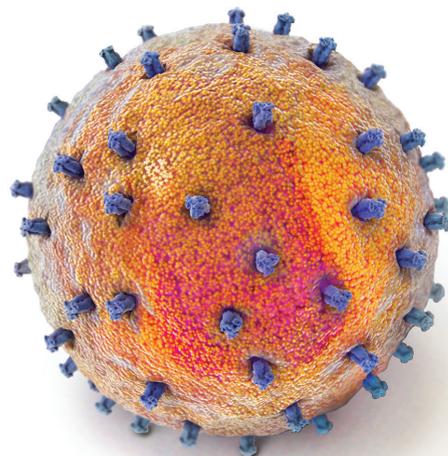


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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

## The WHO Casts a Wider Net

IAS meeting serves as launching pad for new HIV treatment guidelines *By Andreas von Bubnoff*

No good deed, it is often said, goes unpunished. But one exception to this otherwise airtight rule may well be a needle-exchange and methadone maintenance program set up recently by Malaysian authorities to reduce HIV transmission among injection drug users (IDUs). It was partly in recognition of that feat that the International AIDS Society (IAS) picked Kuala Lumpur, the capital of the East Asian nation, as the venue for its annual meeting, according to local meeting co-chair Adeeba Kamarulzaman, who is dean of the faculty of medicine at the University of Malaya in Kuala Lumpur. The selection also made Malaysia the first Muslim country—and the first in Asia—to have hosted the conference, which took place from June 30 to July 3.

Kamarulzaman said the needle-exchange program, which she helped establish in 2006 in the face of vociferous opposition from cultural and religious conservatives, has prevented thousands of infections and helped reduce the number of new infections each year among people who use drugs from about 5,000 at the start of the program (most of which were due to IDUs) to just over 1,000 last year.

But that wasn't quite the focus of the conference. Rather, new treatment guidelines announced by the World Health Organization (WHO) on the opening day of the conference became a major subject of dis-

cussion for the remainder of the meeting.

The new guidelines recommend that antiretroviral therapy (ART) be initiated in HIV-infected adults when the CD4<sup>+</sup> T-cell count of HIV-infected patients reaches 500—up from the previous threshold of 350. They also recommend that, in some cases, ART should be started whatever the CD4 count happens to be: people infected with HIV who qualify for such aggressive treatment include children under five, pregnant and breastfeeding women, and those who are in a relationship with someone who is not HIV positive. (Unchanged is a previous recommendation that HIV-infected people with active TB disease, or hepatitis B co-infection with severe chronic liver disease should also be treated irrespective of CD4<sup>+</sup> T-cell count.)

The guidelines pose a considerable challenge, especially to developing countries, which have been disproportionately hit by HIV. Tsitsi Mutasa-Apollo of the Ministry of Health & Child Welfare in Harare, Zimbabwe, said they raise the number of eligible patients worldwide from 17 million to almost 26 million, compared with just 9.7 million people who were enrolled in ART at the end of 2012.

Another thing that might make implementation of the new guidelines difficult is the stigma associated with HIV infection in many countries and cultures. “People are still afraid to get tested. Stigma and discrimina-

tion are still very much alive,” said Andrew Tan, the founder and current elected president of myPlus, a network of HIV-positive Malaysians.

Homosexual sex is illegal in Malaysia, according to Tan, who chose the opening night of the conference to go public as an HIV-positive gay man, but told the audience that he was afraid of the repercussions. “It’s about time we had a law against discrimination in the workplace based on HIV status,” he said, adding that the Malaysian program of mandatory pre-marital HIV testing for Muslim couples is also “ultimately discriminatory.” Such programs, he said, “remind us that systemic stigma and discrimination remain the single greatest obstacle to slowing the spread of HIV.”

Most observers seemed to welcome the new WHO guidelines, but some felt they didn't go far enough. Bill Bahlman, a long-

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term treatment advocate and associate producer at Gay USA TV in New York, said that given that the US guidelines already recommend treating all infected people immediately, irrespective of CD4 count, the WHO should have done the same. “I welcome the new treatment guidelines from WHO,” he said, “[but] I think they are unfortunately too conservative. I think the sooner we treat people with HIV, the less new infections we are going to have worldwide.”

But Gottfried Hirnschall, who directs the HIV department at the WHO and co-chaired the guidelines process, said there is currently not enough high quality evidence from randomized trials to recommend treatment at higher cell counts than 500. One such trial, called START, is currently underway: It examines whether net health benefits are different if patients start ART above 500 CD4+ T cells or defer treatment until CD4+ counts have dropped to levels below 350. The WHO also weighed factors such as availability of the drugs and concerns about side effects, Hirnschall said.

