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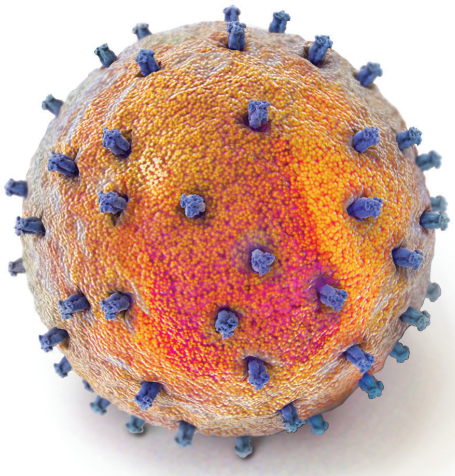

[SPOTLIGHT]

PrEP Works

The annual Conference on Retroviruses and Opportunistic Infections offered a broad survey of the state of HIV research, with new oral prevention results as the highlight. ***By Richard Jefferys***

The 2015 Conference on Retroviruses and Opportunistic Infections (CROI) is likely to be remembered as a watershed moment for pre-exposure prophylaxis (PrEP)—the use of antiretrovirals to prevent HIV infection. Just as the 1996 International AIDS Conference launched highly active antiretroviral therapy into the mainstream, some attendees viewed this year's CROI, held February 23-26 in Seattle, as the one that proved once and for all that PrEP is an effective HIV prevention strategy. PROUD and IPERGAY, two studies which were designed to evaluate PrEP's effectiveness in men who have sex with men (MSM) in relatively real-world settings, reported reductions in HIV incidence that surprised even the investigators. However, the need to improve the implementation of PrEP still looms large.

News from the vaccine research realm was not as dramatic, but an array of presentations described progress, including advances in analyzing antibody functions. Meanwhile, the pursuit of a cure remains at an early stage but is increasingly a focus at CROI, with several sessions addressing the state of the field, including areas of overlap with vaccine research.

Oral PrEP results are easy to swallow

Using oral antiretrovirals (ARVs) to prevent HIV infection is hardly a new idea. Back in 2010, investigators first showed that orally administered Truvada (a pill combining two antiretrovirals: tenofovir and emtricitabine) was 44% effective at preventing HIV infection in MSM and transgender women. This year at CROI, Sheena McCormack, professor of clinical epidemiology at the Medical Research Council Clinical Trials Unit at University College London, debuted results from the PROUD study, conducted in the UK, which was designed to assess how PrEP would perform in routine practice.

To that end, investigators recruited high-risk MSM over 18 years of age. Being at high risk of HIV infection in this study was defined as having had anal sex within the last 90 days without a condom and anticipating it would occur again in the next 90 days. Participants were randomized to receive Truvada immediately or after a year, in addition to standard prevention services. Follow up occurred every three months, in accordance with normal clinic practice.

The initial phase of the trial was intended as a pilot to explore whether recruitment and retention would be sufficient to embark on a larger efficacy trial, but in April 2014 the Data Safety Monitoring Board (DSMB) recommended evaluating efficacy due to the high HIV infection risk observed in the cohort. The DSMB then intervened again in October 2014 because the divergence between the number of HIV infections in the immediate and deferred PrEP groups was so significant that it would have been unethical to continue. Truvada was then offered to all participants.

At that point, 545 individuals were enrolled. The effectiveness analysis was based on 267 volunteers in the group that received Truvada from the start and 256 volunteers in the deferred group. The difference in the number of HIV infections was striking: 3 in the group receiving Truvada from the start and 19 in the other group. This equated to an efficacy of 86%.

Furthermore, two of the three infections that occurred in the group that received PrEP immediately may have actually been infected just prior to enrollment in the study.

ALSO IN THIS ISSUE

The other infection occurred in a participant who defaulted from follow up after receiving an initial Truvada prescription. When he was later diagnosed with HIV infection, he informed medical staff that he'd stopped taking PrEP. Six of the infections in the deferred-PrEP group could also have represented infections that occurred prior to study entry, but even if all such cases were excluded from the analysis the reduction in incidence was still highly significant.

