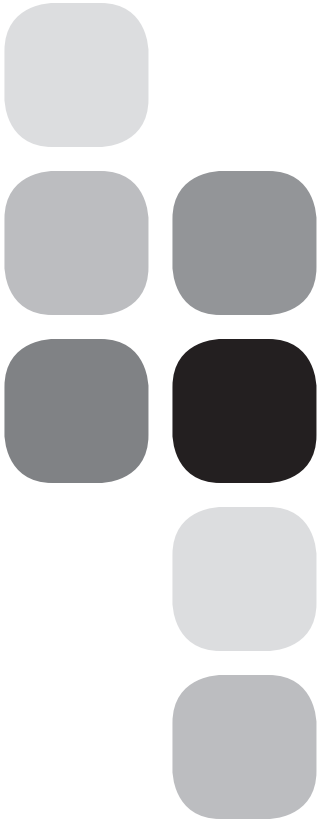

Strategies for Using Pre-Exposure Prophylaxis (PrEP) to Lower HIV Incidence in Select Populations

Policy Considerations and Suggestions of the National PrEP Committee:
Project Inform, AIDS Vaccine Advocacy Coalition, Community HIV/AIDS Mobilization Project, National Alliance of State & Territorial AIDS Directors

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As the number of new HIV infections in the United States holds steady at about 56,300 per year, strategies that supplement behavioral approaches to prevention are needed. In the past year, positive results have come from PrEP, microbicide and vaccine trials. Data related to the potential efficacy of PrEP, in particular, argue for immediate consideration of approaches to its implementation.

Accumulating data strongly support the idea that effective treatment of HIV infected individuals helps to prevent transmission, and the National HIV/AIDS Strategy released on July 13, 2010 is focused on expanded testing and treatment both to improve the health of HIV-positive individuals and reduce HIV incidence. [1] Data from the CAPRISA study strongly suggest that an antiretroviral-based microbicide may be successful in preventing new infections. [2]

Another potential biomedical prevention strategy is oral pre-exposure prophylaxis (PrEP), using antiretroviral drugs, combined with risk reduction counseling in sexually active HIV-negative individuals or those who share drug injection equipment, to reduce the likelihood of acquiring HIV infection. Results from the iPrEx study of gay and bisexual men and transfemales who took TDF (tenofovir) plus FTC (emtricitabine) strongly suggest potential benefits from the implementation of PrEP in these risk populations. (The brand name for TDF is Viread, and the brand name for TDF+FTC is Truvada.) Overall iPrEx efficacy was 43.8 percent. Adjusted for 50 percent adherence to medication or more, it was 50.2 effective. For individuals with 90 percent adherence, efficacy appears to have been 72.8 percent. [3]

PrEP is not a novel idea. Medications are used to prevent other infectious diseases such as malaria. However, PrEP would require longer courses of therapy in many cases, and its administration, which includes ongoing medical observation to monitor for side effects, HIV testing and behavioral counseling, would be much more rigorous.

At the present time, there is an ambitious clinical trial agenda in addition to iPrEx to determine whether PrEP is safe and effective in various populations, with results expected in early 2011 and beyond. [4] The current efficacy studies are evaluating TDF with or without FTC.

This policy document responds to the efficacy of PrEP as demonstrated by iPrEx and anticipates the results of additional PrEP trials. It is intended to present a range of ideas and foster discussion among interested individuals or organizations about PrEP implementation in the United States. It may later inform official proposals for policymakers and guide the implementation of PrEP interventions in the US, assuming that studies continue to demonstrate sufficient safety and efficacy.

Here we offer specific ideas regarding individuals who may be candidates for PrEP, possible sources for its delivery, its financing, and other important considerations for advocates and policymakers. We realize that many questions regarding the use of PrEP will remain unanswered for some time. Therefore, this document is not intended to be comprehensive. Rather, it should provide an immediate framework for stakeholders (including local health departments, public and private medical providers and public and private insurers) to begin considering PrEP implementation as additional clinical trial results become known.

