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The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

Prevent and Conquer

Research updates that headlined this year's Conference on Retroviruses and Opportunistic Infections *By Kristen Jill Kresge*

THE SUCCESS OF ANTIRETROVIRALS (ARVs) for the treatment of HIV/AIDS is a remarkable victory in the now 29-year-old battle against the pandemic. In his plenary talk at the 17th Conference on Retroviruses and Opportunistic Infections (CROI), which was held February 16-19 in San Francisco, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), called ARV therapy “one of the best success stories in biomedical research as it gets translated to the patient.”

At the end of 2008, approximately four million HIV-infected people in low- and middle-income countries were receiving ARVs. “As the years go by we’re doing better in getting drugs to people who need them,” said Fauci. “That’s the good news.”

“The sobering news,” Fauci continued, “is that it’s not sustainable.” Despite this progress, there is still a huge gap between the number of people who need treatment and those who receive it—a gap recently widened by the World Health Organization’s (WHO) decision to revise treatment guidelines in response to mounting evidence for the benefits of earlier initiation of treatment. Based on the updated guidelines, only 30% of the HIV-infected people in the world who qualify for therapy are receiving it.

Closing this gap is a huge priority in battling HIV/AIDS, and critical to that is reducing

the number of new infections. Fauci outlined a triumvirate of HIV prevention strategies that top the research agenda at NIAID, including the development of a preventive HIV vaccine; test and treat, which calls for universal HIV testing and immediate treatment for those infected; and pre-exposure prophylaxis, which involves delivering ARVs orally or in a microbicide gel to uninfected individuals. Several research updates on these three areas dominated the discussions at this year’s CROI.

Building on RV144

One of the main planks in the HIV vaccine research agenda is building on the results of RV144, the first AIDS vaccine trial to show any evidence of vaccine-induced protection against HIV. The results of this large efficacy trial in Thailand showed that a combination of two vaccine candidates provided about 31% protection against HIV infection.

In his remarks at CROI, Fauci made it clear that, in his opinion, a much higher efficacy should be the goal. “I think we’ve got to do better than 60%-70%,” he said. “We’re setting the bar very high, but the history of AIDS tells us we’ll clear that bar with the best minds, resources, and political will.”

The RV144 results may also affect the design of future trials. “We really have to focus future trials on the prevention of acquisition,” said Fauci. “Understanding the

T-cell response [through trials of candidates that are solely designed to impact viral load] is very important, but when we do a large clinical trial in humans, it is my opinion that we’ve really got to look at acquisition.”

One obvious way to improve upon the RV144 results is to try to determine the immune correlates of protection—the specific types of immune responses induced by the vaccine that had a protective effect. Nelson Michael, director of the US Military HIV Research Program (MHRP), said work on trying to determine the correlates of protection is just getting underway. In the meantime, researchers are continuing to analyze the RV144 data. At CROI, Michael provided results from an RV144 analysis that showed that the level of vaccine-induced protection

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against HIV was significantly lower in individuals who reported behavior that put them at risk of HIV infection at any time during the three-year trial. But Michael warned against over-interpretation of these results since the analysis was not part of the initial trial design. Michael also suggested that the association between risk behaviors and lack of protection may have more to do with the seemingly transient impact of vaccination—the protective effect of the vaccine candidates appears to have been concentrated almost entirely during the first year—than with risk, as the reporting of risk behaviors continued throughout the trial.

The test and treat approach

When researchers at the WHO published results from a mathematical model showing that universal annual testing and immediate ARV treatment for all HIV-infected individuals could make a major

dent in the number of new HIV infections, the model ignited much discussion and debate. Despite the attention test and treat has received, there is limited data to support the premise. “All of the mathematical models assume much lower HIV transmission rates when on ARV therapy but there is very little empiric evidence,” said Deborah Donnell, deputy director of the HIV Prevention Trials Network (HPTN) statistical center.

This is beginning to change. At CROI, Donnell presented data that helps bolster the connection between ARV treatment and prevention. In an observational sub-study of the Partners in Prevention Study, Donnell and colleagues analyzed HIV transmission rates among 3,381 serodiscordant couples, in which one person is HIV infected.

