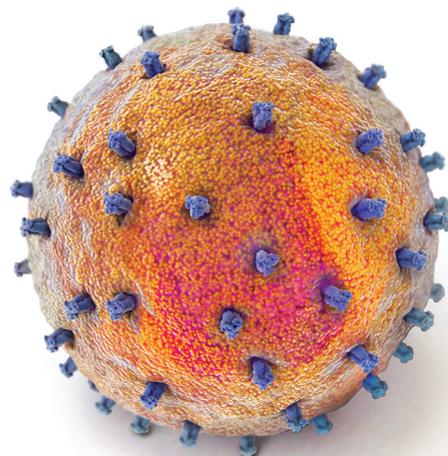


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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

Much Accomplished, More to Achieve

Despite tremendous gains in the realms of HIV treatment and prevention, the focus at AIDS 2014 was on what still needs to be done.
By Neil McKellar-Stewart

The 20th International AIDS Conference (AIDS 2014), held July 20-25 in Melbourne, Australia, commenced on an even sadder and more reflective tone than this biannual meeting typically conjures. The nearly 14,000 delegates from over 200 countries began by commemorating those who died on their way to the conference as passengers aboard the Malaysian airline flight brought down in eastern Ukraine (see *Remembering the Researchers and Activists Lost Aboard MH17*).



Although this terrible loss cast a shadow over the entirety of the conference, researchers and advocates turned their focus to recent progress in the realms of HIV treatment and prevention research, as well as what is still needed to achieve an AIDS-free world.

Salim Abdool Karim, director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA) spoke convincingly of the possibility of controlling the HIV pandemic even in the absence of an effective vaccine or functional cure. He referenced modelling studies that suggest voluntary medical male circumcision (VMMC), earlier initiation of antiretroviral therapy (ART), and pre-exposure prophylaxis (PrEP; the use of antiretrovirals to prevent HIV infection)—all recently

proven methods of blocking the spread of HIV—if implemented in combination and at ambitious coverage levels could produce a six-fold decline in global HIV incidence by 2025. However, Karim acknowledged that this would not stop HIV transmission completely.

Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID), concluded that a world without AIDS would require both a vaccine and a cure. Although there was little new data on vaccine research to speak of in Melbourne, cure research once again received top billing as the conference was preceded by the *Towards an HIV Cure* symposium, the fourth such pre-conference meeting on the topic.

A long road ahead

At the main conference, Jintanat Ananworanich, associate director for therapeutics research at the US Military HIV Research Program, highlighted a multitude of recent cure-related studies, including the recent cases in which transient but encouraging remission from HIV infection was achieved: the two adults from the US city of Boston who were HIV free for a short period of time following stem cell transplants, and the case of a toddler (born in the US state of Mississippi)

who remained HIV free for several years following early initiation of ART. The Mississippi infant's relapse was reported just before the opening of the conference (see VAX July 2014 *Spotlight* article, *Melbourne's Rallying Cry: Step Up the Pace*).

While in these cases the remission period was short-lived, suggesting an HIV cure is far from reality, these and a multitude of other studies indicate that the pace of HIV cure research has picked up. The HIV Vaccines and Microbicides Resource Tracking Working Group, which released their latest report at the conference (www.avac.org/resource/global-investment-hiv-cure-research-and-development-2013), confirmed this. They estimate that global funding for cure-related research increased by 16% from 2012 to 2013, reaching a total of US\$102.7 million, although this number underestimates the contribution by industry as companies with known programs in cure research did not provide input. Most of the funding comes from the public sector, with less than \$5 million contributed by philanthropies such as

ALSO IN THIS ISSUE

- ▶ Remembering the Researchers and Activists Lost Aboard MH 17

Aides Fonds, amfAR, the Campbell Foundation, and Sidaction.

