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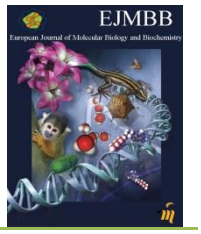

CHALLENGES AND FUTURE OF HIV PREVENTION

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ABSTRACT
HIV prevention is the "ensuring that the appropriate mix of evidence-based prevention strategies achieves a sufficient level of coverage, uptake, intensity and duration to have optimal public health effect Although global attention to HIV and AIDS remains strong, particularly regarding treatment initiatives, until recently HIV-prevention has garnered scant attention. Treatment alone will not reverse the epidemic, and current prevention efforts have not been successful in halting HIV transmission.

INTRODUCTION

Currently, for every two people who go on treatment for HIV and AIDS, five people become infected. In 2007 the Global HIV Prevention Working Group (PWG) had projected that 60 million new cases of HIV will occur by 2015 unless comprehensive HIV prevention is sufficiently increased. Those infected will require costly treatment, care and support. It is expected that scaling up combination prevention efforts would avert more than half of all new HIV infections expected to occur between 2005 and 2015, thereby disabling the epidemic and leading to a long-term decline.

In June 2006, the United Nations General Assembly adopted a political declaration on HIV and AIDS which included a commitment to pursue all necessary efforts towards the goal of universal access to comprehensive prevention programs, treatment, care and support by 2010 [1].

To meet the goal of global universal access by 2010, available financial resources for HIV and AIDS must reach up to US$ 42.2 billion– more than quadruple the resources that were available in 2007. While a lack of resources for HIV and AIDS in general is an issue, there has been debate regarding the relative allocation of HIV and AIDS funding—how much should go towards treatment and how much towards prevention. Although resource constraints make decisions about allocation inevitable, there is an emerging consensus that treatment and prevention are best viewed as complementary strategies rather than in competition with one another.

Increased access to treatment improves opportunities for HIV prevention through increased HIV-testing— and increased testing can reduce stigma and act as an entry point to prevention services. Recent research findings also indicate that providing treatment and lowering individuals' viral load can decrease risk of infection and act as a method of prevention. It is clear that reducing new infections—prevention—goes hand -in-hand with treatment [2].

Scaling up is key to realizing the potential of prevention Coverage levels for prevention services are extremely low. It is estimated that in 2005 a condom was used in only 9% of sex acts involving a non-regular partner

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and prevention programs reached a mere 20% of sex workers, 9% of men who have sex with men and 8% of injecting drug users globally.

Only 11 % of HIVinfected pregnant women in low- and middle-income countries received antiretrovirals to reduce the risk of mother to child transmission. Globally, less than half of all school attendees receive school-based HIV education

Watson-Jones et al. report anxiously awaited findings about a strategy for preventing infection with the human immunodeficiency virus (HIV) by pharmacologically suppressing herpes simplex virus type 2. Despite a sound rationale for the intervention, the results represent yet another disappointment in efforts to reduce the spread of HIV with the use of a biomedical agent.

Indeed, apart from important advances in preventing mother-to-child transmission, primarily through the use of antiretroviral drugs, and in preventing the acquisition of HIV in men by means of circumcision, only one late-stage randomized biomedical trial — involving the treatment of sexually transmitted infections — has shown a beneficial effect on the risk of HIV infection, and this benefit was not corroborated by subsequent studies.

Other late-stage biomedical HIV-prevention trials that failed to demonstrate a benefit examined the use of vaginal microbicide gels, the diaphragm as a cervical barrier, preexposure prophylaxis with antiretroviral medications, and two types of HIV vaccines. Although several behavioral interventions have been shown to reduce self-reported high-risk behaviors and some have reduced the rates of certain non-HIV sexually transmitted infections, none have demonstrated a reduction in the incidence of HIV infection [3].

Shortcomings in research design have inhibited progress in identifying effective HIV-prevention interventions. Design deficiencies led to premature termination of some trials because of inadequate research before the trial began, poor site preparation, or lack of community engagement. Other trials with inconclusive results raised the possibility that interventions had modest effects that could not be detected.

In light of these problems, the Bill and Melinda Gates Foundation asked the Institute of Medicine (IOM) to review the methodologic challenges of trials of nonvaccine biomedical interventions for HIV prevention and to recommend ways to improve the likelihood of success of future trials — an effort in which we participated.

Methodologic challenges make late-stage biomedical HIV-prevention trials more difficult to conduct and interpret than many other types of research on preventive or therapeutic interventions [4,5].

