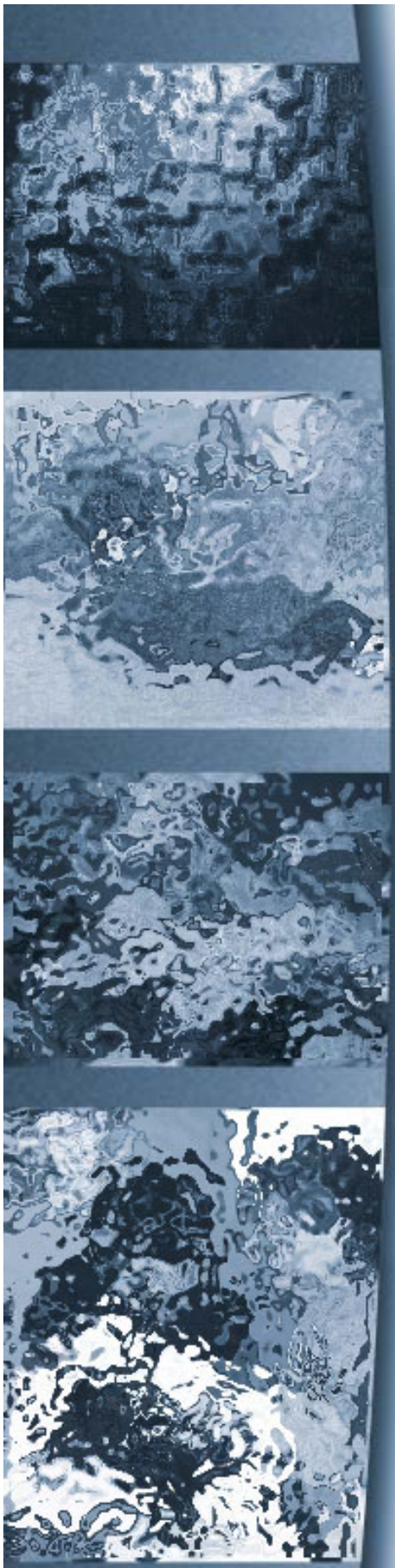

ANTICIPATING THE EFFICACY OF HIV PRE-EXPOSURE PROPHYLAXIS (PrEP) AND THE NEEDS OF AT-RISK CALIFORNIANS

Center for HIV Identification, Prevention, and Treatment Services (CHIPTS)

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November 2004

Funded by:
AIDS Partnership California

APC
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CHIPTS
UCLA • Drew University • RAND • The LA Community
Center for HIV Identification, Prevention, and Treatment Services

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About AIDS Partnership California

AIDS Partnership California (APC) is a statewide public/private collaboration that includes private foundations, corporate funders, and the State Office of AIDS, plus a strategic alliance with CompassPoint Nonprofit Services. Through grantmaking, convening, training, and the dissemination of findings, APC supports the development of a system of HIV prevention for Californians of color with HIV; strengthens the capacity of community organizations to provide HIV services; advances research on the future of the HIV epidemic in California; increases the effectiveness of HIV public and private grantmaking; and supports efforts to shape California's HIV/AIDS-related public policy. Together, these activities aim to help arrest the escalating rate of HIV in California, inform sound policy decisions, and strengthen the system of HIV care and treatment. This work benefits persons with HIV or at risk for HIV, community-based organizations providing HIV services, health departments, and foundations.

About The Center for HIV Identification, Prevention, and Treatment Services

The Center for HIV Identification, Prevention, and Treatment Services (CHIPTS) is a collaboration of researchers from UCLA, Charles Drew University of Medicine and Science, Friends Research Institute, and RAND working with the broader Los Angeles community toward a common goal: to enhance our collective understanding of HIV research and to promote early detection, effective prevention, and treatment programs for HIV. Funded by the National Institute of Mental Health, CHIPTS serves as a bridge among researchers, government, service providers, and people with HIV in responding to the changes in the HIV epidemic and in shaping sound public policy.

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EXECUTIVE SUMMARY

Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection. PrEP should be distinguished from postexposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection. Studies to evaluate the safety and/or efficacy of PrEP among various risk populations in sub-Saharan Africa, Southeast Asia, and the United States are currently being planned or are beginning to enroll participants.

This monograph examines other prominent biomedical prevention strategies, including HIV PEP, prevention of mother-to-child transmission of HIV, hormonal contraception, epidemiologic treatment of sexually transmitted diseases, and malaria chemoprophylaxis, to explore possible parallels with PrEP. An overview of the major PrEP studies that are currently planned or underway is also provided. Five such studies will evaluate the safety and/or efficacy of HIV PrEP among high-risk women (Cameroon, Ghana, Nigeria), high-risk men (Malawi), female sex workers (Cambodia), sexually active young adults (Botswana), injection drug users (IDUs) (Thailand), and men who have sex with men (MSM) (United States). The earliest results of these trials should start to become available in mid-2006.

If PrEP proves to be safe and effective, numerous clinical questions will need to be resolved in order to implement the intervention in California. Issues would include how and by whom the drugs will be administered, how people wanting to use PrEP would be selected, screened, and monitored, and how people who might seroconvert while taking PrEP will be managed. There would be a need to rapidly develop clinical and counseling guidelines that provide recommendations to providers on all aspects of PrEP delivery.

Based on an analysis of who is at risk for HIV in California, a safe and effective PrEP intervention would likely need to be targeted to MSM, female partners of MSM, and IDUs and their partners. Other individuals who might be considered for PrEP would be those placed in situations or locations where risk of HIV acquisition might be heightened for a period of time, such as prisoners, commercial sex workers, or those trying to conceive with a serodiscordant partner.

Any recommendations for using PrEP would need to take its level of efficacy into account, as it is unlikely to be 100% efficacious. Modeling of the potential impact of PrEP on California's HIV epidemic shows that it is extremely unlikely that PrEP will result in the eventual elimination of HIV from at-risk communities. However, the models tested indicate that introduction of PrEP may quickly reduce incidence, with effects on prevalence being less dramatic and over a longer period of time. Potential benefits could be offset if risk behavior increases as a result of PrEP availability or if people on PrEP stop taking medication correctly.

Some prevention and care providers may oppose PrEP, either due to bias against the intervention or from concern about the potential strain on resources; as such, any planning for PrEP implementation will need to include providers and affected communities if it is to be successful.

An effective PrEP intervention would need to be accessible to all at-risk Californians for whom it is indicated. It is not clear how payment for PrEP would be covered, however. Insurers, Medi-Cal, and other payers will need to address how such coverage would occur. The cost-effectiveness model provided in this monograph suggests that PrEP is more cost-effective for individuals who engage in high and extremely high rates of risk behaviors and for instances when the efficacy for PrEP is greater than 50%. Beyond paying for PrEP, other potential barriers to accessing the intervention may include racial and socioeconomic disparity, being a minor, having a mental disability, having undocumented status, clinician bias, and fear of discrimination. These potential barriers will need to be addressed if PrEP is to be distributed equitably.

As the results of PrEP clinical trials will not be available until the studies are completed, and as limitations may exist as to the degree that data from these studies can be generalized to the HIV epidemic in California, it is important that restraint be used in making assumptions about whether PrEP will be appropriate for use in at-risk Californians. Data from currently planned and future studies will be needed before such determinations can be made.

In the meantime, an opportunity exists to consider the critical steps that will need to be taken in California if studies of PrEP prove it to be a viable HIV prevention strategy. Anticipating the key issues likely to be raised by PrEP will facilitate rapid planning and implementation of PrEP programs that are as successful and equitable as possible, if a determination is made that PrEP should be made available to at-risk Californians. A list of recommendations for optimal implementation of PrEP programs in California is provided in Section VI.

Introduction

Significance

Worldwide, approximately 60 million people have been infected with HIV since the beginning of the pandemic, and over 20 million have died. In 2003, there were an estimated 38 million people living with HIV; in that same year, nearly 5 million people became newly infected.[1] As in many countries, HIV infections in the United States are on the rise—an estimated 950,000 people were living with HIV in 2003, up from 900,000 in 2001.[1] Although HIV infections have only been reportable in California since 2002, it is currently estimated that approximately 128,000 Californians are HIV infected (with or without an AIDS diagnosis.)[2,3] There have been over 136,000 cumulative AIDS cases reported in the State through July 2004, with over 80,000 deaths.[3]

Although behavioral interventions (including abstinence, reducing number of sexual partners, partner selection, use of male and female condoms, and needle hygiene) have shown efficacy in preventing HIV infection in diverse populations and settings, they are not always consistently implemented by individuals, are not universally effective, and have not ultimately been able to contain the pandemic. It is widely believed that, in addition to effective behavioral interventions, biomedical approaches to HIV prevention will be required to adequately curb the spread of the virus. The two most prominent technology-based HIV prevention strategies, however—HIV vaccines and vaginal and rectal microbicides—lack candidate agents that are likely to prove successful in the near- to midterm. Other practical options are desperately needed in the meantime.

It is likely that successful HIV prevention efforts will rely on multiple techniques and strategies used in combination. Just as the success of combination antiretroviral therapy relies on multiple drugs that may target more than one step in the viral life cycle, so too might prevention be enhanced by the synergistic use of social, behavioral, biomedical, and barrier methods.

Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention that has recently generated considerable interest. PrEP involves the use of antiretroviral drugs (ARVs) by an individual prior to potential HIV exposure, in order to reduce the likelihood of HIV infection. PrEP should be distinguished from postexposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection. It has been hypothesized that, in various international settings, PrEP could be a viable prevention strategy for certain people at high risk of HIV infection, such as commercial sex workers, those in serodiscordant relationships, and members of high-risk groups who choose not to use condoms or for whom consistent condom use has proved difficult.[4,5] It is not yet known whether PrEP is a safe or effective approach to HIV prevention, however, as studies for its evaluation in several populations are just preparing to begin. These planned studies and future, yet-to-be-planned clinical trials will determine whether and to what degree PrEP is safe and effective. If safety and efficacy are demonstrated, post-marketing (Phase IV) studies will be needed to assess how PrEP gets used in clinical practice.

There are two contrasting positions that might be taken with regard to PrEP. Some might argue that it should be an intervention of last resort, as it requires that healthy people be medicated chronically, or perhaps episodically if the data warrant that the medications be used in that way. Others might counter that it is an intervention that should be added—routinely—to the prevention armamentarium and used for those who do not or will not use condoms, or in combination with other approaches. Data is presented later in this monograph (see "Effects of PrEP on HIV Incidence and Prevalence in California" in Section IV) that demonstrate that population-level effects (ie, reducing prevalence and incidence) might require broad coverage as well as high efficacy. We also present data to demonstrate that PrEP might be cost-effective, relative to other preventive strategies and certainly relative to treatment for particular high-risk populations (see "Cost and Cost-Effectiveness of PrEP" in Section IV). There are likely to be a variety of strongly held positions with regard to PrEP. The goal of this monograph is to provide an overview of the key research issues, as well as the critical clinical, prevention, and economic questions that would need to be addressed prior to any implementation of PrEP programs in California.

