Px Wire: A Quarterly Update on HIV Prevention Research

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AVAC's Take

The science tells us we can begin to end the AIDS epidemic. Yet the global ledger sheet of investment in AIDS and public health suggests a looming shortfall in the resources. For biomedical prevention research advocates, the challenge is clear and urgent: communicate the need to invest in today's tools *and* in research for next-generation strategies, including long-acting PrEP and microbicides, and a vaccine. This issue of *PxWire* is designed to help advocates make the case with stories on critical advances in vaccine and microbicide research, and a centerfold detailing trends in HIV prevention research funding in 2011. We hope you'll take these tools and use them for effective advocacy. As always, send questions to *avac@avac.org*. Enjoy!

Data Dispatch

Understanding the RV144 "Sieve Analysis"

One of key presentations at the AIDS Vaccine 2012 conference detailed the latest insights into the partial protection seen in the RV144 "Thai Prime-Boost" AIDS vaccine trial.

Morgane Rolland of the US Military HIV Research Program (MHRP) presented data on what is known as a "sieve analysis" (the data were simultaneously published in the journal *Nature* doi:10.1038/nature11519). RV144 tested vaccine safety and efficacy in 16,000 Thai volunteers. The sieve analysis focused on samples taken from 110 of the trial participants who acquired HIV during the trial. This group included 44 vaccine recipients and 66 placebo recipients. All of them received counseling, condoms and other behavioral prevention tools.

The purpose of a sieve analysis is—as the name suggests—to understand what types of viruses get blocked by, or get through, a filter of partial vaccine-induced protection. The theory behind such an analysis is that even a vaccine that doesn't protect against all strains of HIV might block viruses with specific genetic characteristics. If this were the case, then the genetic make-up of the viruses infecting placebo recipients and vaccine recipients would be different.

This is exactly what the RV144 team found when it undertook the latest in a series of analyses to understand the trial result.

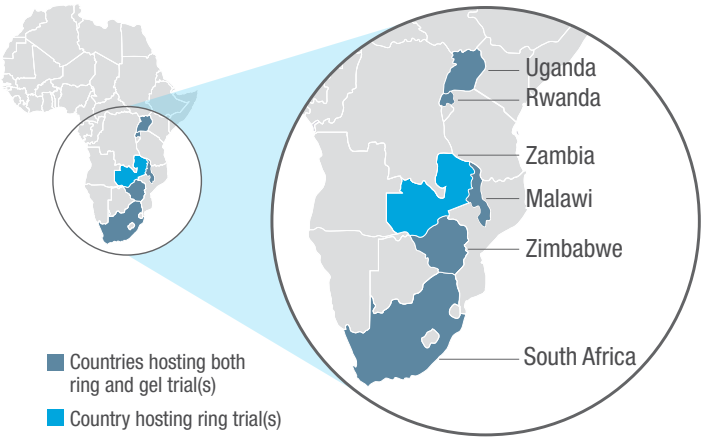
A team of researchers from MHRP, the University of Washington and SCHARP sequenced nearly 1,000 viruses isolated from the 110 vaccine and placebo recipients from RV144 who became HIV-infected during the trial. (Every person who is infected with HIV acquires a "swarm" of viruses with subtle variations in genetic structures. This is why so many viruses were sequenced, compared to the small number of HIV-infected trial participants.)

Researchers compared the genetic sequences from vaccine and placebo recipients. They looked, in particular, at the specific sections ("genetic signatures") that determine the shape and structure of the V1/V2 loop on the HIV envelope. They were guided to this region by the results of the RV144 correlates analysis. Published in 2011, this was an in-depth survey of immune responses in placebo and vaccine recipients. One finding was that antibodies targeted at the V1/V2 loop were associated with decreased risk of HIV infection. This is why the sieve analysis focused on responses to that region.

Antibodies fit onto parts of the HIV virus in a lock-and-key type configuration. So it was possible to search through the genetic signatures for viruses whose V1/V2 loop "matched" the antibodies found in vaccine recipients.

In a tricky bit of logic, a sieve analysis is attentive to which viruses *aren't* present. If the vaccine-induced V1/V2-targeting antibodies were effective, then they would block viruses whose V1/V2 loop "fit" their shape. Viruses with a V1/V2 loop matching the effective antibodies could not be present in vaccine recipients—and might be present in placebo recipients, who lacked the "sieve-ing" immune responses.

