moved through the product development pathway. A number of questions were raised about the product itself and about its effectiveness when used in different dosing strategies, which put it on a pathway that includes ongoing randomized trials. The wisdom of continuing with randomized trials was borne out by the VOICE finding that women counseled to use 1% tenofovir gel daily had the same rate of HIV infections as women counseled to use the placebo gel daily. At press time, there was no explanation as to why the gel did not reduce HIV risk among participants in the active arm. These conflicting data, while disappointing, are exactly the reason that placebo-controlled trials are often needed after an initial proof of concept.

Oral PrEP using TDF/FTC

What we know: In the iPrEx oral PrEP trial, daily oral TDF/FTC was effective at reducing risk of HIV infection by 42 percent overall in gay men, other MSM and transgender women. These data have prompted demonstration projects and a move in the US to seek a prevention indication for TDF/FTC for MSM. The data are mixed in heterosexual populations, particularly among women. The Partners PrEP trial found clear and significant prevention benefits for HIV-negative men and women who used either TDF/FTC or TDF daily—with no statistically significant differences between the two drugs or between men and women in terms of level of protection. FEM-PrEP was halted early after a DSMB review found no evidence of benefit of daily oral TDF/FTC among heterosexual women; the daily oral TDF arm of the VOICE trial was halted after a similar DSMB review and recommendation.

Topical PrEP using 1% tenofovir gel

What we know: At present, we know that in the CAPRISA 004 trial, South African women counseled to use 1% tenofovir gel before and after sex had a 39 percent overall reduction in HIV risk compared to participants counseled to use the placebo. CAPRISA 004 also found that the gel reduced risk of herpes simplex virus type 2 (HSV-2) by over 50 percent among women who were not infected with HSV-2 at the beginning of the trial. In the VOICE trial (conducted in South Africa, Uganda and Zimbabwe), women counseled to use tenofovir gel daily had the same risk of HIV infection as women counseled to use a placebo gel. This leaves the field with urgent questions about where, how and for whom gel might be an effective HIV prevention tool. Key information will come from analysis of the VOICE trial data and from the ongoing FACTS 001 trial, which is testing the same dosing strategy used in CAPRISA 004.

A new rectal formulation of tenofovir gel is being evaluated in a Phase II trial, MTN 017. Coordinating rectal and vaginal research agendas and implementation plans is a must.

key, then policy makers and implementers need to understand where oral and/or topical PrEP fit in and not how they compare to a single intervention—e.g., treatment as prevention. WHO, UNAIDS, Imperial College London, Georgetown University and the London School of Hygiene and Tropical Medicine have received substantial grants from the Bill & Melinda Gates Foundation for PrEP preparedness work—and they should accelerate activities that help define, in practical terms, how holistic ARV-based prevention (for HIV-positive and –negative individuals) might work.

- **Define the costs—and bring them down.** The cost of tenofovir disoproxil fumarate (TDF) and/or TDF plus emtricitabine (FTC) (combination TDF/FTC), the two agents that have shown effectiveness in PrEP trials, could potentially be a major barrier to implementation of oral PrEP programs. Gilead’s licensing agreements with generic manufacturers have helped ensure that these drugs are available at a low cost in countries with the least resources, but the prices need to be established and reduced for lower-middle-income countries too. For 1% tenofovir gel, work clarifying a firm cost estimate for the gel and applicator should continue, even as the gel’s effectiveness is elucidated.

Plan for Success: Oral tenofovir-based PrEP

AVAC and our partners are actively involved with an array of activities focused on accelerating targeted implementation of and/or follow-up research on oral PrEP based on tenofovir, while also emphasizing the need for next-generation, long-acting products.

There are urgent questions about where, how and for whom 1% tenofovir gel could be an effective prevention tool.

These are some key recommendations:

- **Develop a plan for clarifying if and how tenofovir-based oral PrEP can be used in women.** The current data are complex and even contradictory for both oral and topical tenofovir-based products in women. Analysis of completed trials will shed light on biological or behavioral factors that might explain the various findings. The field also needs to determine what additional trials might be needed going forward.
- **Plan and implement pilot projects.** There is a follow-on, open-label trial—iPrEx OLE—as well as demonstration projects being planned in the US. The findings from these efforts should trigger further implementation action in relevant countries. The positive results from Partners PrEP (see p. 31) and HPTN 052 should be explored in projects with serodiscordant couples that evaluate combination HIV prevention including earlier ART for the HIV-positive partner and PrEP for the HIV-negative partner. Such projects should gather information in decision making, adherence, behavior and other issues.
- **Move swiftly on regulatory review.** The US Food and Drug Administration should proceed with review of available data on PrEP using TDF/FTC for gay men and other MSM recognizing that it may take longer to understand how tenofovir-based oral PrEP works for heterosexual men and women.

Plan for Success: Topical PrEP*—1% tenofovir gel

As the box on page 26 explains, 1% tenofovir gel—the product that showed effectiveness in CAPRISA 004, and no benefit in VOICE—is a novel candidate. No other topical HIV prevention strategy has been brought to market. One percent tenofovir gel is being developed by a group of partners, rather than a single pharmaceutical company. We’ve tracked and analyzed the development of 1% tenofovir gel extensively—and as this report went to press, we were grappling with the results of the VOICE trial. Please visit www.avac.org/tenofovirgel for a forthcoming full-length report and the most up-to-date information and advocacy tools. In the meantime:

- **Clarify leadership.** Identify which organization or structure will assume leadership and final decision making in driving forward all aspects of 1% tenofovir gel development. Clarity in the messages regarding VOICE and its implications for CAPRISA 004 and FACTS 001 is of the utmost importance for this coordinating entity or team.
- **Develop and share a strategy** that includes projected timelines for all clinical regulatory, commercial and policy activities to provide a realistic sense of timing, funding and effort.
- **Incorporate rectal formulation research.** The strategic plan should include priorities and funding needs for research on and potential implementation of 1% tenofovir gel as a rectal microbicide.
- **Clarify the manufacturing pathway and confirm the cost of goods** (and the potential for cost reductions) and the timelines, for 1% tenofovir gel with its current applicator to

| AVAC "PLAYBOOK" 2012 | | | | |
|----------------------|---|-------------------|---|------------------------|
| DELIVER | Testing/Diagnostic | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| DEMONSTRATE | PrEP | Microbicides | | |
| Microbicides | GLOBAL GOALS | | AVAC PRIORITY | |
| | <ul style="list-style-type: none"> › A clear and accelerated product development pathway for clarifying the effectiveness of 1% tenofovir gel. › Donor decisions and actions about future trials and overall pipeline are accessible to, and shaped by, civil society and other stakeholders. | | <ul style="list-style-type: none"> › Amplify civil society demand for a firm and cohesive plan for 1% tenofovir gel and future products. | |

inform policy making, advocacy and planning by donors and country programs.