This paper was developed by the National PrEP Committee, established in 2008 by Project Inform, Community HIV/AIDS Mobilization Project (CHAMP), the AIDS Vaccine Advocacy Coalition (AVAC) and the National Alliance of State & Territorial AIDS Directors (NASTAD). The PrEP Committee is a coalition of researchers, public health experts, and HIV prevention and treatment advocates that addresses the research, community engagement/outreach, financing, and implementation issues related to PrEP. The PrEP Implementation Subcommittee looks specifically at the challenges and opportunities related to PrEP delivery and access.

Various stakeholders were consulted in the development of this paper, through conference calls and individual consultations. They included HIV-experienced physicians (with HIV-infected and uninfected patients), representatives of federal agencies, health policy experts from national HIV advocacy organizations, prevention advocates, and physician researchers.

While there are a number of important considerations for the beneficial and judicious use of PrEP, the use of antiretroviral drugs delivered in various ways to prevent HIV infection (treatment as prevention, microbicides and PrEP) represents one of the most promising approaches to HIV prevention under consideration today.

CONSIDERATIONS

Despite the potential for PrEP to be an effective intervention to prevent HIV infection, several significant concerns are likely to remain even after completion of clinical trials and cannot be fully addressed until PrEP is attempted and evaluated in various communities. We discuss these overarching concerns before addressing them and making recommendations.

SAFETY: Data from a trial of the biological and behavioral safety of daily oral TDF use for HIV prevention in gay and bisexual men in three US cities were released in July 2010 and suggested no significant safety issues on the part of participants. An earlier study among young women in Ghana, Nigeria, and Cameroon also provided data showing daily oral PrEP with TDF to be both safe and acceptable for use by African women. Neither study included long-term safety data nor was looking to assess potential effectiveness.

Data exist from the use of TDF in high concentrations for the treatment of HIV suggesting that it can be associated with renal disorders, most often in those at risk for, or with a history of, renal dysfunction. Depending upon the duration of PrEP or how many courses of PrEP one engages in over a lifetime, it is possible to have similar concerns about the safety of PrEP. Current clinical trials are not of sufficient duration to address this question fully and additional data are necessary to establish safety in all high-risk populations. While iPrEx made generally favorable observations about safety of TDF/FTC, no long term studies have been conducted to assess the safety of this medication for use in PrEP.

"Behavioral disinhibition" or "risk-compensation": Concerns have been raised that taking antiretrovirals might lead some individuals using PrEP to think that they do not also have to continue to practice safer sex or syringe use, which could lead to increased risk of HIV exposure. The CDC safety study among gay and bisexual men in the US mentioned above reported that behavioral disinhibition or risk compensation did not occur in this group. iPrEx study participants self-reported increased condom use and fewer sex partners. However, it is important to note that study participants received significant behavioral counseling and reinforcement for safer sex behaviors; more perhaps than will generally be available if PrEP is widely implemented.

Although any future PrEP programs must include a counseling component that reinforces the importance of continued condom use and/or use of sterile syringes for injection drug use, there could be some people for whom ongoing counseling is unavailable or insufficient to reduce and maintain low levels of risk behaviors. These factors could vary for different groups, such as the broad population of gay and bisexual men compared to serodiscordant couples. Therefore, many more data are needed about potential behavioral effects of PrEP among at-risk groups.

DRUG RESISTANCE: Much may also remain unknown until this strategy has been used for some time about the possible development of drug resistance in those who, despite using PrEP, nevertheless become HIV-infected. Experts currently disagree about the potential for drug resistance to develop as a result of PrEP use. Thus far, resistance has not been observed in seroconverters in either of the completed safety trials of PrEP. No participants who seroconverted during iPrEx and were quickly switched to a standard three drug treatment regimen were observed to develop resistance. Three individuals who did develop resistance were later found to have been infected at the time the study began and were not switched to a three drug regimen.

ADHERENCE: iPrEx demonstrated that adherence to a PrEP regimen increases its efficacy. However, there is concern about the ability of PrEP recipients to adhere to the daily oral PrEP regimen. For some individuals, life situations such as a lack of stable housing, mental health or substance use issues, may interfere with adherence to PrEP. Non-adherence could contribute to drug resistance if the virus establishes an infection and continues to replicate while an individual is on a one or two drug regimen that is suboptimal for treatment.

In the ongoing PrEP clinical trials, participants generally have much more support for adherence than may be available in real-life situations where PrEP could be implemented. On the other hand, trial participants are told that efficacy is unknown and that they may be receiving a placebo. Adherence may actually be higher when people taking PrEP in real world situations know that is has been demonstrated to be effective enough to prescribe and that they are receiving actual medication.

