
AVAC's Take

AIDS vaccines are the focus of the updates in this issue of *Px Wire*—and our centerspread shows how a country's rate of antiretroviral treatment (ART) scale-up can propel it towards an epidemic "tipping point". In the near-term, increasing the pace at which people with HIV start ART is a critical goal. In the long-term, an effective preventive HIV vaccine would be a critical tool for ending the epidemic. Along the way, we need innovation in prevention and treatment including therapeutic vaccines, which could be used by HIV-positive people as an additional immune-boosting strategy (see below for more). – AVAC

Data Dispatch: AIDS vaccines

Therapeutic vaccine research takes off

For two days in September, AVAC, the Treatment Action Group (TAG) and the Global HIV Vaccine Enterprise convened a meeting of nearly 100 scientists, funders and advocates to discuss the state of therapeutic HIV vaccine research. Therapeutic HIV vaccines are designed for HIV-positive people with the goal of prompting immune responses that control or eliminate the virus. They are distinct from preventive vaccines, which are designed for HIV-negative people, with the aim of preventing infection or reducing viral load in people who receive the vaccine and later acquire HIV.

It is hard to measure the direct effect of therapeutic vaccines on the virus because people with HIV who are taking effective ART do not have large amounts of HIV in their blood. There are major ethical and feasibility questions about taking someone off of ART to test a vaccine that may or may not work as well as treatment. However, as the meeting showed, there is also strong interest in developing such strategies.

The meeting reviewed the data to date—including results from promising non-human primate research and early-stage human clinical trials. Participants also discussed the different ways an effective therapeutic vaccine might be used. Improving treatment outcomes is one possibility—

e.g., a vaccine plus ART combination. Therapeutic vaccines might also be used in cure strategies that seek to flush latent HIV out of the body's reservoirs. Vaccine-induced immune responses could eliminate the activated virus.

This meeting helped frame some common areas for advocacy, scientific-agenda setting and resource mobilization at a time when the field has renewed momentum. The final recommendations will be available in a paper that AVAC, TAG and the Enterprise hope to publish later this year.

Ad5 is dead—but vectored vaccines live on

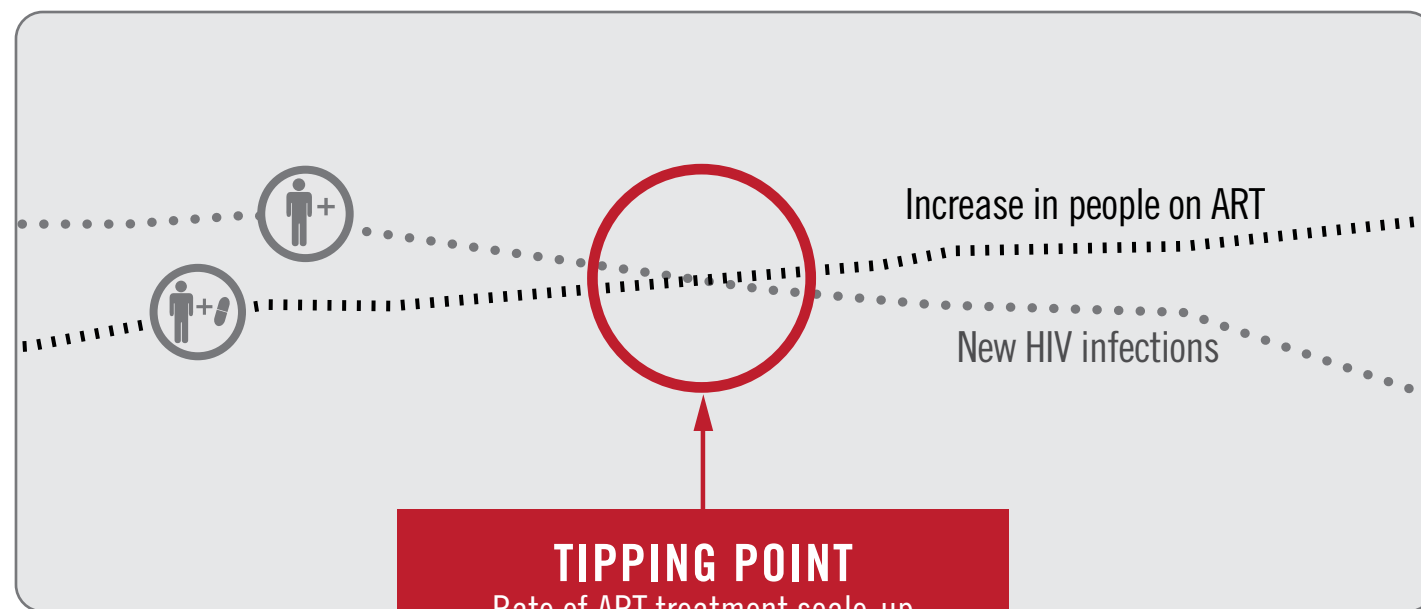
Also in September, the US National Institute of Allergy and Infectious Diseases (NIAID) convened a mini-summit on adenovirus platforms for HIV vaccines (the webcast can be viewed at www.totalwebcasting.com/view/?id=niaid). The meeting was a public reckoning with findings that have surprised and challenged the field in recent years—particularly three trials that tested two different vaccine strategies using adenovirus type 5 (Ad5) as a vector. None of these trials found benefit and data from two of the trials suggested that the vaccine might have increased some volunteers' risk of HIV infection.