- **Identify and follow up on practical ways to lower the cost of 1% tenofovir gel**, including accelerating and supplementing specific plans to develop a less expensive applicator.
- **Develop implementation research strategies and budgets** in key areas, such as service delivery, provider training and marketing. Yes, there are still questions about 1% tenofovir gel. But if the product does move into wider use and the field waits to develop implementation plans until all of these questions are addressed, it will be too late.

Plan for Success: Next-generation products

There are plans underway for essential trials of second-generation products, including the dapivirine ring and a long-acting injectable form of PrEP. Key next steps include:

- **Have a community-informed plan for success at the outset of every trial.** Each new efficacy trial should have a road map for next steps to be taken under various scenarios, such as moderate, high and marginal effectiveness. A draft version of the road map should be presented for input to stakeholders

* As the box on page 19 shows, there's a range of terminology for describing ARV-based prevention. We're using topical PrEP, rather than microbicide, to describe 1% tenofovir gel to emphasize the importance of including both oral and topical formulations in conversations about PrEP and its place in the HIV prevention tool kit.

who are being asked to support or participate in the trial.

- **Build strong product-development teams.**

For products that are developed by non-profits or public-sector actors, establish leadership structures that set aside individual agendas and establish clear priorities. It's also essential to bring in the right skill sets early on, including those of social marketers and manufacturing and regulatory experts, so that they can help shape the plans and lead their implementation.

The responsibility for planning next steps does not solely rest on the shoulders of the trial teams. National governments can plan in advance for how they will assess and respond to emerging data. Donors and implementers can map out the steps that would lead to eventual product introduction. And civil society advocates can establish advocacy positions on various scenarios including follow-on trials, potential implementation, cost and licensure. All of this is work that can be initiated before the results of a trial are known.

Mind the Gap: Ethics and access to emerging strategies

Good news can bring tough questions. As biomedical prevention trials demonstrate effectiveness, there is intense attention on the gap between the end of the trial and the next step to access—especially regarding access for participants in the original study that provided positive results. Many of the questions have been addressed in previous discussions, but new data and more concrete ideas about how well some of these strategies work have intensified conversations, such as those that occurred at a July 2011 meeting arranged by AVAC along with the World Health Organization, UNAIDS and the International Partnership for Microbicides. In the coming year, AVAC will work with these and other partners to convene a consensus-building dialogue on these and other key questions:

- What are the post-trial obligations regarding participant access to products that show initial effectiveness? At what point in the life cycle of the trial should funding be set aside for post-trial access?
- What factors should be considered by stakeholders defining the “standard of prevention” for new trials? Should voluntary medical male circumcision or partner testing and counseling be a requirement for inclusion in future HIV prevention trials?

- What are the ethical implications of the HPTN 052 trial on future studies? Should all participants in stable partnerships be offered couples testing and, if serodiscordant, HIV treatment?
- What are best practices for communicating with trial participants, their communities and broader stakeholder groups about the key steps that will occur from the time a trial's positive result is known to the time trial participants and the larger community can access the intervention?
- When there is a limited quantity of product after a positive result in an effectiveness trial, such as an agent that's been evaluated in a PrEP trial, should placebo recipients be prioritized for post-trial access since they didn't benefit during the course of the trial? Should all participants in the trial receive the agent? For how long?
- If the informed consent process emphasizes that it may be years before participants would gain access to any intervention that shows benefit, does that sufficiently address post-trial access expectations when actual results showing benefit are available? Will discussion of gaps between study closure and post-trial access affect enrollment or community support for the trial?

Prioritize

Adherence matters. This may be the most important finding to emerge from recent HIV prevention trials. The effectiveness of ARV-based prevention clearly depends on its correct and consistent use. The top priority for the prevention research field in the coming years will be to act on this awareness in two ways:

- **Improved methods of adherence support must be developed to translate clinical trial data into real-world effectiveness.** Different types of expertise, including social marketing, social and behavioral science, need to be applied to the task of turning topical and oral PrEP and earlier ART for HIV-positive people into effective public health strategies. New and existing funders also need to invest in the types of activities that will clarify where and how first-generation products can be used, building on innovative approaches to HIV testing, an essential component of safe and effective ARV-based prevention.
- **Build and maintain a pipeline of longer-acting options.** The robust pipeline of longer-acting, less adherence-dependent products needs to remain on track for swift results and follow-up action. Several ARV-containing vaginal rings are currently in development, with the first vaginal ring efficacy trial set to begin in early

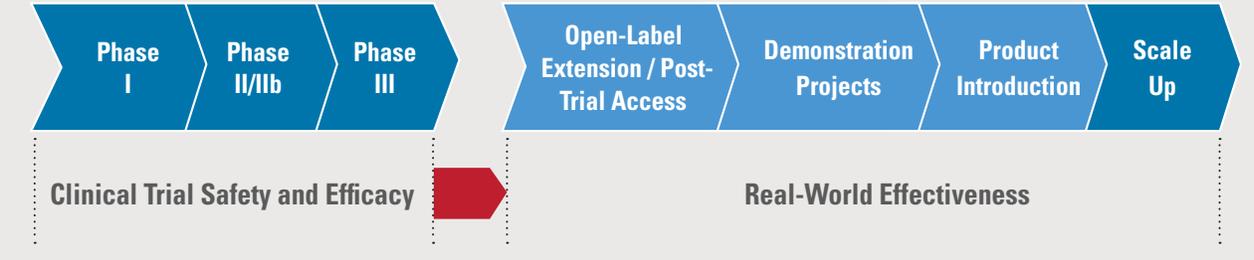
Emerging Data: Injectable hormonal contraceptives and HIV risk

In the month before *AVAC Report 2011* went to press, new data collected during the Partners in Prevention trial with serodiscordant couples suggested that use of injectable hormonal contraceptives doubled women’s risk of acquiring and transmitting HIV compared with women using other contraceptive methods. The trial was not designed to explore this correlation as a primary endpoint. While there have been conflicting data about this correlation historically, these observational data were consistent with other data that have raised this concern. Moreover, the data seized attention from advocates, particularly women, around the world.

- What do the data mean for an individual woman’s family planning choices?
- Given that there are conflicting data from other studies about hormonal contraceptives and HIV risk, what is the research agenda to clarify this issue?
- What do the data suggest about the pipeline needed for multi-purpose prevention strategies that might protect against HIV and prevent pregnancy?
- What are the implications for future biomedical HIV prevention trials, which often have use of a reliable (non-barrier method) form of contraception as an enrollment criterion?

WHO is convening a consultation on these and other key questions in early 2012. AVAC and partners will be working to develop a clear civil society voice at this consultation, supported by educational materials and advocacy priorities in specific countries.