COST: Cost will be a major factor in the broad use of PrEP. Daily doses of TDF alone for HIV treatment can cost as much as $7,100 per year and TDF/FTC can cost as much as $14,400 per year, depending upon the source paying for the drug. In addition to the drug itself, an effective PrEP regimen also includes regular HIV testing, ongoing blood work to monitor possible side effects, and counseling, making overall cost quite high. Some of these costs are incurred by HIV-negative people who already test regularly, off-setting the total cost of PrEP. In any case, some prevention advocates are concerned that only people who can afford the drugs or with access to private health care insurance will have access to PrEP, and that the cost of PrEP could cut deeply into other forms of prevention.

EFFECTIVENESS: Willingness to invest in daily oral PrEP as a prevention strategy (by patients, public and private insurers, and public health providers) will also be directly related to the degree of protection that PrEP confers. If PrEP can reduce the chance of infection by some 75 percent or more compared with behavioral strategies alone, its cost may be palatable. However, if it reduces the chance of infection by less than 50 percent, a PrEP regimen may be too costly compared to other prevention methods, except possibly in the highest risk individuals. Nor will PrEP be as appealing to most potential users if its efficacy is low.

Data from clinical trials will have to be evaluated by analyzing clinical efficacy in relation to the entire cost of PrEP delivery to determine the feasibility and cost-effectiveness of widely implementing this intervention in various risk groups and settings. We do not currently make specific recommendations in this regard at this time, although the hopeful results of iPrEx appear to call for decisions sooner rather than later.

PrEP: FOR WHOM AND FOR HOW LONG?

Because of the previously mentioned concerns about safety, adherence, resistance, cost, and delivery, PrEP might ideally be targeted to individuals who are at the highest risk of HIV infection and for whom other interventions (e.g., condom use, behavioral counseling) alone are not effective or realistic. Such individuals might include those in any of the following groups who also have high risk factors:

- Members of high-risk groups who live in locations with high prevalence rates of HIV infection and are therefore more likely to encounter an HIV-positive sex or needle-sharing partner.
- Members of a group where annual incidence is high (e.g., gay and other men who have sex with men; young men and women of color; injection drug users; and male-to-female transgenders)
- Members of a group where community viral load, or the average CD4 and viral load of all treated and untreated HIV-positive individuals in a specific population or jurisdiction, is high.

High risk factors might particularly include self reports of multiple sex partners, particularly with people of unknown or HIV-positive status; engagement in unprotected receptive vaginal or rectal intercourse; history of vaginal or rectal STIs, and concurrent mental health or substance abuse issues.

These suggestions are intended to focus the use of daily oral PrEP in those for whom the intervention would prevent the greatest number of infections. Focusing utilization reduces the risk that PrEP could be *overused* by the so-called "worried well" who have low individual behavioral risk factors or are not especially likely to encounter HIV-positive partners and underused by those who would most benefit from it. To be certain, however, any person who fits within a group that trials show could be protected and requests PrEP should be seriously considered as a candidate for its use as the US seeks to build a toolbox of prevention options for at risk populations.

Because an individual's level of risk is temporal and varies during their sexually active life, PrEP might, in many or most instances, be temporary or episodic and not require lifetime use of prophylactic drugs. By not using daily oral PrEP indefinitely, the likelihood of long-term toxicity and the potential for the development of drug resistance in the subset of individuals who acquire HIV are decreased. Furthermore, the cost of PrEP as an intervention will vary in relation to the length of time it is used.

Individuals considering PrEP should be evaluated for their ability to adhere to treatment and supported to be adherent, if possible. Ability to adhere should not be used as a criterion to

deny access to daily oral PrEP. Instead, individuals may need to be linked to adherence support services, including counseling, mental health and substance use services, housing, etc. to reduce high-risk behavior and increase the likelihood of their adherence to PrEP. Additionally, people who discontinue PrEP may need services to support adherence to other preventive behaviors that obviate the need to begin taking PrEP once again.