Countries in sub-Saharan Africa Conducting Microbicide Gel and Ring Trials



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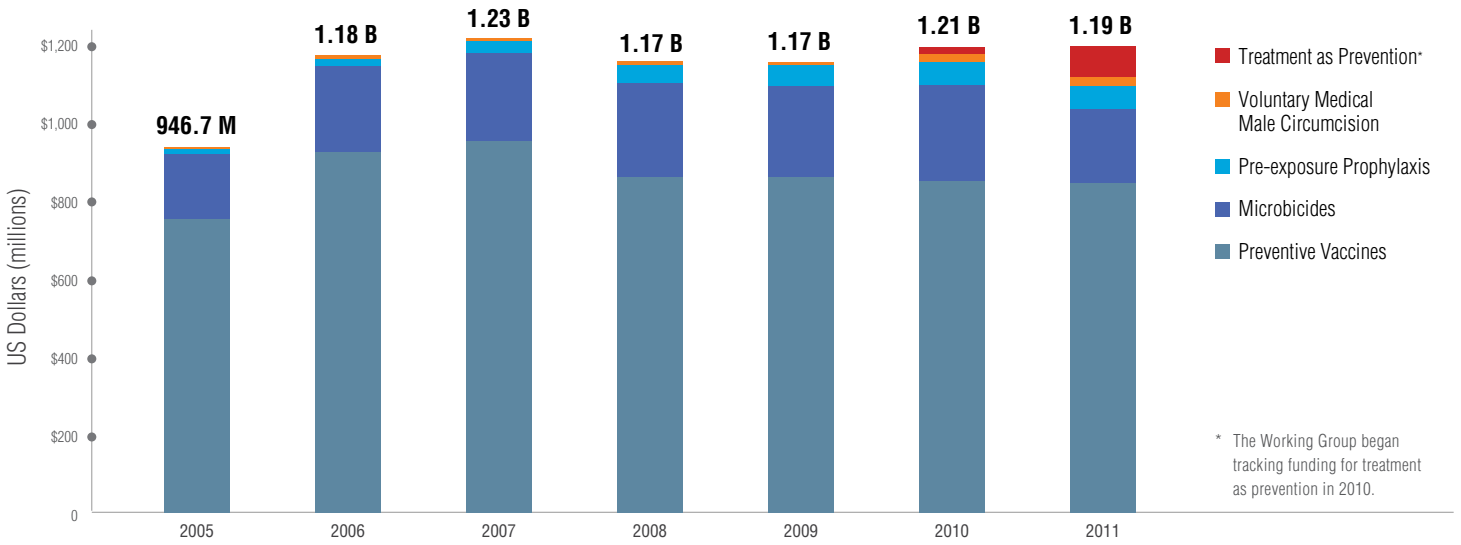
INVESTING TO END THE AIDS EPIDEMIC

The HIV Vaccines and Microbicides Resource Tracking Working Group, comprised of AVAC, the International AIDS Vaccine Initiative (IAVI), the International Partnership for Microbicides (IPM) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), uses a comprehensive methodology to track annual research and development (R&D) investment trends in biomedical HIV prevention. Information collected in previous years has been used by the Working Group and others to monitor levels of effort, analyze the significance of investment trends and assess the impact of public policies aimed at accelerating scientific progress towards new prevention tools against HIV.

The Working Group has expanded its tracking activities to include investment in HIV therapeutic vaccines, other new HIV prevention options such as pre-exposure prophylaxis (PrEP), cure research and operations research to support efficient implementation of existing interventions such as voluntary medical male circumcision. The full report can be accessed at *www.hivresourcetracking.org/*. Below, some of the highlights from this year's report in graphics and concise analysis.