Research to Rollout: A schematic road map



In this graphic, we’ve highlighted, in darker blue, the areas where biomedical HIV prevention research has the most experience to date. The “gap” between positive effectiveness data and access for trial participants and their communities is less familiar territory—as are the steps in lighter blue.

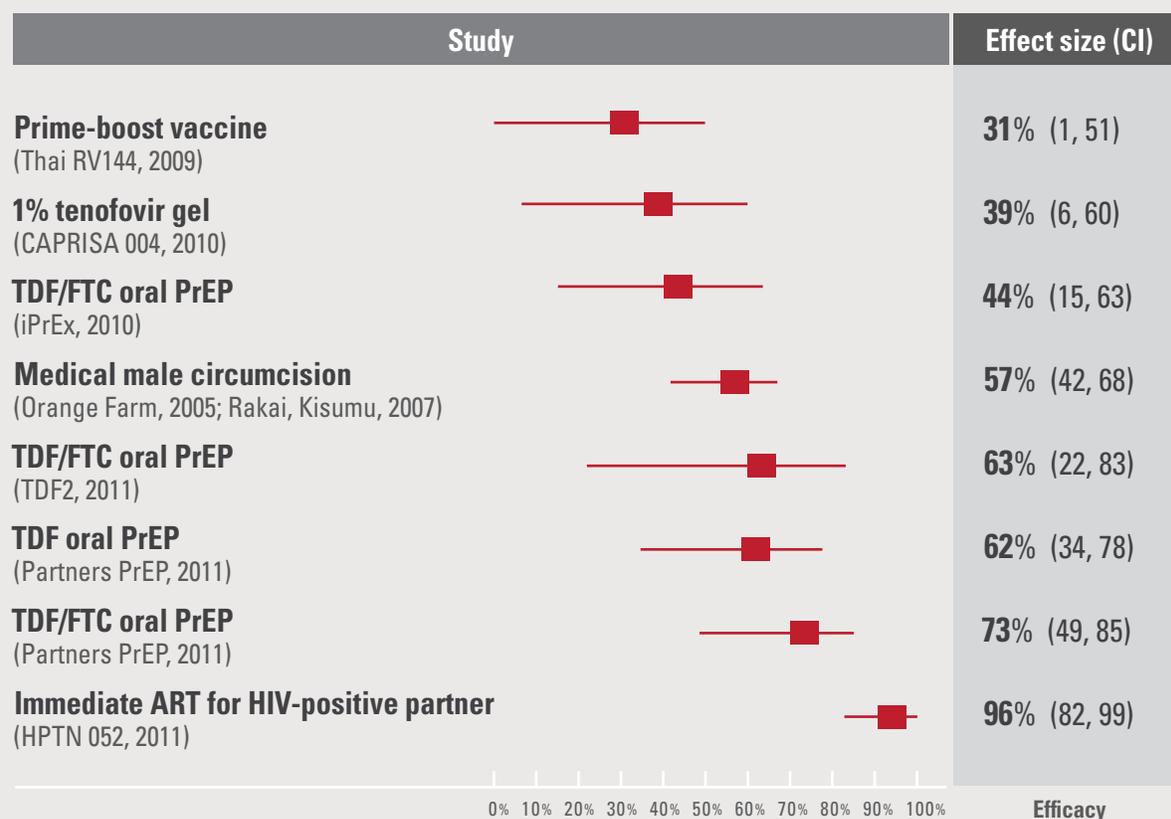
2012. There are also early-stage trials of a long-acting injectable ARV. These and other novel delivery methods may be important innovations for HIV prevention. The history of family planning teaches us that uptake of all methods increases as the range of choices expands. The biomedical HIV prevention field needs a robust pipeline to understand which methods will work best biologically and, ideally, provide a range of choices for different users at different times in their lives.

Perhaps most importantly, any innovations in product development need to be understood in the context of product delivery, promotion and use. The product developers and the research teams that conducted a successful clinical trial

The responsibility for planning next steps does not solely rest on the shoulders of the trial teams.

certainly have invaluable insights, but they do not have all of the information or skills needed to bring a product to market. The discussions about how to move forward on the basis of the results from CAPRISA 004, iPrEx, HPTN 052 and Partners PrEP have, so far, involved too few stakeholders from the worlds of innovative program design and social marketing—and these individuals need to be part of, if not leading, conversations going forward.

What Works in HIV Prevention – November 2011



Visit www.avac.org/timeline to find links to the publications and/or presentations associated with each of these findings as well as information on studies that showed flat or insignificant results.

Building an Evidence-Base for Combination Prevention

Combination prevention is the key to ending the AIDS epidemic. But there's a lot to learn about how options work in synergy, how to deliver a range of services in resource-constrained settings and how to select the most effective, high-impact combinations for a given community. The following research initiatives, including the US National Institute of Health's Methods for Prevention Packages Program (MP3) and a recently announced US\$60 million PEPFAR program, will help to gather this information.

| Study name | Study population | Setting | Package elements |
|--|--|-------------------------|--|
| MP3 I (First round of grants awarded in 2008) | | | |
| Acute HIV Infection in Heterosexuals | Persons with acute HIV infection | Malawi | Standard vs enhanced counseling vs behavioral intervention plus 12-week ART to reduce viral load |
| An HIV Prevention Package for Mochudi | All reproductive-age persons in a single village | Botswana | Behavioral interventions: VCT, partner notification, concurrency reduction, VMMC, condoms and ART for those with high viral load |
| Enhance Prevention in Couples (EPIC) | Serodiscordant heterosexual couples | Lesotho | Behavioral counseling, ART for prevention (CD4<500) plus couples counseling, VMMC |
| HIV Prevention Packages for Injection Drug Users | Injection drug users | Estonia | Potentially syringe exchange, pharmacy sales, methadone, STI screening/treatment, PrEP (if efficacious) |
| Methods for Prevention Packages (MP3) Prevention Rx | Rural heterosexual populations, including serodiscordant couples | South Africa and Uganda | Home-based HIV testing and targeted referrals for VMMC, ART, STI treatment, couples counseling, and topical and oral PrEP (if efficacious) |
| Prevention Umbrella for MSM in the Americas (PUMA) | MSM | North and South America | Potentially PrEP, VCT and interventions addressing adherence, substance use, risk compensation, disclosure and serosorting |
| MP3 II (Second round of grants awarded in 2011) | | | |
| CHAMPS: Choices for Adolescent Methods of Prevention in South Africa | Young men and women | South Africa | Potentially PrEP, microbicides, HCT and circumcision—plus messaging and social marketing around these approaches |
| Comprehensive HIV Prevention Package for MSM in Southern Africa | African MSM | Zambia and South Africa | Package of behavioral, biomedical and community-level interventions |
| Gender-Specific Combination HIV Prevention for Youth in High-Burden Settings | Young men and women | Kenya | Gender-specific HIV packages for female and male youth (MP3-Youth) delivered using community-based mobile health teams |
| Multi-component HIV Intervention Packages for Chinese MSM | MSM | China | Package of TLC-based interventions utilizing a series of short text messages and social networking to reach out to MSM population; participants who test positive are linked to clinics or programs for care and ART |
| US President's Emergency Plan for AIDS Relief (PEPFAR) awards to examine the effectiveness of combination approaches to HIV prevention (awarded September 2011) | | | |
| PopART – London School of Hygiene & Tropical Medicine and the HIV Prevention Trials Network with funding from NIH | | South Africa and Zambia | Examine a strategy linking household-based HIV testing to universal community-based HIV treatment |
| Harvard School of Public Health, with funding from the CDC | | Botswana | Evaluate the impact on HIV incidence of expanding population coverage of an integrated set of HIV prevention interventions |
| Johns Hopkins University, with funding from USAID | | Tanzania | Evaluate the impact of an integrated set of biomedical, behavioral and structural prevention interventions to reduce HIV incidence |

