

# Treatment

## Understanding the results of RV144, the Thai prime-boost AIDS vaccine trial

By Deirdre Grant and Emily Bass

In September 2009 the world learned the initial results of RV144, known as the Thai prime-boost AIDS vaccine trial. This study was the largest AIDS vaccine trial to date, with over 16,000 participants. It evaluated the efficacy of a vaccine regimen consisting of two candidates, known as ALVAC HIV and AIDSVAX B/E. The trial data indicated that the vaccine regimen reduced HIV risk by approximately 30 percent. This is the first time a trial has found evidence that it is possible to reduce the risk of HIV infection with a vaccine. While this does not mean that an AIDS vaccine will be available in clinics anytime soon, the evidence that a vaccine can protect against infection is unprecedented. Scientists will spend the coming months reviewing the data, and testing blood samples from the trial to discover how the vaccine may have protected some trial participants. Researchers are already working hard to understand what these findings mean and to identify key next steps.

### What was the Thai prime-boost trial and how was it designed?

The Thai prime-boost test-of-concept trial began in 2003 and enrolled more than 16,000 HIV-negative Thai men and women between the ages of 18 and 30. A number of Thai and U.S. government collaborators worked on the trial. A combination of two vaccines was tested: ALVAC HIV vaccine (the prime) and AIDSVAX B/E vaccine (the boost). The trial was designed to evaluate whether this vaccine regimen reduced risk of HIV infection and/or whether participants who received the vaccine and later acquired HIV had lower viral loads than those who received the placebo and acquired HIV.

The trial was supported by the World Health Organization (WHO) and UNAIDS, whose HIV

Vaccine Advisory Committee (VAC) found that the trial was conducted to the highest scientific and ethical standards and with active community participation.<sup>1</sup>

### What data are available?

The initial data analysis was published in the *New England Journal of Medicine* in October 2009. The trial team used various statistical methods to compare rates of infections in vaccine and placebo recipients to determine whether the vaccine regimen had any effect on HIV acquisition or viral load in those who seroconverted. It is standard to use three different ways of analyzing the data: Intent to Treat (ITT), modified Intent to Treat (mITT) and Per Protocol (PP)<sup>2</sup>. The use of multiple statistical analyses helps scientists understand the data in greater detail in light of the complexities and realities of clinical trials.

Each of these three analyses looked at a different number of individuals and therefore yielded slightly different results. However, all of the analyses' findings followed the same trend of fewer infections in the vaccine recipients compared to the placebo recipients. One of the most important facets of the Thai data is that all three analyses show the same trend. In every case, there were fewer infections in the vaccine treatment group as compared to the placebo treatment group, indicating a reduction in risk of acquiring HIV between 26.2% and 31.2%. While only one of the three analyses was statistically significant (which means that the observed difference is very likely due to the effect of the vaccine, and not to chance), the fact that all analyses trend in the same direction provides strong evidence that the vaccine did reduce the risk of HIV infection in some volunteers.

The vaccine regimen had no effect on post-infection viral load levels among the recipients who became

infected. This vaccine was developed with the aim of preventing new infections and thus was only tested in HIV-negative individuals. There are trials of therapeutic vaccines that are being studied to determine their effectiveness at treating people currently living with HIV.

### Regional data limitations

The trial data are from a single trial in Thailand. The data from the trial do not provide information on whether this specific strategy would have a benefit in areas where other HIV virus subtypes predominate. The vaccine included synthetic fragments of genetic material from HIV subtypes B and what is often referred to as subtype E, but is more accurately classified as CRF01\_AE. These are two of roughly nine circulating subtypes, or clades, of HIV worldwide. Subtype E is common in Thailand and Southeast Asia, while different subtypes predominate in other regions of the world. The trial data indicated the vaccine had a protective effect in an area with HIV subtype E, which is prevalent in Southeast Asia. There is not yet evidence that the vaccine would be effective in areas where other subtypes are prevalent.

### What happens next?

The RV144 trial steering committee has convened a scientific steering committee and a product development advisory group. Independent scientific advisory groups ensure that the expertise of the broader AIDS vaccine field is brought to bear on challenging, potentially field-altering results.

The scientific steering committee for the RV144 trial consists of four working groups, each including a range of scientists from outside the trial team. Those groups will explore the implications of the Thai trial data for the evaluation and design of other AIDS vaccine candidates and studies and make recommendations for the field. The trial steering committee plans to establish an online submission process for researchers to propose potential studies using lab samples collected from the trial. The product development working group is currently considering the options and implications for future clinical development of the ALVAC-AIDSVAX regimen.