Rationale: Examining Other Key Biomedical Prevention Strategies

Use of ARVs as a prevention strategy in people who are HIV negative may seem like a provocative idea, and indeed there are legitimate concerns that arise from such an approach, many of which this report will outline. There are, however, many instances in medicine in which pharmaceutical or biological agents are used to prevent disease. Examples include vaccinations to prevent a host of infectious diseases; prophylactic use of antibiotics, antifungals, and antivirals in people with HIV at risk for opportunistic infections; and the use of cholesterol-lowering drugs to reduce the risk of coronary heart disease. A few examples, because they involve behavior and/or use ARVs, may be particularly illustrative with regard to PrEP. The use of ARVs for postexposure prophylaxis, mentioned earlier, and for prevention of mother-to-child transmission are two key examples from the HIV milieu. Other illustrative examples of the use of pharmaceutical agents in a pre-exposure context are epidemiologic treatment of sexually transmitted diseases (STDs), hormonal contraception, and chemoprevention of malaria.

HIV Postexposure Prophylaxis (PEP)

Postexposure prophylaxis (PEP) emerged as an accepted HIV prevention strategy in a select group of individuals—those with occupational exposures—following the report in 1995 of a nonrandomized, retrospective, case-control study of health care workers having occupational, percutaneous exposure to HIV-infected blood. The study showed that postexposure use of zidovudine (ZDV or "AZT") was associated with an approximate 81% reduction in the odds of acquiring HIV.[6,7] Subsequently, studies were initiated that examined PEP for nonoccupational (ie, sexual and drug use) exposures to HIV. Two studies have shown that it is feasible and cost-effective to deliver PEP to individuals with nonoccupational HIV exposures, predominantly men who have sex with men (MSM).[8-11] One of the studies has shown that PEP attracts individuals who mostly engage in safe sexual or injection practices, experience a lapse, and seek PEP as a result.[8] Moreover, this study showed that it is difficult to deliver PEP in a timely manner following exposure to HIV,[8] perhaps diluting its efficacy.

> *It is widely believed that, in addition to effective behavioral interventions, biomedical approaches to HIV prevention will be required to adequately curb the spread of the virus.*

Several countries, including France,[12] Italy,[13] Spain,[14] Switzerland,[15] Australia,[16,17] and South Africa,[18] have issued official policies that recommend PEP for nonoccupational exposures.[19] In the United States, the CDC has issued guidelines for occupational PEP.[20] Despite the lack of controlled studies evaluating its effectiveness, the CDC has issued less formal recommendations on nonoccupational PEP,[21] although these do not go so far as to advocate its use. State guidelines for nonoccupational PEP have been issued in New York and Rhode Island,[22,23] and Massachusetts has issued a clinical advisory recommending that clinics create protocols that address key PEP concerns.[24] In California, recent legislation has established the structure for preparing and promulgating guidelines for nonoccupational PEP.[25] Recommendations for provision of PEP following sexual assault have also been issued for California.[26] Although some guidelines exist for nonoccupational PEP, the safe and effective delivery of PEP remains complex, and reliable data on the use of PEP in settings in the United States is not available.

Prevention of Mother-to-Child HIV Transmission (PMTCT)

The use of ARVs for PMTCT has perhaps been the most successful HIV prevention strategy to date. Administration of ARVs to an HIV-infected mother during labor (and sometimes earlier in pregnancy as well) and to the infant postpartum has been shown to dramatically reduce the odds for perinatal HIV transmission. A landmark 1994 study of zidovudine (AZT) prophylaxis before, during, and after delivery resulted in vertical transmission rates declining from 25.5% to 8.3%.[27] Since then, similar approaches using nevirapine and combinations of agents in both research and clinical practice have driven vertical transmission rates even lower. The mechanism for this effect likely includes both pre- and postexposure prophylactic components. Pre-exposure prophylactic components include the prevention of cross-placental and intrapartum HIV transmission by lowering the viral load of the mother and, for drugs that cross the placental barrier, by providing drug exposure to the fetus. Administering drug to the infant postpartum comprises the postexposure prophylactic component. The use of antiretrovirals for PMTCT has greatly reduced the number of HIV-positive children born to infected mothers in the settings in which such treatment is available.

Epidemiologic Treatment for Sexually Transmitted Diseases (STDs)

Epidemiologic mass treatment is an approach to STD control in which antibiotics are administered to a population based on increased risk of exposure rather than STD symptoms or test results. As rates of exposure to STDs are typically high in high-prevalence populations, epidemiologic treatment likely works both by preventing and treating infections. Although epidemiologic mass treatment is not currently standard practice in the United Stated, the approach has been studied in diverse international settings for prevention and control of a variety of STDs, including syphilis, gonorrhea, chancroid, and chlamydia.[28] While incidence and prevalence of STDs in high-prevalence populations can be decreased through epidemiologic treatment, they may approach returning to baseline once treatment is withdrawn. The degree to which this approach is effective may depend on the particular pathogen, with some responding better to epidemiologic treatment than others. Continuing treatment, as well as supportive STD services, may be necessary to sustain the benefits. Problems encountered with the approach have included the costs of providing continuous treatment, the potential for development of antibiotic resistance, and difficulties with enlisting the ongoing support and cooperation of affected communities.[28,29] Similar issues arise with regard to PrEP for HIV, and these are discussed in more detail throughout this report.

Hormonal Contraception

A widely accepted model of pre-exposure chemoprophylaxis in the field of sexual and reproductive health can be found in hormonal contraception. Sexually active women of childbearing potential have the option of taking prescription hormonal therapy (synthetic progestin with or without estrogen) as a means of birth control to prevent unplanned pregnancy. Methods of delivery include oral contraceptives ("the pill"), an injectable formulation (Depo-Provera), a transdermal patch (Ortho Evra), and an intravaginal ring (NuvaRing). A subcutaneous implant system (Norplant) was also available until its recent discontinuation by the manufacturer. Hormonal therapy may also be used as postexposure prophylaxis—referred to as emergency contraception—to prevent fertilization or implantation after unprotected vaginal intercourse.[30] The advent of birth control pills in the early 1960s was a watershed event, as the preventive contraceptive method was disconnected from the risk behavior (ie, vaginal sex) for the first time, and contraception subsequently became simpler, more effective, and more widely accepted. If PrEP proves to be safe and highly effective, it could have a similarly profound impact on HIV prevention.

Malaria Chemoprophylaxis

Another parallel to HIV PrEP is the case of malaria, an infectious agent for which chemoprophylaxis is a standard preventive measure. Malaria prevention for travelers to endemic areas combines behavior

modification (avoidance of mosquitoes, protective clothing and nets, application of DEET-containing repellants) with prophylactic drugs (examples include chloroquine, mefloquine, doxycycline, and atovaquone/proguanil). Although the drugs do not prevent infection with the malaria parasite, they can help to prevent clinical illness by killing malaria parasites as they exit the liver and enter the bloodstream. As this event can happen several weeks after infection, malaria chemoprophylaxis is generally continued for a period of time after leaving an endemic area. Taking prophylactic drugs is not a guarantee against malarial illness, however, and the medications may cause significant toxicities in certain individuals and can incur considerable cost. Despite these shortcomings, chemoprophylaxis combined with mosquito-avoidant behavior modification is considered the standard of care for people traveling to malaria-endemic areas, and has allowed them to visit and live in these areas more safely.

Although not a perfect model, Malaria chemoprophylaxis may be able to provide a framework for thinking about HIV PrEP. As with HIV, malaria is a serious, potentially fatal illness for which no effective vaccine currently exists. Both diseases share the characteristic of risk exposure being generally episodic rather than continuous. Malaria chemoprophylaxis is typically used when an individual enters an endemic area; similarly, a chemoprophylactic strategy for HIV may largely be needed when an individual enters a period of high risk (ie, while engaging in commercial sex work or beginning a serodiscordant relationship). In addition, the primary strategy for avoiding infection with both pathogens remains behavior modification—avoiding mosquito bites in the case of malaria, and using condoms and managing sexual partners in the case of HIV. Certainly, the parallels are not perfect. For some individuals at risk of HIV infection, their reality may be one of chronic risk and exposure. In addition, allowing oneself to be exposed to mosquito bites does not bring with it many perceived rewards, whereas having unprotected sex may provide people with pleasure, the perception of increased intimacy, and the ability to reproduce. Thus, the fundamental ways that people approach risk with each condition may differ. While antimalarial drugs have been shown to be an important component of malaria prevention, it is not yet known whether PrEP can be used with similar efficacy for HIV prevention in at-risk populations.

In Summary

Whether or not HIV PrEP will come to play as significant a role in HIV prevention as the use of ARVs for prevention of perinatal transmission, or the use of hormones and chemoprophylaxis, respectively, for contraception and malaria prevention, will largely depend on the outcome of current and future studies evaluating the safety and effectiveness of PrEP as an HIV prevention strategy. It will also rest on how acceptable such a strategy, if effective, is to program planners, care providers, and the public. As with all interventions, a careful risk-benefit analysis would be required to determine in which contexts such an approach would be warranted. This report outlines some of the major PrEP research currently being planned, and highlights many of the key clinical, prevention, and economic issues that should be considered with regard to potential future PrEP implementation in California.

Overview of Planned PrEP Research

As of September 2004, there were several major PrEP studies involving human subjects being planned or currently underway. These studies include investigations of the safety and/or efficacy of PrEP in high-risk women (Cameroon, Ghana, Nigeria), high-risk men (Malawi), female sex workers (Cambodia), sexually active young adults (Botswana), injection drug users (IDUs) (Thailand), and MSM (United States). A summary of these studies is provided in Table 1.

TABLE 1. Major Planned PrEP Studies

Sponsor	Study Location	Population	Enrollment Target	Study Aims	Timeline
FHI/Gates	Cameroon, Ghana, Nigeria	High-risk women	1,200	Evaluate biological safety of TDF for PrEP Assess efficacy of TDF for PrEP Determine acceptability of PrEP among participants, their partners, and the community Identify barriers and facilitators to translating study results into effective HIV prevention planning	Enrollment began in summer 2004 (Malawi to begin in spring 2005). Study to last approximately 2 years.
	Malawi	High-risk men	400		
NIAID	Cambodia (Phnom Penh)	Female commercial sex workers	960	Evaluate safety and efficacy of TDF for PrEP Evaluate safety of using TDF in participants with hepatitis B Assess adherence to study drug Evaluate changes in risk behavior	Scheduled to begin enrollment in fall 2004; currently on hold.
CDC	Botswana	Sexually active young adults	1,200	Evaluate biological and behavioral safety of TDF for PrEP Evaluate efficacy of TDF for PrEP Measure bone density and bone metabolism in subset of your participants Assess adherence to study drug Evaluate TDF resistance in participants who seroconvert Assess acceptability of TDF and study procedures	Study enrollment may begin in fall 2004. The trial is scheduled to last 32 months.
CDC	Thailand (Bangkok)	IDUs	1,600	Evaluate biological and behavioral safety of TDF for PrEP Evaluate efficacy of TDF for PrEP Assess adherence to study drug Evaluate TDF resistance in participants who seroconvert	Enrollment is planned for fall 2004; the study is scheduled to last 30 months.
CDC	United States (San Francisco & Atlanta)	High-risk MSM	400	Evaluate biological and behavioral safety of TDF for PrEP Assess adherence to study drug Analyze effect of TDF on HIV drug resistance profiles in participants who seroconvert	A 9-month recruitment period is scheduled to begin in fall 2004; participants will be followed for 2 years. (Men who seroconvert during the study will be followed for 12 months after diagnosis.)

