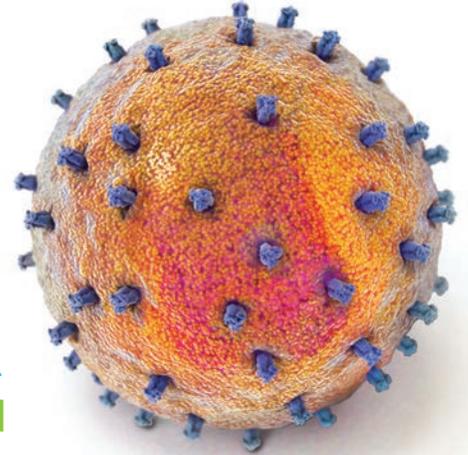


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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

An Antiretroviral Renaissance

Impressive findings from ARV-based prevention trials cause some at the biannual AIDS conference to declare treatment *is* prevention

By Regina McEnery and Kristen Jill Kresge

THE MERCURY IN ROME this July was already high when the International AIDS Society's Sixth International Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011) got underway. But the encouraging data surrounding HIV prevention made it even hotter. "I've never seen something explode like this," said Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID).

The heat wave was fueled by overwhelmingly positive results from three recent international studies evaluating the role of antiretrovirals (ARVs)—which have been wildly successful in extending the lives of HIV-infected individuals—in also preventing HIV transmission. One study (HPTN052), results from which were first released in May but presented publicly for the first time in Rome, showed that earlier ARV treatment of HIV-infected individuals leads to a dramatic 96% decrease in HIV transmission. Two other studies (Partners PrEP and TDF2), results from which were released just days before the opening of IAS 2011, showed that pre-exposure prophylaxis (PrEP)—the administration of ARVs to HIV-uninfected individuals—resulted in a 62%-73% reduction in HIV transmission among heterosexual men and women.

"We are now on solid scientific ground

that even without a vaccine or a cure, we could turn around the trajectory of the pandemic," said Fauci. "That's huge." Several scientists and policy makers compared the momentum for using ARVs for prevention to the original fervor that surrounded combination ARV therapy, introduced in 1996. "Rome is the watershed for treatment as prevention," said Stefano Vella, a co-chair of the conference, which was held July 17-20 and drew more than 5,000 delegates.

But perhaps more interesting will be what happens after Rome. In a time of constrained resources, there will likely be generous debate over how to implement earlier HIV treatment or PrEP. "These are the challenges we've longed for," said Mitchell Warren, executive director of AVAC, the HIV prevention advocacy group. "For many years we've been asking what if. Now we're asking what now."

Hitting the virus earlier

Soon after combination HIV therapy was introduced, the dogma was hit the virus early and hard. That meant starting treatment sooner rather than later, and using a power-packed combination of ARVs. Then, primarily because of drug toxicities, the strategy changed and clinicians advocated for treating later in the course of HIV infection when the immune system becomes severely compromised. Grad-

ually, in rich countries where access to ARVs is not as scarce, the approach to therapy has started to shift back to starting treatment earlier. And, because ARVs can suppress HIV replication in most cases to below detectable limits, researchers have for many years speculated, based on the results from several observational studies, that getting HIV-infected individuals on therapy earlier would also have the fringe benefit of making them less likely to transmit HIV to others. But there had never been a randomized, controlled clinical trial to study the prevention benefits of earlier treatment until HPTN052. "The HPTN052 study is the definitive proof of a concept," said Myron Cohen, the trial's principal investigator. "As we put people on treatment we render them less infectious. That's a given now."

The Phase III HPTN052 study was launched in April 2005 and conducted at 13

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clinical research centers in Africa, Asia, and North and South America, at a cost of US\$73 million. In May, the study's independent data safety monitoring board (DSMB) informed the study's funder, NIAID, to release the results showing that earlier treatment reduced HIV transmission by 96%, four years ahead of the study's scheduled completion date. The study enrolled 1,763 serodiscordant couples—in which one partner is HIV-infected and the other is not—with CD4⁺ T-cell counts between 350 and 500. Half of the infected partners were randomized to start ARV therapy immediately, and for the others treatment was delayed until their CD4⁺ T-cell counts dropped to below 250 or they had developed an AIDS-defining illness.