Still, Hirnschall believes the WHO will eventually move towards recommending treatment above 500, provided there is enough evidence. “My personal view,” he said, “is this is the direction in which we will be going, in which we should be going.”

## Hitting HIV hard—and early

Meanwhile, evidence for the benefits of early treatment initiation keeps accumulating. This theme pervaded the main IAS meeting and was one focus of a two-day symposium on strategies to cure HIV infection that preceded it. Such strategies largely involve targeting T cells that have HIV DNA integrated into their chromosomes, since they form a viral reservoir that makes HIV infection incurable. A growing body of evidence suggests aggressive treatment helps in that regard. Laurent Hocqueloux, a French researcher, reported that, when

followed up after several years of treatment, people who started therapy at T cell counts over 500 had lower levels of integrated HIV DNA in blood cells, and higher CD4+ T-cell counts, than those who started later.

Starting treatment even earlier, during the acute phase of infection, could have even greater benefits. According to early results from a 90-patient French trial called OPTIPRIM, patients who started treatment within three months of infection had a roughly 20-fold reduction in the HIV DNA reservoir in blood cells after one year of treatment. This means that early treatment initiation could bring patients closer to an eradication of viral reservoirs, the most important goal of strategies for curing HIV infection.

Such strategies involve inducing HIV replication in latently infected, resting CD4+ T cells, with the expectation that they will then die as a result of renewed viral replication or become vulnerable to antiretroviral drugs and immune responses. One drug family researchers use to lure the virus out of hiding are HDAC inhibitors. One of these, known as SAHA, has been shown in human trials to stimulate the production of HIV hiding in latently infected T cells. However, this effect was only partial, because it did not result in production of viral particles by these cells.

But Martin Tolstrup of Aarhus University in Denmark reported that a more potent HDAC inhibitor named Panobinostat increased the levels of free HIV RNA in the blood of people on highly active antiretroviral therapy, which suppresses HIV enough to make it undetectable in typical tests. “We believe that we see an increase in the amount of free virus being produced,” Tolstrup said.

“I think [the study] is profoundly important,” said Steven Deeks of University of California, San Francisco, who co-chaired the cure symposium. It is, he said, the first time anyone has shown induction of latently infected cells to make virus *in vivo* in humans.

Once latently infected cells are reactivated to make virus, the virus production alone might suffice to kill the cells. But that might not be enough, and researchers are examining additional strategies to kill such cells. One involves vaccinating people on ART to boost immune responses targeting HIV. Another involves using modified HIV-specific antibodies—the roughly Y-shaped proteins that can bind to viruses and inactivate them—that carry and deliver

## Other cases of a cure?

One thing that had everybody excited in Kuala Lumpur was the announcement that researchers might have replicated the HIV cure achieved in Timothy Brown—the so-called Berlin patient, who is so far the only chronically infected patient who is believed to have been cured of the infection.

Last year, Timothy Henrich, an infectious disease doctor at Brigham and Women’s Hospital in Boston, announced that two HIV-infected patients, who, like Brown, received bone marrow transplants from HIV-negative donors, no longer had signs of an HIV DNA reservoir—at least while they were kept on antiretroviral therapy (ART). This suggested that the virus might not come back if treatment is interrupted.

In Kuala Lumpur, Henrich reported that since stopping ART eight weeks earlier in one patient and 15 weeks earlier in the other, he had not yet detected any HIV RNA in either patients’ blood. He and his colleague Daniel Kuritzkes cautioned, however, that it will take years of follow up to be reasonably sure that the virus isn’t coming back. What’s more, the treatment remains far too risky to be used routinely.

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a toxic bacterial molecule that kills virus-producing cells.

To kill reactivated cells that produce virus, however, one needs to be able to detect them in the first place. One approach to this problem is to seek out cells that produce a key HIV protein known as the viral Envelope on the surface of infected cells. But that might be easier said than done. Richard Koup of the National Institute of Allergy and Infectious Disease's Vaccine Research Center, reported that when he isolated a population of CD4<sup>+</sup> T cells from individuals not on ART that were rich in cells actively producing HIV, he found it to be very difficult to detect Envelope expression on the surface of these cells.

### Control as a kind of cure

The meeting also featured updates on so-called post-treatment controllers, who started treatment during early infection and

subsequently controlled the virus after stopping treatment. So far, such cases are only anecdotal, such as the 14 patients of the VISCONTI cohort in France, or the so-called Mississippi baby, who started ART about 30 hours after birth and appears to have been functionally cured.