These studies all make use of tenofovir disoproxil fumarate (TDF) as the investigational PrEP agent. TDF is a prodrug of tenofovir, a nucleotide analogue reverse transcriptase inhibitor, and has been approved by the Food and Drug Administration (FDA) since 2001 in combination with other antiretroviral agents for the treatment of adults with HIV-1 infection.[31] Starting in the mid-1990s, studies with simian immunodeficiency virus (SIV) in macaques, a useful model of human HIV infection, have shown that tenofovir is effective at preventing infection with SIV when used either as pre- or postexposure prophylaxis.[32,33] Research has also been conducted with a topical vaginal tenofovir gel. In macaques, application of tenofovir gel before or after vaginal challenge with SIV protected 100% of the macaques[34]; studies of tenofovir vaginal gel are now underway in humans.[35] As oral TDF is an available agent with relatively low toxicity that can be administered once daily, considerable interest arose in evaluating its safety and efficacy as PrEP for prevention of HIV infection. TDF is discussed in more detail in Section III.

FHI/Gates Study (Cameroon, Ghana, Malawi, Nigeria)

Family Health International (FHI), with funding from the Bill and Melinda Gates Foundation, is conducting a Phase II study of PrEP in high-risk, HIV-negative adults in Cameroon, Ghana, Nigeria, and Malawi. The study is double-blinded, randomized, and placebo-controlled, and consists of a 6-month screening phase, a 6-month recruitment phase, and 12 months' use of study drug for each participant. The endpoints of this study are the safety of using TDF for PrEP (determined by laboratory measures of kidney and liver function and reports of adverse events) and the efficacy of TDF for PrEP in this population (determined by HIV seroconversion). The study is currently powered only to detect a powerful treatment effect; as such it would not be expected to demonstrate efficacy. The study began the screening phase in Ghana in June 2004, and in Cameroon and Nigeria in July of 2004; following screening, 1,200 women will be enrolled and randomized to receive either TDF or placebo. Enrollment began in Ghana and Cameroon in July 2004, and in Nigeria in August 2004; as of September 2004, the sites had enrolled approximately one-third of their planned participants. A site in Malawi, scheduled to start in spring 2005, will enroll 400 high-risk HIV-negative men. Participants in the FHI study will be counseled that this is an experimental procedure and that they may be receiving a placebo. They will also receive instruction in methods of HIV prevention, be provided with condoms, and receive counseling that stresses safer sexual practices. In tandem with this safety/efficacy trial, FHI is conducting overlapping formative research in the study sites with the goals of preparing sites for the Phase II study; determining the acceptability of the intervention among participants, their partners, and the community; and identifying barriers and facilitators to translating the results of the Phase II trial into effective HIV prevention program planning. Study closeout is scheduled for mid-2006, after which trial results will begin to become available.

NIAID Study (Cambodia)

The National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring a randomized, double-blinded, placebo controlled study of TDF for HIV PrEP among female commercial sex workers in Phnom Penh, Cambodia. FHI has collaborated to sponsor the preparatory work for the study. The study would seek to enroll 960 HIV-negative adult women who have received money or gifts in exchange for sex in the year preceding enrollment. Participants would receive TDF or placebo for 12 months. The study would provide condoms and appropriate counseling on HIV prevention to all participants, and would evaluate the safety and efficacy of TDF for PrEP, as well as adherence to study drug and changes in HIV risk behavior. In addition, the study is planning to evaluate the safety of using TDF in participants with hepatitis B. This study was planned to begin in October or November of 2004. In August 2004, however, the Cambodian Prime Minister ordered a stop to the planned trial. Publicly, concerns had been raised by sex worker advocacy groups regarding medical follow-up for trial participants. While the study investigators and sponsors remain committed to working with government and community groups to try to resolve issues of concern, at the time of writing, the status of the trial was unclear.

CDC Study (Botswana)

The prevalence of HIV infection in young adults in Botswana is extremely high—approximately 50% of women aged 25-29 are HIV infected, as are approximately 28% of men in the same age range. Sponsored by the Centers for Disease Control and Prevention (CDC), this randomized, double-blinded, placebo-controlled Phase II/III study of TDF for PrEP will seek to enroll 1,200 male and female participants, with 20% or participants in the 18-19 age group and 80% in the 20-25 age group. Following randomization, participants will be followed on study drug for 12-24 months, and then off drug for an additional 2 months. Oral HIV tests, interviews, laboratory monitoring, and adherence counseling will occur at monthly study visits. Although participants must already be sexually active in order to participate in the study, intensive risk reduction counseling will be conducted quarterly by professional counselors. A subset of participants will receive measurement of bone density and bone metabolism, as studies of very high-dose TDF in young animals was associated with osteopenia (decreased bone mass). The study's Data and Safety Monitoring Board (DSMB) will assess the safety of the study after 100 person-years of follow up to determine whether to enroll additional participants and proceed to Phase III of the study. The trial may begin in fall 2004, and is scheduled to last 32 months. Efficacy data may be available late in 2006.

CDC Study (Thailand)

This CDC-sponsored study is a randomized, double-blinded, placebo-controlled Phase II/III study of TDF for PrEP in 1,600 HIV-negative IDUs in Bangkok, Thailand. Participants will be eligible if they are healthy and report injection drug use in the last 6 months. As with the CDC trial in Botswana, the study in Thailand will be assessing the effectiveness and biological safety of TDF for PrEP, evaluating changes in HIV-associated risk behaviors, and examining adherence to study drug and the development of resistance among participants who seroconvert. Behavioral assessments, laboratory analysis, and physical examinations will occur at screening, baseline, and every 4 weeks during follow up. The study will include 12 months of enrollment, 12 months of follow up, and 6 months of off-drug evaluation. If enrollment begins in fall 2004 as planned, study close-out should occur in early 2007.

CDC Study (San Francisco & Atlanta, United States)

The CDC has plans to begin a randomized, double-blinded, placebo-controlled study of PrEP using TDF in high-risk, HIV-negative MSM in two cities in the United States in the fall of 2004. The study will seek to recruit a diverse sample of 400 MSM (200 each in Atlanta and San Francisco) over a 9-month period, with 2 years of follow up (men who seroconvert during the study will be followed for 12 months after diagnosis). This Phase II extended safety study will examine biological safety (clinical safety and tolerability) and behavioral safety (affect on risk behaviors), and as such will not include an evaluation of efficacy. Participants will be randomized to one of 4 study arms—daily TDF, daily placebo, no treatment for 9 months followed by daily TDF, or no treatment for 9 months followed by daily placebo. Behavioral risk assessments, laboratory monitoring, and physical exams will be conducted at screening, enrollment, weeks 2, 4, 8, 12, and then every 3 months for the duration of the study. Free rapid HIV testing will be provided at each visit, and additionally as often as participants wish during the study. Risk reduction counseling will be conducted at each study visit, and more often if necessary. Adherence to study medication will be assessed, and analysis of any study participants who seroconvert will be conducted to determine if TDF has an effect on the resistance profile of the transmitted virus. Should this study demonstrate safety, a larger efficacy trial in this population would be required to demonstrate its effectiveness. The study is expected to begin enrolling in fall 2004.

<u>In Summary</u>

The major HIV PrEP studies currently planned or underway are designed to evaluate the safety and/or efficacy of TDF when used as PrEP in several high-risk populations. As such, they should be able to answer some key

questions about the potential to use TDF as PrEP, and about the overall acceptability of PrEP as an HIV prevention intervention. Given that these studies are still in the planning stages or have just recently begun, however, final data will likely not be available until mid-2006, at the earliest.

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Currently, only the CDC-sponsored safety study of MSM in Atlanta and San Francisco involves a U.S. population, so while the studies in Africa and Asia are likely to provide useful data on the efficacy of PrEP (and in the case of the African sites on a research outcomes assessment examining the translation of study results into programs), it is unclear to what degree the results of these studies will be useful for evaluating whether PrEP is a viable intervention for high-risk groups in the United States in general or California in particular. It is likely that additional research would be necessary before definitive determinations are made regarding PrEP implementation. Economic and policy analyses might also be required to examine how PrEP programs could be funded, structured, monitored, and evaluated in California, and what the potential economic, social, and medical impacts of such programs might be.

Clinical Issues

The clinical issues that would need to be considered for offering PrEP in settings in California include what drugs to use, what the safety issues are from an individual patient perspective, how the drugs might be administered, how people wanting to use PrEP would be screened and monitored, and what the concerns may be for people who might seroconvert while taking PrEP.

A major issue to be resolved is "who decides?"— is it the patient or the provider or some combination of both? The issues to be decided include who is provided with PrEP, for what indications, and with what types of monitoring. An additional issue is who delivers PrEP. We suspect that there will not be a single answer, and that practice modes and models will vary. Nonetheless, there may be a need for professional and other groups to begin drafting practice guidelines to provide recommendations to individuals and providers in the optimal use of PrEP.

Available Versus Optimal Drugs for PrEP

There are currently 20 antiretroviral drugs approved for treating HIV infection in the United States. In addition, there are four fixed-dose formulations available that combine more than one drug in a single pill. Currently available agents fall into four antiretroviral drug classes: nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTIs), nonnucleoside analogues (NNRTIs), protease inhibitors (PIs), and fusion inhibitors. While all of the available drugs could potentially provide some efficacy as PrEP, not all of them are

ideal candidates. To be ideal for use as PrEP, a drug should be potent, able to be dosed once daily, have a favorable toxicity profile, and not promote development of high-level viral resistance based on a single mutation. In addition, drugs whose mechanisms of action focus on pre-integration phases of the viral life cycle (prior to completion of effective viral integration into host cell DNA) are, at least in theory, likely to be more effective than those that focus on post-integration.

Protease inhibitors have a post-integrational mechanism of action—inhibiting the functional processing of viral proteins. Coupled with a side effect profile that includes possible fat redistribution and lipid abnormalities, this makes PI drugs seem less than ideal as candidate PrEP agents.

