SAFETY CONSIDERATIONS IN THE PREVENTION OF TRANSMISSION OF HIV BY PRE-EXPOSURE PROPHYLAXIS (OR "PREP")

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The use of oral tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (TDF/FTC) to reduce the risk of acquisition of HIV represents a major breakthrough in HIV prevention research. Results from recent pre-exposure prophylaxis (PrEP) trials have demonstrated the efficacy of TDF and TDF/FTC in preventing HIV acquisition in different populations, including men who have sex with men (MSM) and heterosexual men and women.[1]

A need for understanding and developing the safe use and implementation of antiretrovirals (ARVs) for prevention remains. How does PrEP best fit into the prevention toolbox with other critical tools such as condom use and risk reduction counseling?

The Forum for Collaborative HIV Research provided a neutral space where questions such as these could be discussed openly and where input from experts from each stakeholder group could be gathered to inform regulators and other public health leaders. Safety data of five clinical trials covering more than 6,000 individuals exposed to oral TDF or TDF/FTC were reviewed. Discussion included: 1) medical risks of PrEP in a population without HIV infection; 2) socio-behavioral risks such as disinhibition and reduction in use of condoms as an adjunct safety measure; and 3) risks of development of drug resistance. These discussions led to an assessment that controlled distribution of PrEP to avoid development of resistance following seroconversion is unwarranted at this point. The stakeholders agreed, however, on the need for targeted educational programs for providers and patients, and for further post-marketing clinical studies to assess the safety and effectiveness of PrEP in a real world setting. Clinical studies would potentially include assessment of safety and effectiveness in adolescents, young black MSM, and women especially in the context of pregnancy and breast-feeding. Further study is also warranted to assess drug-drug interactions. In addition, while little evidence was found of adverse behavioral changes in clinical trial participants, further behavioral study in the post-marketing environment would be important.

Finally, stakeholders concluded that PrEP should be part of a larger package of HIV prevention activities to reduce the number of people who become infected with HIV. The National HIV/AIDS Strategy of the United States emphasizes the need for improvements in HIV prevention and the need for combination approaches, such as PrEP [1]. PrEP as an intervention, in combination with other proven, effective HIV prevention activities, can reduce the numbers of new infections in the U.S. Moreover, as part of a package of services, the wider implementation of PrEP could increase access to HIV testing among those most at risk of infection. Increased HIV testing would identify more individuals with HIV infection, identify them sooner, and allow them earlier access to HIV care.

[1] Some studies (discussed below) have been unable to demonstrate efficacy of oral prophylaxis in women.

SUMMARY OF SAFETY DATA FROM PRE-MARKET STUDIES OF PREP

Safety data of five clinical trials covering more than 6,000 individuals exposed to oral TDF or TDF/FTC were reviewed. See Table 1 for a summary.

Pre-Exposure Prophylaxis Initiative (iPrEx)

The iPrEx study enrolled 2,469 HIV-negative MSM and 30 transgender women who were randomized 1:1 to receive TDF/FTC or placebo. The study demonstrated a 44% reduction in risk of acquisition of HIV on an intention-to-treat basis, but a calculated 92% reduction when detectable drug was found in the blood of study participants from a pre-planned sub-group analysis.

1,226 participants in the TDF/FTC arm contributed 2,124 person-years of exposure [2]. No difference was detected between active and placebo arm with respect to depression (3% versus 5%; p=0.07), serious adverse events (5% in both), Grade 3 or 4 adverse events (12% versus 13%; p=0.51), or death (<1% in both). Active arm participants experienced a significantly higher incidence of nausea (2% versus <1%; p=0.04) and weight loss (2% versus 1%; p=0.04), but not diarrhea (4% in both) or other clinical adverse events, compared to participants in the control arm. The gastrointestinal events tended to occur in the first month and resolved thereafter similar to the experience in patients with HIV treated with TDF/FTC.

Among a panel of clinical laboratory measurements, the only observed difference was an elevation of creatinine in the active arm at any visit (2% versus 1%; p=0.08). When assessed through a second creatinine level at the next visit, seven creatinine elevation events were confirmed in five individuals in the active arm and none in the placebo arm. All five individuals had creatinine levels return to normal after stopping medication and creatinine elevation did not recur on re-challenge.