A key problem has been accurately estimating the expected incidence of HIV in the trial population, which is crucial to determining a planned trial's necessary size and duration. Some researchers substantially overestimated the expected incidence, which resulted in an inadequate sample size and thus inconclusive trial results. Trials have also been adversely affected by high rates of nonadherence to prescribed regimens and of attrition among participants, which reduce a trial's power to detect an effect and can bias the results. Accurate assessment of the adherence and risk-taking behavior of participants, which is key to interpreting results, has also proved challenging [6,7].

A particularly vexing problem relates to high pregnancy rates among participants. Women who become pregnant are routinely required to discontinue use of study products, and researchers sometimes cease to follow these women to track HIV and pregnancy outcomes, both of which exacerbate attrition problems and preclude the evaluation of effects on pregnant women and fetuses. Since any successful product introduced into the community would most likely be used by women after they became pregnant, this practice creates a clinical and ethical dilemma.

HIV-prevention trials also lack reliable surrogate end points for HIV infection or product activity and must therefore use HIV infection as the end point. Thus, effectiveness trials cannot be preceded by smaller studies using surrogate end points to demonstrate proof of concept and efficacy under ideal circumstances. As a result, such studies need to be large and sometimes lengthy, making them both costly and challenging [8,9].

The Joint United Nations Program on HIV–AIDS (UNAIDS) estimates that 2.5 million persons (range, 1.8 million to 4.1 million) became infected with HIV in 2007. The Projected Numbers of New HIV Infections before a Vaccine Becomes Available, Assuming a 2.5% Annual Decrease in the Number of Infections in 2007. shows the cumulative number of people who would become infected over the next two decades if there is a 2.5% annual decrease in incidence in the coming years (a decrease based roughly on UNAIDS estimates from 1998 through 2007). These estimates suggest that in the 15 to 20 years it may take to develop and evaluate a highly efficacious vaccine, the world may be facing 20 million to 60 million new HIV infections. Such projections emphasize the urgency of finding effective nonvaccine approaches to prevention. Since any such advances will probably be modest in magnitude or limited to particular subpopulations and settings, it is critical to learn how to optimize the use of multiple, partially effective biomedical and behavioral interventions in the settings and populations in which they are most effective [10].

Beyond continuing the vaccine search, researchers and sponsors can take some steps to accelerate advances in HIV prevention in the coming decade. First, the research community should intensify its investment in the development of safe, easy-to-use biomedical interventions. Second, preclinical and early-stage clinical testing and prioritization of products for later-stage testing need to be improved to make the most efficient use of research resources and to minimize large-scale testing of unsafe or ineffective products. Because having a reliable surrogate end point could greatly accelerate product evaluation,

investigators should prioritize research toward identifying such surrogates. In addition, cross-sectional biomarkers that can be used in standard and less sensitive assays to estimate HIV incidence, which could be extremely valuable but are not yet sufficiently reliable, should also be a focus of research. Better methods for accurately assessing adherence and risk-taking behavior and better strategies for improving adherence are also needed [11].

Several problems that have plagued late-stage HIV-prevention trials must be overcome. Future trials should include adequate planning to ensure community acceptance and sustainability of the intervention, should involve proper preparation of sites to ensure adequately trained staff and sufficient physical infrastructure, and should include reliable estimation of the rates of HIV infection, pregnancy, loss to follow-up, and nonadherence to determine an adequate sample size and trial duration. Trials must be carefully monitored, with the use of event-driven timetables, and researchers must capture reliable information on adherence and risk-taking behavior.

Young women are disproportionately affected by the HIV epidemic in many regions, particularly sub-Saharan Africa, and high rates of pregnancy are common in many target populations. Therefore, sponsors and researchers must take additional steps to evaluate the safety and efficacy of preventive products in pregnant women. These steps include completing studies of reproductive toxic effects and other appropriate preclinical research, ideally before phase 2 studies begin; identifying circumstances in which it might be safe to continue using the product during pregnancy; and developing plans for the collection of key safety information during trials and at their completion [12,13].

Identifying and implementing improved behavioral interventions to reduce the risk of HIV infection represent an important opportunity that has not been adequately exploited, in part because most of these studies have been too small to permit evaluation of HIV infection as an end point. The IOM report advocates integrating research on behavioral interventions into biomedical intervention trials by using factorial and other study designs. Such integrated strategies could be effective in reducing risky behavior and promoting condom use, thereby enhancing the ultimate effectiveness of a biomedical intervention.1

Evaluating multiple interventions and collecting more reliable outcome information, as well as conducting trials of adequate size, place additional demands on trial sites — underscoring the importance of investing in the human, physical, and regulatory capacity at study locations, ensuring their sustainability. We believe that sponsors need to reconsider the traditional financial and time constraints that have been placed on investigators conducting HIV-prevention trials [14-17].