In Rome, the complete analysis of the HPTN052 trial was presented. Cohen noted that 39 new infections occurred, with genetic analyses confirming that 28 of these infections were linked to the infected partners. Of those, 27 occurred among those who were randomized to the delayed treatment arm of the study. And Cohen said evidence suggests that the one infection that occurred while the infected partner was on therapy may have occurred before the virus was fully suppressed in this individual. Seven of the infections were not linked to the HIV-infected partners, while four are still being analyzed. Since the findings were first released, another new infection has been identified in the delayed treatment arm. Of the 28 total new infections, the majority (64%) occurred when the infected partners' CD4⁺ T-cell counts were above 350, the current cut-off recommended by the World Health Organization (WHO) for initiating treatment.

Researchers found that ARVs were effective at suppressing HIV replication no matter when treatment was initiated, but noted that the absolute CD4⁺ T-cell levels ultimately achieved in the delayed treatment arm were lower than in the early treatment arm.

Cohen also provided more detail on the demographics of the participants in the trial:

954 couples were from Africa, 531 were from Asia, and 278 were from North or South America. Interestingly, of the HIV infections that were confirmed to have occurred between the couples, 82% of the infections occurred among couples in sub-Saharan Africa, even though they accounted for only 54% of the couples enrolled in the trial. This may be explained, in part, by the different behavioral characteristics observed in the couples enrolled at the African clinical research centers and the differences in baseline viral load (a measure of the amount of virus circulating in blood), which was significantly higher at the centers in sub-Saharan Africa, according to Mina Hossainpour, one of HPTN052's site investigators. The rate of unprotected sex reported at the African sites was 9%, compared to only 4% among couples at sites in the Americas and Asia. There were also a higher percentage of individuals who reported multiple sex partners at the African sites. Hossainpour reported that the level of viral suppression that occurred on ARVs was similar across the sites and the adherence to the daily drugs was 99% at both African and non-African clinical sites.

Beatriz Grinsztejn, an investigator from a study site in Brazil, also reported that earlier treatment was associated with a 41% reduction in HIV-related clinical events. There were just 17 cases of tuberculosis—a common opportunistic infection among those with HIV—in the early treatment arm compared to 33 cases in the delayed treatment arm, a statistically significant difference. Overall, these results led Cohen to conclude that earlier treatment “should be applied aggressively in the population we studied.”

PrEP findings

PrEP was the other newsmaker at IAS 2011. Results from the Partners PrEP study of 4,758 heterosexual serodiscordant couples at nine clinical research centers in Kenya and Uganda showed that a daily dose of the ARV tenofovir (TDF) reduced the risk of HIV

infection by 62%, while daily dosing of the ARV Truvada—a combination of TDF and emtricitabine (FTC)—performed even better, reducing HIV infection risk by as much as 73%. Both ARV regimens were effective in preventing infection in men and women, and the differing efficacy between the two arms was not statistically significant. This sparked one researcher to ask whether TDF, which in monkey studies was less protective than Truvada, might actually not be inferior and therefore a cheaper PrEP approach.

The results from the Partners PrEP study were so favorable that the trial's DSMB suggested releasing the results and discontinuing the placebo arm of the trial 18 months before the trial's scheduled end date. This news came just eight days before the data was presented in Rome.

Jared Baeton, associate professor of global health at the University of Washington, reported that retention in the study was “incredibly high” at 98%, and that based on monthly pill counts, the adherence rate to the daily pill was also 98%. Baeton also noted that there were no significant safety events during the trial. The study, which was funded by the Bill & Melinda Gates Foundation, is the largest PrEP study conducted thus far, but not the first to show efficacy. Last year, the iPrEx trial showed that Truvada was 44% effective in preventing HIV infection among nearly 2,500 men and transgendered women who have sex with men, making it the first oral PrEP study to show efficacy.

The other results presented in Rome came from a PrEP trial known as TDF2, which involved 1,219 sexually active men and women in Botswana. Led by BOTUSA, a partnership of the US Centers for Disease Control and Prevention (CDC) and the government of Botswana, the study found that daily administration of Truvada reduced the risk of HIV infection in both men and women by approximately 63%. If individuals who stopped taking Truvada for some period of

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time during the study were excluded from the analysis, the efficacy was approximately 78%.

TDF2 was originally planned as a Phase III efficacy trial but was scaled back to an expanded safety trial after the HIV incidence in Botswana dropped and investigators concluded they would need to double enrollment to meet the pre-specified endpoint of 57 new infections among volunteers. Despite this, the TDF2 study did yield statistically significant results. Only nine infections occurred among 601 participants who received Truvada, while 24 infections occurred among the 599 individuals who received placebo.