NNRTIs may also be problematic in that high-level viral resistance to drugs in this class can be conferred by single mutations, which can be quickly selected when these agents are used alone.[36] This could have implications for people who are exposed to viral strains possessing such mutations, as well as for people who might seroconvert while on PrEP. In addition, the NNRTI nevirapine has caused severe dermatological and liver toxicities in HIV-negative people using the drug as PEP, and has thus been deemed unsuitable for use in PEP.[37]

Fusion inhibitors, the newest antiretroviral class to receive approval in the United States, have a mechanism of action that makes them attractive as possible PrEP drugs—preventing HIV from entering the target host cell. Enfuvirtide, the only drug in this class currently licensed, must be injected intramuscularly twice daily and commonly causes painful nodules at injection sites. Other fusion, entry, and coreceptor-inhibitor drugs are currently being studied and may eventually prove to be more practical to use, both for treating HIV infection and possibly for PrEP. For example, the CCR5 antagonist UK-427,857 can be dosed orally and is currently in development at Pfizer, which has initiated human trials evaluating the safety of the drug and its effect on viral load.[38]

Of the NRTIs, several drugs have characteristics that may limit their potential as PrEP candidates. Lamivudine (3TC) and emtricitabine (FTC) cause few toxicities and may be taken once daily, but both are susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone. Most of the other drugs in this class, including abacavir, didanosine (ddI), stavudine (d4T), zalcitabine (ddC), and zidovudine (ZDV, AZT), are associated with rates and types of adverse effects that may not be acceptable for chronic use in HIV-negative individuals.

Tenofovir disoproxil fumarate (TDF) is the NRTI that is currently most suitable for use as PrEP. TDF is potent, can be dosed once daily, and has a relatively favorable toxicity profile. The drug is not without risks, however, including possible emergence of resistance due to selection of the K65R mutation. TDF is the investigational agent in the major PrEP studies currently planned or underway. TDF was approved by FDA in 2001 to treat HIV infection and is formulated as a once-daily, 300 mg oral tablet (Viread®); a once-daily, fixed-dose combination tablet of TDF and emtricitabine (Truvada™) was approved in August 2004 (both Gilead Sciences, Inc., Foster City, CA).

TDF Safety

The incidence of adverse effects with TDF is low and similar to placebo; gastrointestinal side effects (ie, nausea, diarrhea) are most common. It is important to note, however, that data on TDF safety to date have been from HIV-infected patients, and that unanticipated toxicities could result from chronic use of TDF in uninfected patients, as was the case with nevirapine use for PEP.

Lactic acidosis and hepatic steatosis, serious and potentially fatal conditions that can be caused by NRTIs, have not been reported with use of TDF monotherapy in clinical trials. Post-marketing, however, cases of lactic acidosis (a condition in which the mitochondria in cells generate abnormally high levels of lactate)

have been reported with use of TDF in combination with other antiretroviral drugs, and similar cases of hepatic steatosis (in which fat droplets accumulate in the liver) may exist from combination of TDF with other antiretroviral drugs. There have been cases of renal (kidney) toxicity with TDF, although the majority of these cases were in patients who had underlying systemic or renal disease or were taking nephrotoxic drugs (those which damage the kidneys).

In addition to HIV, TDF has some activity against hepatitis B virus (HBV) but is not approved for use in treating hepatitis B disease, and use of TDF has not been evaluated in HIV/HBV-coinfected patients. There have been reports of severe acute exacerbations of hepatitis B in coinfected patients taking TDF upon discontinuation of the drug.[31] Thus, use of TDF for PrEP would require HBV screening, and should not be used in HBV-infected patients without active involvement of an expert in HBV disease and treatment.
There are relatively few drug-drug interactions involving TDF. The doses of atazanavir and didanosine should be adjusted when coadministered with TDF, but as these drugs are only used for treating HIV, such interactions would not be of concern for HIV-negative people taking TDF as PrEP. As TDF is primarily cleared by the kidneys, caution should be used when taking TDF with drugs that inhibit renal tubular secretion or are themselves eliminated renally. No significant interactions with food or nonprescription, nutritional, herbal, or recreational agents have thus far been reported in the scientific literature, but it is possible that such interactions are yet to be discovered. In cases of renal insufficiency, the dose of TDF needs to be adjusted, and this requires screening and ongoing laboratory monitoring.

TDF is pregnancy category "B"— animal studies have revealed no evidence of harm to the fetus, but there are no adequate, well-controlled studies in pregnant women. As there is interest in evaluating TDF for use in preventing mother-to-child transmission of HIV (intrapartum, early postpartum, and breastfeeding), studies are currently underway and in development to evaluate the safety and pharmacokinetics of TDF in HIV-infected pregnant women and their infants.

As prescription medicines go—and HIV drugs in particular—TDF appears to be a relatively safe agent with few adverse side effects and interactions with other drugs. As TDF has been used in clinical practice in the United States only since 2001 (and in the European Union since 2002), however, it is possible that other notable toxicities, drug interactions, or concerns about resistance will be reported as more people use the drug and more time passes. Also, TDF has to date been evaluated for use in treating people with HIV infection. Studies examining whether TDF is acceptably safe from the risk-benefit perspective of an HIV-negative person using TDF for PrEP are just beginning to get underway. While these studies have a limited follow up period in which to look for adverse effects, it is hoped that the results of these studies will begin to shed light on the safety of using TDF for PrEP.

Provision of PrEP

The PrEP studies described in Section II are providing participants with 300 mg TDF tablets (or placebo) to be taken once daily during the study period. It is not yet known what the optimal strategy is for providing PrEP, should it prove effective, to various populations. How it would be determined whether PrEP use should be episodic or continuous, or for how long use of PrEP should continue for a given population or individual, are questions that are currently unanswerable and may or may not be clarified by currently planned studies.

It is not yet known what the optimal strategy is for providing PrEP, should it prove effective, to various populations.

It cannot be assumed that the mechanisms of drug provision that may work in the controlled circumstances of a clinical trial will necessarily translate into "real world" settings. Many of the groups most at risk for HIV in California, such as IDUs, young people of color, and young MSM, are often those who may be less likely to have health coverage, and this could affect their ability to access PrEP. Agents such as TDF are currently prescription products that require some degree of clinical monitoring, which can be particularly complex in the case of HBV-coinfection or renal insufficiency. Should PrEP prove to be effective, it is unclear whether or how high-risk individuals would be able to access PrEP outside of mainstream health care channels—or even if this would be advisable—as there are few precedents for use of prescription drugs without formal medical oversight. While some of the studies will be tracking adherence to PrEP, drug adherence generally tends to be higher in the research context, and the actual experience in non-research settings and with populations other than those being studied may vary.

Some at-risk individuals may use inappropriate means to acquire PrEP drugs (ie, medication sharing, Internet sales) with the intended purpose of using PrEP while avoiding medical monitoring and behavioral prevention strategies. Active preparation of the care communities and prevention agencies may help limit this, but it is likely that a highly effective result for the PrEP trials will increase the desirability of acquiring the medication among HIV-negative individuals. As in the cases of sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra), Internet sales and sharing of medication are not only possible, but likely. It is unlikely that legal sanctions will prove to be effective at addressing these unauthorized transactions. Strategies that promote the value of integrating behavioral supports that encourage compliance and that facilitate sustained health-related behavior change may increase the utility of PrEP and decrease the occurrence of Internet sales and medication sharing. For example, communities will need to be educated that PrEP will not likely be a "magic bullet" against HIV infection.

PrEP Screening and Monitoring

The goal of PrEP is to prevent HIV infection in high-risk seronegative people. It is important that persons seeking PrEP who are HIV infected be identified, as PrEP is inadequate therapy for someone with HIV infection. PrEP monotherapy could allow for disease progression and limitation of future therapeutic options due to viral resistance. Planned studies of PrEP will screen for HIV infection prior to enrollment; the FHI study in Africa will conduct HIV testing and pre- and post-test counseling during screening, and then repeat HIV testing at monthly follow-up visits for the duration of the intervention. In the U.S. CDC study, HIV testing will occur at each study visit (at screening, enrollment, weeks 2, 4, 8, 12, and then every 3 months for the duration of the study), plus more frequently if a participant wishes.

HIV screening will continue to be necessary should PrEP eventually be offered outside the research setting. Screening for HBV and renal insufficiency will also be necessary for safe PrEP implementation. In addition, engaging high-risk people to evaluate them for PrEP may oblige care providers to screen for other comorbid conditions (such as hepatitis C virus or STDs), and provide vaccinations to prevent hepatitis A and B. An acceptable standard for baseline and follow-up screening for PrEP would need to be developed. As persons accessing PrEP would be doing so through some sort of care mechanism, it is unlikely that HIV testing for this purpose would be anonymous. It may need to be determined whether a requirement for confidential HIV testing in this regard, coupled with California's law mandating reporting of HIV infections, could act as a barrier to accessing PrEP for some of those at high risk for HIV.

If PrEP is implemented, a standard will also need to be developed to address how those taking PrEP will be monitored for adverse effects, and how often such monitoring needs to occur. Clinical trials of PrEP will carefully monitor laboratory values (such as kidney and liver function) and have detailed methods for reporting study-related adverse events. The results of these trials may shed light on the type of monitoring necessary and the required frequency of monitoring. Post-marketing Phase IV studies or other mechanisms for reporting adverse events that may occur if PrEP is implemented will be desirable. A National Nonoccupational HIV Postexposure Prophylaxis Registry was established by the CDC to collect data on drug toxicity and other

variables related to PEP for sexual and drug-use exposures to HIV, allowing providers to send in reports by fax or through the registry's Web site (http://www.hivpepregistry.org). To date, however, this registry has not collected many reports, and so other models to collect such data for PrEP need to be considered.

While it is too early to determine many of the details about the type and frequency of monitoring for HIV infection and PrEP-related side effects required for widespread PrEP implementation in California or other locations in the United States, it is reasonable to expect that the currently planned studies will provide at least some direction in this regard. If PrEP becomes a viable intervention, government or professional bodies should convene expert panels to issue guidelines on screening, toxicity monitoring, and other facets of PrEP management, similar to those that have been issued for other aspects of HIV prevention and care, although whether or not this would occur is subject to conjecture.

Adherence

The issue of adherence will be an important one to explore, both in the research context and, if shown to beeffective, with clinical use of PrEP. The issues with PrEP may be more complex than those encountered in analogous prophylaxis situations, and different from many treatment situations. Malaria prophylaxis, for example, usually requires short-term use while an individual is traveling in an endemic area. Individuals using antiretrovirals for PEP take the medications for a brief period of time only. Those taking antiretrovirals to treat HIV infection are aware that lapses in adherence can lead to resistant virus, the need to change medications, and perhaps disease progression. The two situations most analogous to PrEP for HIV are the use of contraceptives to prevent unplanned pregnancy, and the use of antimalarials for individuals living in endemic areas for long periods of time. Nonetheless, it is impossible, at this point, to specify the kind of adherence necessary for effective PrEP, and it will not be possible to do so until we have good data on the frequency and dosing levels necessary for PrEP to work. Once these parameters are defined, the kinds of support systems needed to ensure that individuals take PrEP in a way to maximize efficacy will become clearer.