IMPLEMENTATION OF PrEP

Results from iPrEx established efficacy of PrEP in gay and bisexual men and transfemales. Results from the PrEP study in IDUs are expected in 2011. These early clinical trials are likely to result in immediate demand for the intervention. The real level of that demand will obviously depend upon recognition of how rigorous the PrEP regimen is, the ability to secure reimbursement for it, and full recognition that this intervention does not replace the need for the ongoing practice of safer sex or syringe use.

The entire health delivery system — from physicians in private practice to community health clinics to private and public insurers — may be asked by HIV-negative people to provide and/or pay for PrEP. It will be important for government agencies and community groups to communicate broadly and thoughtfully to at-risk HIV-negative people about whether and how it is advisable to attempt to access PrEP until a thoughtful and comprehensive implementation program is in place.

Our concerns are that PrEP is implemented in an equitable way so that those who might benefit most receive it, and also that it is available in a manner that does not unduly burden already taxed infrastructures (particularly in the public sector). Physicians are legally able to prescribe PrEP off-label. However, because Tenofovir and Truvada are currently approved only for HIV treatment, it is likely that coverage will be denied for an unapproved use by many private insurers. Access through the AIDS Drug Assistance Program (ADAP) is not possible because, by statute, this already underfunded program only serves HIV-positive people. Other public programs to pay for PrEP medications are not currently available. Some possible short-term ways to implement PrEP in both the public and private sectors are considered below.

First, *priority should be given to highest risk populations in which the greatest benefit has been established as a result of clinical trials.* Appropriate caution must be taken when extrapolating clinical trial results from one population to another. Therefore, implementation should first begin in highest risk populations studied in clinical trials and for whom efficacy has been established. Implementation should also be based upon analysis of issues including background prevalence and incidence levels (discussed above), confidence intervals, subgroup analyses, adherence levels, durability of effect, safety, resistance and others. This approach helps to assure that PrEP is distributed equitably across different populations and communities, rather than just to those who can most afford it.

Local demonstration projects should be rapidly implemented to establish optimal ways to deliver PrEP. The results of iPrEx suggest that CDC and NIH should quickly implement demonstration projects in several diverse jurisdictions throughout the country (perhaps through the newly announced CDC 12-city prevention planning initiative) to assess the feasibility and effectiveness of delivering PrEP to gay and bisexual men and transfemales. Demonstration projects of PrEP in all populations in which studies show efficacy would also help to assure greater equity because they could provide early access to PrEP across several high-risk populations that could benefit from it. They would provide other jurisdictions with information about the logistics and cost of administering PrEP interventions, financing, community and user acceptance, and utilization rates. They could provide early information about the impact of PrEP delivery on existing HIV testing, risk reduction counseling and other HIV prevention and treatment programs. Furthermore, demonstration projects would provide additional information about efficacy, adherence, safety, resistance and impacts on behavior outside of controlled clinical trials. Medicare, Medicaid and other payers would likely consider the results of these demonstration projects as part of their decision-making about whether to cover services of a daily oral PrEP program.

With effectiveness established in clinical trials like iPrEx, some individuals perceiving themselves to be at risk will seek

it out through well-established and trusted community-based clinics funded through federal and/or local health departments, as well as university research programs. These would make ideal sites for demonstration projects. Because they will be called upon to deliver PrEP, as well, it would be beneficial to include private physicians and their patients in demonstration projects in order to assess delivery issues specific to this setting.

The Public Health Service, CDC and other appropriate medical groups should issue guidelines for daily oral PrEP use as soon as efficacy is demonstrated. Given the generally favorable results of iPrEx, and if additional PrEP studies show efficacy, at risk HIV-negative people will want to access it immediately and should not automatically be turned down pending the results of demonstration projects. PrEP guidelines are needed quickly by physicians and could help to further legitimize PrEP, as well as increase the likelihood of reimbursement by private and public payers.

FINANCING PrEP

Early use of daily oral PrEP may be influenced much more by provider and patient acceptance of it than by the decisions of insurers about whether to generally or universally pay for it. However, given the results of iPrEx and the potential for additional PrEP studies to show that this is an effective intervention, at least some HIV-negative individuals will seek it out and advocates will have to work hard to assure that those who would benefit from it can access it. The cost of the drugs themselves, clinical monitoring and adherence support required to support it are significant and will undoubtedly be carefully scrutinized.