Even as cure funding increases, there is still some confusion about what an HIV cure will actually mean. Ananworanich discussed what an HIV cure means to those living with the virus. She said HIV-infected individuals expect that eradication would mean living free of disease, with no long-term adverse consequences of HIV and diminution of stigma and discrimination. She referred to an Australian study that sought to identify the outcome priorities of clinical trial participants. In this study, the four highest-rated priorities for participants were: Not passing HIV onto others (47%); being considered uninfected (32%); not getting HIV a second time (32%); and stopping ART (25%). These priorities were congruent with those from a larger European community survey of 452 people living with HIV presented at AIDS 2012.

Fauci noted that the term cure generally denotes permanent remission from disease following cessation of therapy. In the case of infectious diseases, this classically involves eradication of the microbe, but in cancer, it means an absence of relapse for life or for a pre-defined period of time.

After reviewing what is known about the various hideouts HIV stakes out in the body, collectively referred to as the HIV reservoir, Fauci suggested that sustained remission from HIV might be the most likely scenario for an HIV cure. But even this won't come easily. Fauci said sustained remission would most likely be achieved in individuals whose virus is suppressed by ART very early on in the course of infection, who are stimulated to induce natural HIV-specific immunity following cessation of therapy, and who also receive passive transfer of HIV-specific antibodies or therapeutic vaccination.

Implementing PrEP

Discussion of PrEP is hardly new at this biannual gathering, but as evidence of its effectiveness in at-risk populations mounts, recom-

mendations for its use are now being strengthened. The recently released World Health Organization (WHO) guidelines now strongly recommend PrEP use based on what the organization classifies as high-quality evidence. In Melbourne, Chris Beyrer, incoming International AIDS Society president, emphasized that the guidelines refer to PrEP as "an additional prevention option for men who want it," as part of a comprehensive set of interventions. He explained that HIV prevention options, like contraceptive options for women, may change over an individual's lifetime, and PrEP is now another possible option.

Bob Grant, director of the Gladstone Institute of Virology and Immunology at the University of California, San Francisco, presented additional evidence of PrEP's efficacy in late-breaking findings from the iPrEx OLE study, an opt-in open-label extension phase of the original iPrEx trial that showed the combination antiretroviral Truvada (tenofovir and emtricitabine or FTC) was an effective PrEP strategy in men who have sex with men and transgendered women.

Among study participants who elected to take PrEP (regardless of the frequency and regularity with which they did so) the annual HIV incidence rate was 1.8%, compared to 2.6% for those who opted out of taking the drug. Overall effectiveness of PrEP during this study was about 50%. Among participants who took at least four doses of drug weekly, there were no new HIV infections.

But as in the original iPrEx study, poor adherence was strongly associated with incident infections. Only about one-third of OLE participants took the drug regularly, with younger people being less likely to have measurable drug levels in blood, suggesting they took the drug irregularly. However, adherence was better among people who reported more high-risk sex or more sexual partners.

Intermittent PrEP

Given the overall poor adherence to PrEP in clinical trials, The Agence nationale de recherches sur le sida et les hépatites

virales (ANRS) is conducting a study known as IPERGAY to evaluate the efficacy of intermittent or "on demand" PrEP. This randomized, double-blind, placebo-controlled trial began enrolling gay and bisexual men in France and Quebec in early 2012. Participants are randomly assigned to take two Truvada or placebo pills 24 hours before they expect to have sex, and one pill at both 24 and 48 hours afterwards. As the trial is still ongoing, data on effectiveness are not yet available, however, Jean-Michel Molina, from Saint-Louis Hospital reported early findings on adherence at the conference.

This interim analysis included 129 men with an average age of 35 who reported having a median of two instances of sexual intercourse per week (with a range of between zero and 31 partners), and a median of 10 partners over the previous two months. About 80% of participants reported that they had used PrEP the last time they had sex. Based on pill counts, they took an average of 15 pills per month, meaning they were on PrEP about half the time. At any clinic visit, approximately 86% of participants had detectable levels of tenofovir in their blood, and 82% had detectable levels of emtricitabine. Drug levels rose consistently as the trial progressed.

