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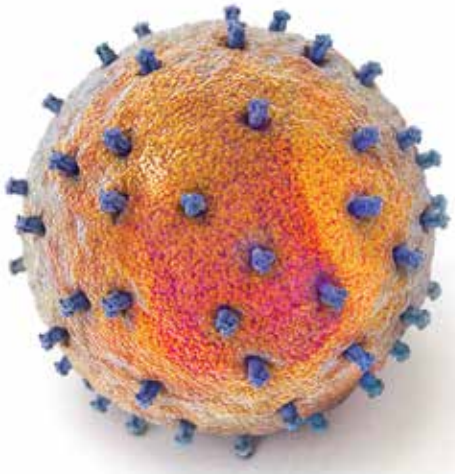
The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

Stepping Up the Pace

Two years ago, the focus of the International AIDS meeting shifted to ending AIDS. In Melbourne, the theme is getting there faster. But how?

The 20th International AIDS Conference (AIDS 2014), which will be held July 20-25 in Melbourne, Australia, already looks and feels a bit different than previous meetings. For one, it's going to be significantly smaller, due primarily to a sharp decline in registrations from North American participants who may have been deterred by the steep travel costs and long flight times to the land Down Under.

The International AIDS Society (IAS), the Geneva-based group that sponsors the biannual meeting, expects about 12,000 delegates this year, roughly half the number that attended the conference two years ago in Washington, DC. The meeting will, however, include more delegates than usual from Asia, Africa, and the Pacific.

Regardless of its size, the conference offers researchers and advocates a world stage, and the issues that will likely resonate the loudest in Melbourne are related to social justice and discrimination, sustaining funding for HIV/AIDS treatment and prevention programs, and efforts toward an HIV cure. In contrast, talks on vaccine research will be relatively sparse. Italian immunologist Antonio Lanzavecchia, a founding director of the Institute for Research in Biomedicine in Switzerland, will deliver a plenary on what needs to be done to accelerate AIDS vaccine discovery efforts.

Social justice issues are of particular importance given the recent passage of anti-homosexuality legislation in several countries. Prior to the meeting, organizers circulated the Melbourne Declaration, a petition urging the "immediate and unified opposition to discriminatory and stigmatizing practices" that they say exist in over 80 countries and threaten universal access to HIV prevention, treatment, care, and support. The declaration says AIDS funders should not support organizations that promote intolerance and discrimination.

The long road to a cure

Long considered a neglected area, momentum in HIV cure research, as well as the funding to support it, is building. But in Melbourne, the reports will be mixed.

Just weeks before the conference's start, a disappointing setback was reported regarding the "Mississippi baby"—a child born in the US state of Mississippi who was considered potentially cured of HIV following early initiation of antiretroviral therapy. But more than two years after discontinuing therapy, the child now has detectable levels of virus.

According to Anthony Fauci, the director of the US National Institute of Allergy and Infectious Diseases, who will be speaking at the Melbourne meeting, these recent findings are certainly disappointing. "Scientifically, this development reminds us that we still have much more to learn about the intricacies of HIV infection and where the virus hides in the body," said Fauci in a public statement.

According to Australian researcher Sharon Lewin, co-chair of AIDS 2014, data from four Canadian babies who seem to be in a prolonged HIV remission following early initiation of therapy will also be reported in Melbourne. These cases likely would have generated more optimism if not for the sobering news about the Mississippi baby. Discussions about the feasibility of curing HIV will undoubtedly occur at the two-day symposium focused exclusively on cure research that the IAS is hosting prior to the conference.

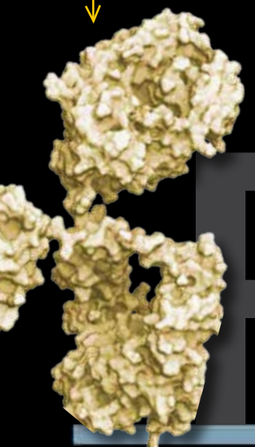
Steven Deeks, a professor of medicine at the University of California-San Francisco who is studying different HIV cure strategies, says the Mississippi baby, as well as very similar cases of adults from the US city of Boston who had experienced a prolonged absence of detectable virus after receiving stem cell transplants for cancers, provide dramatic proof of how even a single virus can persist in a quiescent state for months and even years, and then come roaring back. "Based on this case as well as the Boston cases, I am wondering if eradicating the virus will ever be possible," says Deeks. "We will likely need to enable the immune system to help control what little virus persists after a curative intervention."

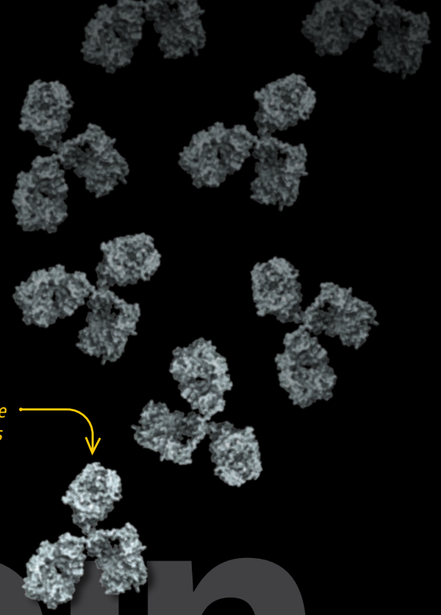
But rather than derailing research efforts, Deeks views the recent developments as instructive. "As I believe has been the case in vaccine research, these setbacks

Continued on back page...