Neither Medicare nor Medicaid is likely to be a large provider of PrEP in their current form. In order to be eligible for these programs today, an individual must be of retirement age or disabled, and the vast majority of those at highest risk for HIV infection would not meet those requirements. However, by 2014 when Medicaid has been expanded to cover millions of non-disabled individuals pursuant to health care reform legislation, it could become a significant source of reimbursement for PrEP. Medicare and Medicaid might agree to cover PrEP for low-income patients if a sufficiently high level of efficacy continues to be established, the CDC and/or US Preventive Services Task Force recommend it, and demonstration projects establish its effectiveness and affordability. However, individual states will partially control decisions about reimbursement for PrEP by Medicaid, necessitating both national and state level advocacy for this coverage.

There are anecdotal reports that private insurance companies are currently paying for drugs used for daily oral PrEP (for both short-term and long-term use) in the small number of instances where clinicians are prescribing it off-label. Insurance companies do not necessarily require a diagnosis or indication with prescriptions. If the drugs are on their formulary, insurance companies do sometimes cover their cost. However, most people would be unable to secure payment for PrEP through their private insurers at this time in large part because both Viread and Truvada are currently approved by the FDA for treatment but not prevention purposes.

Health care reform will also expand private health insurance coverage to a significant percentage of individuals who would benefit from PrEP. Since health care reform is essentially an expansion of current health care coverage, with new protections and affordability measures, the same issues that apply to coverage of PrEP today will continue to apply under the new system. In order to assure that insurance companies uniformly pay for PrEP, CDC and US Preventive Services Task Force guidelines recommending it and supporting reimbursement for it, as well as community advocacy to insist upon it, may also be required.

Even if private insurance covers the cost of PrEP, many insured individuals may be afraid to receive it through their own physicians and insurance companies out of fear of judgment about their behaviors. As is frequently the case with HIV testing, some privately insured individuals may be more likely to use PrEP if it is made available through community-based, publicly funded sources. Building and financing a new program of this kind may be difficult in the current economic and political climate, and given concerns about a growing ADAP waiting list. But advocacy to build a distinct funding stream to pay for PrEP for those individuals who are not included in health care reform or who will not rely on their private insurance may be necessary, wise and cost-effective.

Some percentage of existing CDC and SAMHSA HIV prevention dollars should perhaps be redirected from less effective prevention programs to a new PrEP program if this strategy continues to show effectiveness. However, decisions about financing a standalone PrEP program should be made as part of an overall analysis about which HIV prevention interventions are most efficacious and cost-effective in various populations of at-risk individuals.

RECOMMENDATIONS

Based upon the results of iPrEx, and if PrEP continues to demonstrate effectiveness and feasibility as an HIV prevention intervention:

- Government agencies, AIDS service organizations and/or other resources need to be immediately prepared to advise HIV-negative people about whether and how they can access this intervention in the short term as decisions about widespread access are made and programs instituted.
- CDC and US Preventive Service Task Force guidelines should be developed that support the delivery of daily oral PrEP to high-risk HIV-negative people in the populations for whom efficacy and safety have been demonstrated in clinical trials.
- Both public and private insurers should fund PrEP regimens for high-risk individuals in the populations for whom efficacy and safety are demonstrated in clinical trials.
- Sufficient new federal funding should be made available to deliver daily oral PrEP if existing payers fail to cover it. In addition, consideration should be given to supporting PrEP delivery from existing prevention sources.
- Gilead Sciences, the manufacturer of Viread and Truvada should seek FDA approval for use of these drugs for daily oral PrEP, contingent upon ongoing results of clinical trials. Such a label modification would reduce regulatory risks for Gilead, increase physician confidence in prescribing PrEP, and make it easier to gain insurance coverage and additional financing to ensure access for those who need it.

FINAL CONSIDERATIONS

Current PrEP effectiveness studies are evaluating daily use of PrEP as a long-term strategy over the course of 1 or more years in the clinical trial setting. Additional studies of safety, adherence and efficacy of intermittent PrEP use are planned, and these studies are critical to understanding ways to increase acceptance of this intervention, as well as opportunities to decrease cost, drug-related side effects and resistance. A comprehensive PrEP research agenda is needed that puts these different pieces of the puzzle together and will need to be modified on an ongoing basis as more data are collected.