Seroconversion During PrEP

In the planned PrEP trials, regular monitoring for HIV infection serves as a determinant of the efficacy of the intervention. It also provides the opportunity to discontinue study drug quickly if a participant becomes HIV infected while enrolled in the study, and to refer the participant to appropriate counseling and care. The efficacy of PrEP is not yet known. If PrEP is not 100% effective when used properly, or if doses are missed, then it is possible that people may still seroconvert while taking PrEP. In the case of PEP, Roland et al found a substantial number of seroconversions among those taking ARVs for nonoccupational PEP.[39] Cases of seroconversion despite occupational PEP have also been reported.[40-43] Ideally, someone taking PrEP who seroconverts would be identified as soon as possible following infection so that the person could be immediately evaluated for optimal clinical management. As monotherapy is not suitable for treating HIV disease it is likely that, in a case of seroconversion, the PrEP agent would be discontinued or substituted with combination antiretroviral therapy, depending on the needs and preferences of the patient.

It is possible that taking PrEP could affect disease course in cases of subsequent seroconversion. PrEP could have an impact on HIV resistance patterns in those taking it who seroconvert. The selection of the K65R mutation in HIV-infected patients taking TDF in combination with other antiretroviral drugs has been seen with increasing frequency.[44] Additionally, if PrEP use resulted in significant transmission of TDF-resistant viral strains, it could reduce the drug's effectiveness as both a therapeutic and prophylactic agent. Some have speculated that, should HIV infection occur while taking PrEP, the presence of antiretroviral drugs in very early infection may reduce HIV-mediated destruction of virus-specific T-cell clones, thus helping to preserve antiviral immunity. While some data in primates may lend support to this theory, such attenuated disease has not been seen in health care workers who have seroconverted while taking PEP for occupational exposure to HIV.

In Summary

The primary goal at this stage is for clinical trials of PrEP to get underway and produce high-quality safety and efficacy data over the next couple of years. Results of the studies will be eagerly anticipated and closely followed. Should studies determine that PrEP is safe and effective, care will need to be taken to ensure that people who use PrEP in real world settings are adequately screened and monitored, that appropriate strategies for supporting adherence are available, that any effects on subsequent seroconversion while on PrEP are considered, and that the potential risks and benefits to a given individual considering PrEP can be weighed as for any medical intervention.

Prevention Issues

Target Populations for PrEP

In the United States and in California, racial and ethnic minorities are at high relative risk for HIV infection (Table 2).[45] California is second only to New York in the cumulative number of AIDS cases reported through December 2002 (128,064 in California compared to 155,755 in New York).[45] California demographics differ somewhat from national demographics (Table 2).[45-47]

TABLE 2. AIDS Cases by Race/Ethnicity: United States & California

	United States AIDS Cases[a]		**California AIDS Cases**
	Through 2002		*Through July 2004*[b]
African American	39%		18%
Asian/Pacific Islander	<1%		2%
Caucasian	41%		58%
Latino	18%		22%
	In 2002		*In 2003*[c]
African American	51%		20.6%
Asian/Pacific Islander	1%		3.5%
Caucasian	31%		40.5%
Latino	17%		34.4%

Sources

a. Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention. HIV/AIDS Surveillance Report: Cases of HIV Infection and AIDS in the United States, 2002. CDC; 2003.

b. California Department of Health Services, Office of AIDS. AIDS Reporting Registry: Surveillance Report for California, July 31, 2004.

c. California Department of Health Services, Office of AIDS. California - AIDS Cases Reported from January 1, 2003 through December 31, 2003. Data query performed by Office of AIDS, August 2004.

Gender distribution differs in California from the rest of the nation as well (Table 3). It is important to note that a substantial proportion of AIDS cases among minorities in California are among MSM or MSM-IDU. A breakdown of AIDS cases in men in California in 2003 is given in Table 4.

TABLE 3. AIDS Cases by Sex: United States & California

	United States AIDS Cases (in 2002)[a]	California AIDS Cases (in 2003)[b]
Male	74%	87.3%
Female	26%	12.7%

Sources

a. Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention. HIV/AIDS Surveillance Report: Cases of HIV Infection and AIDS in the United States, 2002. CDC; 2003.

b. California Department of Health Services, Office of AIDS. California - AIDS Cases Reported from January 1, 2003 through December 31, 2003. Data query performed by Office of AIDS, August 2004.

For AIDS cases in women reported in California in 2003, HIV was almost always acquired through heterosexual transmission or injection drug use, although there remains a substantial percentage of cases in which the risk behavior group is "unknown." Table 5 provides a breakdown of AIDS cases in women in California in 2003.

Prevalence estimates indicate that HIV remains concentrated primarily in individuals in specific risk behavior groups—MSM, IDUs, or their combination. Estimates of the number of MSM in California range from a low of 400,000 men who identify as gay or bisexual to 800,000 men who have ever had sex with another man.[48,49] Approximately 200,000-300,000 Californians are injection drug users.[49,50] Rates of new HIV infections from counseling and testing settings in California have also remained stable or decreased slightly since 1990, with the rate of incident infections across the State hovering above 1%. Among MSM, the group at highest risk for new HIV infection, however, incidence rates remain at 3-4%.[51] There is no indication that HIV is migrating from groups of individuals who engage in these behaviors to the general population. A prospective, NIDA-funded cooperative agreement with UCLA, Research Triangle Institute, RAND, University of Illinois at Chicago, and Yale University is underway to study incident infections in these core risk groups, the sexual partners of these core-group individuals, and the sexual partners of these adjacent individuals to address the question of diffusion of HIV transmission from individuals with known HIV risks to those with no known risks.

Methamphetamine use, along with use of other drugs and alcohol, is strongly linked to high-risk behavior and the acquisition of HIV among MSM. The most recent example of this comes from Project Explore.[52] Colfax et al determined that substance use during sex was independently associated with increased sexual risk in this cohort. They found that the following substances used just before or during sex increased the probability of serodiscordant unprotected anal intercourse: alcohol (OR 1.11 per drink), inhaled nitrites ("poppers") (OR 1.9), amphetamines (OR 1.5), and sniffed cocaine (2.4).[53] In a follow-up analysis using only MSM from San Francisco, Colfax et al found that high-risk sex (unprotected anal sex with an HIV-infected or unknown-status partner) over time increased during times that use of methamphetamines, inhaled nitrites, or sniffed

TABLE 4. AIDS Cases in Men in California in 2003

Among Men	
MSM	65.4%
MSM-IDU	7.6%
IDU	9%
Heterosexual	4.8%
Unknown	12.3%
Among African American Men	
MSM	48.8%
MSM-IDU	6.6%
IDU	16.6%
Heterosexual	6.8%
Unknown	20.4%
Among Asian/Pacific Islander Men	
MSM	70.9%
MSM-IDU	4.1%
IDU	4.1%
Heterosexual	7.0%
Unknown	5.3%
Among Caucasian Men	
MSM	73.7%
MSM-IDU	10.1%
IDU	7.4%
Heterosexual	2.6%
Unknown	5.3%
Among Latino Men	
MSM	63.7%
MSM-IDU	5%
IDU	7.2%
Heterosexual	6.3%
Unknown	16.6%

Source

California Department of Health Services, Office of AIDS. California - AIDS Cases Reported from January 1, 2003 through December 31, 2003. Data query performed by Office of AIDS, August 2004.

TABLE 5. AIDS Cases in Women in California in 2003

Among Women	
Heterosexual	47.2%
IDU	23.7%
Unknown	25.4%
Among African American Women	
Heterosexual	43.4%
IDU	27.7%
Unknown	26.2%
Among Asian/Pacific Islander Women	
Heterosexual	65.4%
IDU	0.0%
Unknown	23.1%
Among Caucasian Women	
Heterosexual	43.6%
IDU	38.7%
Unknown	16.0%
Among Latina Women	
Heterosexual	52.1%
IDU	11.6%
Unknown	31.7%

Source

California Department of Health Services, Office of AIDS. California - AIDS Cases Reported from January 1, 2003 through December 31, 2003. Data query performed by Office of AIDS, August 2004.

cocaine also increased.[54] Finally, Koblin et al examined predictors of seroconversion in the Project Explore cohort. The use of amphetamines accounted for 17.4% of seroincidence, with an adjusted hazard ratio of 2.11. Heavy alcohol use accounted for 5.5% of seroconversions, with an adjusted hazard ratio of 1.81.[55]

Mental health variables have also been associated with high-risk behavior and with seroconversion. Again, in the Project Explore cohort, depression accounted for 15.3% of the seroconversions, with an adjusted hazard ratio of 1.42.[55]

Many of the cases of HIV transmission among injection drug users may be caused by sexual activity. Kral et al conducted a nested case-control study of IDU seroconverters and control subjects who remained seronegative. Men who had sex with men were 8.8 times more likely to seroconvert than heterosexual men. This could be because of the drug of choice (methamphetamines) and also because of sexual transmission. Another predictor of seroconversion among female IDUs in San Francisco was having traded sex for money (OR 5.1); women who had a steady sex partner who also injected drugs were 68% less likely to seroconvert than women without a steady sex partner.[56] Similar findings about sexual transmission being the predominant mode of transmission among injection drug users have been found by Strathdee et al[57,58] and other studies pointing to risks of seroconversion among sex workers.

Immigration is also an important consideration for the HIV epidemic. In Los Angeles, for example, 24% of persons living with AIDS as of 1999 were born outside of the United States.[59] In a recent study of STD clinics run by the Los Angeles County Department of Public Health, analyses of data from blinded HIV testing of 61,120 specimens for routine syphilis testing revealed that 38% of clients were born outside of the United States. The majority (87%) were from Mexico or Central America, with no difference in HIV prevalence between U.S. and foreign-born clients.[60]

Finally, diagnosis with an STD is an important marker for those at risk for HIV acquisition. In the Project Explore cohort, Koblin et al found that prior self-reported gonorrhea accounted for 4.2% of seroconversions, with an adjusted hazard ratio of 2.41.[55]

From these analyses, PrEP in California would need to be directed at the following groups:

- MSM, particularly:
    - MSM of color, particularly Latinos and African Americans
    - MSM who are also IDUs
    - MSM who use alcohol, methamphetamines, or other drugs
    - MSM diagnosed with an STD
    - MSM who report depression
- Female sexual partners of MSM
- IDUs
- Sexual partners of IDUs

Other individuals who might be considered for PrEP would be those being placed in situations or locations where risk of HIV acquisition might be heightened and PrEP use potentially considered for a period of time, for example:

- Persons in serodiscordant relationships
- Persons wishing to conceive with a serodiscordant partner
- Prisoners, while they are incarcerated
- Commercial sex workers, while they are engaged in sex work
- Actors in adult films, while they are filming
- Relatively low-risk persons traveling to areas of high prevalence when sexual activity is possible

Additional research may be needed to determine, based on specific risk behaviors, which individuals within these populations might be especially good candidates for PrEP. It should be emphasized that, if it is shown to be effective, use of PrEP among risk populations is likely to have the most benefit when it is promoted as part of a comprehensive prevention strategy that includes condoms and other methods of risk reduction. PrEP is unlikely to be 100% effective, either due to inherent limitations with the approach or to lack of proper adherence.