DISCUSSION

CDC enumerates certain issues in HIV Prevention as follows :

Too Few People with HIV Are Aware of Their Infection Of the approximately 1.2 million people living with HIV in the United States, CDC estimates nearly one in eight (more than 161,000 people) do not know they are infected. Because many new infections are transmitted by people who do not know they are infected, undiagnosed infection remains a significant factor fueling the HIV epidemic. HIV testing has never been quicker or easier than it is today, and more people have been tested than ever before. But fear and misperceptions can still keep people from finding out their HIV status: Many people, even those who engage in high-risk behavior, do not get tested because they do not believe they are at risk for HIV infection. Others misunderstand the testing process, not realizing that rapid HIV tests can be done with a simple cheek swab or finger prick and provide results in as little as 20 minutes. Some are concerned that other people will find out that they have tested positive (or that they sought testing at all), although testing is completely confidential. Some may avoid testing simply because they are afraid their test will be positive. Today, more than half of American adults have not yet been tested [18,19].

Many People with HIV Do Not Receive Ongoing Treatment Ensuring that people living with HIV receive ongoing care and treatment is one of the most effective ways to protect their health and prevent the further spread of HIV. Treating people with HIV lowers the amount of virus in their body and can dramatically reduce their risk of transmitting HIV to others. Of those living with HIV, just 40 percent receive regular medical care, and only 30 percent are successfully keeping their virus under control through treatment [20,21].

Diverse Populations Need Equal Access to Prevention Information and Tools Prevention programs must serve a diverse population that includes gay and bisexual men of all races and ethnicities – particularly those who are young, transgender women, and African Americans and Latinos – and help provide those populations with equal access to accurate prevention information and effective prevention tools. With more people than ever before living with HIV, it has also become increasingly important for prevention programs to address the needs of HIV-infected people and their partners [22,23].

Disparities in HIV Rates Are Fueled by Social and Economic Inequities A wide range of complex social and economic factors drive the HIV epidemic and place African Americans and Latinos at greater risk for this disease. Many of the contextual factors that increase risk for other diseases (such as heart disease and diabetes) also fuel the spread of HIV within these communities: High community rates of HIV: Because the burden of HIV is greater in some communities, African Americans and

Latinos are at increased risk of being exposed to HIV infection with each sexual encounter. Therefore, even with similar levels of individual risk behaviors, African Americans and Latinos are at higher risk of infection than other races and ethnicities. Poor access to health care: Having health insurance can enable a person to more easily access HIV care and treatment – but nearly 20 percent of African Americans and 30 percent of Latinos lack consistent health insurance, compared with 11 percent of whites. Low socioeconomic status: CDC research shows that those who cannot afford the basics in life may end up in circumstances that increase their HIV risk. Census data indicate that in the United States poverty is not evenly distributed – nearly a quarter of African American and Latino families live in poverty (compared to 10 percent of white families). While each individual has a personal responsibility to protect his or her own health, as a nation we have a shared responsibility to tackle the root causes of these disparities [24].

Limited Resources for HIV Prevention Today, the need to do more with existing resources is greater than ever. To achieve a higher level of impact with every federal prevention dollar, CDC is pursuing a High-Impact Prevention approach that works to match cost-effective, scalable interventions to heavily affected populations and geographic settings to maximize reductions in HIV incidence.

Many people Have Become Complacent about HIV Too many people no longer view HIV as a serious concern. A recent survey by the Kaiser Family Foundation found that the percentage of Americans who rank HIV as a major health problem is substantially lower than it was a decade ago. Even more troubling are studies showing that among some of the populations with the highest rates of infection (including gay and bisexual men and African Americans), many people do not recognize their risk, or they believe HIV is no longer a serious health threat. Each new generation needs to be reminded of the still-serious nature of HIV and the importance of prevention. More than three decades after CDC reported the first cases of AIDS, the sense of national crisis may have waned – but our resolve cannot. We have to think about scaling of HIV Prevention efforts which could be thought of as follows :

Launching of the HVTN 702 HIV vaccine trial – Earlier this week, the first participant enrolled in HVTN 702, the largest HIV vaccine trial ever to take place in South Africa, and the only vaccine efficacy trial currently taking place worldwide. HVTN 702 will test the safety and efficacy of an HIV vaccine strategy based on the combination evaluated in the RV144 trial, which took place in Thailand and reported results in 2009. RV144 found modest benefit using a two-vaccine combination. This has been updated and adapted for the genetic variants of HIV circulating in Southern Africa. The efficacy trial, which is scheduled to run through 2020, is just one important milestone in the larger HIV vaccine research and development agenda. Gratitude, encouragement and thanks to volunteers and trial staff!

