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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

Deadly Synergy

A Keystone Symposium on TB and HIV emphasized the need to tackle the diseases in tandem



By Andreas von Bubnoff

ALTHOUGH TUBERCULOSIS (TB) is thought to be the leading cause of death among people with HIV/AIDS, scientific conferences often focus on these two deadly diseases separately. This changed recently, when over 300 scientists and clinicians gathered in Arusha, Tanzania, from October 20-25 at a Keystone Symposium on “Overcoming the Crisis of TB and AIDS.”

Tuberculosis, a disease caused by a bacterial infection, is responsible for between one-third to a half of AIDS deaths, and at least a quarter of the approximately two million people who died of TB last year were co-infected with HIV, conference co-organizer Anne Goldfeld of Harvard Medical School said in the opening session. “Each infection and its solution cannot be separated from each other,” she added. “By bringing together scientists and clinicians who work at the cutting edge of each disease, it’s the aim of this conference to serve as a catalyst to generate new ideas and to identify new ways of solving our global humanitarian disaster.”

The presentations at the symposium spanned many topics including the mechanism of the synergy between HIV and TB, and the treatment and prevention of both diseases.

A lethal dance

Given that the meeting convened both TB and HIV experts, one central topic was

how the two infections interact and synergize in individuals that are HIV/TB co-infected. Each infection enhances the other infection’s ability to cause disease: HIV by compromising the immune system and weakening the body’s defenses against other pathogens like the bacterium that causes TB, and TB by driving HIV’s ability to replicate or produce more virus.

Goldfeld showed the results of test-tube studies that address how TB infection increases the quantity of HIV circulating in blood, known as viral load, by enhancing the ability of HIV to replicate. Her data suggest that TB infection in certain kinds of white blood cells induces a protein—one of several—that stimulates HIV replication.

Goldfeld is also involved in the CAMELIA clinical trial in Cambodia that is studying the timing of HIV therapy in co-infected individuals who have already begun therapy for TB. When to initiate highly active antiretroviral therapy (HAART) in co-infected people is a conundrum for scientists and clinicians. Starting co-infected people on HAART too late results in higher mortality because the immune systems of these individuals become too compromised by HIV and therefore they cannot withstand the onslaught of many infections that people with healthy immune systems can typically control. Yet there have also been concerns

that starting HAART early might result in adverse drug reactions and interactions. “[There] was a tremendous bias that people couldn’t take seven different types of medicines at once,” Goldfeld said. “So the recommendation was to wait until after the intensive phase of TB therapy was finished to initiate HAART.”

In addition, TB symptoms can sometimes worsen when HAART is initiated. For reasons scientists don’t completely understand, some co-infected individuals develop immune reconstitution inflammatory syndrome or IRIS, an inflammatory disease thought to be associated with an increase in the number of infection-fighting immune cells—known as CD4⁺ T cells—that, ironically, is one of the benefits of HAART. Gold-

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feld said that IRIS typically kicks in six to eight weeks after initiation of HAART.

The aim of the CAMELIA trial, which just finished enrolling 661 co-infected volunteers, is to see if early HAART initiation will increase survival in co-infected, immune-compromised individuals despite the perhaps more complex initial clinical management of issues such as IRIS, Goldfeld said. In the trial, some co-infected volunteers start HAART two weeks after starting TB therapy, while others delay initiation of HAART until two months after starting TB therapy. Results of the trial, which evaluates survival one year after initiation of TB therapy, are expected in mid-2010.

Some volunteers enrolled in CAMELIA are also enrolled in another trial called CAPRI-T, which is designed to evaluate whether certain characteristics of CD4⁺ T cells are involved in causing IRIS. Investi-

gators are analyzing blood samples from participants at several time points after they start TB therapy and at the time IRIS occurs, if this condition develops. Results of this trial are also expected in 2010.

Alan Sher, chief of the laboratory of parasitic diseases at the US National Institute of Allergy and Infectious Diseases (NIAID), presented data from a study in mice that suggest IRIS depends less on the quantity of CD4⁺ T cells than on their activity.

