A US Policy Perspective on Oral Preexposure Prophylaxis for HIV

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Orally administered preexposure prophylaxis is an innovative and controversial HIV prevention strategy involving the regular use of antiretroviral medications by uninfected individuals.

Antiretroviral medications protect against potential HIV infection by reducing susceptibility to the virus.

Recent clinical trial results indicate that preexposure prophylaxis can be safe and efficacious for men who have sexual intercourse with men, yet there remain policy considerations surrounding costs, opportunity costs, and ethical issues that must be addressed before broad implementation in the United States. Resources for HIV prevention are limited, thus cost-effectiveness analyses of PrEP implementation in nonexperimental situations are needed to allocate prevention funding most productively. Findings from the randomized clinical trials that PrEP is efficacious should mark the beginning of the policy discussion, not its end. (*Am J Public Health.* 2011;101:982–985. doi:10.2105/AJPH.2010.300066)

A NUMBER OF BIOMEDICAL interventions now becoming available will move HIV prevention well beyond admonitions to adhere to ABC (abstain, be faithful, and use condoms). Rather than relying exclusively on behavior change, these novel prevention strategies combine medical with behavioral approaches. Preexposure prophylaxis (PrEP), postexposure prophylaxis (PEP), and test and treat or testing with linkage to care (TNT/TLC+) have enormous potential to leverage the power of antiretroviral medications (ARVs) to limit the spread of HIV by reducing an individual's susceptibility to HIV or by reducing community viral load. As we move into the post-ABC world, weighing policy concerns of cost, opportunity costs, and ethical issues of these new biomedical strategies is important.

Orally administered PrEP is an innovative and controversial HIV prevention strategy that involves the regular use of existing ARVs to protect uninfected individuals against potential HIV infection. Using antiretroviral agents to decrease the risk of HIV transmission has already been successful in reducing transmission from HIV-positive mothers to their infants, curbing HIV infection through breastfeeding of uninfected infants, and protecting against occupational exposure.[1]

The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) are supporting randomized clinical trials of PrEP in 13 countries (including the United States) that involve more than 20 000 participants.[2] Results on PrEP use by men who have sexual intercourse with men (MSM) from the Pre-Exposure Prophylaxis Trial Initiative (iPrEx) were released in late 2010.[3] The study results generated a great deal of enthusiasm and optimism because they indicated that HIV incidence was 44% lower in MSM receiving PrEP compared with controls. Participants who took the medication on 90% or more of days had a 79% decrease in HIV incidence.[3]

These randomized clinical trial results suggest that PrEP is a promising strategy, but we must temper this promise with a healthy dose of caution. PrEP is an intensive intervention for which cost, feasibility, and behavioral considerations may be as important as clinical efficacy. Thus, we must continue to examine the viability of PrEP as an HIV-prevention strategy, especially considering the development of competing biomedical prevention modalities.

The iPrEx results provide strong clinical evidence that PrEP can reduce seroconversion rates in experimental participants. However, the trials have not been designed to address crucial policy issues involved in full-scale implementation. Attendees at the Preparing for PrEP Conference in 2009 rightly called for "proof of deliverability" before PrEP implementation.[4] We would like to add that proof of desirability is equally important and should be considered.

Before launching full PrEP implementation, a window of opportunity exists to consider the pragmatic policy issues PrEP presents within the current political and financial context. The interpretation of the PrEP randomized clinical trial results and the desirability of PrEP promotion must be considered from the perspective of costs, associated opportunity costs, and ethical dilemmas created.

THE HIGH COST OF PrEP

The high cost of PrEP therapy would present the first challenge to full implementation. The wholesale cost of medicinal PrEP therapy is approximately $900 per month in the United States.[5] In addition to these direct costs, ongoing counseling and testing or surveillance for adverse side effects and the development of resistant viral strains would be required.[6,7] Targeting PrEP to the 100 000 persons in the United States at highest risk for HIV is estimated to cost more than $1 billion annually.[8] Thus, PrEP implementation would most likely require new resources. This begs the question, from where?