Circumcision continues to deliver

Male circumcision as an HIV prevention strategy continues to produce encouraging results, some of which were discussed in Melbourne. Both the WHO and the Joint United Nations Programme on HIV/AIDS recommend VMMC as an effective intervention for prevention of heterosexually acquired HIV, particularly in settings with generalized HIV epidemics. The most recent data from Uganda show that in the five years since the Rakai trial of male circumcision, the protective effect was maintained among the men who were circumcised, with a 73% protective effect against HIV infection.

Kévin Jean, a postdoctoral fellow at the Institut national de la santé et de la recherche médicale (INSERM), presented data from

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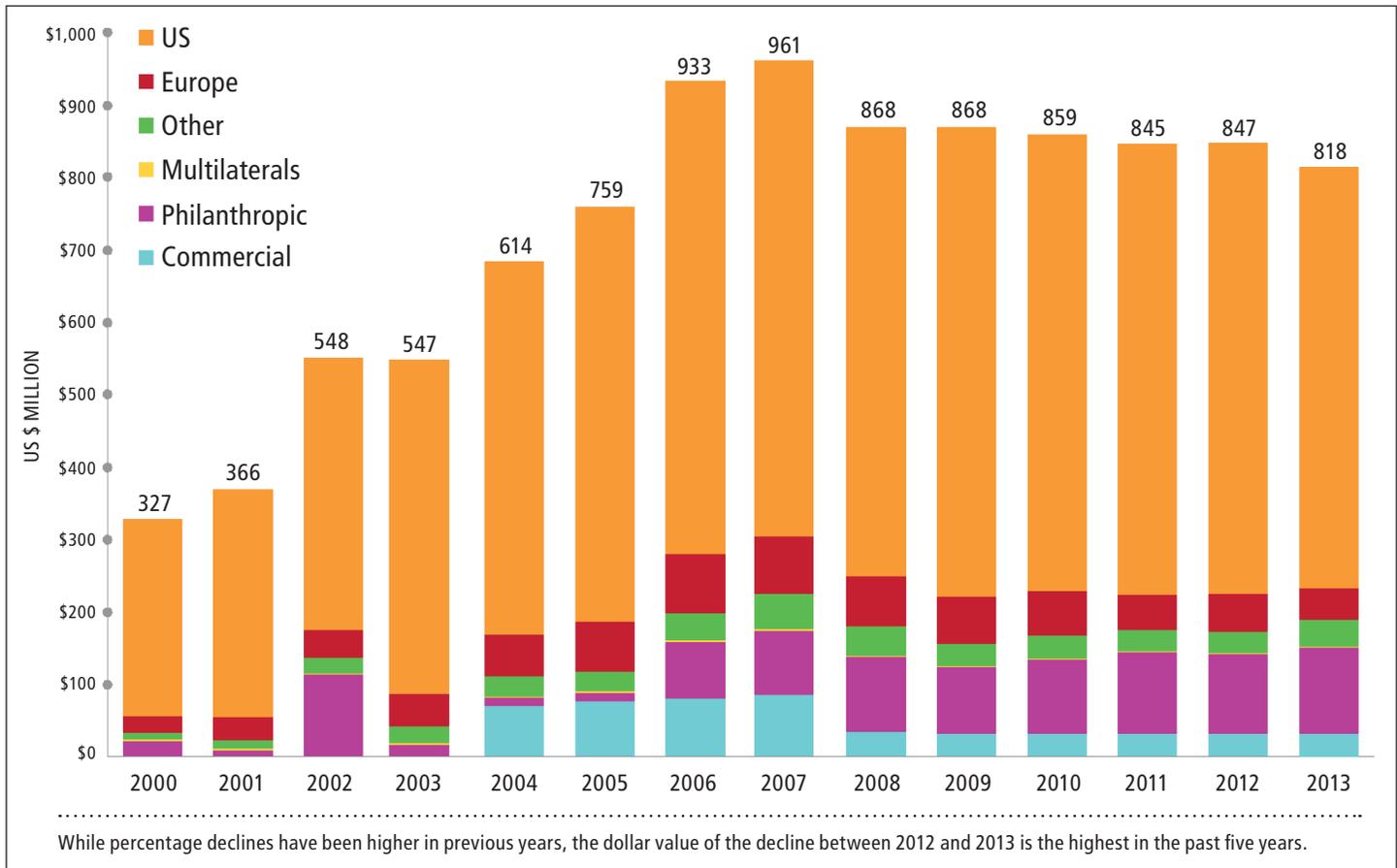
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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with 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.