Adverse events were uncommon: of 13 cases where PrEP use was interrupted due to a side effect (mostly gastrointestinal events were reported), 11 volunteers successfully restarted PrEP. Rates of other sexually transmitted infections (STIs) were not significantly different between the arms, and rates of reported condom use did not change over the course of the study. Reported adherence to PrEP in this study was high, and this was confirmed by measuring drug levels in a 57-person sub-study.

McCormack pointed out that the HIV incidence in the deferred PrEP arm of PROUD was three times higher than investigators had anticipated, based on analysis of the overall MSM population attending the clinics where volunteers were recruited. This suggests that those at the very highest risk had chosen to volunteer for the study. "People who needed it really came forward," McCormack said, and this emerged as a theme in PrEP presentations at CROI, raising the hope that if PrEP is made widely available, it will be accessed by populations that stand to benefit the most.

The resounding success of PROUD was duplicated—to the percentage point—in the results of the IPERGAY trial, which were presented by Jean-Michel Molina, chief of infectious diseases at the University of Paris Diderot. The purpose of this trial was to test whether "on demand" PrEP might be both efficacious and convenient. Participants were instructed to take two Truvada (or placebo) pills two to 24 hours prior to sex followed by two additional doses 24 and 48 hours afterward, in addition to receiving standard prevention counseling and condoms. The trial involved high-risk MSM in France and Canada.

As was the case for PROUD, the IPERGAY DSMB ended the randomized comparison in October 2014 due to the observed difference in HIV infections between the groups, and at that time PrEP was offered to all volunteers. The efficacy analysis was based on 176 participants from the Truvada-treated group and 177 placebo recipients.

Molina revealed that two HIV infections occurred in participants taking Truvada while 14 occurred among placebo recipients. The estimated efficacy was therefore 86%. Incidence was higher than anticipated in the placebo group, echoing PROUD's suggestion that the volunteers who enrolled were cognizant of their elevated risk of acquiring HIV. As with the primary results, the analyses of adherence, adverse events, STI rates, and sexual behavior over time all closely mirrored those of the PROUD study. The average number of Truvada pills consumed during the study was four per week, meaning monthly usage was close to half that of daily dosing. Molina concluded that "on demand" PrEP represents an attractive alternative to daily use for high-risk MSM.

A double-pronged strategy

Jared Baeten, professor of allergy and infectious diseases, epidemiology and global health at the University of Washington, addressed the use of both PrEP and antiretroviral therapy (ART) in a different population: heterosexual serodiscordant couples, where one partner is HIV infected and the other is not. Baeten's goal was to investigate whether a combined strategy of PrEP use by the HIV-uninfected partner and ART initiation in the HIV-infected partner was feasible and reduced HIV transmission in serodiscordant couples in Kenya and Uganda. In this setting, PrEP was administered on a time-limited basis, as a "bridge" until the HIV-infected partner had been on ART for six months (unless there were adherence issues or the individual's viral load remained detectable despite treatment).

A total of 1,013 couples were enrolled, deemed to be at high risk of transmitting HIV based on a scoring system developed by Baeten and colleagues. Of the HIV-uninfected partners, 33% were female and 67% male, and over 95% initiated PrEP with good adherence. ART was started by 80% of the HIV-infected partners, with more than 90% achieving viral load suppression. ART was prescribed in accordance with new guidelines recommending treatment for all HIV-infected individuals in serodiscordant relationships. Rather than employing a control group, which was considered unethical, Baeten constructed a model to predict likely HIV incidence in serodiscordant couples not using PrEP, and in whom ART was prescribed based on previous guidelines ($CD4^+$ T-cell count less than 350). The model was based on data collected from previous studies involving over 5,000 people.