The high cost of PrEP is likely to be publicly financed. Although private insurance coverage will grow with the implementation of the Affordable Care Act, private insurance is unlikely to cover the cost of PrEP unless recommended by the US Preventive Services Task Force.[9] The Health Resources and Services Administration (HRSA), through the Ryan White HIV/AIDS Program, provides treatment of HIV-positive individuals, and the CDC is tasked with the allocation of national prevention resources. However, the use of ARVs for prevention falls somewhere between HRSA's and CDC's responsibilities.[10] Both HRSA and state resources are

extremely taxed and highly unlikely to be an option for the financing of PrEP, and the fiscal year 2010 federal allocation to CDC prevention resources was $878 million less than that recommended by the National Alliance of State and Territorial AIDS Directors.[11]

Regardless of the funding source, responsible implementation would require a long-term involvement in an intensive medical intervention for large numbers of HIV-negative individuals. This involvement includes, but is not limited to, counseling and support services to ensure compliance and to maintain other preventive strategies, frequent testing to monitor seroconversion, and active surveillance for side effects and resistant strains.[6,7]

Costs of Compliance Counseling

Data from the randomized clinical trials are beginning to confirm predictions that sustained and effective counseling is imperative to maintain ARV adherence.[6,7,12] The very intense levels of counseling that participants in randomized clinical trials receive are unlikely to be available for nonexperimental implementation, particularly in community-based organizations in low-income areas that are currently struggling with inadequate funding for the current patient load.[6] Providing counseling for patients on PrEP will further strain the capacity of the HIV-related delivery system.

Results from randomized clinical trials are unlikely to be fully informative about adherence levels if PrEP were to be implemented outside the trial context.[4,6] First, to promote adherence, randomized clinical trials set up specific mechanisms, in addition to the extensive counseling and case management services, to support participants' compliance (e.g., medication bottles with pill caps that were monitored by the researchers).[3,10] The iPrEx study sites went to extraordinary lengths to retain participants, engaging them with movie screenings, pageants, and open houses.[13] Second, as noted by the director of the Atlanta-based PrEP trial, the individuals who agreed to participate in the trial were a selected group that was more likely to commit to taking a pill a day than were individuals who refused to participate.[10] Nonetheless, the iPrEx results indicated that only 49% of participants took their medication on 90% or more of the days (and the 51% of participants who took their medication with less regularity experienced a nonsignificant 21% decrease in HIV infection).[3] Third, trial participants may also be more adherent because they feared losing the incentive they received for being a randomized clinical trial participant. If full PrEP implementation required even nominal cost-sharing for medication, the adherence incentives would be reversed; rather than anticipating financial gains for being adherent, individuals on PrEP could reduce their out-of-pocket costs by taking their medication less consistently.

Surveillance

Public health concerns underscore the importance of maintaining active surveillance for resistant viral strains.[4,6] If compliance is weak, resistant strains may develop and undermine current treatment strategies that depend on the two drugs currently used in PrEP trials, tenofovir (TDF) and emtricitabine plus tenofovir (FTC/TDF).[6] The small and targeted nature of the clinical trials limits their statistical power to detect the development of resistant strains. Programs designed to monitor resistance would have to be established and the cost of these programs factored into a comprehensive cost-effectiveness analysis of wider PrEP implementation.

THE OPPORTUNITY COST OF PrEP

Resources for prevention are always limited; thus, efficient allocation of public funding is crucial to avert the greatest number of new infections within a given budget particularly if existing prevention resources are redirected to support PrEP.

Prevention Strategies

The high cost of PrEP makes it imperative to ensure that it does not displace existing, effective, and lower-cost prevention strategies. PrEP is not a substitute for other prevention strategies, and we must continue to use the effective, low-cost strategies among people who can successfully use them. In fact, PrEP interventions require the maintenance of conventional prevention strategies because (1) the emerging data indicate that PrEP is not 100% effective at preventing HIV infection,[3] (2) PrEP will not provide protection against other common sexually transmitted infections, and (3) epidemiological modeling has begun to underscore the importance of stability in risk behaviors to PrEP efficacy.[14]

Increasing rates of risky transmission acts are a major unknown and potentially iatrogenic outcome associated with PrEP.[6,7] Currently, MSM account for a growing share of incident HIV infections in the United States.[15,16] Increasing incidence of sexually transmitted infection and risk-taking behaviors among MSM suggests that perceptions of less severe consequence to high-risk sexual activity can reduce safe-sex practices.[15,16] Indeed, qualitative studies suggest that many MSM see biomedical prevention as an alternative to using condoms. In a recent study of high-risk MSM in New York City, 35% of participants reported that PrEP would decrease personal condom use.[17] Whether PrEP can be characterized as "harm-reducing" depends crucially on risk compensation (or behavioral disinhibition) that may offset the protective effect of PrEP.[14,17]