“There’s little doubt about the power of ARV-based prevention strategies among heterosexuals,” said Michael Thigpen, a TDF2 study investigator who presented the results in Rome. But the TDF2 data do suggest there may be a difference in the protective efficacy in men and women. Of the 33 new infections that occurred in both the Truvada and placebo arms, the protective efficacy was 80% among men and only 49.4% among women.

Researchers also presented findings confirming that the scale-up of adult male cir-

cumcision within a community is effective at reducing HIV incidence. The data, gleaned from a study conducted in the South African community of Orange Farm, where one of the first studies of adult male circumcision was conducted, found 55% reduction in HIV prevalence and a 76% reduction in HIV incidence among circumcised men.

Moving forward

Buoyed by the encouraging findings of earlier treatment and PrEP, researchers are now faced with the challenges of implementing these strategies. The CDC says it is reviewing data from all of the trials involving heterosexual men and women and will begin working to develop guidance on the use of PrEP among heterosexual men and women in the US. Meanwhile, the WHO delayed the release of guidelines on testing, counseling, and treatment for serodiscordant couples—which was scheduled to occur in Rome—because of the latest data, but expects these guidelines will be available by the end of the year.

With money tight, there will likely be serious discussions about which of these

strategies is most feasible. “The next step is trying to figure out with the resources we have, how to implement this,” said Fauci. “We can’t do everything.”

The HIV vaccine and microbicide resource tracking working group’s 2010 report, released at IAS 2011, noted that funders in 2010 invested \$1.19 billion in research and development for preventive HIV vaccines, microbicides, PrEP, and operations research related to adult male circumcision, about \$40 million less than 2007 when funding peaked. Global HIV vaccine research funding, which totaled \$859 million last year, declined 1% from the previous year, while funding for microbicides, male circumcision, and PrEP increased—in some cases by as much as 124%—though total spending for each of these categories was considerably less than for vaccines.

One thing everyone agreed on was that HIV prevention strategies should not be pitted against each other. “This either/or argument is going to make us fall flat on our faces when we should be running forward,” said Robert Grant, principal investigator of the iPrEx trial. ■

GLOBAL NEWS

Margaret McGlynn Selected as New Chief Executive Officer of IAVI

Margaret McGlynn, a former executive with pharmaceutical company Merck, is IAVI’s new president and chief executive officer. McGlynn, whose appointment was announced July 7, succeeds IAVI’s longtime CEO, president, and founder Seth Berkley, who left in June to head up the GAVI Alliance, a Geneva-based global health partnership launched in 2000 to increase access to immunizations.

“Margie has a wealth of experience in both the vaccine industry and the HIV field, a deep understanding of global health, public policy and development issues, and strong business acumen,” said Paul Klingenstein, chairman of IAVI’s board of directors.

McGlynn, who goes by Margie, is no stranger to IAVI, having served as a member of its board of directors since 2010. As president of Vaccines and Anti-infectives at Merck, McGlynn was responsible for a US\$7 billion portfolio of products and oversaw the launch of several vaccines and drugs, including the first vaccine to prevent cervical cancer and the first in a new class of AIDS drugs that blocks a key enzyme needed for HIV replication. She also helped form the

Merck Sharp & Dohme (MSD)-Wellcome Trust Hilleman Laboratories, a partnership between Merck and the Wellcome Trust that has led to the establishment of a research center in India that will focus on developing vaccines most applicable in developing countries. While at Merck, McGlynn also endured the disappointing failure of Merck’s adenovirus serotype 5 (Ad5) AIDS vaccine candidate in a large international study known as STEP.

“I have long been passionate about ensuring that people in the developing world can access life-saving medicines and vaccines, and I am delighted that, in my new role as CEO of IAVI, I will be able to contribute to advancing the search for an effective AIDS vaccine that one day will be available to all of those who need it,” said McGlynn.