Pilot

There are too many theoretical debates about which interventions will be feasible to roll out and which interventions potential end users of various products will be most interested in and likely to adopt. Some of these debates can be informed by field research led by experienced epidemiologists, social scientists and behavioral scientists in consultation with policy makers and advocates. But most often, investigation through innovative demonstration projects and/or phased implementation plans will be necessary. This work provides a truer picture of how a new strategy might actually work in the context of life outside of what can be a research bubble. Necessary steps include:

- **Pilot projects in HIV-serodiscordant couples** that look at provision of both PrEP and earlier treatment when offered in combination.
- **Preparation for pilot projects in women**—including strategies for describing the new and emerging HIV prevention hierarchy for women. This expanding suite of options still needs to be defined but would build on standard prevention programming with information about couples counseling and the health and

prevention benefits of ART, regardless of CD4 cell count, for HIV-positive women and for the HIV-positive partners of HIV-negative men. Expanded prevention programming for women would also address HIV risk associated with injectable hormonal contraceptives (see box, p. 30). In the future, topical and oral PrEP could be added to the conversation.

- **Funding for outreach and education** targeting key constituents, including health professionals, community clinics and community-based organizations that work with individuals and communities who could most benefit from new prevention strategies.
- **Coordinated information sharing**, such that country-level decision makers can easily understand what information is being gathered in various planned or ongoing pilot and demonstration projects—and identify what additional data, if any, should be gathered in local projects.

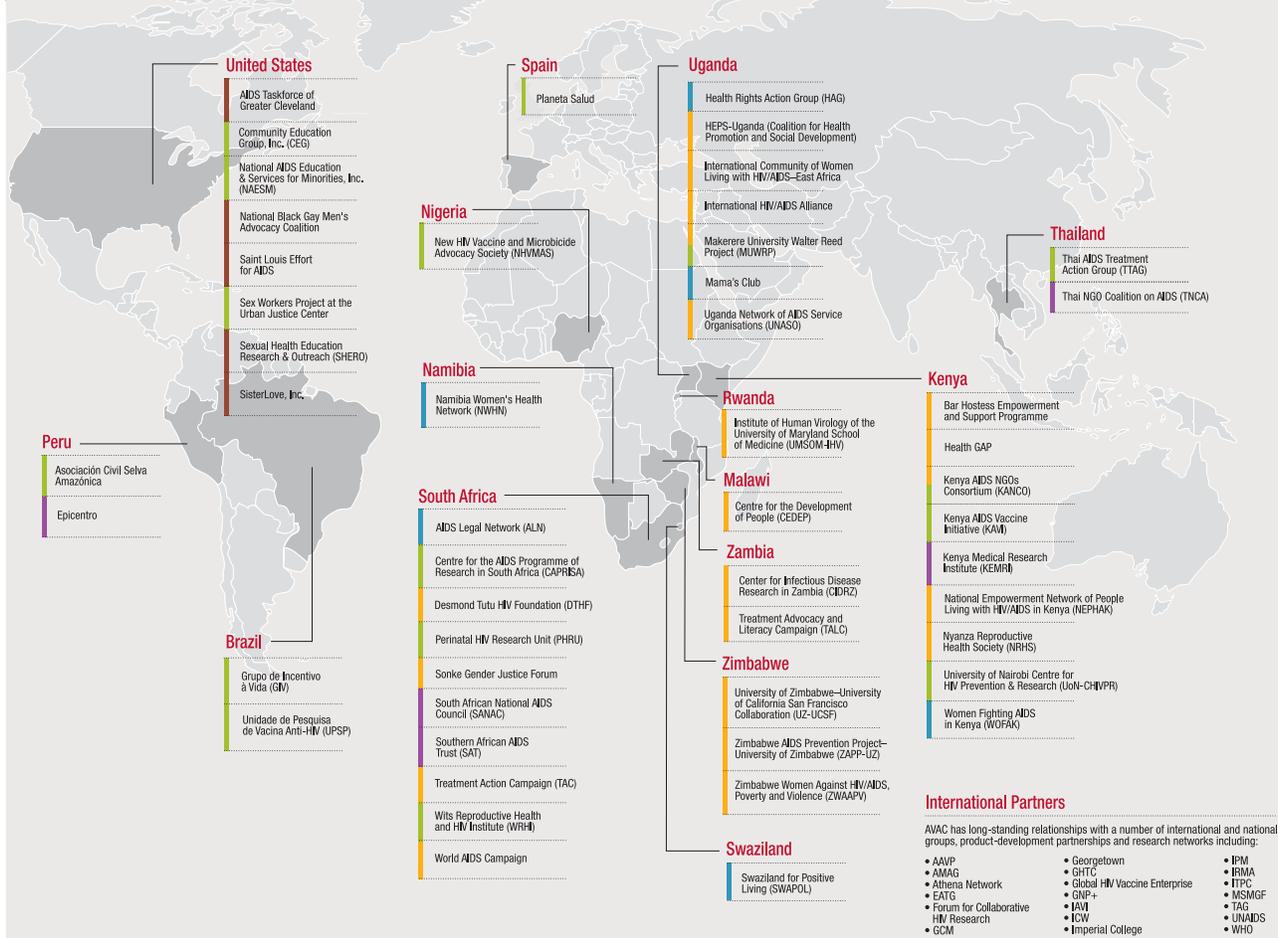
It is also important to develop decision-maker tools to help assess when a demonstration project is warranted and when a country or community might move straight into a plan for phased implementation. A demonstration project should plan for what will happen after it has been completed and analyzed. It shouldn't be a stand-alone initiative with no plans for follow-up. ■



ART – antiretroviral therapy; HCT – HIV counseling and testing; MSM – men who have sex with men; NIH – National Institutes of Health; PrEP – pre-exposure prophylaxis; STI – sexually transmitted infection; TLC – test and link-to-care; VCT – voluntary counseling and testing; VMMC – voluntary medical male circumcision

- A Kurth et al. "Combination HIV Prevention: Significance, Challenges, and Opportunities," *Current HIV/AIDS Reports* (Mar 2011) 8(1):62-72.
- enGrant Scientific, <http://search.engrant.com/>, accessed Nov 11, 2011.
- "PEPFAR Announces Largest Study of Combination HIV Prevention," PEPFAR (press release, Sept 14, 2011), <http://www.state.gov/r/pa/prs/ps/2011/09/172389.htm>.