In the current study, only two HIV infections were observed. By contrast the model predicted 40 HIV infections. The estimated reduction in HIV transmission when PrEP use was coupled with ART initiation compared to the model was therefore 96%.

In response to a question from Glenda Gray, executive director of the Perinatal HIV Research Unit at the University of the Witwatersrand and current president of the South African Medical Research Council, Baeten reported that both the HIV infections in the PrEP/ART group occurred in women. Gray's point was that there might still be some uncertainty about oral PrEP efficacy in women compared to men—one

SENIOR PRODUCTION MANAGER
Nicole Sender

CONTRIBUTING EDITOR
Kristen Jill Kresge

CONTRIBUTING WRITERS
Richard Jefferys
Mary Rushton

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concern is possible differential penetration of the ARV tenofovir in the vaginal versus rectal mucosal tissues. But Baeten said that in this study there appeared to be other explanations for the two HIV infections occurring in women.

Microbicide news disappoints

The encouraging news about oral PrEP that emerged at CROI was, unfortunately, accompanied by another blow to hopes that the ARV tenofovir administered as a vaginal microbicide might be similarly efficacious. In 2010, researchers reported results from the CAPRISA 004 trial, which showed a statistically significant 39% reduction in HIV incidence associated with use of 1% tenofovir gel by South African women at high risk of infection. Study participants were instructed to apply the gel within 12 hours before and 12 hours after sex. However, a subsequent trial of daily tenofovir gel administration in the VOICE study was unable to demonstrate efficacy. Now, a confirmatory study known as FACTS 001, designed to evaluate the original CAPRISA 004 approach in a larger number of women in South Africa, also failed to show efficacy, as reported at CROI by Helen Rees, executive director of the Wits Reproductive Health and HIV Institute in Johannesburg.

The trial was conducted at nine sites and enrolled 2,059 women aged 18-30 years. Because the results from VOICE indicated inconsistent use of the vaginal microbicide contributed to the lack of efficacy, intensive adherence support was incorporated into the FACTS 001 design. The efficacy analysis included 1,015 women in the tenofovir gel group and 1,014 who were randomized to receive a placebo gel. There was no significant difference in the number of HIV infections in the two groups, with 61 and 62 occurring in each group respectively. Analyses of adherence bolstered previous findings that suggest the gel is not user-friendly—a paltry 13% of the participants applied it during more than 80% of sexual activity.

Rees said that the results, while disappointing, represent important science that highlights the urgent need for prevention options that are easier to integrate into women's lives. Study sponsor CONRAD is analyzing results from all three tenofovir gel trials to see if there might be a subpopulation of women that might benefit from the product, but it is very unclear whether regulatory authorities would consider approval based on such an approach.

Striking an upbeat note for vaccines

In the self-described role of motivational speaker, Galit Alter, professor of medicine at the Ragon Institute of the Massachusetts Institute of Technology, Massachusetts General Hospital and Harvard, delivered an upbeat overview of recent advances in HIV vaccine science at a workshop for new investigators and trainees on the opening day of the conference. Alter delineated two approaches to successful vaccination: completely blocking HIV entry, or rapidly killing virus-infected cells at the site of exposure before systemic infection ensues. Citing recent data, Alter noted that the window of opportunity for extinguishing an HIV infection at the site of entry before HIV has the opportunity to establish a hideout from the immune system, known as the reservoir (where it can persist indefinitely) is indeed very narrow. Studies suggest this window is certainly less than three days in monkeys exposed to simian immunodeficiency virus (SIV, the monkey equivalent of HIV).

Hopes for blocking HIV entry with broadly neutralizing antibodies (bNAbs) that can inactivate a large swath of HIV variants have been bolstered by the discovery that a substantial proportion of HIV-infected individuals develop these antibodies over a period of two to three years after initial infection. Alter emphasized that this demonstrates the human immune system is capable of generating such bNAbs, and that it therefore should be possible to recapitulate the process with immunization.

