

## Spotlight

### Deadly duo

*Joining forces to fight TB and HIV*

An astonishing one-third of the world's population is infected with the bacterium that causes tuberculosis (TB), *Mycobacterium tuberculosis*. In most people it remains inactive or latent but in about 10% of people an active case of TB disease will develop within their lifetime. Simple antibiotics can prevent and treat most of these cases, yet 8-10 million people develop an active TB infection annually and two million die from it.

In recent decades the risk posed by TB and its consequences have been far greater due to the relentless spread of the HIV/AIDS pandemic. Stephen Lewis, the former United Nations Special Envoy for HIV/AIDS in Africa, has called the two diseases a "combination made in hell." HIV-infected individuals have a 20-fold greater risk of developing active disease, and TB is now the leading cause of death among HIV-infected people around the world. The TB bacterium and HIV are a deadly combination because both pathogens attack the immune system. "Both diseases suppress the immune system independently," says Jerald Sadoff, president and chief executive officer at the Aeras Global TB Vaccine Foundation, an organization developing improved TB vaccines. This compounds the damage to the body's defense system.

The relentless spread of the HIV epidemic is also making it impossible

to continue to confront TB through traditional approaches. In response, the global health community is changing how it confronts these two diseases, incorporating more collaboration between historically separate TB and HIV/AIDS programs. A major goal of the World Health Organization's (WHO) new Stop TB Strategy, launched in 2005, is to decrease the burden of TB and HIV in populations affected by both diseases, and the plan is endorsed by a coalition of organizations involved in TB and HIV care. This new initiative combines the traditional approach to TB therapy, known as directly observed therapy short-course or DOTS where individuals are observed taking their medications, with a greater awareness of the interaction between HIV and TB.

The Stop TB policy recommends more thorough surveillance and prevention, both of HIV among TB patients and of TB in people living with HIV/AIDS. "TB prevention, diagnosis, and treatment services need to be core functions of HIV prevention, treatment, and care services, and vice versa," says Haileyesus Getahun, secretary of the TB/HIV working group at the WHO.

#### Identifying and treating TB

The majority of TB infections are acquired when an individual inhales bacteria shed via the coughing or sneezing of an individual with active TB infection. The bacteria then lodge deep in the lungs where they are kept in check by the immune system, resulting in a latent infection.

The transition from latent to active TB infection can happen on its own but is far more likely in individuals with com-

promised immune systems. HIV-infected individuals are particularly susceptible, making it one of the most common infections that occur in individuals with AIDS. During active infection the TB bacteria multiply and enter the bloodstream. They can also settle in internal organs, such as the kidneys and brain.

While HIV can be detected through a relatively simple antibody test, diagnosis of latent or active TB infection presents many challenges. Antibody tests for *M. tuberculosis* have proven useless and in many regions of the world the techniques used for diagnosing TB have remained relatively unchanged for the past hundred years.

The most common test for latent infection is a skin test where proteins from killed TB bacteria are injected just beneath the skin. A hypersensitivity reaction occurs in people with prior exposure to the bacterium, causing inflammation at the injection site. Though quick and easy, roughly 25% of those with active TB may have negative skin tests, meaning that people who need antibiotics to prevent the transition from latent to active TB will not receive them.

The test also does not work in newborns and infants due to their immature immune systems or in individuals with compromised immune systems, who may be unable to mount the necessary immune response. There is also the

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possibility of false-positive test results with the skin test, especially in people who were previously vaccinated against TB. The vaccine, known as bacille Calmette-Guerin or BCG, is used to immunize infants but its protection only lasts through childhood, which is why TB infection remains so common.

If latent TB is detected by the skin test, treatment with a single antibiotic (isoniazid) can dramatically reduce the chance of developing active TB. Diagnosis of active TB is done with a chest X-ray, but it must be confirmed by other methods. The gold standard is the smear test, which involves taking a sample of coughed-up sputum and smearing it onto a microscope slide and then examining it for the distinctive appearance of the *M. tuberculosis* bacterium.

Preventing the conversion from latent to active TB with isoniazid can reduce morbidity and improve survival, and the WHO recommends that all individuals with latent infection, including people living with HIV/AIDS, take isoniazid for six to nine months. But more recent studies indicate that nine months to a year is even more effective. In randomized controlled trials, isoniazid reduced the incidence of active TB by about 60% in HIV-infected patients with a positive skin test and 42% overall.