McGlynn retired in 2009 from Merck after more than 26 years there, and in recent months has been devoting her attention to advocating for more research on potential new therapies for a rare genetic disease that has affected her family. She, her husband Kevin, and their two children, John and Kelly, make their home in Pennsylvania. —Regina McEnery



Understanding How Adjuvants Boost Immune Responses

What have researchers learned about the use of substances called adjuvants that can augment the response to vaccination? *By Regina McEneaney*

A NUMBER OF DIFFERENT STRATEGIES have been used to develop existing vaccines. Some, such as those that prevent influenza or pertussis, contain a whole-killed version of the virus or bacteria itself. Others, including the oral polio vaccine or the combination vaccine that protects against measles, mumps, and rubella, contain weakened or attenuated forms of the viruses against which the vaccines are designed to protect. While this strategy has proven safe for many vaccines, whole-killed or attenuated HIV vaccines are not considered viable strategies partly because of concerns that the virus would mutate and regain its ability to cause disease, therefore making it unsafe. Rather than containing HIV in its entirety, AIDS vaccine candidates contain non-infectious fragments of HIV's genetic material.

Unfortunately, these gene fragments used in HIV vaccine candidates (referred to as antigens) are not as effective at stimulating the immune system as whole-killed or attenuated pathogens. One way to boost the immune response to these vaccine candidates is to add an adjuvant (see *VAX October 2004 Primer on Understanding Vaccine Adjuvants*). The word adjuvant comes from the Latin word *adiuvare*, which means to help, and adjuvants have been called a vaccine's little helper. These substances work by mimicking the danger signals triggered by actual pathogens, thereby activating the body's innate immune response—the first line of defense against viruses and bacteria—which in turn activate the body's adaptive immune responses (see *VAX December 2008 Primer on Understanding Innate Immunity and HIV*). Both innate and adaptive immune responses are thought to be important in vaccine-induced protection. Some adjuvants boost the immune responses enough that less of the vaccine is required to provide protection.

Many licensed vaccines use adjuvants, the most common being alum, which consists of insoluble aluminum salts. Another

adjuvant called AS04—a mixture of alum and a derivative of bacterial endotoxin—is used in a recently licensed vaccine against human papillomavirus (HPV) and was the first non-alum adjuvant to be approved in the US. Meanwhile, another adjuvant, MF59, which contains biodegradable oil, is used in influenza vaccines in Europe.

Innate immunity

Interestingly, while alum has been used as an adjuvant for over 80 years, scientists still do not have a clear understanding of exactly how it works. But the understanding of how adjuvants work is improving as researchers develop a better understanding of innate immunity. In recent years, scientists have learned a lot about this arm of the immune system through the identification of specific proteins on cells, known as receptors, which control interactions between cells and their environment. Dendritic cells and macrophages—two types of innate immune cells that are the body's first responders—rely on these protein receptors to sense pathogens and alert the immune system of their presence.

The first class of protein receptors, called toll-like receptors, was identified about 15 years ago. Since then, researchers have identified 10 human toll-like receptors as well as other receptors that specifically recognize retroviruses, such as HIV. Scientists say identifying and learning about these receptors will enable them to design new and improved adjuvants that work in a more systematic way, which could then lead to an improved stimulation of innate immune responses by adjuvants, and ultimately a more sustained immune response to vaccination.

HIV vaccine adjuvants

Because AIDS vaccine candidates containing fragments of HIV genes may not provoke as robust an immune response, scientists think some AIDS vaccine candidates are likely

to require adjuvants. The exception is viral vector-based approaches, which use modified, non-infectious viruses other than HIV to carry fragments of HIV's genetic material. These candidates typically do not require an adjuvant because they are thought to stimulate stronger innate immune responses.

Several of the AIDS vaccine candidates that have been tested in clinical trials so far have been administered along with the adjuvant alum, most notably VaxGen's AIDSVAX vaccine candidate (a genetically engineered version of HIV's gp120 surface protein) that was used in the VAX003 and 004 Phase III trials in the US and Thailand, as well as the RV144 efficacy trial in Thailand.

However, evidence is building that other adjuvants may be more effective than alum. The follow-up trials of RV144 will likely use MF59 rather than alum because studies of several adjuvants found that alum produced the lowest level of antibody responses. Researchers are also studying another adjuvant, called PolyICLC, which binds to a toll-like receptor and another receptor inside dendritic cells, in a Phase I AIDS vaccine trial.

Other adjuvants are also being evaluated in preclinical studies, including one that is designed to induce innate and mucosal immune responses, which are considered important for protection against HIV because it is most often transmitted sexually.

Choosing the best adjuvants for HIV vaccine development will likely be difficult, however, because it's not clear what kind of immune response a vaccine should induce (see *VAX November 2006*

Primer on Understanding Immune Correlates of Protection, Part I and *December 2006 Primer on Understanding Immune Correlates of Protection, Part II*). ■