With three trials showing flat results and/or possible signs of harm, why did the field need to meet at all? One answer is that there are many different types of adenoviruses, including other serotypes from humans (which cluster into several distinct families) and chimps that are being considered for AIDS vaccine development. So it's essential to question whether the outcomes seen with Ad5 might be repeated with other Ad-vectored candidates. Another reason is that Ad-vectored candidates have produced potent immune responses and intriguing evidence of protection or power to control infection in some non-human primate experiments. While we don't know how an effective vaccine will work, these candidates do some of the things that we think may be protective. Finally, there's a possibility that similar effects could happen with other vaccines that don't have an Ad vector at all.

The Step and Phambili trials of the Merck Ad5 candidate were halted early, in 2007, after an interim analysis of the Step study data showed that there was no evidence of protection and that there

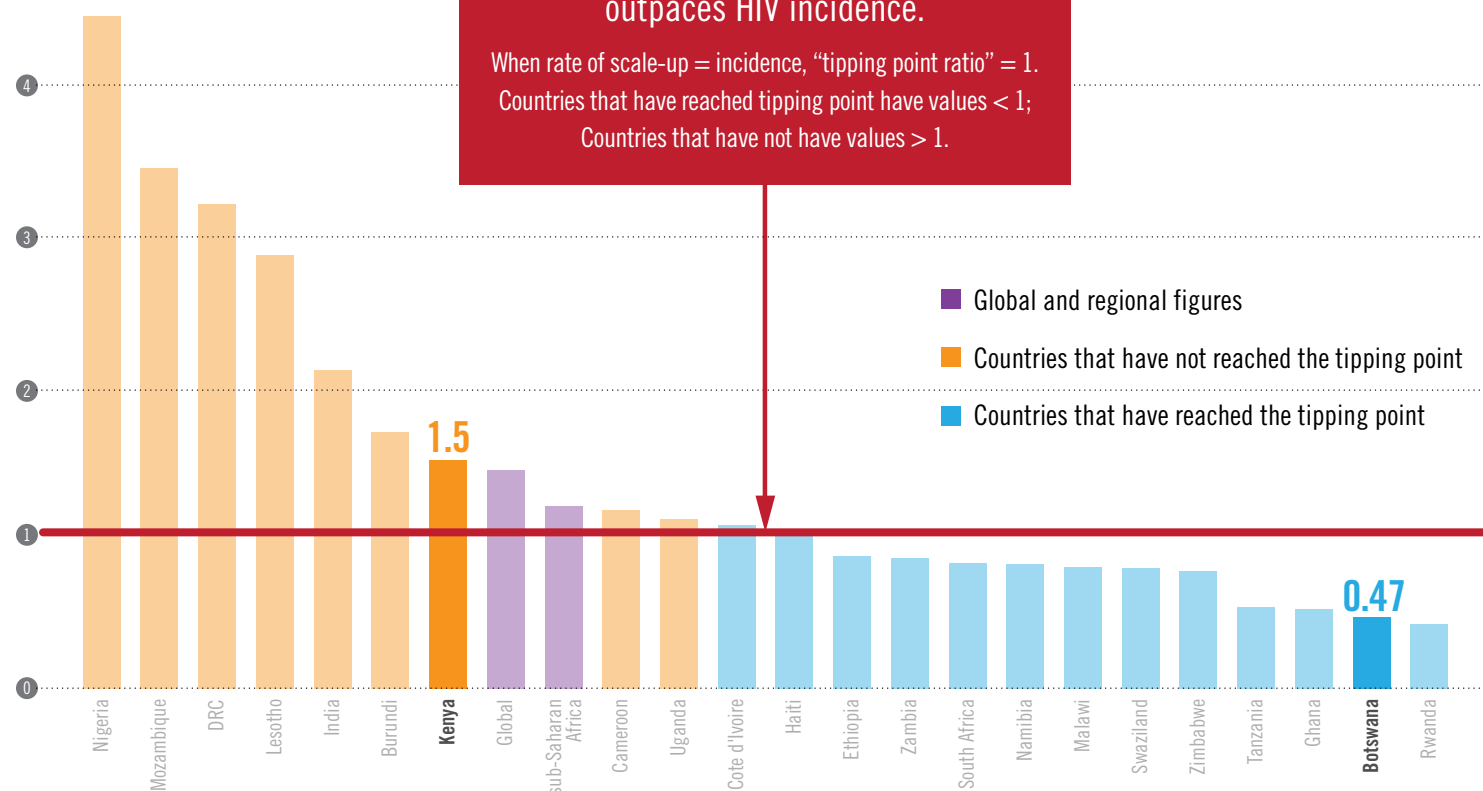
THE TIPPING POINT

Understanding a crucial milestone in the AIDS response



TIPPING POINT
Rate of ART treatment scale-up outpaces HIV incidence.

When rate of scale-up = incidence, "tipping point ratio" = 1.
Countries that have reached tipping point have values < 1;
Countries that have not have values > 1.