A more recent study investigated whether isoniazid, given to all individuals in a community regardless of their prior exposure to TB, could reduce the prevalence of the disease at the community level. Roughly 700 HIV-infected South African miners were given isoniazid preventive therapy for six months, reducing active TB infection by 38% overall, and by 46% in individuals not previously exposed to TB.

A similar effect was seen in a randomized clinical trial involving about 250 HIV-infected South African children. The group receiving isoniazid had a statistically significant lower incidence of TB than did the placebo group—5 cases compared to 13 in those who received placebo. The effect was so significant that the placebo arm was discontinued. Heather Zar, associate professor at the University of Cape Town, conducted this study and said it could have major public health implications. “This could be recommended routinely for HIV-infected children who

do not have access to antiretrovirals and who live in high TB-prevalence areas,” she says.

### ARVs improve survival

Effective antiretroviral (ARV) therapy can dramatically improve the quality of life and survival time of HIV-infected individuals. The drugs’ effective suppression of virus replication allows the immune system to rebound and keep HIV in check. Several studies have also demonstrated that ARVs can reduce the incidence of TB in HIV-infected people by greater than 80%. This effect is greatest among people with lower CD4<sup>+</sup> T-cell counts and those who start ARVs early in the course of their HIV infection (see *Primer*, this issue).

A study presented at the International AIDS Conference in 2006 in Toronto showed that isoniazid plus ARVs may be the best way to prevent active TB disease in people co-infected with HIV and TB. The analysis of over 11,000 HIV-infected men and women in Rio de Janeiro found that isoniazid plus highly active antiretroviral therapy (HAART) is more effective than either therapy alone at preventing active TB disease—67% disease reduction among people treated with both drugs, while isoniazid or HAART alone reduced disease by 32% and 51% respectively.

The study is one of three ongoing projects by the Consortium to Respond Effectively to the AIDS/TB Epidemic, known as CREATE, led by Richard Chaisson of US-based Johns Hopkins University in Baltimore. Chaisson is also looking at the question of how long HIV-infected individuals should take isoniazid. “We are doing a clinical trial funded by the National Institutes of Health that is looking at giving preventive treatment for an indefinite period of time to see if that is more effective in settings where there is more TB transmission,” says Chaisson.

Effectively addressing TB in some countries may even require revising guidelines on ARV therapy. HIV-infected individuals are susceptible to several viral and bacterial infections once their total number of CD4<sup>+</sup> T cells drops below 200 per ml of blood. This is the cutoff point for an AIDS diagnosis and is also the starting point for ARV therapy in many countries. But TB can

switch from latent to active form even at higher CD4<sup>+</sup> T-cell counts of around 250. Effectively preventing development of active TB would therefore require starting ARV therapy earlier. This could be complicated in developing countries where diagnosis of HIV infection often does not occur until a person has developed AIDS.

### Extensively drug resistant TB

Another concern for researchers battling the HIV/AIDS and TB epidemics is a new form of TB that can not be treated with most available antibiotics, making it especially deadly. When this extremely drug-resistant TB (XDR-TB) emerged in a hospital in South Africa’s KwaZulu-Natal province in 2005, its first victims were people living with HIV/AIDS; within a month of diagnosis it had killed 44 HIV-infected people.

The spread of XDR-TB poses an additional threat for efforts to halt the development of TB among HIV-infected individuals. Identification of XDR-TB in HIV-infected individuals is even more difficult than a simple TB diagnosis. Drug-resistant strains are usually diagnosed via sputum culture, yet this may not detect many of the types of TB most common among HIV-infected individuals.

With XDR-TB now present in all regions of the world, global public health officials fear a deadly wave of TB that could spread first among HIV-infected individuals, and then within the general population. About 2% of all TB cases are XDR-TB, defined by WHO as resistance to at least the two most commonly prescribed TB drugs (rifampicin and isoniazid) in addition to several others. An estimated US\$95 million is needed to stop the spread of XDR-TB, according to the WHO’s Stop TB Partnership.

In the end, the success of programs to fight TB and HIV in a concerted manner rests on the availability and quality of services and the coordination between testing for HIV and TB, as well as delivery of ARV and TB therapies. A joint HIV-TB approach could range from referrals between services to the integration of HIV/AIDS and TB clinics. As the example of XDR-TB indicates, failure to implement HIV and TB prevention and treatment will only serve to worsen the toll on human lives.