Global HIV Prevention R&D Investments from 2005–2011



Investment Snapshot for 2011

Prevention Option	Amount 2011	Amount 2010	Change from 2010	Headlines
Preventive Vaccines	US$ 845 M	US$ 859 M	-US$ 14 M (-2%)	The year saw lower US public-sector investment and the end of the US stimulus package, along with lower European investment overall.
Microbicides	US$ 186 M	US$ 247 M	-US$ 61 M (-25%)	The year was one of preparation for clinical trials and decreased investment, due in part to the cyclical nature of clinical trials, with many follow-on and large-scale trials set to begin in 2012 and beyond.
Pre-Exposure Prophylaxis	US$ 62.3 M	US$ 58.3 M	+US$ 4 M (+7%)	PrEP funding in 2011 saw increased funding as a result of the large-scale trials that took place in 2011, with next-generation and follow-on trials getting ready to begin in the following years.
Adult Male Circumcision	US$ 20.3 M	US$ 21.7 M	-US$ 1.4 M (-6%)	While funding for R&D and operations research decreased slightly in 2011, this is due to an increase in implementation, rollout and scale-up of adult voluntary medical male circumcision as a proven HIV prevention option.
Treatment as Prevention	US$ 79.4 M	US$ 19.6 M	+US$ 59.8 M (+30%)	Funding increased substantially due to improved data collection and a post–HPTN 052 focus on scale-up of treatment as prevention worldwide.
All HIV prevention R&D*	**US$ 1.24 B**	**US$ 1.27 B**	**US$ 30 M (-2%)**	Budget constraints and competing priorities led to an overall flatlining of global HIV prevention R&D spending in 2011.

* Total includes investment in prevention of vertical transmission (not shown).

Data compiled by the HIV Vaccines and Microbicides Resource Tracking Working Group
www.hivresourcetracking.org

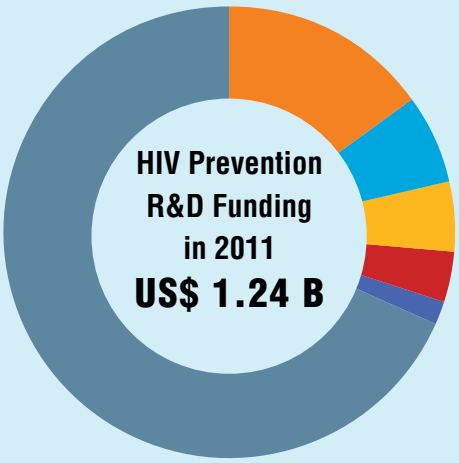
2011 Investments in HIV Prevention R&D to End the AIDS Epidemic

DEVELOP	**Developing new HIV prevention options through research and development**	Vaccines **US$ 845 million**	The field is closer than ever before to an effective HIV vaccine with a range of insights from analyses of RV144, the first trial to show protection in humans. Efforts are underway to improve on this finding and to harness potent neutralizing antibodies. One large-scale efficacy trial, HVTN 505, is ongoing.
DEMONSTRATE	**Demonstrating new HIV prevention options in implementation studies**	Microbicides **US$ 186 million**	Follow-up trials will expand on trials to-date of the vaginal microbicide 1% tenofovir gel. New technologies—a ring and long-acting injectable—are being tested. A marketable product is within reach and the field has formed partnerships and collaborations furthering its efficiencies.
		Pre-Exposure Prophylaxis **US$ 62.3 million**	PrEP has shown efficacy in gay and heterosexual adult men, women and transgender women. The US FDA has approved daily TDF/FTC as PrEP; the WHO has issued international guidance.
DELIVER	**Delivering proven HIV prevention tools**	Treatment as Prevention **US$ 79.4 million**	HPTN 052 proved that treatment as prevention works. Efforts are underway to scale up treatment, maximizing prevention and clinical benefit.
		Male Circumcision **US$ 20.3 million**	The pace of rollout of voluntary medical male circumcision is accelerating in some countries—with much work still to be done.

The above does not include investments in behavioral and structural interventions, or male and female condoms.

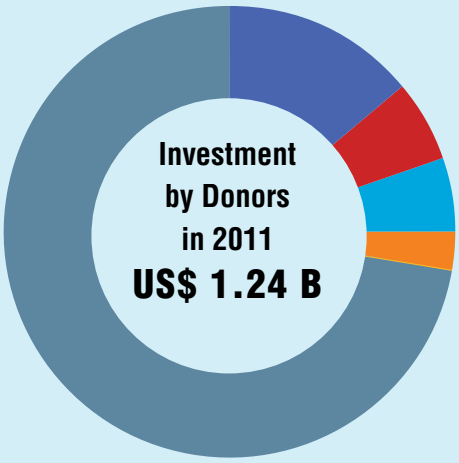
The advances made in 2011 provide a scientific basis for the argument that it is possible to begin to end the AIDS epidemic. Discoveries were made across the spectrum of R&D for HIV prevention options while models forecast the profound impact of scaled-up combination prevention. Despite a growing optimism based on these discoveries, researchers continued to face the challenge of delivering results while their budgets came under increasing pressure. Total funding for all HIV prevention R&D decreased by US$ 30 million from 2010 to 2011. Realizing the full potential of the scientific advances of 2011 will demand sustaining, and perhaps even increasing, funding levels in the years ahead. To retain the momentum achieved so far, the HIV prevention field will need to make an intelligent, realistic, strategic and integrated case for the sustained and flexible funding for each prevention option.

