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HIV Experts Create the Roadmap for Providing PrEP to Uninfected Individuals to Reduce the Risk of HIV Infection

WASHINGTON, DC (August 24, 2011) - To stem the estimated 2.6 million new HIV infections that occur worldwide each year, more than 200 representatives from the scientific and HIV/AIDS communities took an important step in assessing the safety and public health implications of providing antiretroviral drugs to uninfected men and women exposed to HIV through sexual contact - a strategy called pre-exposure prophylaxis, or PrEP.

Assembling August 19 at an open public meeting and interactive webcast convened by the Forum for Collaborative HIV Research, these researchers, HIV/AIDS advocates, members of industry and representatives from National Institutes of Health, the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA) and state public health departments applied the findings from a number of large trials to discuss a roadmap for FDA and CDC to develop guidance on the safe use of PrEP in otherwise healthy individuals at high risk of acquiring HIV. Held with the encouragement of FDA, this meeting has important implications for medical practice in the U.S. because recent data strongly support the efficacy of antiretroviral intervention for this purpose.

Although FDA has not yet approved PrEP to reduce HIV acquisition in uninfected individuals, one form of PrEP recently studied for use in healthy men or in couples where one partner is HIV positive -a daily pill containing tenofovir plus emtricitabine (TDF/FTC) - is FDA-approved for the treatment of HIV infection. In women, studies have also demonstrated the efficacy of prophylactic treatment with tenofovir applied as a vaginal gel.

"We now have findings from large studies that support a conclusion that PrEP is effective in gay and bisexual men, who represent more than half of new HIV infections in the U.S., and now, there is evidence that PrEP may reduce HIV infection in heterosexual men and women, the population hardest hit by HIV worldwide," said Jur Strobos, MD, Deputy Director of the Forum. "We must however, apply these promising data to develop workable strategies that mitigate risk that may be associated with the prophylactic use of antiretrovirals. These include both medical and socio-behavioral risk. We must ensure that people at greatest risk for acquiring HIV receive a comprehensive package of prevention services, including regular HIV testing, condom provision, risk reduction counseling and management of other sexually transmitted infections. The purpose of our meeting was to help identify what the components of a complete package should be."

Among the data reviewed at the meeting were results from the large-scale, multinational iPrEx trial, which found that a daily dose of TDF/FTC provided at least 44 percent protection to men and transgender women who have sex with men (MSM). Among those patients who were most adherent (used TDF/FTC on 90 percent or more of the days during the trial), HIV risk was reduced by 73 percent. Reinforcing these findings, a new CDC trial called the TDF2 study, along with Partners PrEP conducted by researchers at the University of Washington, showed that PrEP reduced the risk of HIV in 63 percent of the uninfected heterosexual men and women in the study population. While unsuccessful in demonstrating efficacy for as yet unknown reasons, data from the FEMPrEP study presented at the meeting also confirmed that there were minimal if any safety concerns associated with daily use of the antiretroviral drugs. As limited studies, none could assess safety problems that may arise with broader use - the purpose of this meeting.

Charting the future use of PrEP as a prevention strategy, the meeting participants considered how FDA's broad authority to require Risk Evaluation and Mitigation Strategies (REMS) could be applied to mitigate the risks associated with the scale-up of prophylactic use of antiretrovirals. The participants focused on several medical complications associated with use of the TDF/FTC combination including a potential impairment in renal function in some patients with long-term use and an early decrease in bone mineral density that could stabilize over time.

Due to the need for further study of the long-term side effects of PrEP, the panel recommended that communication plans be developed for use by clinicians and patients that stress regular testing of renal function and the panel agreed that additional

REMS measures, such as a Medication Guide, would be helpful to ensure adequate monitoring of renal complications - a well-known phenomenon with the use of tenofovir.

Also assessing available data on how tenofovir impacts bone mineral density and vitamin D levels, the panel concluded that additional educational materials are required to address these medical risks, but that the decision to evaluate bone mineral density should be left to the healthcare provider on a case-by-case basis.

Other medical issues included handling of depression, frequent in this population especially during periods of their lives when PrEP might be most important; risks to infants of women who wish to get pregnant on PrEP or who are breast-feeding; and sexually-transmitted infection - which is not treated or prevented by PrEP.

Targeted physicians for education should be infectious disease experts, primary care givers including gynecologists, and physicians who manage sexually transmitted infections even though the latter have not previously been involved in longitudinal care.

At the same time, the panel considered the potential for patients to develop HIV drug resistance to antiretroviral drugs used for prevention, noting that drug resistance has been well documented in HIV/AIDS patients on treatment. Considered by some to be the thorniest issue associated with the scale-up of PrEP, resistant HIV is more difficult to treat and frequently requires a more complicated treatment regimen. Moreover, even though the development of resistance has not been a concern in ongoing PrEP clinical studies, the panel members agreed that less frequent testing for HIV seroconversion that is likely upon scale-up may exacerbate the problem.