## Global News

### AIDS vaccine trial begins in US

Two biotechnology companies, Pharmexa-Epimmune and Bavarian Nordic, recently initiated a Phase I AIDS vaccine trial with funding from the US National Institutes of Health (NIH). This trial started at the end of April and is being conducted by the HIV Vaccine Trials Network (HVTN) at sites in three US cities—Nashville, Rochester, and San Francisco.

Investigators plan to enroll 108 volunteers to evaluate the safety and immunogenicity of two vaccine candidates administered consecutively in a prime-boost combination. The first candidate, EP1233, is a DNA vaccine candidate developed at Pharmexa-Epimmune with funding from the US National Institutes of Allergy and Infectious Diseases (NIAID). The second candidate was developed at Bavarian Nordic and uses a modified vaccinia Ankara viral vector to deliver HIV proteins matching those in the DNA candidate.

### South Africa launches AIDS plan

At the end of April the South African government released a new national AIDS plan, outlining the country's strategy to combat the epidemic. At the end of 2006, there were 5.5 million South Africans living with HIV/AIDS, according to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the number of HIV-infected individuals continues to rise. In response to these grim statistics, the 160-page plan includes a proposal for halving the number of new HIV infections by 2011 through improved prevention programs. It also proposes improving the diagnosis of HIV/AIDS, providing life-saving antiretroviral treatment to 80% of the estimated one million South Africans that are in need, and reducing the rate of mother-to-child transmission of HIV to below 5% over the next five years—all at an estimated cost of US\$6 billion.

The "HIV and AIDS and STI Strategic Plan for South Africa, 2007-2011" was prepared following extensive consulta-

tion with government officials, UNAIDS, research institutions operating in the country, and several civil society representatives. The release of this comprehensive plan was lauded by many organizations, including the Treatment Action Campaign and the AIDS Law Project, which have been critical of the government's sluggish response to the AIDS epidemic, and was also endorsed by the recently restructured South African National AIDS Council.

### 10th annual World AIDS Vaccine Day commemorated

The 10th annual World AIDS Vaccine Day was commemorated on May 18, with many organizations conducting AIDS vaccine education campaigns or events to stimulate awareness and support for the development of a preventive AIDS vaccine. The commemoration of World AIDS Vaccine Day originated in 1997 when then US President Bill Clinton delivered a speech at Morgan State University calling on the world's researchers to develop an AIDS vaccine within the next decade.

Although this goal was not met there has been substantial progress in the field. In the past decade the funding for AIDS vaccine research and development has quadrupled and scientists have made significant advancements in the understanding of HIV and its interaction with the immune system (see March 2007 *Primer on Understanding Why an Effective AIDS Vaccine is Feasible*). Researchers have also advanced promising AIDS vaccine candidates into preliminary efficacy trials, and there are now more than 30 ongoing preventive AIDS vaccine Phase I and II clinical trials.

In an editorial in the *San Francisco Chronicle*, Peggy Johnston, director of the Vaccine Research Program at NIAID, and Tony Fauci, director of NIAID, said, "We now know more about HIV, the virus that causes AIDS, and have more promising vaccines in development than at any other time in the history of the HIV/AIDS pandemic." Still there are many remaining scientific obstacles that must be overcome before Clinton's challenge will be realized (see April 2007 *Primer*

on *Understanding the Challenges of AIDS Vaccine Development*).

The urgent need for a vaccine that could help reverse the relentless spread of the AIDS pandemic remains unchanged since Clinton's speech. Currently 40 million people are living with HIV/AIDS around the world and each day an additional 12,000 new HIV infections occur. A preventive AIDS vaccine, even one that is partially-effective (see *Primer*, this issue), would help to dramatically lower the number of new infections.



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## What is a partially-effective vaccine and how can it limit the spread of HIV?