PrEP at Varying Efficacy Levels

As PrEP is unlikely to be 100% efficacious, any recommendations for its use would need to take its level of efficacy into account. An analogy can be made between PrEP and preventive HIV vaccines. Much theoretical work has been conducted to attempt to understand the relationships between vaccine efficacy, range of coverage, projected increases in risk behavior, and epidemic control. We believe that those results are instructive here, perhaps even more so than attempts to understand the relationship between antiretroviral use among HIV-infected individuals, reductions in infectiousness, and spread of HIV, as in modeling conducted by Velasco-Hernandez, et al.[61] In the absence of any specific current knowledge regarding the efficacy of PrEP, we must rely on assessments of varying levels of PrEP efficacy.

There are two potential scenarios to consider—the impact on the individual and the impact on the community. Anderson and Garnett outline several parameters to define impact on the individual and the community[62]:

- Apparent efficacy—the percentage of individuals who appear to be immunized (in the case of a vaccine) or the percentage who achieve sufficient blood levels of the medication (in the case of PrEP)
- Duration of protection (relevant for vaccines and also relevant for PrEP)
- Vaccine (or drug) failure rate—fraction of vaccinated (or medication-taking) individuals who become infected when exposed to the virus
- Ratio of the infectiousness, if infected, of vaccinated (or PrEP-using) individuals (ie, have "broken through" vaccine or PrEP), relative to that of unvaccinated (or non-PrEP using) individuals
- Ratio of the length of the average incubation period of HIV in infected vaccinated (or PrEP-using) individuals (ie, have "broken through" vaccine or PrEP), relative to unvaccinated (or non-PrEP using) persons

These modelers demonstrate that the impact of an intervention on a community also requires calculating the basic reproductive rate of the virus determined by changes in sexual behavior after the introduction of an intervention like PrEP, the partner exchange rate in the population, sex acts per partner, and sexual mixing patterns. For a vaccine with 80% efficacy, assuming individuals do not change their behavior as a result of the introduction of the intervention, and with life expectancy of sexual activity set at 35 years, eradication of the virus is not possible. The same could hold true for PrEP.

Nonetheless, benefits can accrue to communities even with vaccines of lower efficacy. Low coverage with a highly efficacious vaccine (or PrEP) can have a substantial impact on endemic prevalence, as can high coverage with a vaccine (or PrEP) of low efficacy. Further, encouraging the use of an effective PrEP strategy in combination with other prevention approaches could have a synergistic effect that provides significant benefit.

Even with widespread use, however, PrEP might not have benefit if it is of low efficacy and risk behavior increases substantially. Katz et al examined the relationship between the introduction of highly active antiretroviral therapy (HAART) and HIV seroincidence among MSM in San Francisco. It was concluded that any decrease in per-contact risk of HIV transmission due to HAART use appears to have been counterbalanced or overwhelmed by increases in the number of unsafe sexual episodes.[63] Thus, in this case, other prevention behaviors were reduced with the use of ARVs. It will be necessary to address this issue should the roll-out of PrEP be desirable. The potential effect of PrEP on risk behavior and on HIV incidence and prevalence in California is discussed below.

In the individual case, a highly efficacious PrEP medication would be required to protect individuals engaged in sexual relations with many partners, or engaged in high-risk practices (eg, unprotected receptive anal or vaginal intercourse) with high-risk partners (eg, individuals known to have or HIV, or whose HIV serostatus is unknown but where exposure to and infection with HIV is highly likely). A less efficacious PrEP medication might be useful if individuals combined it with other known forms of protection, such as condoms.

Effect of PrEP on Risk Behavior

Two precedents are illustrative in examining the potential for PrEP to lead to increased risk behavior: postexposure prophylaxis (PEP) and the introduction of HAART into communities.

Evidence of the impact of the introduction of PEP is informative but far from definitive. The available data show that PEP does not appear to increase risk behavior among those receiving it in conjunction with 5 sessions of risk reduction counseling. Martin et al examined whether or not use of PEP lead to increases in risky sex. They followed 397 adults with a high-risk sexual or drug-use exposure and found, after 12 months of follow-up, that the majority of participants did not request a repeat course of PEP (83%). Compared with baseline, 73% of participants reported a decrease in the number of times they had performed high-risk sexual acts, and 13% reported no change.[64] The Praca Onze Study Team in Brazil, which used a counseling protocol that included detailed individual discussions on high-risk exposures, the expected side effects of antiretroviral drugs, and the lack of data on the efficacy of PEP, reported similar findings.[65] Very early in the evaluation of PEP in San Francisco, Waldo, Stall, and Coates examined the impact of the availability of PEP on sexual risk behavior in MSM, and found that hearing about PEP was not related to sexual risk taking, with only a small percentage self-reporting that PEP had the effect of increasing their sexual risk behavior.[66] These precedents may or may not apply to PrEP, as most individuals requesting PEP were relatively low risk, and sought PEP after a lapse in safe sexual or injection practices.[8]

The evidence on the introduction of HAART causing increases in risk behavior is also informative and important to consider. The potential benefits of PrEP on reducing HIV incidence may be short lived if individuals receiving PrEP increase their risk behaviors, particularly if PrEP is only modestly efficacious and there is low coverage in the population. There have been a plethora of reports showing that increased sexual risk-taking, a resurgence of sexually transmitted infections, and increases in incidence of HIV among MSM were reported in San Francisco, the United States, Canada, the United Kingdom, France, the Netherlands, and Australia following the introduction of HAART.[67-71] Reductions in worry about HIV were correlated with increases in risk taking. Katz et al were able to demonstrate the correlation between the introduction of HAART and increases in risk behavior.[63] Focus groups conducted in California by Morin et al to identify perceptions of why HIV risk-taking had increased found the following: (1) HIV is not the threat it once was due to more effective therapies, (2) communication about HIV has decreased among MSM, and social support for being safe has also decreased, and (3) community norms shifted such that unsafe sex was more acceptable.[72]

These implications are important. It will be necessary to study individual and community reactions to PrEP and to determine how to implement it, so that it does not lead to discarding other prevention approaches.

A difficulty, however, is that its use may be simpler for some than condoms or other prevention approaches, and may be favored. It may also become difficult to send complex messages about combination prevention strategies. Finally, economic pressures may reduce spending for traditional condom promotion and other prevention activities in favor of PrEP.

Effects of PrEP on Incidence and Prevalence of HIV in California

The potential effects of PrEP on the HIV epidemic in California can be modeled to the extent that the use of PrEP is analogous to a short-lived, partially effective vaccine with multiple doses required to confer protection. Although modeling of the HIV epidemic has historically not been able to be as accurate as modeling for conditions such as vaccine-preventable childhood illnesses, it can still be useful in estimating the impact of interventions and other variables on the course of the epidemic. We developed modeling equations to test varying assumptions about PrEP efficacy and its impact on the basic reproductive number, a commonly used measure of vaccine efficacy. The reproductive number can be considered as the average number of secondary infectious cases generated by a single infectious case over the entire course of infection in a wholly susceptible population. If the basic reproductive number can be reduced below 1, then infection will eventually die out (the basic reproductive number for HIV in San Francisco has been estimated at between 2 and 5.)[73] The basic reproductive number in the presence of PrEP is related to the fraction of the population treated with PrEP (coverage), the degree of protection provided by the PrEP medication (apparent efficacy), and a variable that describes change in one of the parameters of the basic reproductive number following the introduction of PrEP, for example, changes in the numbers of partners.[73,74]

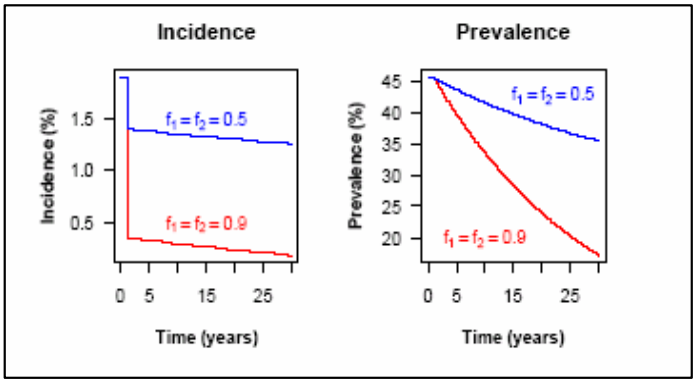
Modeling results indicated that for PrEP to reduce the basic reproductive number below 1, both the coverage and the degree of protection would have to be extremely high (>90%), especially in situations where the basic reproductive number is high, which are the circumstances for which PrEP has been proposed. Hence it is extremely unlikely that PrEP will result in the eventual elimination of HIV from any of the at-risk communities in California. Still, it is worth noting that the models tested indicate that introduction of PrEP may quickly reduce incidence, with effects on prevalence being less dramatic and over a longer period of time.

It will be necessary to study individual and community reactions to PrEP and to determine how to implement it, so that it does not lead to discarding other prevention approaches.

The models tested the dynamics of incidence and prevalence using a number of explicit assumptions regarding the natural history of HIV within a population. These are: (1) the population is homogenous with rates of risky behaviors the same for all individuals; (2) individuals enter the community at a certain rate and leave the population (by death/immigration) at a per-capita rate; (3) there is a short period during acute infection (average 2 months) when the transmission probability is higher followed by a longer asymptomatic period (average 12 years) during which the transmission probability per act is low; (4) individuals become infected at a rate proportional to the number of individuals with acute and chronic infection, weighted by their infectiousness; (5) PrEP is introduced in two waves—first, a proportion of individuals in the community initiate PrEP; second, as new individuals enter the community, a proportion initiate PrEP; (6) treated individuals have a lower probability of being infected per contact.

Figure 1 presents outcomes for models of PrEP on HIV incidence and prevalence in a population with 45% prevalence and 2% incidence. Modeling results were calculated based on a pessimistic scenario (coverage and degree are 50%) and an optimistic scenario (coverage and degree are 90%). A fraction of uninfected individuals initiate PrEP at year 1 in the simulation, after which a fraction of individuals entering the population initiate PrEP.

FIGURE 1. Outcomes for models of PrEP on HIV incidence and prevalence in a population with 45% prevalence and 2% incidence, based on a pessimistic scenario (coverage and degree are 50%) and an optimistic scenario (coverage and degree are 90%)



The models assume that PrEP is administered to individuals entering the population and that individuals take PrEP throughout their sexual lifetimes. A more pessimistic scenario involves a single rollout of PrEP, with no sustained PrEP of new individuals entering the population, and this results in a slow increase in incidence, following an initial drop. The most dramatic effect is seen when individuals stop taking PrEP while still practicing risky behavior. In such a model, the drop in incidence is reversed almost entirely after five years, and the effect on prevalence is negligible. Moreover, these models suggest that although PrEP has the potential to reduce incidence dramatically even at low levels of coverage and efficacy, decreases in incidence can easily be overturned by increases in risk behavior and by failure of individuals to comply with PrEP. While the probability of drug resistance emerging in an individual on PrEP exposed to HIV is likely low, the emergence of drug resistance would be accelerated if individuals continued with PrEP following infection, if individuals failed to comply with the PrEP regimen, and if individuals were not tested for HIV frequently. There is always a risk that the resulting drug-resistant virus could be transmitted to individuals on PrEP at a higher frequency than drug-sensitive virus.