Bone mineral density at the spine decreased by 1% (p=0.049) over the course of the study and transiently at the hip (maximum 0.3%; p<0.001) in the active arm as compared to the placebo arm, but was not associated with an increase in fracture rate (1.2% versus 0.8%, respectively). The bone loss did not progress after the first few months and the degree of bone mineral density loss was less than that previously reported in treatment studies of HIV-infected individuals on TDF/FTC therapy (3% to 4%) (See Viread Labeling).

Two cases of FTC resistance (184I, 184V) in the active arm and one case (184V) in the placebo arm were identified through genotypic resistance analysis– all occurred in study participants who were retrospectively identified as acutely infected with HIV at the time of enrollment. The proportion of resistant virus in both active arm cases waned to below 0.5% within six months of stopping TDF/FTC. The clinical significance of this finding is not known. Minor variant assay analysis of 91 samples from treatment emergent seroconverters revealed two cases of resistance (1 to TDF and 1 to FTC) among the placebo group but none in the active arm.

By patient report, unprotected receptive anal intercourse decreased from 60% to approximately 25% at 144 weeks in both study arms, regardless of whether participants believed they were on active drug or not. Similarly, self-reported condom use in both arms increased from 50% at enrollment to approximately 80% over the course of the study. Thus, no subjective evidence of risk compensation was seen although, given that this evidence is based on self-report, it could be met with skepticism. That said, there was a four-fold decrease in acute HIV incidence among placebo arm participants as compared to historical population estimates supporting the lack of risk compensation.

Partners PrEP

The Partners PrEP study enrolled 4,758 couples from Uganda and Kenya who were randomized 1:1:1 to three arms of oral TDF, oral TDF/FTC or placebo. According to enrollment criteria, participants were serodiscordant couples in which the HIV-infected partner was not eligible for HIV treatment under national guidelines. Participant retention was 95%. Adherence measured by pill counts was 97%. On July 10, 2011 the Data Safety and Monitoring Board (DSMB) for the Partners PrEP study recommended that the study results be publicly reported and the use of placebo discontinued because of clear demonstration of HIV protection based on an interim review of efficacy data through May 31, 2011. Twelve infections occurred before initiation of study drug (3 in the TDF, 3 in the TDF/FTC and 6 in the placebo arms). Of the 78 infections in the primary modified intention-to-treat analysis (infections occurring during the study), 18 occurred in the TDF arm, 13 in the TDF/FTC arm, and 47 in the placebo arm for an estimated efficacy of 62% for TDF and 73% for TDF/FTC. No significant difference in efficacy between TDF and TDF/FTC or between male versus female participants was observed. Based on the recommendation of the DSMB, the placebo arm is being re-randomized to the active arms, which will continue to provide more comparative information on relative efficacy, safety of, and emergence of resistance on TDF and TDF/FTC prophylaxis.

No significant differences by arm in serious adverse events or deaths were observed. There were no differences among groups in confirmed increases in creatinine (1% overall) or decreases in phosphorus (9%). In terms of adverse events, small differences in active arms versus placebo in the first month in nausea (5.9% to 6.3% versus 4.5%) and diarrhea (4.1% to 4.5% versus 2.8%) were observed. A total of 272 participants became pregnant – the same proportion in each

arm – with time off study drug at 1.8% overall. About 20% of the HIV-infected partners met national guidelines for antiretroviral treatment during the follow-up. No evidence of risk compensation was reported, with unprotected sex declining from 27% to 10% or less at 30 months.

Data on pregnancy outcomes, newborn health, drug resistance, plasma viral load, and plasma/intracellular drug levels in seroconverters await further follow-up and analysis.

Phase II CDC Safety Trial of TDF for Pre-Exposure Prophylaxis in Men who have Sex with Men (MSM)

Three sites in the U.S. (San Francisco, Atlanta, and Boston) randomized 400 HIV-uninfected MSM to either oral TDF or placebo. To assess behavioral changes pursuant to pill taking, each arm was further randomized (1:1) to either a lead-in phase of observation with no drug dispensed for nine months or immediate therapy. Three hundred and twenty three (323) men completed all study visits. Seven seroconversions were reported. One of these seven subjects tested negative for HIV-antibody but had a positive viral load at enrollment and thus was determined to be infected at or before study initiation. Of the remaining six seroconverters, three were in the active (delayed) arm and three in the placebo arm. No resistance associated mutations were identified.