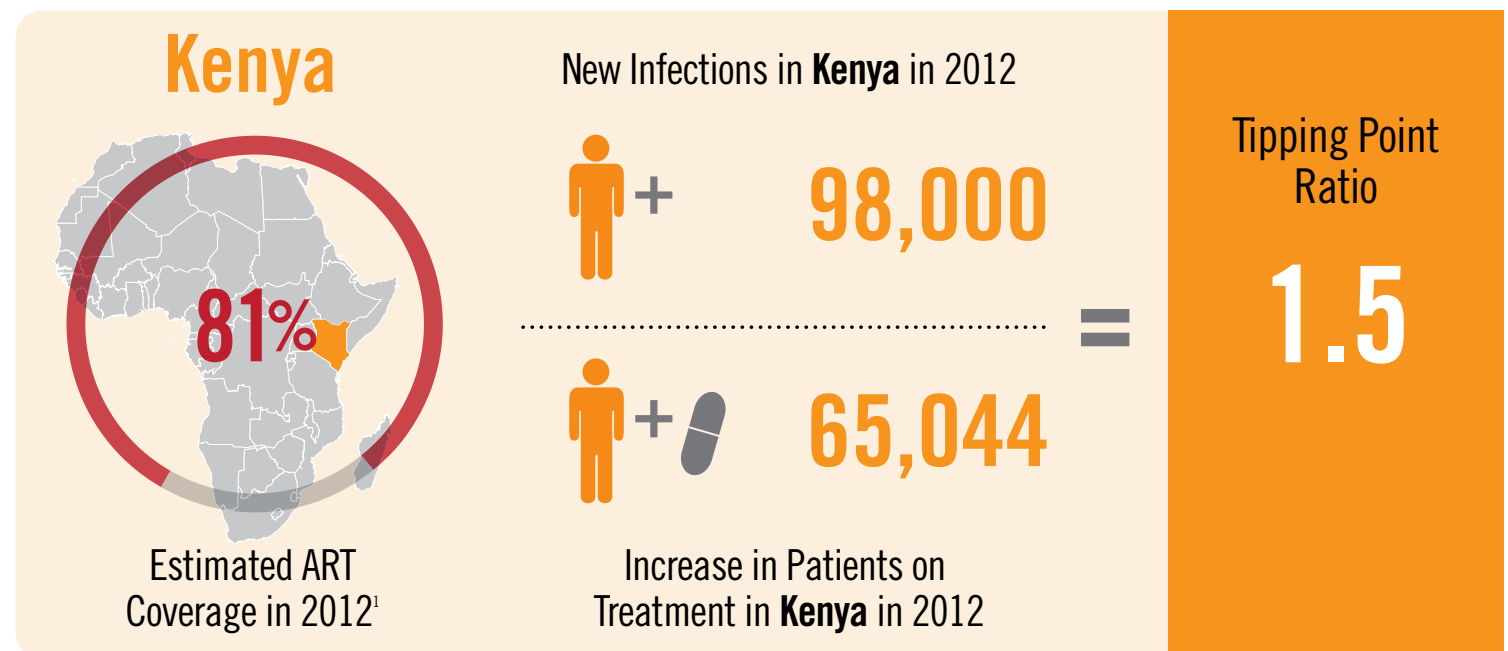
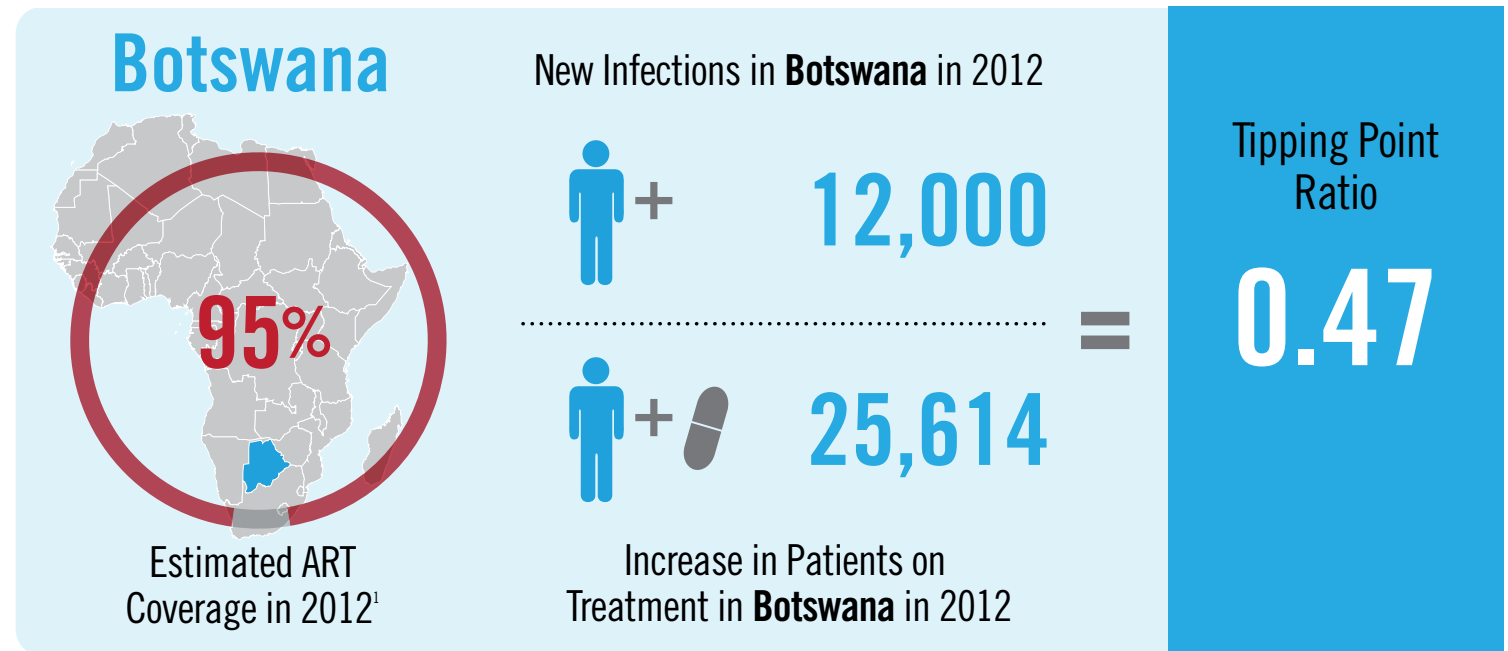
➔ Global progress in reducing new HIV infections and scaling up antiretroviral treatment by 2012

One way to measure progress in fighting AIDS is to compare the number of new HIV infections with the increase in HIV positive people on antiretroviral therapy (ART) over a given time period. An AIDS epidemic reaches its "tipping point" when the number of annual new HIV infections falls below the annual increase in patients starting ART. Coverage matters. A first milestone is treating approximately two thirds of the people in need in a given country. Once that level is reached, countries and advocates can track progress to the tipping point.