Progress is now being made toward designing immunogens, the active ingredients of vaccines, which could engage and activate the immune system to produce such bNAbs. One strategy is to use a series of sequential immunizations with different immunogens designed to guide the antibody response.

Of the approaches designed to rapidly eliminate virus-infected cells and therefore extinguish a localized HIV infection, Alter cited the use of a replicating cytomegalovirus (CMV) vector-based vaccine, which has shown promise in monkey studies and is being prepared for human studies in both uninfected and HIV-infected individuals.

Given all this, Alter concluded that the stage is set for significant progress toward a successful vaccine in the coming years, and several subsequent presentations at the conference expanded on areas touched upon in her talk.

Toward a cure

Interest in bNAbs is not only dominating the vaccine field these days, it has recently extended into efforts to cure HIV, with several clinical trials being planned. At CROI, researchers reviewed the possible role of bNAbs in cure strategies.

But the cure-related finding that garnered the most attention came from James Whitney, assistant professor of medicine at Beth Israel Deaconess Medical Center and Harvard Medical School. Whitney debuted results from a monkey study designed to evaluate whether a Gilead Sciences drug that is in clinical development for hepatitis B and C infections could also help reactivate HIV that is laying latent in hidden cells and compartments of the body that make up the viral reservoir. This novel drug, dubbed GS-9620, was able to stimulate viral replication in monkeys who were on ART, suggesting it was effectively activating latent virus, and seemed to reduce the amount of viral replication that occurred when ART was interrupted. Early-phase human trials have found GS-9620 to be safe, and a pilot study in people infected with HIV on ART has now been launched.

The increasing enthusiasm for HIV cure research remained evident at CROI, with several sessions spilling participants into video-equipped overflow rooms. But at a press conference on the topic, John Mellors, Director of the HIV/AIDS Program at the University of Pittsburgh, sought to quell any misconceptions about immediate prospects. "The reality is that progress will be slow, and will grind out over years to decades until we have a functional cure for a significant fraction of HIV-infected individuals—there are many pieces to the puzzle that need be put together to solve the problem." ■

Richard Jefferys is Coordinator, Michael Palm Basic Science, Vaccines & Prevention Project at the Treatment Action Group.

[PRIMER]

Understanding Community Immunity

What is herd immunity and what happens when it breaks down?

Vaccines are designed to protect the individuals who receive them from infection with various disease-causing agents, such as viruses and bacteria. Widespread vaccination has only led to complete eradication of one virus—smallpox—but routine vaccination has successfully decreased the incidence of many once common diseases.

Part of the reason vaccines are so successful is because of community immunity or herd protection (see figure). It works like this. The more people in a community that get vaccinated, the fewer people who are susceptible to infection (those who remain unvaccinated because they are either too young or immune compromised). When a high enough percentage of people are immunized, the chain of infection for contagious diseases is broken and the spread of disease within the community is contained. Conversely, when immunization rates decline, there are more susceptible individuals and the effects of herd protection can break down, leading to an increase in the spread of disease. Measles is a good example of what can happen when herd protection breaks down.

The measles virus is a highly contagious, airborne pathogen that causes telltale red spots and complications that can include diarrhea, hearing loss, seizures, brain swelling, and pneumonia in about 30% of cases. Before a highly effective vaccine was developed in the 1960s, measles was a nearly ubiquitous childhood disease.

In 1971, a combination vaccine against measles, mumps, and rubella, the so-called MMR vaccine, was introduced, leading to a precipitous decline in all three diseases. Two doses of the combined MMR vaccine are estimated to be 97% to 99% effective at preventing infection with the measles virus. Vaccinating infants and children against measles led to a 75% drop in cases worldwide between 2000 and 2013. Yet because vaccination is far from universal, the measles virus is still responsible for about 145,700 deaths annually.