AVAC's Global Partners in HIV Prevention Research Advocacy



Good Participatory Practice Partners

In November 2007, UNAIDS and AVAC published *Good Participatory Practice (GPP) Guidelines for Biomedical HIV Prevention Trials*, which were created to set global standards for stakeholder engagement in biomedical HIV prevention trials. An updated version of the guidelines was published in 2011. The guidelines provide trial funders, sponsors and implementers with systematic guidance on how to effectively engage with all stakeholders in the design and conduct of biomedical HIV prevention trials. Since 2008, AVAC has supported specific stakeholder groups—our GPP Partners—in Africa, the Americas, Asia and Europe in a process of reviewing and providing critical feedback on the guidelines. A participatory approach was used to design the consultations, which included focus group discussions, interviews, surveys, workshops and consultative meetings.

HIV Prevention Research Advocacy Fellowship Program

The HIV Prevention Research Advocacy Fellowship Program provides support to emerging and mid-career advocates to implement projects related to biomedical HIV prevention research activities in their countries and communities. The program is designed to expand the capacity of civil society advocates and their host organizations to monitor, support and help shape biomedical HIV prevention research worldwide. The Advocacy Fellowship is guided by the belief that effective, sustainable advocacy grows out of work that reflects organizational and individual interests and priorities.

National Stakeholder Engagement

National stakeholder engagement is different from the types of activities undertaken to prepare for and conduct a study in specific locations—although some groups may be involved in both trial-specific outreach and broader stakeholder engagement. One of the main differences is that, in this process, stakeholders are asked to provide input and guidance on steps that can happen in the short, medium and long term to prepare for the results from an ongoing study and/or to take action on implementing new research findings or prevention strategies, such as combination prevention.

Prevention Research, Outreach, Advocacy and Representation (PxROAR)

The PxROAR program is one of AVAC's United States-based programs. The program centers on a small group of advocates working in communities around the US that are hard-hit by HIV. The program is designed to educate its members about HIV prevention research science and advocacy strategies and provide a platform for specific prevention research advocacy campaigns.

Women's HIV Prevention Tracking Project (WHIPT)

WHIPT was launched as a collaboration between AVAC and the ATHENA Network to support women's community-based efforts to monitor, evaluate and develop or expand advocacy around new and emerging HIV prevention strategies. In its first two years, teams in five countries monitored and developed advocacy on VMMC and its implications for women.

For more information on AVAC's programs and partners visit www.avac.org/programs.

The End

Develop

- Vaccine
- Cure
- Sustain the science
- Control the epidemic

Demonstrate

- PrEP
- Microbicides
- Plan
- Prioritize
- Pilot

Deliver

- Test
- Circumcise
- Treat
- Model
- Reprogram
- Fund

DEVELOP

DEVELOP

PART 3

Sustain the science. Control the epidemic. The AIDS epidemic isn't going to end tomorrow. Even with all of the strategies described in the preceding pages, it isn't guaranteed to end at all. The success of the venture will depend in large part on the ability to operationalize—and fund—combination prevention in many different settings. Over the long term, there may also be breakthroughs in the search for a protective AIDS vaccine and a functional cure, strategies that would have an enormous impact on the shape of the epidemic and prevention needs. It is critical that this work be sustained with adequate funding, and a consistent focus.

As the world implements existing tools, we must also maintain scientific investigation. The AIDS vaccine field is as exciting as it has ever been. The results from follow-up work on the RV144 vaccine efficacy trial have framed a new research agenda. Basic scientific exploration of neutralizing antibodies is paying off as new potent antibodies are identified, and their structures and maturation processes are increasingly well defined.

Some might say that when we say we have the tools to end AIDS and yet also urge continued investment in research, we are trying to have it both ways. We think that, over the long term, both implementation and scientific investigation are needed if we are to see the struggle through to the end.

Sustain the science

There is more momentum and direction in the AIDS vaccine field than there has ever been before. Against steep odds, an immune response associated with decreased risk of infection was identified in an analysis of samples from the RV144 Thai prime-boost vaccine trial. The same analysis also offered up a vaccine-induced immune response that seemed to counteract

the protective effects of the vaccine. At the same time, advances in isolation of broadly neutralizing antibodies are being parlayed into vaccine strategies that could reach the clinic in the next few years.¹⁶

A protective AIDS vaccine and a functional cure would have an enormous impact on the shape of the epidemic.

¹⁶ WC Koff. "Scientists Find New Antibodies to Help in HIV Vaccine Quest," IDSA Education and Research Foundation's Center for Global Health Policy (Aug 17, 2011), <http://sciencespeaksblog.org/2011/08/17/scientists-find-new-antibodies-to-help-in-hiv-vaccine-quest/>.

There is also energy and enthusiasm centered on cure research, including both a “functional cure”, one that would not entirely rid the body of HIV, and a “sterilizing cure”, which would eradicate the virus. In July, the International AIDS Society launched the Towards an HIV Cure initiative,¹⁷ which will bring an international group of scientists and other stakeholders together to guide the development of a global cure research agenda.

Optimism about a cure has arisen in reaction to the extremely rare instance of the “Berlin patient”, Timothy Brown, who appears to be virus-free—proof of concept that HIV can be functionally cured. There is new money available for tackling the challenge, including funds for the Martin Delaney Collaboratory at the NIH and the French research agency ANRS. These resources could help address the need for robust assays to measure HIV presence in resting cells; they could also help answer questions, such as whether HIV maintains low-level viral replication or is restricted to quiescent cells.

Now is actually the best and most important time to invest in vaccines.