However, a country can reach the tipping point and then cross back—returning to a situation where incidence outstrips rate

of ART initiation. That's why it is essential to achieve optimal coverage rates of high-impact prevention including voluntary medical male circumcision, male and female condoms and harm reduction. Newer strategies such as PrEP and, eventually, a microbicide or vaccine should also be used for maximum impact.

The pace at which treatment and prevention are scaled up is key. To reach the tipping point the rate at which people are started on treatment should accelerate immediately. To stay on course countries and donors need to increase financial and human resource commitments to strategic combination prevention.



1 Based on WHO 2010 Guidelines; WHO issued updated guidelines in June 2013, Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a public health approach. www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html
 2 UPEPFAR. PEPFAR Blueprint: Creating an AIDS-free generation. November 2012. www.pepfar.gov/documents/organization/201386.pdf
 3 UNAIDS. UNAIDS report on the global AIDS epidemic 2013. www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf
 4 UNAIDS. UNAIDS report on the global AIDS epidemic 2012. www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_with_annexes_en.pdf



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was a trend towards increased risk of infection in some Step volunteers (see www.avac.org/vaccines/ad5 for more information). The trend was not statistically significant and waned over time. In 2013, Phambili researchers reported an increased number of infections in vaccinees compared to placebo recipients—a gap that appeared three and a half years after immunizations were halted.

The HVTN 505 trial tested another Ad5-vectored candidate along with a DNA prime. The trial enrolled only circumcised men with no prior Ad5 infection, given the previous Step result where this group was not at increased risk. The trial was launched in 2009 after extensive discussions about feasibility and ethics. It was halted early in April 2013 after a scheduled data review showed there was no chance the strategy would show efficacy. There was no evidence of vaccine-induced enhancement of HIV risk in HVTN 505.

At the mini-summit, scientists agreed that it is critical to err on the side of caution. Even an unexplained, non-statistically significant trend towards increased risk, such as was observed in Step and Phambili, means that “Ad5 is dead” as an HIV vaccine vector. As to the questions about how to proceed with other vectors—Ad or otherwise—the answers were complex and less clear-cut.

Throughout the day, there was discussion of mechanisms: why might any vaccine increase risk of HIV infection? One of several possibilities is that vaccines send an influx of immune cells—the very cells that HIV targets—to the site of infection. This effect would not be unique to Ad5-vectored candidates. Any vaccine that was not protective could end up increasing susceptibility to HIV simply by increasing these targets, though a potent vaccine could overcome this effect. Participants also discussed the possibility of providing other strategies like PrEP or monoclonal antibodies or a microbicide as an added layer of protection after immunization. One participant suggested that male circumcision could be recommended prior to immunization, since the foreskin could be the site for many target cells.

There was consensus on some of the tasks the field can take to continue with vector research—and on the urgent need to move ahead, even while exercising all possible caution. A full set of recommendations that balance these considerations is forthcoming.

Recently Released

An Action Agenda to End AIDS: Where are we in realizing the promise of beginning to end AIDS?
www.endingaids.org

Global AIDS Response Progress Reporting 2013: Construction of Core Indicators for monitoring the 2011 UN Political Declaration on HIV/AIDS
www.unaids.org/en/resources/campaigns/globalreport2013/index.html

Financing the Response to HIV in Low- and Middle-Income Countries: International assistance from donor governments in 2012
www.kff.org/global-health-policy/report/financing-the-response-to-aids-in-low/

Not to be Missed

October 7–10: AIDS Vaccine 2013: The annual gathering of the AIDS vaccine science field features many webcast presentations and press conferences. You can find the full list at www.aidsvaxwebcasts.org, *Barcelona*

October 16–19: European AIDS Conference, *Brussels*

December 1: World AIDS Day

December 7–11: 17th ICASA Conference 2013, *Cape Town*

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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