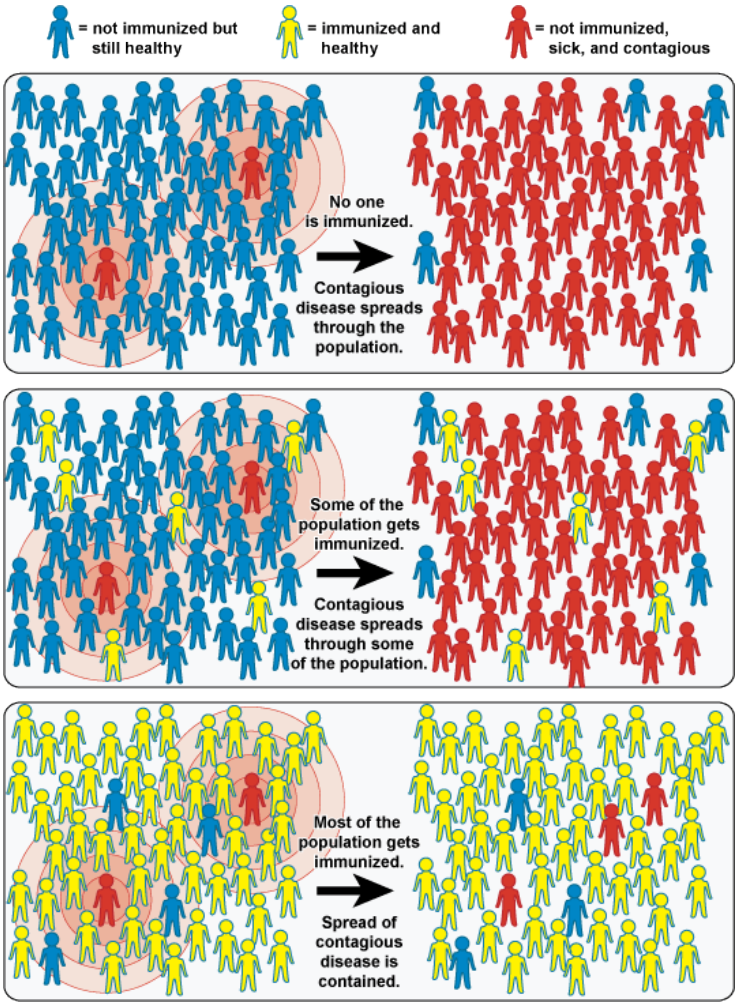

Illustration depicts how poor, partial, or optimal immunization coverage impacts the entire community. Source: National Institute of Allergy and Infectious Diseases

In the US, high vaccination rates, combined with good disease surveillance and rigorous control of outbreaks, resulted in measles being successfully eliminated in 2000, according to the US Centers for Disease Control and Prevention. But the country is once again in the midst of a measles outbreak involving 178 cases in 17 states. Several European countries are experiencing similar outbreaks. These outbreaks occur when vaccination rates decline and herd immunity breaks down.

Scientists can determine how high vaccination rates must be to establish herd protection by figuring out how quickly and efficiently the pathogen can move through a population. Because measles is so highly contagious (a single infected individual can spread the measles virus on average to 12 to 18 people), the threshold of vaccine coverage to maintain herd immunity is around 95%. By contrast, only about 80% to 85% of individuals in a community need be vaccinated to maintain herd immunity against polio. Measles immunization rates in the US, which are 92% and slipping due to a variety of factors including a growing anti-vaccine movement, are no longer high enough to achieve herd protection.

The situation in West Africa is even worse. The ongoing Ebola crisis in Guinea, Liberia, and Sierra Leone has led to an estimated 25% drop in childhood vaccinations between 2013 and 2014. Public health experts estimate that the disruption in health care services, which left as many as 1.1 million children unvaccinated over the past 18 months, has dramatically increased the number of individuals susceptible to measles. They estimate that this could lead to outbreaks of more than 200,000 cases—double what it was before inoculations waned—and as many as 16,000 deaths. For this reason, global public health organizations are now discussing the feasibility of implementing national vaccination campaigns in Ebola-affected countries. ■