Sher first infected mice deficient in T cells with *Mycobacterium avium*, which causes a TB-like infection in the animals. When given CD4⁺ T cells from a normal mouse, to mimic the increase in CD4⁺ T cells that would occur as a result of HAART, the mice indeed got a rapid IRIS-like disease and died. But the injected T cells did not expand more in infected mice compared to uninfected mice. Instead, they produced molecules that may lead to the recruitment of other types of white blood cells to tissues including the lungs, where they can cause damage. He believes that intervening in this process might be a possible way to prevent IRIS in humans.

Insights on HIV transmission

The meeting also featured presentations that dealt with HIV and TB separately, including some that focused on HIV transmission. Much has been learned in recent years about HIV transmission. This includes information about the specific viruses that get transmitted from an infected person to an uninfected person. For example, researchers have found that about 80% of heterosexual HIV infections can be traced back to one transmitted virus variant (see VAX April 2009 *Primer on Understanding the Transmitted Virus*). This is true even though there are numerous HIV variants circulating in the already infected partner. This led researchers to conclude that there is some sort of bottleneck that occurs in HIV transmission that severely limits the number of viruses that can establish an infection. However, how much of a bottleneck there is depends on the route of HIV transmission. Researchers have observed that in men who have sex with men (MSM) and injection drug users (IDUs), there are often more HIV variants that get transmitted and establish a new HIV infection.

George Shaw, a professor of medicine and

microbiology at the University of Alabama, and one of the pioneering scientists documenting these early events in HIV transmission, said that recent studies in IDUs indicate that at least 17 different transmitted viruses have now been found to be responsible for establishing infection. "There [are] so many we can't count [precisely]," he said. This suggests that some routes of transmission may be fundamentally more difficult to protect against.

Antibody PrEP

A much-discussed strategy to prevent HIV transmission is the administration of antiretroviral therapy to HIV-uninfected individuals prior to exposure to the virus, an approach known as pre-exposure prophylaxis (PrEP; see VAX November 2008 *Spotlight* article, *PrEP Work*). David Ho, a professor at Rockefeller University and director of the Aaron Diamond AIDS Research Center, is developing a novel PrEP strategy which involves giving people an antibody rather than antiretroviral therapy. The antibody, called Ibalizumab, binds to a molecule on the surface of CD4⁺ T cells that HIV uses to get inside. By binding to this molecule, the antibody prevents HIV from infecting CD4⁺ T cells, the virus' main target.

Ibalizumab is currently being tested in Phase IIb clinical trials as an HIV therapy, but Ho thinks the antibody should also be tested in uninfected people to see if it has any utility as an HIV prevention strategy. He said this prevention strategy would require less frequent dosing than with antiretroviral therapy and is also typically associated with fewer adverse events.

However, administration of Ibalizumab is not necessarily risk free. One concern with antibodies that bind to this molecule on the surface of CD4⁺ T cells is that they could inhibit the normal function of these important immune cells. But Ibalizumab doesn't seem to interfere with normal immune function, Ho said.

Ho is now testing Ibalizumab in nonhuman primates to see if it can prevent HIV infection, and he is planning to launch a Phase I study in healthy volunteers. He also plans to further improve the antibody so that it would only need to be administered every few months. ■

Regina McEnergry contributed to this article.



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Economy Threatens World Progress on Immunization

THE THIRD EDITION OF THE State of the World's Vaccines and Immunization brought some good news about efforts toward immunizing children against vaccine-preventable diseases and the development of new vaccines, but also some dire warnings about how the global economic downturn might impede progress in immunization programs.

The report, issued in October by the World Bank, the World Health Organization (WHO), and the United Nations Children's Fund (UNICEF), noted that there are now 106 million children receiving the required three doses of DPT (diphtheria-pertussis-tetanus) vaccine before their first birthday—a 74% increase in coverage since 2000. Despite this progress, 24 million children a year still fail to receive even a single dose of the DPT vaccine.

