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Challenges to HIV Prevention — Seeking Effective Measures in the Absence of a Vaccine

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In this issue of the *Journal*, Watson-Jones et al. (pages 1560–1571) 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 dem-

onstrated a reduction in the incidence of HIV infection.¹

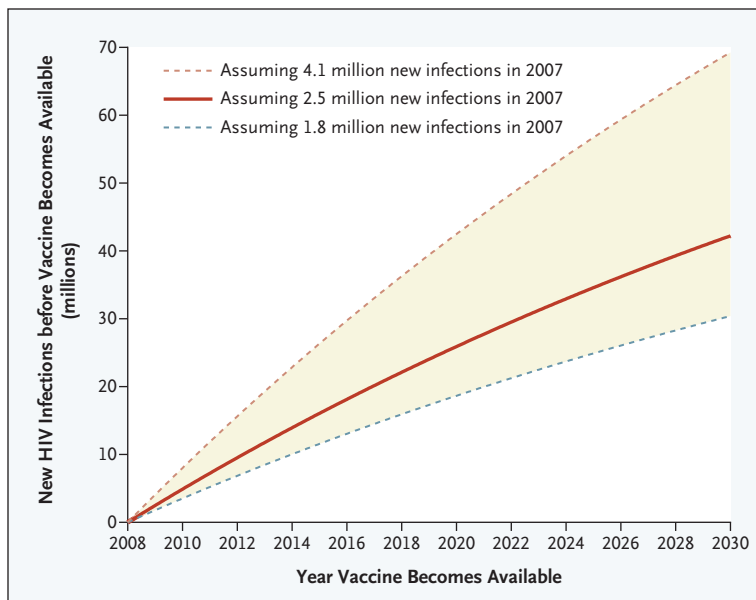
Shortcomings in research design have inhibited progress in identifying effective HIV-prevention interventions.¹ Design deficiencies led to premature termination of some trials because of inadequate research before the trial began, poor site preparation, or lack of community engagement. Other trials with 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.¹

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. 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.

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.



Projected Numbers of New HIV Infections before a Vaccine Becomes Available, Assuming a 2.5% Annual Decrease in the Number of Infections in 2007.

Estimates of the numbers of new infections in 2007 are from the Joint United Nations Program on HIV–AIDS.

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 2007.² The graph 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.

Beyond continuing the vaccine search, researchers and sponsors can take some steps to accelerate advances in HIV prevention in the coming decade.¹ 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.

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,² 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.

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 report¹ 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.

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 nonvaccine biomedical interventions. It is equally important to design, fund, and conduct these trials in ways that give them the best chance of success.

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1. Lagakos SW, Gable AR, eds. *Methodological challenges in biomedical HIV prevention trials*. Washington, DC: National Academies Press, 2008.

2. 2007 AIDS epidemic update. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2007.

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