Still, the excitement was palpable at a session dedicated to such studies. Asier Sáez-Ciri6n from the Institut Pasteur in Paris, one of the researchers working with the VISCONTI cohort, told the standing-room-only crowd that he is now looking for additional cases to build an international cohort of post-treatment controllers. He asked that anyone aware of such cases share them with his team. Additional examples will make it possible, he said, to better understand the mechanism of post treatment control and to find markers that can predict which patients are likely to show such control.

Others are now also planning to look into the VISCONTI effect. John Frater from the University of Oxford said he is recruiting a new cohort of patients, called HEATHER, who started treatment within a few weeks after infection. "We have identified over 100 potential participants, who we can start to investigate. Maybe we have got some VISCONTI-like patients," he said.

Hocqueloux's report on the benefits of early therapy above a CD4<sup>+</sup> T-cell count of 500 prompted one audience member at the cure symposium to ask him whether the START trial should be stopped. "My personal opinion," Hocqueloux responded, "is to treat every patient [who] is not an elite controller. That's what I do as a clinician every day."

It remains to be seen when the WHO will take that view. ■

## GLOBAL NEWS *by Regina McEnergy*

### The US moves its AIDS strategy into higher gear

In an effort to revive an ailing domestic AIDS strategy, US President Barack Obama ordered his administration last month to review all federal AIDS counseling and testing programs and to recommend more effective ways of delivering treatment and care in the US.

A working group chaired by Grant Colfax, director of the Obama administration's Office of AIDS Policy, and Department of Health and Human Services (HHS) Secretary Kathleen Sibelius have 180 days to deliver their recommendations.

The announcement came three years after the Obama administration unveiled the country's first-ever National AIDS Strategy to combat the static US epidemic, where the annual number of new HIV infections is around 50,000. When he rolled out the strategy, Obama set a concrete goal to reduce the number of new infections by 25% within five years, increase access to care and optimize health outcomes for people living with HIV/AIDS.

Yet compared to how the US has responded to the international AIDS crisis—namely through its President's Emergency Plan for AIDS Relief (PEPFAR) launched by George W. Bush and participation in The Global Fund to Fight AIDS, Tuberculosis and Malaria, the national strategy has been seen by critics as lacking in ambition and inadequately funded. Moreover, it paled in comparison to outgoing Secretary of State Hillary Clinton's bold pledge to end AIDS around the world using evidence-based approaches.

"Not only is the US plan not on track to achieve its goals, but they are themselves far less ambitious than what has already been achieved in the past decade in some of the world's poorest countries, such as Cambodia, Ethiopia, or Zambia," remarked Mark Harrington, the executive director of the Treatment Action Group (TAG) in New York, in *The Atlantic* magazine last year.

In the US, only 25% of the 1.2 million HIV-infected people are on effective antiretroviral therapy with an undetectable viral load and only 33% are retained in care, Harrington noted. "Only 82% even know their HIV status—a number that's much lower among young people with the virus," Harrington wrote.

So what was Harrington's reaction to the executive order? In a word, pleased. Harrington said he particularly liked the fact that the Obama administration recognizes the importance of aggressive testing and early treatment in preventing transmission of HIV, as shown in the landmark HPTN052 study of serodiscordant couples in Africa.

Harrington said he was also glad to see the White House all but embrace a model of care—known as the HIV treatment cascade—that identifies key opportunities to improve services for people with HIV. By identifying these "leakages" in care, clinical sites have a better shot of referring people for HIV care after being diagnosed, and making sure they are adhering to HIV treatment and therefore lowering their undetectable levels.

"I'm much more impressed," said Harrington. "I'm feeling like [the administration] has been listening to the science."

Along with stressing a continuum of care, the HHS—which oversees federal HIV/AIDS programs—announced it would be investing US\$8 million to \$10 million a year to support health centers and local health departments in integrating public health practice and clinical care. The project will target areas with high numbers of racial and ethnic minorities disproportionately affected by the epidemic, and communities with a substantial unmet need for comprehensive HIV services. ■

# Understanding the P5 Partnership

How is this research collaboration advancing the development of a safe and effective AIDS vaccine? *By Regina McEnergy*

A clinical trial in Thailand known as RV144 made history in 2009 by establishing that a vaccine can prevent HIV infection (see VAX Sep. 2009 *Spotlight* article, *First Evidence of Efficacy from Large-Scale HIV Vaccine Trial*). Its efficacy was a modest 31% on average—considerably lower than the minimum efficacy of 50% that investigators themselves said was necessary to trigger discussions of possible licensure (see VAX Dec. 2009 *Primer on Understanding Vaccine Licensure*). Still, scientists and advocates alike welcomed, with some relief, the long-sought proof-of-concept for HIV vaccines.