“This report is really a call to action aimed at everyone. We need to stick with it,” said Graeme Wheeler, managing director of operations at the World Bank, at an October 21 report launch in Washington, D.C. Wheeler said an estimated

US\$1 billion is needed annually to ensure that new and existing vaccines will be delivered to all children in 72 of the world's poorest countries. The global economic downturn is causing concern that the United Nations' Millennium Development Goal to reduce deaths among children under age five by 66% between 1990 and 2015 will not be met if countries are forced to curtail their immunization campaigns.

The report noted that continued investments will also be needed to accelerate the development of vaccines against tuberculosis, AIDS, and malaria, which are responsible for more than four million deaths a year, mainly in developing countries. There are currently about 80 vaccine candidates in the late stages of clinical testing—40 of them are aimed at diseases for which a vaccine does not yet exist. Of those, the malaria vaccine candidate known as RTS,S/AS01, which is being developed by GlaxoSmithKline Biologicals and is now being tested in a Phase III trial in Africa, was cited as a high-impact vaccine that was the furthest along in clinical testing.

WHO Meeting to Evaluate Test-and-Treat Strategy

NEARLY A YEAR AFTER a quintet of researchers from the World Health Organization (WHO) published an article in *The Lancet* describing the results of a mathematical model that predicted that a combination of annual HIV testing and immediate antiretroviral (ARV) treatment could potentially end the AIDS epidemic in 50 years, scientists, public health officials, and community activists gathered November 2-4 to talk exclusively about the strategy dubbed test and treat (see *Test and Treat on Trial*, VAX, July 2009).

The WHO convened the meeting in Geneva, Switzerland, to stimulate discussion about the ethical implications, acceptability, and feasibility of implementing the test-and-treat approach in various populations. Although the strategy looks promising based on mathematical models, it has not yet been subjected to the rigors of a randomized, controlled clinical trial.

The experts who gathered in Geneva included Julio Montaner, president of the International AIDS Society, who is a vocal advocate of early initiation of ARV treatment and has been studying the impact that expansion of ARVs has had on lowering community viral load and HIV incidence in Vancouver, British Columbia. Community viral load reflects the mean viral load of a group of HIV-infected individuals. Montaner said a study that looked at the effect of expanding ARV treatment from 3,500 HIV-infected individuals to 5,000 in a community in Vancouver appears to have had an impact on transmission. “All I am prepared to say right now is that new HIV infection rates are going down,” said Montaner.

US researchers are hoping to launch a pilot study next

spring to evaluate the feasibility of implementing test and treat in Washington, D.C., which has the highest prevalence of HIV in the country, and the Bronx in New York City, which has the highest AIDS death rate of the city's five boroughs due to the fact that so many HIV-infected individuals there are diagnosed late. The three-year study will occur in high-risk communities where poverty, racial discrimination, AIDS stigma, distrust of doctors, and other factors can be barriers to accessing medical care. Wafaa El-Sadr, director of the Center for Infectious Disease Epidemiologic Research at Columbia University's Mailman School of Public Health, will be heading up the pilot study, which is being funded by the US National Institute of Allergy and Infectious Diseases (NIAID) and reflects a collaborative effort between NIAID, the US Centers for Disease Control and Prevention, and local health departments in the two cities.

El-Sadr said the goals of the study are to determine the best way to link HIV testing and treatment programs, to retain HIV-infected individuals in treatment programs, and to ensure individuals adhere to their daily ARV regimens.

“What I got from the [WHO] meeting was a collective commitment of the importance of continuing to expand access to treatment,” said El-Sadr. “Only about 40% of people who need treatment today can obtain it. We have a long way to go.”

Mark Harrington, an activist who heads the Treatment Action Group in New York City, said at the very least, test and treat may provide better linkage between prevention and treatment. “Care and treatment and prevention need to be done altogether.”