Results from clinical trials will underestimate the level of risk compensation expected if PrEP were implemented more generally. The observed rate of behavioral offsets in the randomized clinical trials can only be considered a lower bound on the rate in actual implementation. One trial participant remarked that he maintained his usual preventive measures because he did not know if he was receiving active PrEP or the placebo.[10] If PrEP were fully implemented, all patients would know that they are getting active medication and might be emboldened to take more risks. An open-label follow-on to iPrEx is currently being developed to provide information on the magnitude of this effect.[18]

The positive efficacy findings in the iPrEx trial demonstrate proof of concept, but not proof of effectiveness. A decision to implement PrEP may come with a substantial opportunity cost for individuals at risk. Evidence from focus groups suggests that PrEP may be used as a substitute for existing prevention modalities, rather than as a supplement.[17] Thus, there is a potential that individuals on the PrEP regimen may actually increase their risk of HIV infection because statistical modeling suggests that reduction in viral transmission is

highly sensitive to the level of risk taking.[19]

Emerging Biomedical Technologies

Cost-effectiveness analyses are needed that compare PrEP, not only to existing prevention modalities such as condoms, but also to other, new biomedical approaches to prevention that are in development, such as PEP, microbicides, and TNT/TLC+.[6] Although no head-to-head comparison among the biomedical strategies has been conducted, some analyses compare each strategy to the status quo.

Paltiel et al. estimated that the cost in the United States of each additional quality-adjusted life year (QALY) generated by PrEP, assuming 50% efficacy, was $345 200 (after adjusting to 2010 dollars; Table 1).[20] (All sums hereafter are in 2010 dollars.) Desai et al. included the prevention of secondary infections and estimated the cost per QALY of PrEP targeted to very-high-risk MSM in New York City at $35 600.[19]

It is important to note that the results from Desai et al. are sensitive to assumptions about increases in sexual risk taking, and the model indicates that a 4.1% increase in the yearly numbers of sexual partners completely offsets the benefits conferred by PrEP. In addition, one of the target groups for PrEP may be uninfected partners in serodiscordant couples. In this situation the uninfected partner's risk may already be reduced if the infected partner's viral load is suppressed by antiretroviral therapy.[21] Consequently, the cost per QALY for this particular group is likely to be similar or greater than that calculated by Paltiel et al.

In contrast, the cost per QALY of a screening test, followed by treatment of HIV-positive patients in the TNT/TLC+ scenario is estimated to be $46 700.[22] Accounting for reduced transmissions lowers the cost per QALY to $38 700.[22] A four-week PEP treatment has the lowest cost per QALY at $21 600, but its application is limited to those individuals who recognize their risk, suspect infection, and rapidly seek treatment.[23,24] Finally, many behavioral prevention strategies have been found cost-effective.[25]

ETHICAL CONSIDERATIONS

Resource and ethical issues are inextricably linked because resources are limited. Currently, in some state AIDS drug assistance programs, the demand for ARVs is outpacing the funding allocated to pay for them: currently there are more than 6000 HIV-positive people in 10 states on waiting lists for antiretroviral treatment.[26] Could public support be ethically allocated to provide PrEP to high-risk, but uninfected individuals, while public resources were not available to treat all those currently infected?

Will PrEP be available without cost-sharing, as state AIDS drug assistance program services are? Young Black MSM in Atlanta reported that they were unwilling to pay $25 per month for PrEP.[10] If cost-sharing will be required, the implementation of PrEP will likely reinforce racial, ethnic, and geographic disparities.

The difference in the cost per QALY calculated in the Desai and Paltiel studies indicates that targeting to high-risk populations can dramatically lower the cost per QALY of PrEP. In actual implementation, can PrEP be made available to some individuals and not others? Will this lead to an informal market for ARVs, wherein high-income individuals who do not meet the risk criteria for PrEP purchase drugs from low-income individuals who are receiving PrEP or, more alarmingly, who are HIV-positive but willing to sell their drugs?[6]

Finally, it is important to weigh the ethical considerations on a global scale. Through the President's Emergency Plan for AIDS Relief, the US government has made a commitment to expanding access to treatment. Would it be ethical for the United States to expend large sums to provide ARVs to Americans without the disease at the same time that millions of HIV-positive individuals around the world lack access to the treatment?

