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Ethical Challenges of Preexposure Prophylaxis for HIV

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ON JULY 16, 2012, EMTRICITABINE/TENOFOVIR (Truvada; Gilead Sciences) became the first drug approved by the US Food and Drug Administration (FDA) for preexposure prophylaxis (PrEP) of human immunodeficiency virus (HIV) for adults at high risk. Clinical trials have demonstrated that daily use of oral antiretroviral drugs can reduce the risk of HIV acquisition through sexual intercourse. With 50 000 new HIV infections per year in the United States¹ and 2 million per year worldwide,² PrEP could become a major component of “combination prevention” along with condoms, counseling, testing, and treatment.

Behavior and Effectiveness

Emtricitabine/tenofovir is only partially effective for HIV prevention, with the Partners PrEP study of serodiscordant couples reporting a 75% risk reduction in HIV transmission.³ The effectiveness of PrEP correlates with adherence; the iPrEx study of male-to-male sexual contact reported more than 90% protection among study participants with high adherence,⁴ but 44% reduction in HIV transmission overall.⁵ Even a modest 44% reduction, however, would represent a clear benefit in high-prevalence settings and sexual networks. Researchers must closely monitor the results of ongoing open-label studies of PrEP, as well as use in practice, and if necessary, conduct pilot programs to increase adherence over time.

If unsafe sex were to increase with PrEP, it could theoretically offset effectiveness in practice. Behavioral disinhibition, however, was not observed in clinical trials. Moreover, a substantial increase in unsafe sex would have to occur to offset the benefits of PrEP on a population level.

Cost-effectiveness

Daily emtricitabine/tenofovir in the United States has been estimated to cost \$10 000 per year, including screening and physician visits.⁶ This cost is high compared with alternative prevention strategies. However, even high-price interventions become cost-effective when compared with the greater cost (and morbidity) that would occur if individuals became infected.

At a health system level, comparative cost-effectiveness should be a primary consideration for priority setting. Assuming 44% effectiveness, one model estimated that emtricitabine/tenofovir would be cost-effective for those who engage in male-to-male sexual contact who average 5 sexual partners per year.⁶ Additional research is needed to compare cost-effectiveness across different combination prevention approaches.

Patient and Population-Level Risk

If patients who are HIV infected take emtricitabine/tenofovir, drug resistance can occur, thereby compromising therapeutic options and possibly posing a public health threat. Therefore, PrEP requires regular testing and reliable medication use. The FDA Amendments Act of 2007 empowers the agency to approve a drug subject to a Risk Evaluation and Mitigation Strategy, including medical testing. The FDA could have directed physicians to prescribe and pharmacies to dispense this drug only to patients with a negative HIV test result. Such stringent conditions, however, would reduce access. The FDA instead required the manufacturer of emtricitabine/tenofovir to train and educate health care professionals and collect drug utilization data. The FDA labeling recommends HIV testing at least every 3 months, as well as symptom monitoring for acute HIV-1 infection and toxicities (especially kidney impairment and bone density loss).

Equity and Justice

Despite empowering patients and promoting the public's health, PrEP could exacerbate health care inequalities. High cost and intense medical monitoring could exclude individuals with low income, unstable housing, drug dependence, or mental illness. This challenge is even greater in low-income countries with limited resources and infrastructure.

Early PrEP adopters are likely to include gay and bisexual men and heterosexual serodiscordant couples with greater education and resources. Extending PrEP to other groups will require effective public health governance, along with

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research and innovation. Fortunately, a blueprint exists: antiretroviral strategies for both HIV treatment and preventing mother-to-child transmission have relied on advances in science, financing, access, and health care to achieve remarkable success globally.

Underserved Populations. Reaching populations with disproportionate HIV incidence, including young black men who engage in male-to-male sexual contact, is crucial to reduce HIV burdens and promote equity. Although the Affordable Care Act will expand coverage, it cannot ensure testing and PrEP for all vulnerable individuals. Prevention programs should explore synergies with HIV testing campaigns, which currently link to treatment, but they could also link to PrEP for HIV-negative, high-risk individuals.

Women. The FDA approval includes at-risk women, despite mixed evidence of PrEP effectiveness but clear need: 25% of new HIV infections in the United States¹ and half worldwide² occur in women. PrEP addresses the need for a female-controlled prevention mechanism that can be used without a male partner's consent. The efficacy of oral PrEP remains less certain for women than for men, although the results of the VOICE study (clinicaltrials.gov NCT00705679) are expected in 2013 and could alleviate concerns raised by the FEM-PrEP study, which closed early due to futility.⁷ A female-specific prevention method such as vaginal microbicide could enhance the effectiveness of chemoprophylaxis among women. The CAPRISA 004 trial found that topical tenofovir gel, used before and after sexual contact, reduced HIV acquisition by 39%.⁸

Generalized Epidemics. Most new HIV infections worldwide occur in developing countries experiencing generalized epidemics. Although the United States is the only country to have approved a PrEP indication, others may soon follow. PrEP rollout represents a vital test for governments, global health programs (eg, PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria), and normative bodies (World Health Organization). Cost and health care infrastructure could represent major barriers to widespread PrEP availability. Planning for regulatory review, financing, and implementation must therefore continue.

Ethical Resource Allocation. Thousands of Americans with HIV are currently on waiting lists for drug treatment, even though effective treatment significantly reduces the risk of transmission.⁹ Given scarce resources, what are the relative priorities between PrEP for healthy individuals and treatment for currently infected individuals? Although these 2 uses may appear to entail inescapable trade-offs, expanding treatment for all infected individuals (which is now recommended),¹⁰ while selectively offering PrEP to high-risk individuals, is the best public health strategy and could lower health care costs in the long term.

Ethical Research. The FDA's approval of PrEP will trigger scrutiny of HIV prevention trials using placebo

controls. Beneficence requires researchers to minimize risks to study participants—and while regulatory approval alone does not determine the appropriate standard of care, it signals a strong evidence base and shifting clinical norms. Offering PrEP to study participants, however, presents scientific and logistical research challenges, with no consensus on how to balance conflicting obligations. Multistakeholder deliberations should proceed on this topic.

Looking Ahead

Daily oral emtricitabine/tenofovir is likely just the first iteration of PrEP interventions that will reach the market. Dosing PrEP intermittently (before and after sexual exposure, or only during periods of increased sexual activity), rather than daily, could theoretically maintain effectiveness for some users while reducing toxicity and cost. Longer-acting PrEP products such as vaginal rings or injectable agents could also reduce the daily burden for PrEP users. With these biomedical advances, PrEP could transform HIV prevention much like hormonal contraception transformed family planning. Combination prevention and universal treatment makes it possible to dream of an “AIDS-free” generation.

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