What are antibodies?

Antibodies are infection-fighting proteins produced by the immune system. These proteins can inactivate viruses or other disease-causing organisms in multiple ways. Antibodies are also the reason that most vaccines work. In short, a vaccine contains some substance that triggers the immune system to make antibodies, as well as other types of immune cells. The body then retains a "memory" of this, and can quickly activate these immune responses if the actual virus or bacteria enters the body in the future.





Antibodies trigger the destruction of viruses in various ways

Protein power!

Why is the HIV vaccine field in the midst of a renaissance?

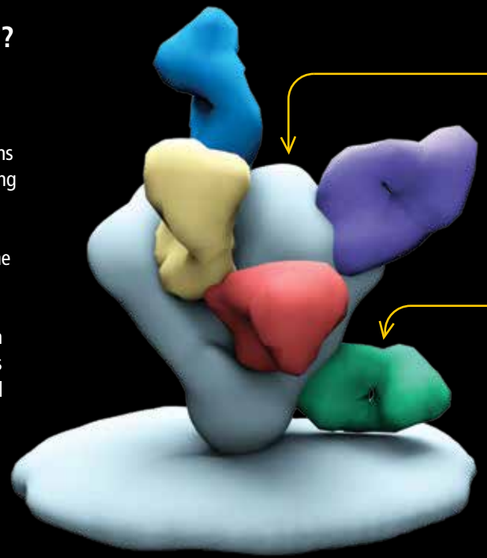
Antibodies.

How do antibodies neutralize HIV?

Five years ago, HIV vaccine researchers isolated a handful of antibodies in blood samples collected from HIV-infected individuals that were extremely good at inactivating, or neutralizing, many of the different strains of HIV in circulation. These are called broadly neutralizing antibodies.

Now, researchers have isolated dozens of these broadly neutralizing antibodies against HIV. The immune systems of about 20% of HIV-infected individuals make them. Recently, researchers started tracking the development of these broadly neutralizing antibodies in real time to learn more about how they develop. Studies show these antibodies develop slowly and have unusual characteristics that make them able to neutralize this notoriously difficult virus.

Studies in animal models indicate some of these antibodies are able to protect against infection.



The surface of HIV is dotted with highly unstable spikes called HIV envelope trimers.

The crop of recently isolated broadly neutralizing antibodies can latch onto the trimer in multiple spots and inactivate the virus.

Image courtesy of Christina Corbaci and Andrew Ward at The Scripps Research Institute

How can we harness antibodies in the fight against HIV?

Vaccine researchers are studying how antibodies bind to HIV and are using this information to design vaccine candidates. Other researchers are exploring whether directly administering broadly neutralizing antibodies could be an effective means of preventing HIV infection, or if they may also have a role in HIV treatment.

VACCINES

Ideally, an HIV vaccine would trigger a person's immune system to make the types of broadly neutralizing antibodies that are generated in about 20% of HIV-infected people. To accomplish this, vaccine researchers must identify what to include in the vaccine to enable the immune system to generate these antibodies.

Several different vaccine components, referred to as immunogens, are currently under study. Many are based on the HIV trimer spikes that are the targets of broadly neutralizing antibodies. Because the broadly neutralizing antibodies against HIV are so unusual, researchers suspect it may take multiple different vaccine immunogens to guide the immune system to make them.

PASSIVE ADMINISTRATION

While vaccine researchers are trying to identify ways to get the immune system to do the difficult work of making broadly neutralizing antibodies against HIV, studies are already planned to see if directly administering these antibodies into people is an effective HIV prevention strategy. Similar to using antiretrovirals—a strategy referred to as pre-exposure prophylaxis—antibody injections might also be a way to stave off infection.

The advantage of antibodies is that, theoretically, a monthly or even quarterly shot in the arm might be sufficient to protect against HIV. Antibody injections might also be useful in combination with antiretrovirals to help further reduce rates of mother-to-child HIV transmission.

TREATMENT/TOWARD A CURE

Broadly neutralizing antibodies might also have a role in HIV treatment. Antibody injections could replace antiretroviral treatment for a period of time, alleviating some if not all of the side effects of the drugs, or be administered in addition to antiretrovirals, augmenting the effectiveness of treatment.