CONCLUSIONS

With regard to costs, opportunity costs, and ethical considerations, the desirability of orally administered PrEP must be established. We have argued that randomized clinical trials may not provide all the needed evidence when the intervention under consideration is one for which the outcome depends not only on physiologic responses to treatment but also on behavioral responses. In the case of PrEP, clinical trials may demonstrate physiologic efficacy but are unlikely to provide definitive information on adherence levels and risk compensation, key parameters in determining whether PrEP will lead to increased rather than decreased HIV transmission.

Significant opportunity costs exist. Available models of cost-effectiveness suggest that including the secondary benefits of reducing community viral load, TNT/TLC+, and PrEP may achieve similar cost per QALY subject to the caveat that models of PrEP did not fully account for the cost of maintaining counseling and compliance monitoring at levels provided in the randomized clinical trials. Such expenditure would be necessary to gain the level of clinical results indicated by the randomized clinical trials. Public health concerns underscore the importance of extensive active surveillance for resistant strains that could undermine existing

TABLE 1—Cost-Effectiveness Comparison of Interventions to Avert HIV Infection

Intervention	Year	Cost per QALY, $ (as Published)	Cost per QALY, $ (2010)	Source
PrEP (50% efficacy)	2006	298 000	345 203	Paltiel et al.[20]
PrEP for high-risk MSM (50% efficacy) 25% coverage rate	2007	31 970	35 594	Desai et al.[19]
TNT/TLC+ (without secondary effects)	2004	37 100	46 653	Paltiel et al.[22]
TNT/TLC+ (with secondary effects)	2004	30 800	38 731	Paltiel et al.[22]
PEP regimen	2000	14 449	21 646	Pinkerton et al.[23]

Note. MSM = men who have sex with men; PEP = postexposure prophylaxis; PrEP = preexposure prophylaxis; QALY = quality-adjusted life year; TNT/TLC+ = test and treat or testing with linkage to care. Constant dollar estimates of alternative biomedical interventions using the "medical care" item of the Consumer Price Index.

treatment regimens. Compromising the effectiveness of current antiretroviral agents could impose huge societal costs.

Implementing PrEP at the expense of TNT/TLC+ would impose a large opportunity cost because TNT/TLC+ involves a relatively low-cost HIV test given to a large population with treatment of the small number of those who test positive. By contrast, PrEP involves dosing large numbers of uninfected individuals with costly medications for an extended period of time.

Studies suggest that PrEP could be cost-effective if targeted to "core transmitters" of HIV. However, success of a targeted strategy depends not only on the efficacy of PrEP, but also on levels of risk compensation. Targeted high-risk individuals may well exhibit more risky behaviors than the highly selected sample of randomized clinical trial participants. The randomized clinical trials provide behavioral risk counseling and incentives to adhere to the ARVs. At the same time, participants may practice safer behaviors because they are uncertain if they are receiving ARVs or placebo medications. The conditions of large-scale implementation of PrEP are substantially different from those in a randomized clinical trial and policy decisions must be made with consideration to cost-effectiveness, opportunity costs, and ethical issues of PrEP in practice.

Additional results from the randomized trials of PrEP are eagerly anticipated, and the CDC and NIH have begun designing communication and adherence strategies, developing eligibility criteria, and planning for the strategic monitoring of drug resistance.[6,10] However, as many others have pointed out, it would be a mistake to treat PrEP or any other biomedical intervention as a silver bullet, applicable to all populations and desirable in all settings.

Orally administered PrEP expands the number of options that a successful prevention program could offer. However, the strategy cannot succeed if made at the expense of consistent reductions in risk-taking behaviors. Combination prevention is desirable, but in a world of limited resources, more spending on PrEP clearly implies less on other effective interventions. Findings from the randomized clinical trials that PrEP is efficacious should mark the beginning of the policy discussion, and not its end. ■

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This commentary was accepted November 4, 2010.

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All authors contributed to the conceptualization of the article, interpretation of data, drafting of the article, and critical revisions.

Acknowledgments

This study obtained support from the UCLA Center for HIV Identification, Prevention and Treatment Services, funded by the National Institute of Mental Health (grant P30 MH 58107; M.J. Rotheram-Borus, PhD, Principal Investigator) and from the California HIV/AIDS Research Program (grant RP08 LA 602).

The authors thank Kevin Farrell and participants in the conference, Preparing for PrEP: A Stakeholder's Dialogue, organized by the Center for HIV Identification, Prevention and Treatment and held on August 23, 2009, in Atlanta, GA.

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