At the start of the study, the HIV-infected partners were not already taking ARVs. During the study, 10% (349) of the HIV-infected partners initiated ARV treatment. At the end of the two-year study, researchers analyzed 103 new HIV infections among the initially uninfected partners and determined that only one occurred when the HIV-infected partner was on ARV treatment. This correlates to a statistically significant 92% reduction in HIV transmission if the infected partner was taking ARVs. “There was a substantial prevention benefit for ARV therapy,” said Donnell. Researchers are hopeful that a randomized, five-year, Phase III clinical trial known as HPTN 052 will provide a conclusive answer about the protective effects of ARV therapy.

Another method researchers are employing to gauge the ability of ARV treatment to reduce HIV transmission rates is estimating the community viral load—the mean viral load of all HIV-infected individuals in a given community. And in some cases, declines in community viral load are correlated with declines in the number of individuals newly diagnosed with HIV.

Moupali Das-Douglas, director of the research unit at the San Francisco Department of Public Health, presented data indicating that a significant 40% decrease in the community viral load among men who have sex with men in San Francisco that occurred between 2004 and 2008 correlated with a 45% reduction in the number of new HIV infections during this same four-year period. The declines in community viral load and the number of new HIV

diagnoses were credited to an increase in HIV testing rates in San Francisco, as well as an increase in the number of infected individuals who are receiving ARVs.

Julio Montaner, director of the British Columbia Centre for HIV/AIDS, reported similar results from a prospective study in British Columbia, Canada, which evaluated the community viral load of all HIV-infected people in the province who are on ARV treatment. Montaner said the rapid uptake of HAART in this population is “driving down viral load steadily,” and that this has resulted in a decrease in the number of new HIV diagnoses, particularly among injection-drug users (IDUs).

However, a third study conducted in Washington, D.C., which has the highest HIV prevalence in the US with about 3% of the population living with HIV/AIDS, showed a different trend than what was observed in San Francisco and British Columbia. Researchers from George Washington University School of Public Health and Health Services reported a 17% increase in the number of new HIV diagnoses in Washington D.C. from 2004 to 2007 following a dramatic expansion of routine HIV testing services and efforts to provide those infected with treatment.

Intermittent PrEP

While randomized trials and feasibility studies of test and treat have only recently started, several clinical trials of PrEP will soon be yielding results. Kenneth Mayer, an investigator involved in a PrEP trial in the US, said 2010 will be a “major year in our understanding of PrEP.” The results of four PrEP trials should be reported this year. The preliminary results of a pilot feasibility study of intermittent PrEP use, rather than daily administration, are also expected this year.

Meanwhile, two new intermittent PrEP studies (HPTN 066 and 067) are slated to begin this year. These studies will collect extensive pharmacokinetic data, which will hopefully shed light on the optimal dosing regimens for intermittent PrEP. “We have many things to learn about optimal [PrEP] dosing,” said Mayer.

In addition to oral dosing, researchers are also studying the use of gel formulation of ARVs that can be used as microbicides. Several efficacy trials of non-ARV-based microbicides have provided disappointing results. “Microbicides without ARVs aren’t

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a dead issue, but they're definitely on a resuscitator," said Fauci. "The time has come to look at an ARV-based microbicide."

There are two clinical trials underway to evaluate the use of ARVs formulated as topical microbicides, with the first results expected later this year. Meanwhile, researchers are

also experimenting with other ARVs that may be effective topical PrEP agents. One of these is maraviroc, the first licensed ARV that blocks HIV entry into cells. At CROI, John Moore, a professor of microbiology and immunology at Weill Cornell Medical College, reported that maraviroc was able to pro-

tect nonhuman primates against simian immunodeficiency virus (SIV), the monkey version of HIV, in a dose-dependent manner.

Richard Jefferys, Basic Science Project Director at Treatment Action Group, contributed to this article.

GLOBAL NEWS *By Regina McEnery*

US\$10 Billion Pledge for Vaccine Research, Development, and Delivery

THE BILL & MELINDA GATES FOUNDATION announced a US\$10 billion commitment over 10 years to fund research, development, and distribution of vaccines to people in the world's poorest countries. "We must make this the decade of vaccines," said Bill Gates, after he announced the substantial donation during the World Economic Forum's annual meeting in Davos, Switzerland, which took place January 26-31.