These developments are exciting, but no one can say when they will yield dividends in terms of public health interventions. It is clear that the trials to evaluate both cure and vaccine approaches will be highly complicated.

| AVAC “PLAYBOOK” 2012 | | | | |
|----------------------|--|-------------------|--------------------------|---|
| DELIVER | Testing/Diagnostic | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| DEMONSTRATE | PIP | Microbicides | Prevention and Treatment | Prevention and Treatment |
| Vaccines | GLOBAL GOALS | | | AVAC PRIORITY |
| | <ul style="list-style-type: none"> › Maintain funding to build on recent breakthroughs. › Connect the vaccine agenda to combination prevention. › Identify and close funding gaps for RV144 follow-on trials. | | | <ul style="list-style-type: none"> › Make the case for sustained funding, including resources to engage community in discussing future trials. |

Still, now is exactly the time to maintain support for this work. Now is actually the best and most important time to invest: precisely at the moment when there are new hypotheses to test, based on clearer scientific signals than the field has ever seen before. Unfortunately, the vaccine field is entering dangerous financial waters, both because of the global economic recession and because advances in other areas of biomedical prevention research have re-awakened questions as to whether investment in such a complex and long-term endeavor is still warranted.

Though global AIDS vaccine funding declined only one percent in 2010, both US and European donors decreased their commitments by more than that. The overall decline would have been even greater had it not been for US stimulus funding which ends this year.¹⁸



¹⁷ B Audoin et al. “The Rome Statement for an HIV Cure: Major HIV/AIDS Stakeholders Call for HIV Cure Research to be Accelerated,” International AIDS Society (July 18, 2011), <http://www.iasociety.org/Default.aspx?pageId=583>.

¹⁸ *Capitalizing on Scientific Progress: Investment in HIV Prevention R&D in 2010*, HIV Vaccines and Microbicides Resource Tracking Working Group (July 2011), <http://www.hivresourcetracking.org/sites/default/files/Capitalizing%20on%20Scientific%20Progress.pdf>.

Reasons to Believe: Highlights from the year in AIDS vaccine research

It has been a year of movement in the AIDS vaccine field. Leaders Seth Berkley (IAVI), Peggy Johnston (NIAID) and Alan Bernstein (Global HIV Vaccine Enterprise) moved on to new roles. And the science solidified the case for an AIDS vaccine. What follows is a very short list of some of the highlights:

May 2011: The Pox-Protein Public Private Partnership, or “P5” (formed by Sanofi Pasteur, Novartis Vaccines and Diagnostics, Inc., the US NIH, the Bill & Melinda Gates Foundation, the US Military HIV Research Program and the HVTN), debuts with an overarching development strategy designed to move from the RV144 Thai prime-boost vaccine trial result to a potentially licensable product for Thailand and elsewhere.

May 2011: Louis Picker (Oregon Health and Sciences University) and colleagues publish long-term follow-up data showing that non-human primates receiving a vaccine strategy using a persistent CMV vector had sustained, stringent viral control following mucosal challenge a year after immunization.

August 2011: Two groups report new findings on HIV-specific antibodies—one revealing insights into the maturation process that leads to potent HIV-specific antibodies, the other identifying new, broadly neutralizing antibodies gleaned from analysis of samples from HIV-positive individuals.

August 2011: The HVTN 505 trial of a DNA-Ad5 combination expands its scope to include an investigation of whether the experimental vaccine regimen prevents HIV infection.

September 2011: Barton Haynes (Duke University) and collaborators announce identification of two immune responses that may have had an impact on risk of infection among vaccine recipients in the RV144 trial.

Third quarter 2011: Monoclonal antibodies similar to those associated with reduced risk of HIV infection in RV144 are grown and move into animal trials.

“AIDS Vaccine Clinical Developments Can Contribute to an HIV Prevention Revolution,” AVAC’s Statement on HIV Vaccine Awareness Day (May 18, 2011), <http://www.avac.org/ht/d/sp/i/33756/pid/33756>.

SG Hansen et al. “Profound Early Control of Highly Pathogenic SIV by an Effector Memory T-Cell Vaccine,” *Nature* (May 26, 2011) 473(7348):523-27.

LM Walker et al. “Broad Neutralization Coverage of HIV by Multiple Highly Potent Antibodies,” *Nature* (Sept 22, 2011) 477(7365):466-70.

X Wu et al. “Focused Evolution of HIV-1 Neutralizing Antibodies Revealed by Structures and Deep Sequencing,” *Science* (Sept 2011) 16:333(6049):1593-602.

B Haynes. “The RV144 ALVAC/HIV Prime, rgp120 B/E Trial: Immune Correlates Analysis,” presented at AIDS Vaccine 2011 in Bangkok, Thailand (Sept 13, 2011), <http://www.hivvaccineenterprise.org/conference/2011>.

As *AVAC Report 2011* went to press, policy makers, advocates and researchers were bracing themselves for potentially major cuts in the US budget. With the US government’s investment still accounting for over 73 percent of all vaccine investments, even small-percentage declines will have a major impact on the overall funding picture.

To address a particularly worrying turn of events, advocates and scientists are urging the US Army to revisit a decision to substantially cut the budget of the US Military HIV Research Program (MHRP)—the very program that conducted the RV144 trial and is planning a range of follow-up trials. While MHRP is not the only player taking the RV144 result forward, it would be a mistake to make such a crippling funding cut at the precise moment that the program is solidifying the follow-up agenda for the first successful AIDS vaccine effectiveness trial.

The NIH National Institute for Allergy and Infectious Diseases (NIAID) launched the Center for HIV/AIDS Vaccine Immunology and Immunogen Design program (CHAVI-ID) this year, setting aside US\$28 million for one to two awards in the first year—which is about US\$15 million less than in the first year of the original CHAVI project. CHAVI-ID is planned with a seven-year award period, with goals of building on and extending the published results of CHAVI projects and focusing on rational vaccine design. It will be important to track the milestones and outputs of CHAVI-ID and the Bill & Melinda Gates Foundation-funded Collaboration for AIDS Vaccine Discovery (CAVD) (which recently made a second round of grants focused on translational research) to gauge whether funding levels and collaborative structures are sufficient for the task at hand.

The following HIV steps are key for sustaining progress in basic science and clinical trials to advance the search for an AIDS vaccine:

- **Maintain level funding, at a minimum.** An AIDS vaccine with durable protection would have a profound impact on the epidemic in a way that is comparable only to voluntary medical male circumcision (VMMC) in terms of what is available today. There's more reason than ever to think that an AIDS vaccine is achievable. Funding for AIDS vaccine discovery and clinical trials must be protected.
- **Prioritize the evaluation of hypotheses generated by the results of the RV144 trial.** This is the only evidence to date of vaccine efficacy in humans, and the follow-on research—including attempts to boost immune responses in RV144 volunteers, and to repeat or improve on the result in different populations—should be fully funded and put on a fast track.
- **Minimize overlap—make choices of candidates and trials based on new hypotheses.** Until correlates of protection are validated and demonstrated to be broadly applicable across populations (e.g., different vaccine approaches and different subtypes of HIV), it is prudent to proceed in a way that minimizes overlap (i.e., advancing concepts that are too similar into efficacy trials); avoids advancing hypotheses that have previously proven ineffective; and presents a plausible hypothesis as to why this concept might work when a similar one failed.
- **Continue to address HIV genetic variability.** Strategies such as presenting conserved regions of HIV genes/proteins and selecting candidates based on the breadth of immune responses can address the challenge of HIV genetic variability. Selecting candidates on the basis of the breadth of induced immune responses and using bioinformatics immunogen design (e.g., the mosaic approach) are other current strategies for developing candidates that could provide protection against a broad array of viral strains.