A step forward in HIV prevention for women – This week's New England Journal of Medicine includes the final results of the International Partnership for Microbicide's Ring Study, which evaluated the safety and efficacy of the dapivirine vaginal ring. These results (first presented at CROI back in February) stand alongside the ASPIRE results (which also evaluated the dapivirine ring) to show that the ring is safe and partially protective. There is still much to understand from both of these studies and additional work that is ongoing and planned, as nicely summarized by Adaora Adimora in her accompanying editorial, *Preventing HIV Among Women: A Step Forward, but Much Farther to Go*. The results, commentary and a NEJM video summarizing results from both trials are all online.

UNAIDS' timely and urgent prevention-focused resources developed for World AIDS Day – For the past several years, AVAC and other prevention advocates have urged UNAIDS to shine a light on the yawning gaps in funding and strategy for comprehensive HIV prevention. Starting with its *Prevention Gap* report—released in July 2016—the agency has taken this issue on. The materials released for World AIDS Day include print materials, prevention-focused stories and an investment update. The update outlines age and population-specific gaps and quantifies the funding needs.

Dynamic civil society engagement with clinical trial conduct – Gilead's Phase III trial (known as DISCOVER) of the drug F/TAF for oral PrEP has raised concerns among advocates that stakeholder engagement has been insufficient. The study plans to enroll 5,000 participants from 92 sites across the US and Europe. Participants will be randomized to receive either daily TDF/FTC (Truvada), which is a proven prevention option approved by the US FDA for PrEP in 2012, or daily F/TAF, which is a different version of the drug combination that has been approved for treatment but the efficacy for prevention is unproven.

Given the complex messaging of this trial—one that compares an approved option with an experimental one—community engagement over the course of trial planning and execution is imperative. A group of advocates, representing a range of organizations, submitted a public letter to Gilead on November 16 demanding substantial and meaningful improvements to the process of stakeholder engagement, as outlined in the Good Participatory Practice Guidelines. This is the right thing to do and history has shown this process improves the chances for the trial's success [25].

Uncompromising AIDS activism and advocacy – In the United States, the presidential election has raised major concerns about the full range of issues affecting the domestic and international HIV response. Will research continue to be funded? Will healthcare be extended to all who need it, and will communities respond with love and action to outbreaks of hate and discrimination? Will overseas programs continue to be strategic and sufficiently funded? Nothing can be taken for granted. We are grateful to our allies in the US and abroad who are committed to fighting for what is right, just and sound public health. The Federal AIDS Policy Partnership and the Global AIDS Policy Partnership, along with the Congressional HIV/AIDS Caucus, are hosting a Congressional reception in recognition of World AIDS Day. Health GAP and other activists are planning an event on the Capitol Hill lawn to demand Speaker of the House Paul Ryan and the Republican Congress preserve funding that supports global health programming and the Affordable Care Act.

The life and legacy of Jacobus Witbooi – Jacobus Witbooi, coordinator of Pan African ILGA, died in late November, leaving a community in mourning and a remarkable legacy as a human rights defender. In his work for Pan African ILGA and in a wide array of other roles, Jacobus sought with strength and joy to ensure that LGBT rights were viewed as human rights at community, national and international levels. He was a member of AVAC's PxROAR Africa program where he helped define strategies for integrating biomedical HIV prevention and human rights agendas. He was a beautiful soul, inside and out, a great friend and an inspiration to us all. We are grateful for having known him, even as we grieve his untimely loss [21-25].

CONCLUSION

The challenges in HIV-prevention research are enormous, and even the best-designed trials may fail. Yet a staggering number of new HIV infections are likely to occur before a highly effective vaccine becomes available. With so many lives at stake, it is imperative to prioritize the identification and implementation of more effective behavioral and non-vaccine biomedical interventions. It is equally important to design, fund, and conduct these trials in ways that give them the best chance of success. The decline in new HIV infections among adults has stalled.

The UNAIDS *Prevention gap report* shows that worldwide an estimated 1.9 million adults have become infected with HIV every year for at least the past five years and that the number of new HIV infections is rising in some regions. The report shows that HIV prevention efforts must be reinvigorated if the world is to stay on the Fast-Track to ending the AIDS epidemic by 2030.

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