### What are some of the challenges that lie ahead?

The Thai trial results are the beginning of an exciting chapter in AIDS vaccine research. There are unique challenges and opportunities that have already started to emerge. These include (but are not limited to):

**Limited numbers of samples:** Every trial collects specific quantities of blood (and sometimes other samples)

from its participants. At the end of the study, these samples can be used for a range of analyses to learn more about what happened. For the Thai prime-boost trial, the number of questions about the biological mechanisms underlying the observed effect far exceeds the number of samples available for further analysis. This means that there will be challenging choices about which analyses to conduct using the samples available. The steering committee and scientific advisory group described above will help make these difficult choices. It will also be critical for proposals submitted by outside researchers through the online process to be considered. These experiences with data analysis should be used to shape future trials' approaches to sample collection and data sharing.

**Striking the balance between seeking a correlate of protection and developing a product:** Right now the field is interested in finding out what types of immune responses were responsible for the apparent vaccine effect.

There is also interest in developing the regimen—either as is, or with modifications—as a product for

further study on its own. There are many licensed vaccines in use today that work in ways that are not understood. The Thai regimen could be studied in future trials without detailed knowledge of how exactly it provides protection. The challenge facing all of the stakeholders in the field is to map out a way forward that balances both agendas: to learn as much as possible about how the Thai vaccine regimen provided protection and to carefully consider whether the regimen should be studied in future trials.

### What now?

While the field is reinvigorated by the recent Thai prime-boost vaccine results, advocates continue to note the importance of comprehensive prevention. Even if the vaccine regimen had shown to be effective enough to warrant licensure in Thailand, it would not be a replacement for other methods of prevention, including male and female condoms, behavior change counseling, male circumcision, needle exchange and harm reduction. Any new strategy will need to be delivered and used as part of a multi-faceted approach.

The results of the Thai trial are a boon to AIDS vaccine research. While a highly effective licensed vaccine is still many years away, the evidence that one is possible is a new and exciting discovery for the field.

*Deirdre Grant is the Program Manager at AVAC: Global Advocacy for HIV Prevention. Emily Bass is the Program Director at AVAC. References on page 5.*

# Lifting the HIV entry ban: what it means on the ground

By Erin Price

## Background

On January 4, 2009, the final repeal of the HIV travel and immigration ban went into effect. For too long the United States denied HIV positive non-citizens access to citizenship, residency and visiting rights based solely on their HIV status. Since 1987, under section 212(a)(1) of the Immigration and Nationality Act (INA), a non-citizen determined to have a “communicable disease of public health significance” has been inadmissible into the United States. Over the past twenty years, the Human Immunodeficiency Virus (HIV) has been considered a “communicable disease of public health significance.” HIV-positive non-citizens have thus been barred from entry into the United States, and HIV-positive non-citizens already in the US have been barred from adjusting their status to that of a legal permanent resident. Although there was a waiver available for HIV-positive non-citizens, it was only available to those with a parent, spouse or child living in the U.S. as a citizen or legal permanent resident. This restriction was put in place in 1987 at the request of the late Senator Jesse Helms (R-NC) during the height of the homophobic political climate of the late 1980s.

Public health experts have long acknowledged that the HIV entry ban does nothing to prevent the spread of HIV across international boundaries and is in fact out of step with the public health and immigration policies of much of the rest of the world. This welcome change is the result of decades of advocacy and education of public officials. The legislative action needed to repeal the ban occurred in July 2008 when President Bush signed into law the reauthorization of the President’s Emergency Plan for AIDS Relief (PEPFAR II). This amended the Immigration and Naturalization Act, striking the provision that renders individuals with HIV inadmissible to the United States. Congresswoman Barbara Lee and Senator John Kerry led the fight in Congress to repeal the entry ban. This repeal of the statutory bar required the Department of Health and Human Services (HHS) to reconsider whether HIV should continue to be listed as a communicable disease “of public health significance” that renders non-citizens inadmissible to the United

States. A policy change at HHS was the final barrier to a full repeal. A proposed rule change, started in the final months of the Bush Administration and promulgated by the Obama Administration, proposed the removal of HIV from the list of “communicable disease[s] of public health significance.” During a public comment period in July and August of 2009, HHS received an overwhelming positive response to these proposed changes. While 19,000 comments were made in favor of the change, only 500 were made in opposition.

The publication of the final rule was announced by President Obama on October 30, 2009, to go into effect January 4, 2010.

President Obama noted the historic and significant nature of this policy change: “Twenty-two years ago, in a decision rooted in fear rather than fact, the United States instituted a travel ban on entry into the country for people living with HIV/AIDS. Now, we talk about reducing the stigma of this disease, yet we have treated a visitor living with it as a threat. We lead the world

when it comes to helping stem the AIDS pandemic, yet we are one of only a dozen countries that still bar people with HIV from entering our own country. If we want to be the global leader in combating HIV/AIDS, we need to act like it. And that is why, on Monday [Nov. 2], my administration will publish a final rule that eliminates the travel ban, effective just after the new year. ...<sup>1</sup>”