There were no significant differences between active and placebo arms in Grade 3 or 4 adverse events or other specified clinical adverse events. No significant differences in creatinine elevations or phosphorus decreases were observed. At the San Francisco site, change in bone mineral density was assessed. Similar to iPrEx, participants in the active arm experienced a 1% decline in bone mineral density which stabilized over time and was not associated with an increase in fracture rate.

Reported percent unprotected anal sex or condom use did not change, but the number of sexual partners decreased over the course of the trial (6 per month versus 8 per month at enrollment).

Prevention of HIV infection among sexually active young adults in Botswana (TDF2)

The Botswana trial enrolled over 1,200 healthy heterosexual men and women, 18 to 29 years old, who were randomized to oral TDF/FTC or placebo and followed for 12 months or more. Thirty three seroconversions occurred: nine in the TDF/FTC arm and 24 in the placebo arm; a 63% reduction in risk of HIV acquisition according to an intention to treat analysis. Overall adherence by pill count was 79%.

Overall adverse events occurred at a statistically higher rate in the TDF/FTC arm (p=0.019), driven by differences in dizziness (15.3% versus 10.7%; p=0.019), nausea (18.8% versus 7.2%; p<0.0001), and vomiting (11.5% versus 6.8%; p=0.005). No significant differences in Grade 1-4 clinical laboratory adverse events, including creatinine and phosphorus levels, were observed. Self-reported socio-behavioral risks (percentage of participants with greater than one sexual partner in the last month or percentage of vaginal intercourse episodes without condom use) did not differ significantly between the two arms.

Two cases of resistant virus were documented among participants who seroconverted, one in each arm. The placebo arm participant was initially infected with resistant virus. The active arm participant had been enrolled with unrecognized acute HIV (wild type) infection. Multiple mutations (K65R, M184V and A62V) emerged to high levels while on TDF/FTC. Similar to iPrEx, however, no cases of drug resistance were noted among participants with emergent HIV infection during the study. Further analyses are ongoing, including comparative efficacy by adherence, changes in bone mineral density, serum drug level testing for efficacy and adherence, and risk behavior changes over time.

FEM-PrEP

FEM-PrEP randomized 2,120 women at high risk of HIV acquisition to TDF/FTC versus placebo for 52 weeks (followed by two off-product visits) in Kenya, South Africa, and Tanzania. Approximately 80% of participants completed follow-up with 12.6% lost to follow-up and 5.7% with early discontinuation. A recommendation for early closure for futility was made by the Independent Data Monitoring Committee (IDMC) in April 2011, when the data revealed 28 HIV infections in each arm. The incidence rate of 5.1 infections per 100 person-years confirmed the high HIV risk in this trial population. Further to this point was the relatively high prevalence of other sexually transmitted infections (STIs) at baseline, including gonorrhea (5.9%), chlamydia (13.9%), bacterial vaginosis (41.6%) and syphilis (1.9%). Data cleaning and subsequent unblinded analysis per protocol, including assessment of serum drug levels in seroconverters, will likely be completed in November 2011.

Blinded data from both arms on adverse events were presented. Maximum adherence by pill count was 82%. There was a 15.8% overall incidence of gastrointestinal effects including nausea (4.1%), vomiting (2.2%) and diarrhea (1.2%). Preliminary unblinded analyses suggest a higher rate of these gastrointestinal effects in the TDF/FTC group. Clinical laboratory events included an overall increase in serum creatinine among 3.4% of participants (0.3% Grade 2) and a decrease in serum phosphorus among 15.6% of participants (3.6% Grade 3). Overall, serum ALT and AST increases were observed in 6.8% and 12.3% of participants, respectively. Very few of these (<1%) were Grade 3 or higher. However, neither laboratory defined adverse events nor clinical adverse events appear to be different between the arms in a preliminary analysis. Final comparative data on changes in clinical laboratory parameters and socio-

behavioral data will not be available until unblinded analyses are completed.