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- **Use clinical trials to advance knowledge.** There is no substitute for clinical trials in advancing the search for an AIDS vaccine. We don't have the information to focus on animal models or basic science exclusively. The most powerful information about AIDS vaccines and the human immune system will continue to come from clinical trials of novel compounds, including "discovery trials"

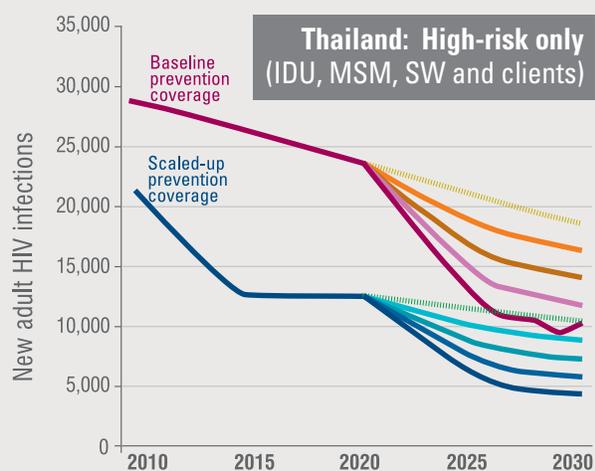
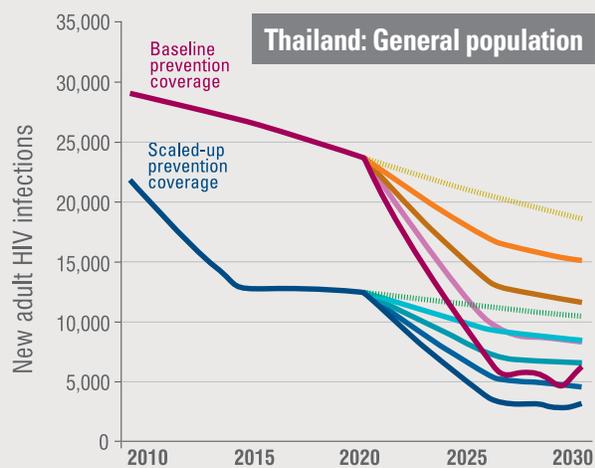
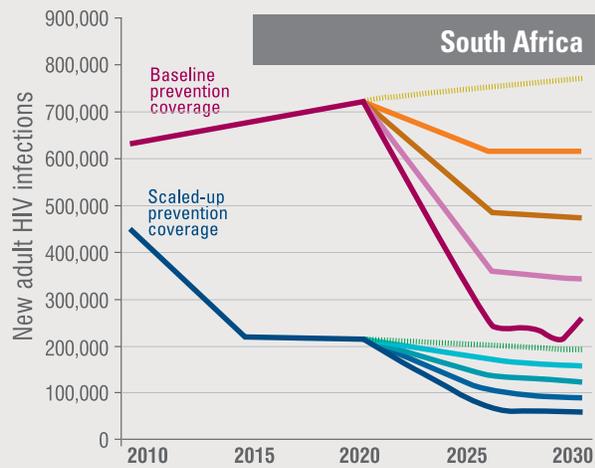
Whither the Enterprise?

In October 2011, the Global HIV Vaccine Enterprise announced a streamlined, scaled-down Secretariat that will focus on three key areas: organizing the annual AIDS Vaccine Conference; convening the field on priority strategic issues where a collective effort is most effective; and organizing an annual Funders' Forum to optimize current resources and efforts and, where possible, to mobilize new resources and efforts in the field.

This structure emerged out of planning and consultation in the wake of Executive Director Alan Bernstein's departure in June. AVAC has tracked the development of the Enterprise from its earliest days and was involved in the discussions that led to the re-structuring.

Will the new Enterprise add value by convening the Funders' Forum and a responsive set of issue-specific gatherings? As an Enterprise partner, we will work to ensure that it does. As a watchdog, we will raise concerns if it looks as if things aren't working out.

Untangling the Threads of Vaccine Impact



that are not on a licensure track. These trials are expensive and complicated to conduct and explain. Yet they are as important as ever. Building support for a well-defined, streamlined AIDS vaccine clinical research agenda will continue to be a major advocacy priority for AVAC and our partners.

- Preserve community engagement budget lines.** The rationale for future AIDS vaccine trials needs to be explained clearly to potential participants and also to the broader community of global advocates. It is going to be highly challenging to marshal funding for future AIDS vaccine trials in an environment of limited resources and expanding enthusiasm for proven interventions, and it is essential that trials network and research sponsors' budgets for community engagement—often the first to go in times of fiscal austerity—are sustained.
- Define how a vaccine could impact combination prevention.** Impact modeling of vaccines as part of combination prevention is also critical. A recent issue of *Vaccine* described various models of the impact of a

These busy graphics show models of what could happen if a moderately effective vaccine were introduced in Thailand or South Africa. The various lines represent the annual number of new adult infections in South Africa and Thailand for different scenarios with the general population vaccination beginning in 2020, reaching target coverage levels by 2025 and maintained thereafter. The top set of lines represents impact on new infections in the context of a baseline prevention scenario in which coverage of all other prevention interventions remains constant at current levels. The bottom set of lines shows the change in new infections in the context of scaled-up prevention, in which all other interventions are scaled up by 2015 and maintained thereafter. The message from these busy figures is one we've stated throughout the pages of this Report: combination prevention is key.

KM Andersson and J Stover. "The Potential Impact of a Moderately Effective HIV Vaccine with Rapidly Waning Protection in South Africa and Thailand," *Vaccine* (Aug 18, 2011) 29(36):6092-99.

partially effective AIDS vaccine strategy with characteristics similar to the ALVAC-AIDSVAX prime-boost strategy evaluated in RV144.¹⁹ The modeling teams looked at various scenarios in South Africa and Thailand, all based on a vaccine with a moderate level of efficacy and rapidly waning protection. The effort was notable, in that the different teams came up with consistent results despite widely different models applied to diverse settings. The general conclusion was that the vaccine strategy could avert between 5 and 15 percent of new infections over a ten-year period, and would be cost-effective at US\$150 in many African settings, and at up to US\$500 in South Africa. Relative to VMMC and treatment as prevention (with sustained adherence and retention—key parameters without which the prevention benefits could be quickly lost), these are relatively modest gains over a long time frame.