## What this means for HIV advocacy

Symbolically, the rule will help reduce HIV-related stigma, and bring the United States into compliance with international health policies regarding HIV immigration and travel. The United States’ HIV entry and immigration ban was at odds with current medical knowledge involving the transmission of HIV, and was also in direct opposition to the U.N.’s International Guidelines for HIV/AIDS and Human Rights.<sup>2</sup> The ban placed the United States alongside only 13 other countries that ban HIV-positive short term visitors: Brunei, Egypt, Iraq, Yemen, Malaysia, Oman, Qatar, Singapore, Sudan, South Korea, Tunisia, Turks & Caicos Islands, and the United Arab Emirates. This put the U.S. in a category with many countries whom the U.S. State Department describes as having either poor or significantly problematic human rights records.<sup>3</sup> The new American policy demonstrates the Obama Administration’s commitment to fight HIV-related stigmatization and treat HIV positive non-citizens with an increased standard of dignity.

*As of the start of 2010 the U.S. no longer bars entry based on HIV status.*

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## What this means for HIV positive non-citizens

HIV will be taken off the list of “communicable diseases” that would normally bar entry without a waiver. HIV-positive non-citizens will no longer have to submit to an HIV test when applying for an American visa. Applicants will still need to undergo a visa-related medical examination, but it will not include an HIV test, decreasing the costs of visa-related medical examinations. In addition, HIV-positive non-citizens applying for entry or adjustment will no longer have to file for a waiver of inadmissibility, which costs a hefty \$545. However, applicants will still be denied for any of the other diseases still on the list of “communicable diseases of public health significance”—including active tuberculosis, infectious syphilis, gonorrhea, infectious leprosy, etc.—unless a waiver is obtained.

This change does not provide amnesty for persons with HIV who previously entered without inspection or were previously denied entry due to their health status. While HIV is no longer a bar to applying for permanent residence, all applicants for a green card must qualify under current immigration law. This means that to get a green card you must have family or employer sponsorship, a current spot in the diversity lottery, asylum, or another recognized means to apply. Many undocumented HIV positive persons who have been living in the United

States still will not have access to residency because they have been in the country without lawful status. The new provision simply means that after January 4, 2010, HIV-positive non-citizens going through an already established path to residency will no longer need to apply for an HIV waiver.

People who are at varying points of applying for residency, waivers, visas and asylum are affected differently by this change. Anyone who has filed an HIV waiver as part of his or her green card application should notify the U.S. Citizenship and Immigration Services (USCIS) that the ban has been lifted, and ask that their application be adjudicated. If you have previously applied for and been denied residency because of your HIV status, you may be able to re-open your case if you are still eligible under current statuses. Anyone applying for asylum on the basis of being HIV-positive should not be affected by this new ruling, because those applications are based upon threat of persecution in country of origin. People previously denied visas because of their HIV status will no longer have that barrier. However, you must still qualify for all other requirements, including a demonstrated intent to return home. While HIV status no longer bars access to immigration, other barriers could affect some people living with HIV. Some people living with HIV whose health poses major barriers may find it difficult to meet USCIS requirements that candidates demonstrate an ability to support themselves, due to the affects of living with HIV. No matter one's relative health, no person is required to bring up their HIV status in the immigration process.<sup>4</sup>

The new rule is not retroactive. The final rule obligates the Centers for Disease Control and Prevention and the Department of Health and Human Services to continue working with the State Department and the Department of Homeland Security to ensure that panel physicians and civil surgeons who conduct the medical examinations are aware of the revision to the current rule.<sup>5</sup>

## Conclusion:

This is a huge victory for human rights and persons living with HIV. The new rule not only eliminates HIV screenings during medical examinations, but also eliminates the need for an expensive waiver application. It also brings the United States into line with international policies regarding HIV and travel restrictions and removes the institutional stigma placed on persons with HIV and AIDS by the old regulation.

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## RV144 vaccine references

- 1 UNAIDS “Largest ever HIV vaccine trial results very encouraging.” UNAIDS: Joint United Nations Programme on HIV/AIDS. September 24, 2009. [http://www.unaids.org/en/KnowledgeCentre/Resources/FeatureStories/archive/2009/20090923\\_vaccine.asp](http://www.unaids.org/en/KnowledgeCentre/Resources/FeatureStories/archive/2009/20090923_vaccine.asp). Accessed: December 10, 2009.
- 2 The Intent to Treat (ITT) analysis included all participants who were randomized and received any injections (the full course was six injections, but not all participants completed the full course).
- 3 The modified Intent to Treat (mITT) included all participants who were randomized and received any injection (as with the ITT analysis) BUT excludes seven individuals who were originally believed to be HIV-negative at baseline, but were later determined to be HIV-positive at baseline.
- 4 The Per Protocol (PP) analysis included only those participants who were HIV-negative at baseline and who followed the protocol procedures exactly, meaning that they completed the full course of injections within the timeframes specified by the protocol.

## HIV entry ban references

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