The \$10 billion pledge is in addition to the \$4.5 billion already committed by the Gates Foundation for vaccines. The Foundation said its increase in vaccine funding was inspired by the remarkable progress in recent years in improving access to existing vaccines and the introduction of new vaccines against rotavirus and pneumococcal disease. The World Health Organization estimates that together pneumonia and rotavirus infection account for 1.3 million deaths every year in children under age five, mostly in developing countries.

The Gates Foundation also estimates that an additional 1.1 million children could be saved with the rapid introduction of a malaria vaccine beginning in 2014. A Phase III efficacy trial of GlaxoSmithKline (GSK) Biologicals' RTS,S malaria vaccine candidate began last year. Depending on the results of this trial, the candidate vaccine could be submitted to the European Medicines Agency for regulatory review by 2011 and be ready for distribution by 2012, according to GSK and the Malaria Vaccine Initiative.

Julian Lob-Levyt, executive secretary of the GAVI Alliance, a Geneva-based non-profit organization that partners with drug companies, health agencies, and charities to provide both financial and programmatic support for vaccination programs in 73 of the poorest countries in the world, noted that the Foundation's \$10 billion pledge set a new precedent in global health. "Vaccines remain the most cost-effective way of saving children's lives," he says.

Journal Retracts Controversial Article that Spurred Anti-vaccine Sentiment

A CONTROVERSIAL 1998 RESEARCH PAPER in *The Lancet*, a prominent medical journal, which prompted an abrupt decline in childhood immunizations, was recently retracted after a UK panel determined that the authors who conducted the study acted unethically.

The 1998 research paper described an unexpected pattern of intestinal lesions in 10 of 12 children with developmental disorders. The authors of the study said the lesions occurred, in most cases, after the children received the measles-mumps-rubella (MMR) vaccine, which is typically given by 15 months of age. The paper also cited previous, unrelated studies that attempted to link patterns of intestinal lesions and another intestinal disorder, ileal-lymphoid-nodular hyperplasia, with sudden behavioral changes, including autism spectrum disorders in young children.

The study did not prove vaccination against MMR caused intestinal disorders. Yet, Anthony Wakefield, a researcher from the Royal Free Hospital and School of Medicine in London who led the study, held a press conference following publication of the study, at which he urged parents to shun the

combination MMR vaccine in favor of having their children vaccinated with the three vaccines individually, with a year interval between each dose.

This study is widely credited with sparking an anti-vaccination movement that resulted in declines in immunizations, particularly in the UK. In 1997, the year before the study was published, 91% of children in the UK were vaccinated. In 2003, the rate had dropped to 60% in some parts of the country.

Ten of the paper's 13 authors—not including Wakefield—submitted a partial retraction in 2004 saying they felt research into the intestinal lesions should continue, but stressed that the paper established no causal link between the MMR vaccine and autism.

Following the retraction in February, the US Centers for Disease Control and Prevention (CDC) released a statement reminding parents that vaccines are safe, effective, and that they save lives. "*The Lancet's* retraction of Dr. Wakefield's study is significant," the CDC noted. "It builds on the overwhelming body of research by the world's leading scientists that concludes there is no link between the MMR vaccine and autism."

Understanding Advances in the Search for Antibodies Against HIV

What are some of the recent developments that are helping researchers identify new targets for HIV vaccine design? *By Regina McEnergy*

VACCINES PROTECT AGAINST DISEASE by priming the immune system to generate the specific types of immune responses necessary to stop an invading pathogen before it causes harm.

Most vaccines induce different types of immune responses, including B cells. B cells produce antibodies—Y-shaped proteins that can latch on to viruses and inactivate or neutralize them—which are considered critical to the protection afforded by many, if not all, vaccines (see *VAX* February 2007 *Primer on Understanding Neutralizing Antibodies*). Antibodies can also help inhibit infection through other mechanisms of action that don't involve direct neutralization (see *VAX* January 2010 *Primer on Understanding Antibody Functions: Beyond Neutralization*).