Vaccine advocates need to explain and rally support for the search for a preventive vaccine—and also help define the niche that a partially effective vaccine might fill. As other prevention strategies are introduced, this niche might become better defined in terms of geography, route of exposure, background combination package and so on, but the AIDS vaccine field needs to take the initiative in bringing this into focus.

The modeling efforts also found that if the efficacy of the regime was more durable (a

| AVAC "PLAYBOOK" 2012 | | | | |
|----------------------|---|-------------------|--|------------------------|
| DELIVER | Testing/Diagnostic | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
| DEMONSTRATE | GLOBAL GOALS | | AVAC PRIORITY | |
| | <ul style="list-style-type: none"> › Increase uptake and utilization of GPP. › Guide new consensus on decision making about when to add emerging strategies to the standard of prevention. › Guide and advocate for post-trial access plans. | | <ul style="list-style-type: none"> › Publish a new consensus statement on standard of prevention in biomedical prevention trials. | |

possible outcome of adding a follow-up boost to the strategy) then there could be significantly greater impact. One of the planned follow-on trials in Thailand will look at whether RV144 participants' immune responses are boosted by a follow-up immunization. The data from this trial can be used in the future to fine-tune and improve impact models even more—a key example of the synergy between research and predictive modeling.

Finally, success in the long-term search for a vaccine, a cure and an end to AIDS depends on the existence of trial sites and infrastructure, including community education and outreach programs, laboratories, testing centers, doctors, nurses and clinic staff. Clinical sites themselves are assets that need to be managed as a long-term investment. An experienced site that loses funding for core activities and readiness for research cannot be easily re-activated. For several years, there has been talk of pluripotent sites that would be able to conduct research on a range of issues—from TB to malaria to vaccines. This approach continues to be a good one to explore, and the ongoing NIH recompetition for new trials networks could help make this a reality for US-supported sites.

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| DELIVER | Testing/Diagnostic | Male Circumcision | Treatment as Prevention | Comprehensive Approach |
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| | <ul style="list-style-type: none"> › Build a movement from all sectors, calling for control of and then an end to AIDS. | | <ul style="list-style-type: none"> › Grow and nurture an array of informed "Ending AIDS" advocates. | |

¹⁹ NJD Nagelkerke et al. "The Potential Impact of an HIV Vaccine with Limited Protection on HIV Incidence in Thailand: A Modeling Study," *Vaccine* (Aug 18, 2011) 29(36):6079-85.

Control the epidemic

If all the proposed steps in the previous 40-odd pages are taken over the next ten years, there will still be people living with HIV and new infections every day. But there will also be many people living longer, healthier lives with HIV—and far, far fewer new HIV infections. The epidemic will finally be under control. This is the first step to ending it, and for some of us it is the goal we will live to achieve.

To control and ultimately end the epidemic, the world needs a comprehensive “Ending AIDS” agenda that spans research and implementation, vaccines, PrEP, microbicides, circumcision, ARV treatment and care. This agenda would constitute a strategic plan that lays out key milestones, budgets and roles, using science and evidence as the guide. AVAC—in concert with many players

The power to achieve is vested not just with the leaders but with all stakeholders.

and stakeholders—looks forward to developing, and ensuring the implementation of, this strategy to end the epidemic.

As NIAID head Anthony Fauci wrote earlier this year:

“If one accepts the tenet that science should inform policy, then the scientific data are speaking loud and clear. Global policy makers must seriously consider these new data in their priority-setting and decision-making. For the first time in the history of HIV/AIDS, controlling and ending the pandemic are feasible; however, a truly global commitment, including investments by those rich and middle-income countries whose contributions have thus far been limited, is essential. Major investments in implementation now will save even greater expenditures in the future; and in the meantime, countless lives can be saved.”²⁰

With all successful movements, the power to achieve is vested not just with the leaders but with all stakeholders. AVAC envisions a near future in which presidents, parliamentarians and policy makers; health professionals and researchers; advocates, people at special risk and people living with HIV and AIDS join in the movement to bring this pandemic to:

²⁰ AS Fauci. “AIDS: Let Science Inform Policy,” *Science* (July 1, 2011) 333(6038):13.



The End

About AVAC

Founded in 1995, AVAC is an international non-profit organization that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and global delivery of biomedical HIV prevention options as part of a comprehensive response to the pandemic. AVAC is dedicated to:

- Translating complex scientific ideas to communities and translating community needs and perceptions to the scientific community.
- Managing expectations about the process of product research and development, testing and delivery.
- Holding agencies accountable for accelerating ethical research, development and delivery of HIV prevention options.
- Expanding international partnerships to ensure local relevance and a global movement.
- Ensuring that policy and advocacy are based on evidence.
- Convening coalitions, partnerships, working groups and think tanks for specific issues.
- Developing and widely disseminating high-quality user-friendly materials.

AVAC focuses in four priority areas:

- Develop and advocate for policy options to facilitate the implementation of available biomedical HIV prevention options as well as the expeditious and ethical development and evaluation of new ones.
- Ensure that rights and interests of trial participants, eventual users and communities are fully represented and respected in the scientific, product development, clinical trial and access processes.
- Monitor HIV prevention research and development and mobilize political, financial

and community support for sustained research as part of a comprehensive response.

- Build an informed, action-oriented global coalition of civil society and community-based organizations that exchange information and experiences.

A major part of AVAC's work is to translate complex scientific ideas to communities through the development and wide dissemination of high quality, user-friendly materials. In addition to *AVAC Report*, which analyzes progress in the field and makes recommendations for actions in the coming year, AVAC publishes *Px Wire*, a quarterly update on HIV prevention research; *P-Values*, a monthly bulletin highlighting advocacy by AVAC partners and other stakeholders; and the *Weekly NewsDigest*, as well as a publications series on anticipating and understanding research results. We also manage the Advocates' Network, an electronic network for organizations and individuals interested and involved in AIDS vaccine and HIV prevention research advocacy.

The AVAC website includes these publications as well as comprehensive coverage of the full range of biomedical HIV prevention interventions in an easy-to-use format that is searchable by intervention and by topic like policy, ethics and community involvement in research. In addition, the site hosts two searchable databases: one on biomedical HIV prevention research clinical trials, products and sites, and one that includes research literacy resources for understanding HIV prevention research. The site is designed to be a central hub of information for the complex array of challenging and exciting issues facing HIV prevention research stakeholders today.

For more information on AVAC's work and how to support it, please visit www.avac.org.

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