The ultimate goal of AIDS vaccine research is to develop a vaccine that will completely protect an individual from HIV infection and the subsequent development of AIDS. Typically, vaccines that protect against other viruses work by inducing strong virus-specific antibody responses that control the virus and prevent development of disease (see February 2007 *Primer on Understanding Neutralizing Antibodies*). However the majority of AIDS vaccine candidates that are currently undergoing testing in clinical trials do not induce broadly neutralizing antibodies against HIV (see February 2007 *Primer on Understanding Neutralizing Antibodies*). Instead these candidates all primarily induce cellular-mediated immune responses, including CD8<sup>+</sup> T cells or cytotoxic T-lymphocytes, which do not attack the virus directly but rather target and kill HIV-infected cells. Without stimulating a robust antibody response, many researchers think it is likely that these candidates will not offer complete protection against HIV infection.

The more realistic goal currently is the development of a vaccine candidate that can induce strong cellular immune responses capable of lowering the levels of virus circulating in the body (known as the viral load) in individuals who do become infected despite vaccination, enabling them to control their HIV infection for prolonged periods of time. This non-classical approach is often referred to as the development of a partially-effective or partially-protective vaccine.

In the past the idea of a partially-effective vaccine has had different meanings—referring to a vaccine that only protects some people who receive it, or a vaccine that only protects against disease some of the time. But in the AIDS vaccine field nowadays a partially-effective vaccine means one that doesn't protect against HIV infection or entirely against the development of disease, but can delay the progression to AIDS in individuals who receive the vaccine and later become HIV infected anyway.

A first-generation vaccine that accomplishes this goal could have many significant benefits. First it could delay the time until a person must begin anti-retroviral (ARV) treatment. It could also help prevent vaccinated individuals who do become HIV infected from transmitting the virus to others. This would be a significant achievement and could shrink the global epidemic by helping to roll back the approximately 12,000 new HIV infections that still occur worldwide every day.

### Delaying therapy

The health of the immune system is characterized by the total number of CD4<sup>+</sup> T cells measured in a sample of blood. These immune cells are responsible for orchestrating the body's defenses against invading pathogens and if too many are lost an individual is susceptible to many serious and potentially fatal infections. Normally an individual will have between 600-1200 CD4<sup>+</sup> T cells in a milliliter of blood. An HIV-infected individual is diagnosed with AIDS when this number falls below 200. On average it takes up to a decade after a person is initially infected with HIV for the virus to deplete the immune system to the point that the onset of AIDS occurs and ARV therapy becomes necessary.

If a partially-effective vaccine is able to suppress the virus during the early stages of HIV infection, it may help preserve some of these critical CD4<sup>+</sup> T cells that are the primary target of HIV. Results from some studies indicate that giving ARVs to an individual very early in the course of their HIV infection correlates with better control of the virus over the long term because it helps spare the immune system from some of the damage inflicted early on by the virus. A similar outcome is predicted with a partially-effective vaccine that could defend the massive number of immune cells in the mucosal tissues that are destroyed by HIV during the initial stages of infection (see *VAX* April 2006 *Primer on Understanding the Early Stages of HIV Infection*).

Such a vaccine could help bolster the immune system and allow an individual

to control HIV for much longer than a decade, postponing the need for ARVs. Although these drugs are incredibly effective at controlling HIV infection and allow HIV-infected individuals to live longer and healthier lives, they can also cause many unpleasant side-effects and are expensive. Delaying ARV therapy could therefore dramatically improve the quality of life of HIV-infected individuals.

### Determining efficacy

It is impossible to follow individuals for more than a decade during clinical trials to see if a vaccine candidate is effective at delaying, or even preventing, the onset of AIDS. So instead researchers rely on indicators that occur much earlier in infection to predict a person's disease outcome. One of these indicators is called viral set-point and it refers to the point during the first weeks of infection when the body's HIV-specific immune responses kick in and, as a result, the HIV viral load drops dramatically. After this drop, the viral load stabilizes at a level called the set-point. Generally, the lower the viral set-point, the longer a person can control HIV. A partially-effective vaccine could help lower the viral set-point even further than in natural infection, extending the time until AIDS develops.

### Reducing infectiousness

There is good evidence suggesting that the likelihood of HIV transmission, both sexually and from mother-to-child, is directly correlated with the viral load of the infected person—the higher a person's viral load, the more likely they are to pass on the virus to others. Therefore a partially-effective vaccine that blunts HIV viral load could reduce the possibility that an individual could infect others.

Although a preventive AIDS vaccine that is able to protect against infection with HIV is the only way to end the AIDS pandemic, developing a first generation, partially-effective AIDS vaccine would be a very important step in rolling back the ever-expanding pandemic.