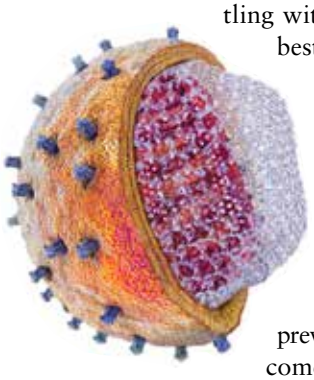
Last year, reports showed broadly neutralizing antibodies could significantly reduce the quantity of virus in the blood of monkeys. This suppression lasted for weeks, as long as antibody levels were maintained. The antibody-treated monkeys cleared the virus faster than HIV-infected humans taking antiretrovirals, suggesting that these potent proteins may help support efforts toward a functional HIV cure, in which the virus level is so reduced that the immune system alone can keep it in check.

are disappointing, but they stimulate lots of very productive discussions, and allow scientists to better focus their research," Deeks says. "Although it would be hard to argue that people will be more optimistic about a cure, I suspect that discussions around this case will lead to better science and more progress."

Implementing and improving PrEP

Recent IAS meetings have been dominated by mostly upbeat findings from an array of HIV prevention trials, including those illustrating the efficacy of pre-exposure prophylaxis (PrEP)— the administration of antiretrovirals to prevent HIV infection.

The Melbourne meeting isn't expected to showcase any blockbuster findings from large studies. Instead, participants will be wrestling with how to make the best use of this growing arsenal of biomedical prevention weapons in today's resource-constrained environment.



Some answers on how best to implement existing prevention strategies will come from an array of demonstration projects and off-label studies that are analyzing how to improve PrEP adherence and make it more widely accessible to high-risk, HIV-uninfected men who have sex with men (MSM), high-risk heterosexual women, or injection drug users (IDUs). There are also studies evaluating the feasibility of test and treat, which calls for universal HIV testing and immediate treatment for those found to be infected, as well as adult male circumcision implementation projects.

"We have the tools to end the epidemic," says Mitchell Warren, executive director of AVAC, the HIV prevention advocacy group based in New York City. "What we need is a business plan."

Ken Mayer, founder, co-chair and medical research director of the Boston-based Fenway Institute, who is delivering a plenary on new HIV prevention technologies, says one of the goals of the meeting is to make sure that donors are aware of all these options and also that they understand why continuing to refine PrEP is crucial to its success.

Efforts to improve PrEP include studying a new generation of PrEP drugs that could potentially improve adherence—the main factor inhibiting PrEP efficacy. These next-generation approaches include vaginal rings that can release an antiviral drug directly into vaginal walls, vaginal rings that double as an HIV preventive and contraceptive, and longer-acting, injectable ARVs that would not have to be taken every day.

Given all of the attention surrounding the initial round of oral PrEP studies—and the recent recommendations to make oral PrEP available to high-risk populations in the US and elsewhere—Mayer says there is a danger in assuming that future efficacy trials are not going to be needed. "This is an exciting time," says Mayer. "We have proof-of-concept that PrEP works and now lots of new technologies [in the pipeline] that will also require large efficacy trials with large numbers of people. I'm concerned about having the resources to do these trials at a time when there is also a lot of attention being given to scaling up treatment."

Financing the response

Indeed, finding the money to end AIDS may be as challenging as the science. Both Deborah Birx, the newly appointed Ambassador at Large and US Global AIDS Coordinator in charge of the US President's Emergency Plan for AIDS Relief (PEPFAR), and Mark Dybul, former PEPFAR ambassador from 2006-2009 and now the executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, will deliver talks and lead discussions that in one way or another address the sustainability of financing the AIDS response. Together, these two powerhouses provide about 90% of the AIDS funding to low- and middle- income countries, but with concerns mounting that the AIDS response is not financially sustainable for the long haul, both programs have begun instituting changes.

According to the Kaiser Family Foundation, US President Barack Obama's fiscal year 2015 budget request for PEPFAR is US$6.4 billion (including the US's Global Fund commitment), a decrease of almost $350 million, or 5% less than the previous year, and the lowest level of funding since 2009. PEPFAR is in the process of trying to strengthen capacity in recipient countries so they can manage their own treatment and prevention programs. Meanwhile, The Global Fund has established new eligibility criteria that limit which countries can seek funding.

David Wilson, who heads the Surveillance and Evaluation Program for Public Health at the Kirby Institute in Australia, says some countries are dealing with these changes better than others. In the Asian AIDS epidemic, which Wilson has studied extensively, China, Thailand, and Malaysia are now financing 90% of their domestic AIDS response, and India has committed to doing the same. Other countries, however, are struggling, he says.

"Many countries are committed to treatment, but prevention is likely to suffer," he adds. "Indonesia is a perfect example. It is now a low- to middle-income country and for that reason graduated from being eligible for Global Fund grants. They are stuck in the middle. There is no way they can fund the AIDS response and they have an increasing epidemic. If prevention programs are scaled back there, it may escalate the epidemic."

Warren hopes the Melbourne meeting can galvanize the global AIDS community to set realistic targets that can then be used as benchmarks for how well communities are doing in the global quest to end AIDS. "I see Melbourne as a real test of leadership. Do we know where we want to go and how will we get there?" ■

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with partners in 25 countries to research, design and develop AIDS vaccine candidates. In addition, IAVI conducts policy analyses and serves as an advocate for the AIDS vaccine field. For more information, see www.iavi.org.