Understanding the Hunt for Immune Correlates of Protection from RV144

How can the recently conducted AIDS vaccine trial in Thailand help inform researchers about the types of immune responses that can provide protection against HIV? *By Regina McEneary*

A RECENTLY COMPLETED efficacy trial in Thailand, known as RV144, showed that two vaccine candidates administered sequentially in what is referred to as a prime-boost regimen could reduce the risk of HIV infection by 31.2% (see *VAX* October 2009 *Spotlight* article, *Vaccine Research Gains Momentum*). This trial provided the first evidence of efficacy for any AIDS vaccine candidate.

Vaccines work because they train the immune system to produce various types of immune cells and proteins, referred to as immune responses, against a specific virus or bacteria. A vaccine can induce many different types of immune responses, including antibodies (Y-shaped proteins that bind to viruses and prevent them from infecting cells), cellular immune responses (CD4⁺ and CD8⁺ T cells that orchestrate the killing of virus-infected cells), as well as natural or innate immune responses. For HIV, researchers do not yet know which types of immune responses are necessary for protection. While the vaccine candidates tested in RV144 only provided a modest efficacy, this trial provides scientists with the first opportunity in humans to try to figure out which immune responses induced by these candidates actually protected some of the volunteers against HIV infection. The specific immune responses that are responsible for protection are referred to as the immune correlates of protection (see *VAX* November 2006 and December 2006 *Primers on Understanding Immune Correlates of Protection, Part I and II*).

If the immune correlates of protection can be identified from RV144, it would be a significant boost for AIDS vaccine research. Scientists could then design AIDS vaccine candidates that induce these specific responses at higher levels, and

thereby improve upon the modest efficacy seen in RV144. But identifying the correlates from this trial will not be an easy task. Overall, relatively few volunteers became HIV infected during RV144, so researchers have a limited pool of individuals in which to search for immune correlates.

The hunt

Researchers will begin the hunt for correlates by screening the thousands of blood and cell samples collected from volunteers during RV144 for different types of immune responses. Specifically, researchers will look closely at the samples taken from the 51 participants who received the vaccine candidates yet still became HIV infected through natural exposure to the virus. Samples from these volunteers will be compared to those from the 8,146 participants who received the vaccine candidates but did not get infected.

Because there are many more uninfected vaccinees than infected vaccinees, scientists will try to match each HIV-infected vaccinee with four to five who are uninfected and who share a similar demographic and genetic profile. Matching the samples as closely as possible in terms of gender, race, age, level of HIV risk, and genetic background will enable researchers to rule out the role these other factors may have played in the immune responses to the vaccine candidates.

Researchers will use multiple laboratory tests, or assays, to try to tease out if a specific immune response—including antibodies or cellular immune responses—occurred more frequently or at a higher level in vaccinated volunteers who did not acquire HIV compared to those who did. Although RV144 showed some efficacy in preventing acquisition of HIV, the prime-boost regimen did not appear to have any impact on the amount of virus circulating in the blood of individuals who became HIV infected despite vaccination. This result has led many

researchers to assume that the modest level of protection was more likely due to antibody responses than cellular immune responses. Antibodies are the key to protection for most, if not all, existing vaccines. Still, researchers will carefully analyze all categories of immune responses in the hunt for correlates from RV144.

Limited samples

Scientists will have to carefully choose which assays to conduct because a limited number of specimens were collected during RV144. This trial was not designed to determine the correlates of protection. No samples were collected until after the six-month vaccination period, and researchers did not collect cell or tissue samples from mucosal sites at which sexual transmission of HIV occurs.

The search for correlates is also hampered by the fact that researchers do not know exactly when people were exposed to HIV and whether the HIV-uninfected vaccinees were even exposed to HIV at all.

Additional studies

There are also additional studies that can help identify the correlates of protection. One of these studies, known as RV152, is already ongoing. It involves the 51 individuals who became infected in RV144 despite vaccination. Information collected from these volunteers may shed light on the characteristics of the virus that infected these individuals. Investigators are also considering whether to conduct a smaller trial with the same prime-boost regimen that is designed specifically to try to determine the immune correlates.

Researchers may also be able to collect valuable clues from studies in nonhuman primates. If they can replicate the protection seen in RV144 in nonhuman primates, they could then use this model to try to identify the immune responses that are responsible for protection. ■