Many scientists believe that an AIDS vaccine will need to induce antibodies, in addition to other immune responses, to be highly effective at protecting against HIV. And because the circulating strains of HIV are so diverse, antibodies that can neutralize a broad array of HIV variants, so-called broadly neutralizing antibodies (bNAbs), have been a major target for HIV vaccine researchers.

To design vaccine candidates capable of inducing these bNAbs, researchers are using a reverse engineering approach. They start by identifying the antibody or antibodies the vaccine should induce and then try to identify precisely where these antibodies attach to HIV. This site is then used by scientists to design vaccine immunogens—the non-infectious fragments of HIV that

bNAbs were identified, limiting the number of targets that could be exploited for vaccine design. However, in the past year, researchers have unearthed a fresh crop of new, and in many cases more potent, antibodies. Five of the eight newly discovered antibodies were isolated from individuals infected with the clades of HIV most prevalent in Africa, where the HIV/AIDS burden is greatest and a vaccine is needed most.

Identifying new targets

The search for new bNAbs typically involves screening blood from HIV-infected individuals to see if it can neutralize a panel of laboratory viruses. These viruses are ranked by how easy or difficult they are to neutralize.

If serum, a component of blood, from an HIV-infected individual can neutralize several different viruses in a laboratory test, then researchers isolate the antibodies present in the serum. While HIV-specific antibodies are common in HIV-infected individuals, bNAbs are much rarer.

Two of the recently discovered antibodies—PG9 and PG16—were discovered by IAVI scientists in collaboration with researchers from The Scripps Research Institute in California. After screening blood from 1,800 HIV-infected individuals in Africa, North America, Europe, Asia, and Australia, researchers identified these two potent bNAbs from a single HIV-infected individual in Africa (see *VAX* October 2009 *Spotlight* article, *Vaccine Research Gains Momentum*).

Three other antibodies—HJ16, HGN194, and HK20—were discovered after screening 400 HIV-infected individuals through the Collaboration for HIV Vaccine Discovery (CAVD), in an effort led by a researcher from the Institute for Research in Biomedicine in Switzerland.

The remaining three antibodies, one known as VRC01, were identified by scientists at the Vaccine Research Center (VRC) at the US National Institute of Allergy and Infectious Diseases.

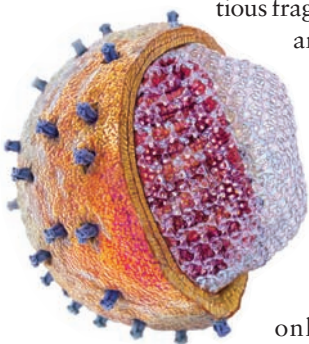
Different laboratory techniques were used to identify these antibodies. For instance, PG9 and PG16 were identified by screening first for neutralization and then for the ability of the antibodies to bind to HIV. This was important because these antibodies bind only weakly to HIV in the form in which it is studied in the laboratory, and had the binding test been conducted first, researchers might not have discovered these antibodies. The VRC01 antibody was found by combining B cells from HIV-infected individuals with virus particles that had been manipulated so that researchers could detect only those antibodies that bind to a specific site on the virus.

Vaccine design

Researchers are now focusing on using these antibodies to reverse engineer vaccine candidates, starting with characterizing where on HIV these antibodies bind. Most of them bind to the spike-like protrusions on the surface of HIV, which is called the Envelope protein because it envelops the virus' genetic material.

Some of the recently discovered antibodies target different parts of HIV's Envelope protein, suggesting to researchers that there are a number of ways to neutralize HIV and thereby prevent infection (see *VAX* October 2009 *Spotlight* article, *Vaccine Research Gains Momentum*). PG9 and PG16 target a section of the virus that is more accessible to bNAbs, making it a promising target for vaccine developers. VRC01 and HJ16, as well as one of the older bNAbs known as b12, all bind to HIV at the site where the virus binds to human CD4⁺ T cells, the preferred target of the virus.

Work is now underway to characterize these sites on the virus and to design immunogens based on them. Although there are still many challenges involved, researchers hope that improved candidates based on these bNAbs will eventually be ready for testing in clinical trials. ■



are included in vaccine candidates. These immunogens are then tested to see if they can elicit these antibodies in people.

Until recently, only a handful of