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Advancing HIV Prevention Science: The Roads from Cape Town

Kenneth H. Mayer, M.D.

The Fenway Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Ma., USA

Because of increasing advances in bio-behavioral HIV prevention science and the need for more cross-talk between investigators, HIV R4P (HIV Research for Prevention) was recently held in Cape Town, South Africa, bringing together almost 1,400 researchers from around the world. The conference's rationale was based on the recognition that all investigators need to understand the latest findings from a wide array of disciplines, if their most promising approaches can be transformed into sustained, cohesive responses that will arrest the pandemic.

In the few years since HPTN 052 trial demonstrated that earlier initiation of antiretroviral therapy by HIV-infected persons decreased HIV transmission to their serodiscordant partners, the concept of "treatment as prevention" has been popularized. Global HIV incidence has decreased by 1/3 annually since the height of the epidemic. Four large community-randomized studies are underway in Africa to understand the population-level impact of earlier treatment combined with other evidence-based prevention services. However, initial successes have been followed by subsequent increased HIV spread in some countries. National trends may mask rising HIV incidence in key populations, i.e. men who have sex with men (MSM), sex workers, people who inject drugs, vulnerable youth, often due to decreased access to services because of stigma and discrimination. Despite annual HIV incidence decreasing over the past decade, there are still about 2 million new infections a year, and with declining mortality among people living with HIV, the epidemic continues to grow. Expansion of treatment is an appropriate aspiration, but research to optimize other prevention approaches is also necessary.

Over the past 5 years, 7 efficacy trials of oral or topical tenofovir-based regimens used for pre-exposure prophylaxis (PrEP) to prevent HIV acquisition have been completed, with 5 demonstrating efficacy. In most studies adherence was the major challenge. Just before and during HIV R4P, 2 European PrEP studies announced they were moving MSM participants from the control conditions (waiting list or placebo) to receive tenofovir-emtricitabine because of demonstrated efficacy. The diverse PrEP efficacy studies demonstrate that chemoprophylaxis works, but many factors may limit adherence. Investigators learned that some participants who enrolled in PrEP trials were motivated by the economic and medical incentives, did not necessarily perceive themselves at increased risk for HIV, and/or did not trust researchers. Further research is underway to develop culturally-tailored programs to enhance adherence for those who can most benefit from PrEP. Several studies suggest that

less than daily regimens can provide high levels of protection, suggesting that careful assessment of pharmacological and behavioral patterns will lead to recommendations for optimized use.

Topical microbicides and intravaginal rings have been under study as ways to minimize systemic antiretroviral exposures, and to serve a dual-use function by providing hormonal contraception. Over the next few months, a third topical tenofovir gel efficacy study will be completed in South Africa, and if successful, should facilitate the path for licensure of the first vaginal microbicide, and will provide additional impetus for rectal gel studies. Two intravaginal dapvirine ring studies will be completed in the next year, and if successful, will offer another prevention modality. Two long-acting parenterally-administered antiretrovirals, rilpivirine and cabotegravir, are in clinical trials, and could obviate the need for daily adherence. Over the next few years, it is hoped chemoprophylaxis will provide a variety of options for HIV prevention, analogous to birth control.

A safe and effective vaccine still remains the Holy Grail for an “AIDS-free generation,” and although no breakthroughs were announced at the meeting, the presentations reflected increasing optimism that progress is being made. The earlier finding that a combination of a canarypox vector boosted by a bivalent mix of HIV envelope antigens was associated with a 31% reduction in HIV transmission in Thailand has led to novel studies of the correlates of protection, suggesting that non-neutralizing antibodies may play an important role in preventing HIV transmission, either by facilitating cell-associated cytotoxicity, by enhancing phagocytosis, and/or by other mechanisms that need further elucidation. These immune correlates studies have also suggested that anti-HIV IgG3 levels are associated with protection while IgA is not. A Clade-C optimized combination vaccine efficacy trial, based on insights from the Thai trial is planned to be conducted in South Africa.

The meeting also highlighted the role that broadly neutralizing antibodies (BNAbs) may play in HIV prevention. Several antibodies have been isolated from long term nonprogressors, rare HIV-infected individuals who retain virological control after living with HIV for decades. More recently, researchers have also postulated that BNAbs might could be administered for immunoprophylaxis. Early studies of parenteral BNAbs administration have demonstrated safety, and efficacy studies of passive immunoprophylaxis are being planned soon for African infants born to HIV-infected, treatment naïve mothers and for high risk HIV-uninfected populations. The current generation of BNAbs may not have sufficient potency, breadth and duration to merit licensure, but proof that the administration of BNAbs could decrease HIV incidence would be a major advance for the field, since vaccine candidates could be developed using the results as benchmarks, and newer, more potent BNAbs could also be developed for immunoprophylaxis.

To the outside observer, the heterogeneity of HIV prevention approaches may seem unwieldy, but most HIV R4P participants appeared to be excited by recent progress, as well as anxious. Resources are a major concern. Until each modality has well-established correlates of protection, the only way to demonstrate efficacy is to conduct randomized, controlled trials. Because HIV transmission is not efficient, and since counseling trial participants attenuates risk, thousands of volunteers are needed for each efficacy trial. This

means that the costs from bench to deployment for each new product are many million dollars. Delegates left Cape Town with renewed optimism, along with the hope that funders and the public will understand that much more work needs to be done.

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