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Decline in Prophylactic Vaccine Funding in 2013



The HIV Vaccines and Microbicides Resource Tracking Working Group in its 2013 report estimates that investment in preventive HIV vaccine research and development declined by approximately 3%, from US\$847 million in 2012 to \$818 million in 2013. This is the largest real decrease in AIDS vaccine investment since 2008, and it follows five years in which funding had either declined or remained stable, from a high of \$961 million in 2007. The Working Group suggests this decrease of \$29 million is primarily because of mandated austerity measures taken by the US government, as well as institutional and policy shifts within international development agencies in Europe and elsewhere. Figure courtesy of AVAC and the HIV Vaccines & Microbicides Resource Tracking Working Group. See the full report at <http://hivresourcetracking.org/sites/default/files/RTWG2014.pdf>.

the ANRS-12126 study in Orange Farm, South Africa, which illustrated that male circumcision not only protected men from acquiring HIV, but was also beneficial to their female partners. While VMMC is known to protect against some sexually transmitted infections in both men and women, including herpes simplex virus-2 and human papilloma virus, as well as both genital ulcer disease and genital cancers, protection against HIV in women is not as well characterized. Modelling studies suggest that reduced HIV incidence in men would result in reduced HIV exposure in women, but until now there was no direct evidence that VMMC had a protective effect in women. The Orange Farm study, however, showed that HIV incidence among women who only had sex with circumcised men was reduced by 17% in women aged 15-49 years, and

20% in women aged 15-29 years—a remarkable outcome in a context where HIV prevalence in women 15-45 years is around 32%.

In a related presentation, Jillian Pintye, an epidemiologist at the Washington State Department of Health Refugee Health Program, reported on new data from the Partners PrEP study, which involved heterosexual, mostly married, serodiscordant couples (in which one partner is HIV infected and the other isn't) in Africa. This data showed male circumcision is also protective against syphilis. She reported that syphilis incidence in participants was a statistically significant 42% lower in circumcised men. When stratified by HIV infection status, the researchers found a significant risk reduction of 62% among HIV-infected men, and a similar non-significant trend among HIV-uninfected men. In women, there was a statisti-

cally significant 59% risk reduction of acquiring syphilis associated with having a circumcised male partner. In sub-group analyses, there was a 48% risk reduction associated with having a circumcised male partner among HIV-infected women, and a 75% risk reduction among HIV-uninfected women. These results confirm the additional preventive health benefits that are associated with VMMC.

Neil McKellar-Stewart is HIV Health Promotion Officer at ACON (AIDS Council of New South Wales) and an active member of the National Association of People with HIV Australia Treatment Officers Network. He is a community representative on the Australasian Society of HIV Medicine Sub-Committee for Guidance in HIV Management in Australia.

Remembering the Researchers and Activists Lost Aboard MH17

By Michael Dumiak

HIV still claims the lives of more than a million people a year. But even within a community so used to mourning, there are lasting signs of shock over the tragedy of July 17, when noted AIDS researcher Joep Lange, his partner and Amsterdam Institute for Global Health and Development communications director Jacqueline van Tongeren, former AIDS Action Europe workers Lucie van Mens and Martine de Schutter, lobbyist Pim de Kuijer, and World Health Organization (WHO) media coordinator Glenn Thomas died along with 292 others in the downing of Malaysian Air flight 17 en route to the 2014 International AIDS Society Conference in Melbourne, Australia (see *Spotlight*, this issue).