Potential Opposition from Prevention and Care Providers

Resistance to implementing PrEP could come from providers if it results in decreases in funding for organizations or traditional prevention programs that could occur if limited resources in California require the diversion of funds for PrEP from other prevention strategies. A similar outcry has occurred with the CDC's shifting of funds from traditional programs to programs emphasizing HIV counseling and testing and a focus on prevention for positives.[75-77] It may not be possible to distribute PrEP through typical prevention channels, as it is a medical intervention that would require a prescription and clinical screening and monitoring. Issues of cost and financing for PrEP medications and services are discussed in Section V.

Opposition could come from prevention providers who fear that the entirety of HIV prevention will be "medicalized," avoiding difficult issues such as condom promotion for high-risk groups, comprehensive sex education for adolescents, needle and syringe exchange for injection drug users, and outreach to individuals in high-risk environments. Favorable funding allocations should be considered for providers capable of delivering supportive behavioral prevention interventions, in which PREP is only one part of a comprehensive risk-reduction strategy aimed at keeping HIV-negative people uninfected.

Care providers may also oppose widespread implementation of PrEP, particularly if additional resources are not available. Many research efforts are being focused on technological prevention strategies including, in

addition to PrEP, male circumcision, microbicides, routine voluntary counseling and testing for HIV, use of acyclovir, the diaphragm, and use of antiretrovirals to reduce infectiousness. None of these strategies are likely to approach the traditional goal of vaccines, namely nearly perfect protection against infection and disease. This will mean that these strategies will inevitably have to be used in combination, and together with more traditional behavioral and social prevention strategies. Medical providers might fear that the entire prevention effort will fall entirely on their shoulders, and that the task is impossible without additional resources or better reimbursement rates for clinical visits.

Agencies serving minority populations might well oppose PrEP, as the populations they serve are the same populations that have limited access to medical services and, as such, are less likely to have access to PrEP through regular medical providers. Any plan for implementing PrEP must take into account the needs of minority communities and populations, and figure out how to ensure that PrEP reaches those most in need of prevention.

In Summary

Based on available data regarding populations at high risk for HIV infection in California, some speculation can be made as to what groups might be good candidates for PrEP if it is shown to be safe and effective. Ultimately, however, data from planned PrEP studies will be needed before it can be determined for whom PrEP is an appropriate strategy. Further studies may be necessary to elucidate, within risk groups, what specific risk behaviors might make one eligible for PrEP. As with HAART, it is possible that an effective PrEP therapy could increase individual and/or community risk behavior, thereby reducing the effectiveness of the intervention. The degree to which PrEP is effective on a biological level, and the extent to which coverage of the therapy is extended to those at risk, will be important determinants of how PrEP affects the incidence and prevalence of HIV in California. Opposition to PrEP may arise from a variety of prevention and care providers, either from bias against the intervention or from concern about the potential strain on resources. Any plans to implement PrEP will need to include providers and affected communities if they are to be successful.

Issues of Economics and Access

Paying for PrEP

The outcomes of the PrEP studies currently being planned and implemented will likely influence the degree to which widespread adoption of PrEP for Californians at high risk for HIV infection is considered. For developing countries with high prevalence of HIV infection, study outcomes indicating that PrEP is safe and effective may lead to consideration of provision of lifelong chemoprophylaxis for large portions of their populations. The relatively low costs and low risks of this approach may be preferable in countries unable to provide lifelong combination treatments for most of those who become infected.[4]

There is not a high-prevalence, generalized HIV epidemic in the United States as there is in some African and Asian nations, and so there is likely to be debate in California over whether the costs for paying for biomedical prevention approaches are justifiable. There are cost benefits from avoiding HIV infections, including contributions to the tax-base from uninterrupted productivity and avoidance of costs to the AIDS Drug Assistance Program (ADAP) and Medi-Cal for each individual who remains HIV negative. If PrEP demonstrates a high degree of efficacy in preventing HIV infection, there will be a need to rapidly determine which people the intervention should be offered to. PrEP must be accessible to all Californians for whom it is deemed appropriate. Questions remain, however, as to how such coverage would be provided. A substantial number of Californians have reduced access to or minimal coverage of health care

that may restrict access to PrEP—it is estimated that 18% of California adults aged 18-64 were uninsured in 2001.[78] The role of the State in ensuring PrEP coverage may include covering the costs for the medication and medical monitoring using Medi-Cal or ADAP. This may be difficult, however, as these programs are already strained, and ADAP is currently only configured to provide medications to those with an HIV diagnosis.

It is unknown whether the FDA would approve a labeling change for TDF to include prevention of HIV infection, based on the studies currently being fielded. While all of the currently planned studies are being conducted with standard ethical and study monitoring procedures that would facilitate consideration by regulatory authorities in many countries, only the NIAID Cambodian trial currently meets FDA investigational new drug (IND) specifications, and at the time of writing, this study was on hold. While clinicians would be free to prescribe TDF "off-label" for PrEP, the lack of inclusion of HIV prevention as an FDA-approved indication could affect the willingness of insurers to cover TDF for PrEP. Inoculation against diseases using vaccines is routine in the United States, with the costs for these inoculations typically borne by most insurance companies and health maintenance organizations. One reason contributing to this is that the approach is extremely effective in preventing the occurrence of disease and related costs, thereby justifying the coverage. Should trials demonstrate that PrEP effectively prevents acquisition of HIV infection, there would be some precedent for insurance companies and health maintenance organizations covering the costs of providing PrEP medication and monitoring, although this comparison is far from perfect—inoculations are generally given once or a few times, whereas PrEP may need to be taken daily, and paid for, for long periods of time. It remains to be seen what policies companies would enact with regard to such coverage.

Cost and Cost-Effectiveness of PrEP

The cost and cost-effectiveness of PrEP are important factors in considering the value of the intervention as part of a comprehensive HIV prevention strategy in California. The expected yearly per-case cost for TDF ($6,292/yr) was calculated using the average of the retail charges for one month (30 tablets) of TDF as quoted by three large pharmacies in California. While it is likely that insurance companies and other large-scale payers for PrEP may successfully negotiate a lower yearly per case cost (which would lead to a lower cost-effectiveness estimate), use of the retail cost provides an estimate that is at the higher bounds.

The cost-effectiveness of PrEP was estimated as the cost to avert one infection given varying levels of apparent efficacy of PrEP (between 30% and 75% effective) and given varying levels of frequency of commission of a limited set of sexual risk behaviors over a one-year period (unprotected receptive anal intercourse, unprotected insertive anal intercourse, receptive anal intercourse with condom, insertive anal intercourse with condom, unprotected receptive oral intercourse). Published estimates of the per-act HIV transmission probability[79,80] and estimates of condom effectiveness[81] were used for this analysis. Base-rates of the average number of times per year individuals engage in specific risk behaviors were provided by Project Explore.[52] Average rates of risk behaviors were defined as 12 of the specific acts per year, high rates defined as 24 acts per year, and extremely high rates defined as 48 acts per year. As shown in Figure 2, the cost effectiveness of PrEP for each infection averted varies as a function of the frequency of risk behaviors and of the efficacy of PrEP. This analysis suggests that PrEP is more cost-effective for individuals who engage in high and extremely high rates of risk behaviors and for instances when the putative efficacy for PrEP is greater than 50%.

Barriers to Access

Racial and Socioeconomic Disparity

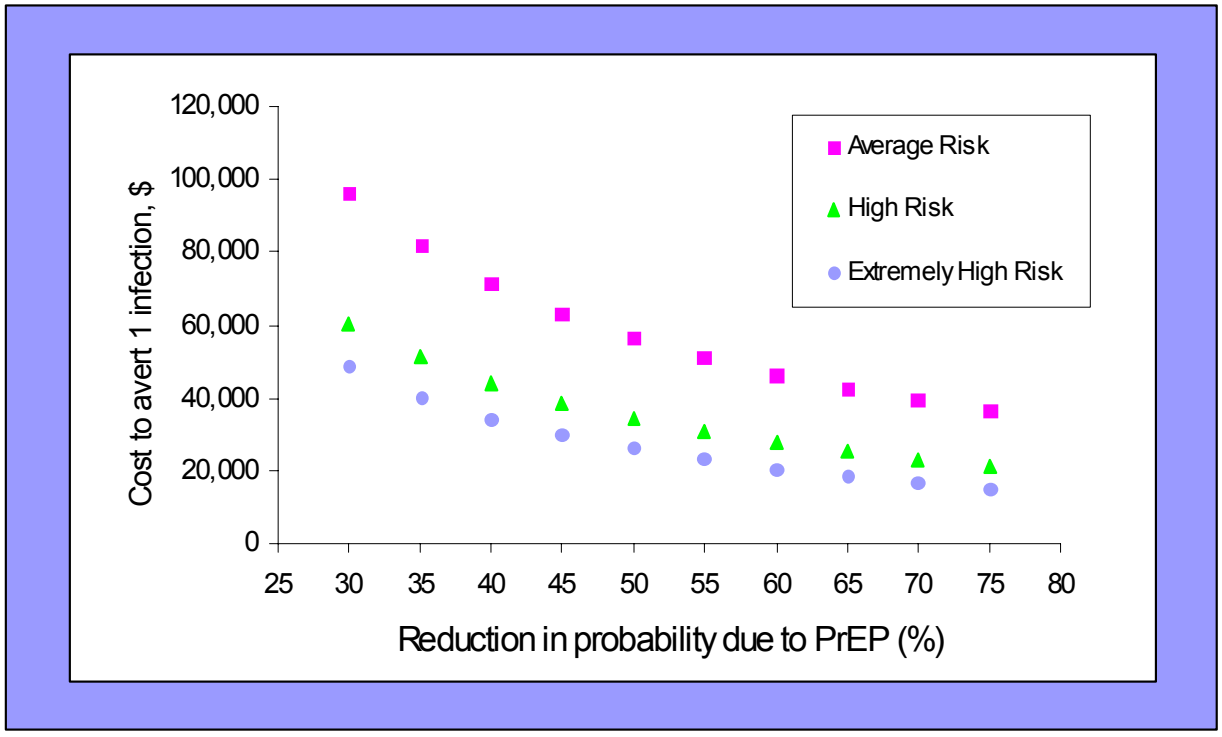
It can be expected that, without explicit intervention, African Americans, Latinos, and those of lower socioeconomic status will be the least likely to have access to PrEP. This certainly has been the case in accessing PEP in San Francisco.[8] Research on access to antiretroviral medications for treatment of HIV has

shown that African Americans, Latinos, and members of lower socioeconomic groups with HIV infection were less likely than others to access antiretrovirals after HAART became available in the late 1990s.[82] Socioeconomic status is certainly operative, as low-income HIV-positive individuals have competing demands (eg, needing money for food, clothing or housing; postponing care because of not having money for transportation; not being able to get out of work) that may prevent these individuals from keeping physician visits. Marked disparities also existed in the distribution of AZT prior to the advent of HAART.[83] Minorities and lower socioeconomic groups are under-represented in clinical trials for anti-HIV drugs. In the nationally represented HIV Cost and Services Utilization Study (HCSUS), lower rates of clinical trial participation by African Americans, Latinos, and lower socioeconomic groups was explained in part by lack of trust, lack of access to care, belief in AIDS conspiracies, and discrimination.[84] In San Francisco, African American ethnicity was associated with being likely to die sooner from AIDS than Caucasian or Latino ethnicity.[85] Of course, racial and socioeconomic disparities in health access and outcomes are not unique to HIV/AIDS and have been documented for a wide variety of diseases for a long time.