Even if PrEP continues to be shown effective and implementation feasible, very little is known about its acceptability at this point. Few surveys or studies have been done to predict how much interest there would be in PrEP use among members of various risk groups if it were to become available. Very little is known about the concerns, fears, hopes, and misconceptions of those who could benefit most from daily oral PrEP. Despite the availability of hepatitis A and B vaccines as well as non-occupational post-exposure prophylaxis (nPEP) for HIV, these preventive measures have been underutilized in many communities, especially among gay and bisexual men. Furthermore, there is little to no knowledge about acceptance among legislators, policymakers, insurance company decisions makers, etc.

Stigma and politics will likely affect broader support for PrEP, particularly among legislators and policymakers. nPEP, for example, is reimbursed by Medicaid only for victims of sexual assault. Adolescent use of the human papillomavirus (HPV) vaccine met resistance among certain political constituents in the abstinence-only environment that permeates much of America. However, these barriers — which HIV advocates have faced since the beginning of the epidemic— should not prohibit the implementation and financing of a potentially effective public health program. After all, substantial public funds are being used to pay for prevention, care and treatment of a range of medical conditions Americans know how to prevent, but to which they are nevertheless vulnerable.

There are likely to be objections to paying for a costly prevention intervention at a time when those already infected with HIV are not universally able to access comprehensive health care, antiretroviral medications, and social services. However, it could also be argued that it is in the best interest of the ability to finance the care and treatment of existing HIV-positive people to sharply limit continued growth of the epidemic.

PrEP is most likely to gain acceptance among various communities, including AIDS service organizations, if it is thought of as one item in the HIV prevention toolbox — perhaps the intervention of last resort when behavioral change alone is insufficient for the high-risk factors described earlier. Still, a few weeks, months, or even multiple years of daily oral PrEP that prevents an HIV infection and its related complications and significantly higher treatment cost is, in our opinion, something to be quite hopeful about .

People who successfully use PrEP could be spared HIV infection and a life-time of antiretroviral drug treatment, frequent laboratory work, co-morbidities, adjustments to drug regimens, the stigma of HIV infection and an unnecessarily shortened lifespan. Furthermore, the same individuals who are at high risk of acquiring HIV infection may also be at high risk of transmitting HIV should they become HIV-positive and not engaging in effective treatment. Using PrEP to prevent the exponential transmission to multiple individuals and their sex partners may be one way to move toward a remarkable decrease in annual HIV incidence.

SUMMARY

If it continues to be proven efficacious and feasible:

- PrEP might best be recommended for those individuals who are at the highest risk of HIV infection and for whom other interventions (e.g., condom use, behavioral counseling) alone are not effective or realistic.
- Priority in delivering PrEP should be given to those populations studied in clinical trials.
- Because an individual's level of risk is temporal, daily PrEP could, in many or most instances, be temporary or episodic and not require a lifetime of prophylaxis with antiretroviral drugs.
- Additional studies to address short-term use and less-than-daily PrEP regimens are needed.
- Local demonstration projects involving private and public providers should be used to evaluate effectiveness of the delivery of PrEP and related services before more widespread use is contemplated.
- HHS, CDC and appropriate medical groups should issue clinical guidelines for the use of daily oral PrEP as soon as possible.
- Both public and private insurers should reimburse the full cost of PrEP regimens for high-risk individuals. A new federal program funded exclusively to facilitate the delivery of PrEP might be necessary if there are gaps in coverage for this intervention, and existing HIV prevention funds might be looked to to support PrEP programs if it is as effective or more effective than other prevention interventions.
- Gilead Sciences, the manufacturer of Viread and Truvada should seek FDA approval for daily oral PrEP, contingent upon results of additional clinical trials. Such a label change would reduce regulatory risks for Gilead, increase physician confidence in prescribing PrEP, and make it easier to secure PrEP financing. Gilead should also agree to favorable pricing of Viread and Truvada in order to support widespread access to a potentially powerful new prevention intervention.

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1. http://www.projectinform.org/pdf/tlc_caps.pdf2.
2. http://www.caprisa.org/joomla/index.php/component/content/article/1/225
3. http://www.nejm.org/doi/full/10.1056/NEJMoa1011205
4. www.avac.org/ht/d/sp/i/354/pid/354