As that summer day fades, Elly Katabira, a medical professor at Makerere University in Uganda, has no problem conjuring his first meeting with Lange. “He came to Kampala for a site visit in 1992. This was his first travel to Africa,” Katabira remembers. “He had just joined the World Health Organization and was in charge of a clinical trial.” The KEMRON trial, which Lange recalls in a moving essay called *Africa on the Rise*, debunked a fake AIDS remedy being peddled by Kenyan strongman Daniel Arap Moi. Katabira worked with Lange as principal investigator. “I remember his desire to see better health care delivered to the poor, through better access to medicines and well-trained health workers.”

Joep Lange, who was 59, started his clinical career in 1981 after receiving his medical degree from the University of Amsterdam. He was an early backer of the “cocktail” approach to antiretroviral therapy, and a powerful force in efforts to both lower overall treatment costs and ensure

access in poor communities in the west and in sub-Saharan Africa. Michael Merson, now director of the Duke Global Health Institute, recruited Joep to the WHO to run drug development for the Global AIDS Program. “Advocating for greater access to antiretroviral drugs is one of his greatest contributions to the fight against HIV/AIDS,” he says. “I came to know him as an extremely kind, intelligent, and compassionate man.”

Chelsea Polis, a young epidemiologist now taking up a senior research associate’s post at the Guttmacher Institute, met Lange and van Tongeren this summer in Lusaka, Zambia, at a workshop called INTEREST: the International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-poor Settings. Lange had invited Polis to speak. “I’m sensitive to how folks treat people in service industries. I noticed they were both very considerate,” she recalls. “I liked them both right away.” Lange had a steely side as well, says Gregg Gonsalves, co-director of Yale University’s Global Health Justice Partnership. “He was a scientist. But the way he talked about the need to get therapies to developing countries, he was like an activist.” He wasn’t afraid to lead amid controversy—such as in criticizing protesters who were trying to disrupt trials on pre-exposure prophylaxis, the use of antiretroviral drugs to prevent HIV infection.

Everyone who spoke about Lange for this article mentioned his exceptional desire and ability to be a part of both high-level research and the everyday world of people bearing the brunt of the HIV pandemic. He showed these qualities early on, as North Carolina Museum of Natural Sciences communications director David Kroll shows in writing about Lange’s basic research. For his first peer-reviewed published research, the 1984 *Lancet* article *Amprolium for Coccidiosis in AIDS*, Lange chose a case study based on his clinical work that shows his creativity with ideas and how he treats

people who are suffering.

Lucie van Mens, who also died on MH17, found her calling working with outsiders as well. A former program director with the Dutch STOP AIDS NOW! group, van Mens set up outreach and health care initiatives for sex workers and people in red light districts across Europe before joining the Female Health Company to make female condoms available, especially in African countries. “We lost so many people who work on HIV/AIDS in that crash,” Gonsalves said.

International HIV/AIDS Alliance director Alvaro Bermejo worked with two others lost in the downed plane, lobbyist Pim de Kuijer and Bridging the Gaps’ Martine de Schutter. “‘I’m Pim, I’m passionate about policy’ was definitely his catchphrase,” Bermejo says. “You could just tell he got into the nitty-gritty of political processes and thrived on them. And we recently saw Martine on a sunny day in June in Amsterdam. She was talking about her hopes for what she could bring to the work with marginalized groups most at risk of HIV.”

Both Gonsalves and Bermejo mourn the hurt to what is still an HIV community, what Bermejo even calls a movement. “The AIDS response loses many of its leaders: to stigma, violence, planes, to AIDS itself. It might not feel like this in some places but we continue to lose 1.5 million people to AIDS every year,” he says. “We often take our colleagues for granted, and when you lose them and reflect on the work that they do, you really appreciate the difference they make.”

Merson looks back to Lange’s June visit to the Duke Global Health Institute. Together they planned a new health and technology initiative focused on urban settings. It will launch later this fall.

Michael Dumiak reports on global science, technology, and public health and is based in Berlin.