HIV Prevention R&D Funding in 2011



- Preventive vaccines **US$ 845 M**
- Microbicides **US$ 186 M**
- Treatment as prevention **US$ 79.4 M**
- Pre-exposure Prophylaxis **US$ 62.3 M**
- Prevention of vertical transmission **US$ 43.1 M**
- Medical male circumcision **US$ 20.3 M**

Investments by Donor in 2011



- US **US$ 894.5 M**
- Philanthropic **US$ 172.5 M**
- Europe **US$ 71.1 M**
- Other **US$ 65.1 M**
- Industry **US$ 32.3 M**
- Multilaterals **US$ 0.6 M**

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This sieve analysis found just such an effect: vaccine recipients had far fewer viruses with specific genetic sequences related to the V1/V2 loop compared to placebo recipients. This is evidence that vaccine-induced immune responses had a selective effect on certain HIV-1 variants.

Next up for the vaccine field: seeking to improve the protective effect of an RV144-like strategy and to ensure that the protection is seen across a broader range of viruses. For now, the search continues.

At a Glance

The Next Big "Ring"

Remembering to use a product consistently is a major challenge—whether it is a daily vitamin, a condom during sex, or a birth control or pre-exposure prophylaxis (PrEP) pill that is taken daily. Biomedical prevention is seeking long-acting strategies to reduce the need to adhere. Among the options being tested are ARV-containing vaginal rings, including one that entered efficacy trials earlier this year.

The two trials, ASPIRE (MTN 020) and the Ring Study (IPM 027), are looking at a flexible ring containing the antiretroviral drug dapivirine, an NNRTI that has been licensed to the International Partnership for Microbicdes (IPM) by Janssen R&D Ireland for its exclusive development as a vaginal ring. IPM is implementing the Ring Study, while the NIH-funded Microbicide Trials Network (MTN) is implementing ASPIRE. Both trials will take place in sub-Saharan Africa. For details visit *www.avac.org/pxrd*.

ASPIRE and the Ring Study are part of a suite of studies designed to generate the data needed to seek regulatory approval. Other planned trials include safety studies in adolescents and peri- and post-menopausal women, condom compatibility and possible drug-drug interaction studies. All trial results are expected by or during 2015.

Recently, a non-human primate trial of a vaginal ring containing another ARV, known as MIV-150, showed evidence of protection. The trial, supported by the Population Council, involved 33 macaque monkeys challenged with SHIV, a lab-constructed, monkey version of HIV. Two of the 17 macaques with MIV-150 rings became infected, compared to 11 of 17 with placebo rings. This trial finding represents protection of 83 percent in macaques who received the ring. There are many limitations to animal studies—and this model has not been widely used to evaluate vaginal rings. However, these data add to the hope that a vaginal ring strategy will also benefit women at risk of HIV worldwide.

Recently Released

An Action Agenda to End AIDS – We have a plan. It's strategic. It's ambitious. It can work. We can end AIDS—from amfAR and AVAC, *www.endingaids.org*.

A Call to Action on Voluntary Medical Male Circumcision – AVAC, NEPHAK, Sonke Gender Justice and UNASO analyze the current state of VMMC rollout, *www.avac.org/malecircumcision*.

Investing to End the AIDS Epidemic – The latest on financial investments in HIV prevention research and development from the HIV Vaccines and Microbicides Resource Tracking Working Group, *www.hivresourcetracking.org*.

Good Participatory Practice: Guidelines for TB Drug Trials – First developed by AVAC and UNAIDS for biomedical HIV prevention research, guidelines are now available for tuberculosis drug trials from the Critical Path to TB Drug Regimens (CPTR), *www.bit.ly/SiLzAb*.

What Works for Women & Girls – A comprehensive review of data from HIV/AIDS interventions for women and girls, *www.whatworksforwomen.org*.

Not to be Missed

October 29–31: HVTN Full Group Meeting, *Seattle, WA*

November 15–18: National Harm Reduction Conference: From Public Health to Social Justice, *Portland, OR*

December 1: World AIDS Day

About AVAC

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

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