Summary of safety data reports

Clinical adverse events, including serious adverse events, other than such gastrointestinal events such as nausea, weight loss, and diarrhea in the early stages of therapy, do not appear to be different between placebo and drug study groups and are similar to labeled events for TDF and TDF/FTC use in HIV-infected patients. Modest increases in serum creatinine were occasionally noted, but these did not persist on re-challenge when present. Decreases in bone mineral density were also observed in planned sub-studies, but these decreases were generally less than that observed in HIV-infected individuals treated with the same drugs and appeared to stabilize over time. No differences in fracture rates were seen. There was no clinically significant development of drug resistance in participants on drug with newly emergent HIV infection, although there were a few cases among participants with acute HIV infection at study entry (identified retrospectively). Thus, care should be taken to ensure individuals are not infected at the time of initiation of biomedical prevention. There was no evidence of change in socio-behavioral risk (e.g., frequency of condom use, unprotected receptive anal intercourse in MSM, or number of sexual partners). Indeed, there was a trend toward decreased sexual risk behavior but this finding is based on self-reporting in a clinical trial setting.

SAFETY CONCERNS

Generally, the threshold for risk should be low when the proposed intervention is preventative, because the population being exposed to drug therapy is otherwise healthy – drug therapy might be considered "unnecessary" in this context. Consideration should therefore be given to whether the disease against which the biomedical prophylaxis is implemented would otherwise result in increased mortality and life-long therapy. Another key consideration is the level of risk of disease acquisition for an individual or a population. In the setting of high individual risk, some degree of side effects or toxicity may be acceptable given clear individual benefits. Among some high-risk populations, such as the young black MSM population in the U.S. that experienced a 48% increase in HIV incidence from 2006 to 2009 and where the prevalence of HIV infection may be as high as 28%, ARV-based prevention for uninfected individuals could be considered as valuable as ARV therapy is for HIV-infected individuals[3][4]. However, the individual should be informed about the risks and potential benefits and make his/her own decision about whether to start PrEP. What may be an unacceptable safety risk in some populations may be more acceptable in others. Acquiring HIV infection is a significant and serious risk to these persons. Thus, panelists agreed that in populations at highest vulnerability, such as young black MSM, discordant couples, or women in exploited settings, safety issues associated with PrEP should be balanced against the substantial benefit provided by drug exposure. While the risk-benefit assessment will likely vary depending on the targeted population, the same calculus may also apply to specific individuals who may not identify as part of a high-risk group. Clinicians should be attentive to individual risk/benefit concerns and determine what is most appropriate for that person.

Medical Risks

Well-appreciated medical risks associated with PrEP included gastrointestinal effects, such as nausea, vomiting and weight loss, and decreases in renal clearance and bone mineral density. Gastrointestinal side effects were considered transient or of insignificant risk as compared to the potential benefit to an individual at high risk for HIV acquisition. For individuals with decreases in renal clearance, continuing on TDF could lead to renal insufficiency or failure. Providers who prescribe TDF for PrEP should follow individuals for changes in creatinine clearance. Safety risks not identified in the substantial number of trial participants enrolled, but potentially seen in different or larger populations, may also include changes in lipid parameters, hepatitis B flares, or interactions with antidepressants. The safety issues in special populations, including African-Americans, adolescents, pregnant women, neonates and breast-feeding infants, also remain to be elucidated by further follow-up or by enrolling different target populations. Another special issue is whether these or other new side effects will arise with periodic or intermittent episodes of dosing. When accompanied by appropriate counseling, PrEP ideally should not be expected to be a long-term therapy. Many individuals are likely to start and stop PrEP depending on their risk assessment at different periods in their lives. For instance, many persons who enter a primary long-term relationship may not need to stay on PrEP although this must be assessed on a case-by-case basis. In heterosexual serodiscordant couples, risk may change depending on whether conception is being considered. Under the assumption that most individuals will have periods of intermittent or varying vulnerability during their lives, does nausea and weight loss become a recurring or increasingly severe phenomenon on re-administration or is there accommodation? Similarly, given early but stabilizing changes in bone mineral density, is there recovery or recurrence when PrEP is administered on a periodic basis? Evaluation of the safety of periodic dosing would provide valuable information.

Socio-Behavioral Changes and Related Risks

Existing studies have not shown an increase in risk behavior with pre-exposure prophylaxis. Thus, this concern is theoretical at present. Currently available data are based largely on subjective reporting, but iPrEx did record a lower seroconversion rate in the placebo arm than was expected from population studies, objectively supporting overall risk reduction. The iPrEx study, however, was a placebo-

controlled study in which the protective activity of the administered agent was stated to be unknown, participants were told they might be on placebo, and intensive risk-reduction counseling and condoms were regularly provided.