Because FDA can require a restricted distribution plan under REMS, the panelists debated the use of this system for PrEP, including requiring physician qualification and registration, pharmacist distribution limitations, and mandatory patient testing before a refill can be ordered and dispensed. Although restricted distribution systems have proven effective in reducing the risks associated with potent teratogens, like thalidomide, or to assure the appropriate use of narcotics, panel members concluded that a restricted distribution plan for PrEP could not be successfully introduced when the same drug combination is available for treatment and would impose substantial burdens on healthcare providers and patients. Further, such a system would impair access to needed preventative therapy.

The panelists also considered the issue of risk compensation. Risk compensation would be the engagement in higher risk encounters or lower use of condoms based on the false belief that these protections are no longer necessary. While existing clinical trial data suggests that risk behavior reduces and condom use increases with PrEP, this was a topic that the panelists agreed should be addressed in demonstration projects.

The panel members recognized that there are a number of questions that still need to be answered through post-market and ongoing studies, including the recommended frequency of HIV testing; continued vigilance in assessing the development of resistance on scale-up; and the possibility of risk compensation. Until these findings are available, however, the panel urged the development of a communications plan that will emphasize the need and importance of regular testing, counseling, and, for medical risks, close monitoring.

With regard to testing patients on PreP therapy for HIV infection, the panelists expressed caution about requiring complicated testing that may not be available in public health clinics. In almost all settings, panel members agreed that routine rapid enzyme-linked immunoassay testing should be sufficient. Addressing the costs of testing, payors on the panels provided assurance that, in covered patients, the cost of recommended quarterly testing will most likely be reimbursed or compensated, thus reducing the financial barriers to regular testing and to PrEP. However, panel members urged the development of mechanisms that will ensure access to regular testing for PrEP patients without financial resources.

Next Steps

As FDA considers the findings from this public meeting, conference participants urged healthcare providers and the public to await further guidance from the CDC and FDA before considering using PrEP. However, if providers believe that initiating PrEP is urgent for a specific patient, CDC recommends following the cautions and procedures previously published for PrEP use in MSM (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm?s_cid=mm6003a1_w).

At the same time, CDC recommends that any healthcare provider considering PrEP be apprised of the following precautions:

- PrEP should only be used among individuals who have been confirmed to be HIV-negative. Initial and regular HIV testing is critical for anyone considering using PrEP. All individuals considering PrEP must also be evaluated for other health conditions that may impact PrEP use.
- PrEP should never be seen as the first line of defense against HIV.It was only shown to be effective in clinical trials when provided in combination with regular HIV testing, condoms, and other proven prevention methods.
- Taking PrEP daily is critical. No other dosing regimen was evaluated in these studies.

- PrEP must be obtained and used in close collaboration with health care providers to ensure regular HIV testing, risk reduction and adherence counseling, and careful safety monitoring. Anyone considering using PrEP should speak with his or her doctor.
- PrEP has only been shown in clinical trials to reduce HIV infection among heterosexual men and women and among men who have sex with men. At this time, there are no data on its benefits or risks among injection drug users.
- Because pregnant and breastfeeding women were excluded from participation in PrEP trials, further evaluation of available data will be needed before any recommendations can be made regarding the use of PrEP for women considering conception or in those who are breastfeeding infants.

As a next step, the Forum for Collaborative HIV Research will post the webcast early next week and will publish the proceedings of this public meeting to advance the regulatory agenda. Once published, the report will be distributed widely to the Forum's many constituencies -government, industry, patient advocates, healthcare providers, foundations, health insurers and academia -with the goal of advancing research on PrEP and driving public policy.

About the Forum for Collaborative HIV Research

Now part of the University of California (UC), Berkeley School of Public Health and based in Washington, DC, the Forum was founded in 1997 as the outgrowth of a White House initiative which called for an ongoing collaboration among stakeholders to address emerging issues in HIV/AIDS and set the research strategy. Representing government, industry, patient advocates, healthcare providers, foundations and academia, the Forum is a public/private partnership that is guided by an Executive Committee that sets the research agenda. The Forum organizes roundtables and issues reports on a range of global HIV/AIDS issues, including treatment-related toxicities, immune-based therapies, health services research, co-infections, prevention, and the transference of research results into care. Forum recommendations have changed how clinical trials are conducted, accelerated the delivery of new classes of drugs, heightened awareness of TB/HIV co-infection, and helped to spur national momentum toward universal testing for HIV. http://www.hivforum.org