Since then, a global coalition of researchers has—with some success—been trying to identify the immune responses provoked by the RV144 regimen that provided protection from HIV (see VAX Nov. 2009 *Primer on Understanding the Hunt for Immune Correlates of Protection from RV144*). The hope, of course, is to use that information to build a better vaccine. Another cadre of researchers has, meanwhile, pushed ahead with a project to test variants of the vaccine regimen evaluated in Thailand in clinical trials. This group, which formed in 2010, is known as the Pox-Protein Public-Private Partnership, or P5, in the jargon of the field.

The P5 team includes representatives from six organizations: the US National Institute of

Allergy and Infectious Diseases, the Bill and Melinda Gates

Foundation; the HIV Vaccine Trials Network; the drug companies, Sanofi-Pasteur and Novartis; and the US Military HIV Research Program, a key collaborator in the RV144

trial. Two efficacy trials are planned, one in men

who have sex with men (MSM) in Thailand and another in heterosexual men and women in South Africa, to see if a candidate similar to the one used in RV144 holds up as well, and perhaps improves protection, in a high-risk population.

The vaccine regimen used in the RV144 study of 16,000 at-risk individuals consisted of a canarypox vector-based vaccine candidate ALVAC-HIV (vCP1521) and AIDS-VAX B/E, a genetically engineered version of HIV's gp120 surface protein, also known as the Envelope protein. The two vaccines were paired sequentially in a prime-boost regimen and administered over six months.

That the regimen worked was significant. But researchers were even more encouraged to see that efficacy reached as high as 60% after one year. This intrigued many researchers and suggested that improving the durability of the immune responses induced by this vaccine regimen might dramatically increase the efficacy.

## A boost to RV144

So the P5 is trying to do just that with their follow-up trials. In the efficacy trial planned for heterosexual men and women in South Africa, researchers will test a prime-boost candidate that targets the most common subtype of HIV in the region, known as clade C. This differs from the RV144 vaccine regimen, which targeted the recombinant clade A/E strain that is dominant in Thailand. The design of the South African trial also differs from RV144 in two other important ways. It adds a fourth injection at 12 months and employs a different adjuvant—MF59—than the standard alum used in RV144 and most licensed vaccines.

Researchers want to see whether these changes in protocol improve the immune responses in vaccinated volunteers, and whether the improvement is sufficient for the vaccine candidate to be licensed. The P5 is also planning to conduct an efficacy trial among MSM in Thailand that will use the same ALVAC/gp120 B/E candidate as the one used in RV144. Like the upcoming South Africa trial, this study will also include a boost 12 months after the first injection, and use MF59 rather than alum as an adjuvant.

The P5 hopes to launch the South Africa trial in early 2015, and the Thai MSM trial a year after that. But challenges remain in meeting these goals—including uncer-

tainty about the funding and difficulties in finding the right antigens for use in each of the candidate vaccines.

## A different viral vector

The P5 is also interested in exploring other promising vectors in hopes of identifying new vaccine candidates and unearthing the so-called correlates of protection—the immune responses that prevent HIV acquisition.

One vector that the P5 is looking at is NYVAC, an altered vaccinia virus that is used in the smallpox vaccine. It is highly attenuated and is not infectious in humans. The P5 selected NYVAC based on previous data that, admittedly, is a bit mixed. In one Phase I study, NYVAC was found to stimulate HIV-specific immune responses, though they were weak. A later Phase I study found that when NYVAC was used in combination with a DNA-based candidate it induced much better immune responses.

Will NYVAC hold up in a larger study? The P5 is hoping to launch a large Phase IIb trial in South Africa of NYVAC alone or in combination with a gp120 candidate. The goal of the study is to see what immune responses are elicited and identify any biomarkers associated with reduction in HIV infection.

The P5 is also involved in two smaller trials. RV305, which began in 2012, is evaluating the impact of an additional boost in volunteers who participated in the RV144 trial. Results from this study are expected in the fall. In the companion study known as RV306, investigators will look at what effect additional boosts of the original RV144 regimen has on 360 volunteers who were not previously enrolled in RV144.

Finally, the HIV Vaccine Trials Network—which is part of the P5—recently began a study, HVTN097, evaluating the safety and immunogenicity of the original RV144 regimen in 100 HIV-uninfected men and women from South Africa. It enrolled its first participant on June 18.

It's too early to say whether the P5's multi-pronged approach will bring the world closer to a licensed vaccine. But stay tuned. ■