Age (Adolescent Minors)

While it is generally in the best interests of all concerned that physicians and other care providers obtain parental/guardian consent and child assent for health care decisions for children aged 13 years and older,[86] children at risk may either not wish to request this consent from their parents/guardians or may be runaways and not have access to parents or guardians to provide consent. In California, minors of any age may consent to medical care related to pregnancy, contraception, or abortion; minors 12 years of age or older may consent to medical services for diagnosis and/or treatment of infectious or communicable diseases (including STDs), and for HIV/AIDS testing and treatment. In these instances, providers may not inform a parent or guardian

FIGURE 2. Cost-Effectiveness of PrEP



without the minor's consent.[87] Despite these policies, adolescent minors in California that are most at risk of HIV infection may have difficulty accessing PrEP and its related care due to lack of insurance, lack of familiarity with or trust of the medical system, and denial of their risk.

Mental Disability

Persons with mental disabilities who engage in HIV risk behaviors may be unable to provide fully informed consent or to even be aware of this prevention intervention and its potential benefits. Should a PrEP intervention for at-risk populations be implemented, consideration should be given to educating guardians of those with mental disabilities and staff members who work at agencies charged with maintaining the welfare of these individuals (ie, the California Regional Centers for developmental disabilities, agencies who work with the homeless). Adherence problems common to individuals with mental disabilities should also be a consideration in formulating recommendations to these individuals. While those individuals who live with families or in more controlled settings may easily comply with the minimal adherence necessary to maintain protection, those individuals with mental disabilities who are homeless or transitionally housed may require extra supports (eg, directly observed therapy).

Undocumented Status

Undocumented immigrants at risk for HIV infection present an especially difficult policy issue. While the rate at which HIV-infected undocumented immigrants access care at California AIDS care clinics is unknown, there would be obvious benefits to using public resources to provide an effective medical prevention for HIV to HIV-negative undocumented immigrants at high risk of HIV. Moreover, given the relative ease by which individuals cross the border between California and Mexico, there may be important policy implications for recommending or even supporting effective PrEP interventions in Mexico for HIV-negative MSM and IDU through existing border health initiatives. The situation is complex, however, as some amount of ARVs intended for PrEP, including those given to immigrants in the United States, are likely to be routed to HIV-infected people in their home countries who need treatment but cannot access it.

Clinician Bias

The literature on adherence in general, and adherence to anti-HIV drugs in particular, has demonstrated convincingly that physicians are not good at predicting who will and who will not adhere well to medications. Especially important in this literature are the findings that homeless and marginally housed individuals are as good as clinic populations in maintaining adherence to antiretroviral medications,[88] as are individuals in developing countries.[89,90] Research is needed on medical care provider biases in use of PrEP for various population groups, and educational strategies that might best ensure that PrEP is not distributed differentially on the basis of demographics. Aside from bias in patient selection, clinician bias against PrEP in general, perhaps based on legitimate concerns about the intervention, would have an effect on whether patients are informed about or offered PrEP in the clinics in which they routinely seek care.

Stigma and Discrimination

Given that risk for HIV often carries socially stigmatizing associations—being gay, using drugs, being sexually promiscuous, etc—a request for PrEP may represent a tacit admission that one engages in behaviors that carry such stigma. The perception, perhaps sometimes correct, among some of those at risk for HIV infection may be that accessing PrEP could lead to sanctions ranging from disapproval of their clinician to discrimination in the workplace to preventing acquisition or retention of health or life insurance. The HIV testing that would be necessary to screen patients for PrEP is unlikely to be anonymous, and this may also cause anxiety for those who are wary of their HIV infection being reported. It is possible that such concerns could prevent a segment of the at-risk population from accessing PrEP, even if it shown to be an effective prevention intervention.

In Summary

Ultimately, resource issues may prove to be relatively minor variables in the consideration of whether to adopt PREP as a biomedical prevention strategy, compared to the overall efficacy of the approach. The more effective the intervention is shown to be, the stronger the policy arguments will be for implementing PrEP as part of a comprehensive HIV prevention approach. If widespread implementation becomes desirable, however, it will be necessary to ensure that such resources are in place to provide the intervention to those that need it, and that any barriers to access are anticipated and addressed proactively.

Conclusion and Recommendations

Reliable information on the effectiveness and biological and behavioral safety of PrEP as an HIV prevention intervention will not be available until the studies currently being planned and implemented are completed and their data analyzed and reported. Given current study timelines, this is unlikely to occur prior to mid-2006. If PrEP is shown to have acceptable biological and behavioral safety, efficacy, and cost-effectiveness, it can be expected that programs to implement PrEP in California would be advocated for by key stakeholders. It is also possible that some communities and organizations would oppose PrEP, based on concerns of its potential to affect risk behavior, or on other economic, moral, or ethical grounds.

As the results of PrEP trials will not be available for some time, there is an opportunity to examine what the response in California ought to be if the intervention proves successful. Should clinical trials show that PrEP is effective, the following are recommended as ways to ensure optimal implementation of PrEP programs in California:

- A statewide panel should be convened to address whether and how PrEP programs would be implemented and covered in California. The panel would need to include all key stakeholders, including State government, clinicians, HIV prevention providers and program planners, PrEP researchers, affected communities and their advocates, health care organizations, and third-party payers.

- Additional clinical research is needed in order to develop sound clinical and counseling guidelines as to how PrEP should be administered to prospective patients. An expert panel comprising government, PrEP researchers, clinicians, prevention providers, and affected communities would issue recommendations covering all aspects of PrEP use, including patient selection, screening, dosage, monitoring, and evaluation.

- If TDF is shown to be effective as a PrEP agent and becomes indicated for this purpose, Phase IV (post-marketing) studies will be valuable in tracking adverse effects related to prophylactic TDF use.

- It is likely, with the attention given to PrEP, that its use may already have begun among some members of risk groups with access and resources. Studies should be initiated to determine the extent of its use, the sources of medications for individuals, the ways in which individuals are using PrEP (eg, episodically or chronically), and whether or not it is being used instead of or in combination with other prevention strategies.

- Studies will be needed to determine (1) if PrEP use will result in decreased use of other prevention strategies (eg, condoms, microbicides, vaccines); (2) how to communicate the need for combination prevention strategies; and (3) how to communicate about PrEP efficacy in the case that studies demonstrate that PrEP is of low or moderate efficacy in preventing HIV acquisition.

- Research will need to be conducted to determine the best ways to introduce and market PrEP in at-risk communities, so that risk behavior does not rise as a result.

- Favorable funding allocations should be considered for providers capable of delivering supportive behavioral prevention interventions in which PREP is only one part of a comprehensive risk-reduction strategy aimed at keeping HIV-negative people uninfected.

- Prevention and care providers need to be brought together with public health officials to discuss the implications of the "medicalization" of prevention, and to discuss alternative strategies to ensure that combinations of approaches—behavioral, social, and biomedical—are used optimally in all settings.

- Evaluation of PrEP provision in nontraditional care settings will be useful to ensure that high-risk individuals with poor access to health care can still avail themselves of PrEP.

- Research will be required that examines medical care provider biases in use of PrEP for various population groups, and provider education strategies will need to be developed that ensure that PrEP is not distributed differentially on the basis of such biases.

- Any plan for implementing PrEP must take into account the needs of minority communities and populations, to ensure that PrEP reaches those most in need of HIV prevention.

- Organizations serving youth, people with mental disabilities, and undocumented immigrants will need to be included in planning for PrEP implementation, to ensure that ways are found to ensure access to PrEP for these groups. Organizations working with IDUs (including needle exchange programs) will also need to be included. Ongoing outreach and education with agencies serving these populations will likely be necessary.

- Stakeholder communities, including those that would be likely to use PrEP if it shown to be effective, as well as their providers, will need to be deeply involved in all aspects of any PrEP research or program planning and implementation that is conducted in California.

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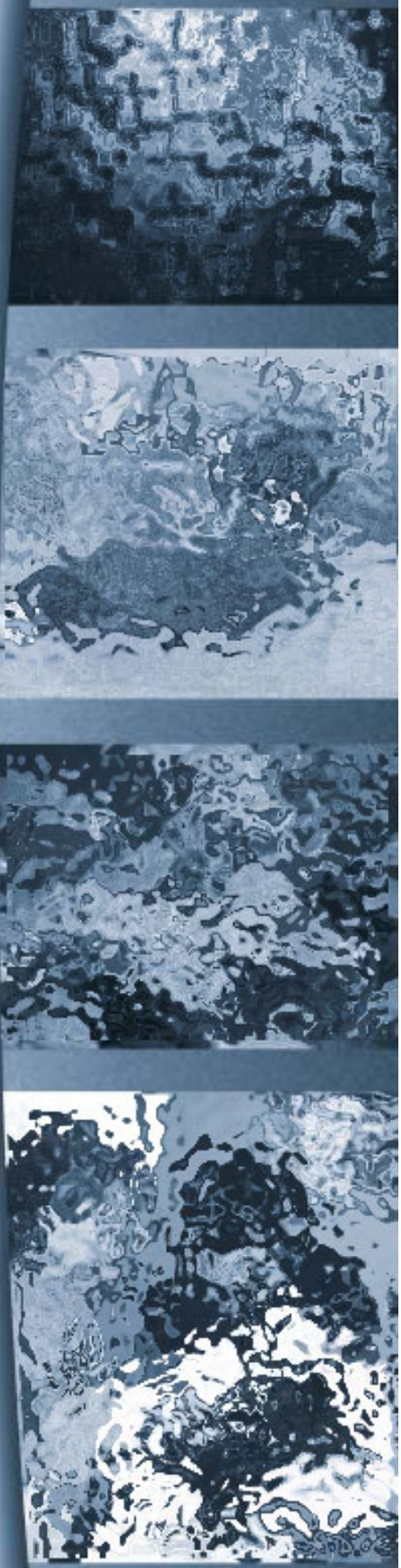

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