In a potential post-approval setting, individuals would be advised of the efficacy of the product and might receive less reinforcement with regard to risk behavior. In that setting, there may be an increased rate of sexually transmitted infections if risk compensation were to occur. Since PrEP does not prevent nor treat other sexually transmitted infections, such risk compensation could actually increase the likelihood of HIV transmission if PrEP efficacy is less than 100% or adherence is insufficient. To the latter issue, apparent non-adherence in iPrEx reduced efficacy from a theoretical 92% to 44%. How much of this reduction in efficacy was also due in part to the effect of any socio-behavioral changes is not known. The potential interplay of increased risk compensation and poor adherence to PrEP, therefore, is concerning. Regardless, non-adherence represents an independent and important concern.

That said, many panelists voiced concern that regulatory decisions have not historically been made based on secondary changes in risk behavior or adherence, which could occur with any number of products, from cholesterol-lowering agents to agents for erectile dysfunction. Both of these interventions may increase socio-behavioral risk which could counterbalance the desired benefits, but this issue was not a part of the regulatory decision-making process. Furthermore, there may be an element of prejudice as similar concerns were expressed over the introduction of birth control and syringe exchange programs.

Risk identification and risk-reduction counseling should be a part of PrEP therapy. Biomedical interventions are never panaceas. PrEP intervention must be part of a comprehensive package that includes counseling on risk-reduction in addition to a prescription. The most vulnerable populations are those not currently using condoms and whose risk is increased by higher HIV prevalence in their social and sexual networks. For many of these persons, the question is not whether they will become infected but, in the absence of PrEP and effective counseling, when they will become infected. When such persons are recruited to PrEP there is an opportunity for counseling that may have the potential for risk reduction (through increase in condom use or reduction in number of partners). That said, caregivers must be attentive to secondary changes in risk behavior, test and treat for sexually transmitted infections, and provide appropriate counseling. Consideration should be given to inclusion of socio-behavioral experts as an integral component of the PrEP team of caregivers. One approach for clinicians may be to initiate PrEP with a five-day supply with refills dependent on ensuring that socio-behavioral counseling has been obtained.

Another social risk is that provision of PrEP might expose vulnerable individuals to stigma or to social harms, especially from those who may believe that the pill-taking implies HIV infection. Informal discussions with vulnerable individuals have frequently shown more concern about this stigma than the risk of HIV infection itself. Changing the name of the pill when used for prevention could help mitigate this risk.

Drug Resistance

The emergence of infection with drug-resistant virus is increased in a setting of inadequate or partial treatment of HIV. Since the prophylactic regimen is not a full treatment regimen, resistance could develop in a number of potential settings. For an individual, these include: unrecognized acute infection at PrEP initiation, non-adherence leading to HIV infection and intermittent PrEP use after infection, and infrequent HIV testing that may miss seroconversion. On a community level, while decreasing overall transmission of HIV, PrEP may proportionately increase the risk of transmission of drug-resistant virus, especially in communities where there is widespread resistance to ARV drugs used for PrEP. The risk of resistance development among persons with undiagnosed HIV infection who inadvertently start PrEP as a result of drug sharing should also be noted. In the current studies, which followed a large number of participants for a considerable time, development of drug resistance during treatment with monthly testing for seroconversion was not identified as a substantial risk. Two studies reported cases of drug resistance in individuals already infected at randomization, but in the iPrEx study at least, the specific mutations identified were reduced to undetectable levels when PrEP was ceased and would not be expected to endanger future treatment. In a real world setting, the risk of drug resistance may be minimized by ensuring that PrEP is not initiated in the setting of acute infection and by regular HIV testing at an interval that is both safe and reasonable for the individual. In those sites that do not have RNA testing available for detection of acute HIV infection, consideration should be given to repeat testing one month after drug initiation.

Intermittent drug exposure, potentially due to non-adherence, drug sharing, or drug diversion, may result in development of resistance in individuals who seroconvert. Defining the duration of protection around a dosing period remains a critical unanswered question. Pharmacokinetic studies could address this question.

Insights from mathematical modeling may help assess the risk of increased community drug resistance [5,6]. These models suggest PrEP will contribute significantly to the reduction in HIV transmissions, but may increase the proportion of drug resistance among the smaller population that does become infected. That said, HIV treatment, rather than PrEP, remains the most likely cause of drug resistance in the community, especially in communities where ARV options are limited. The

concern of substantial increases in community drug resistance as result of PrEP is tempered by the reduced need for treatment afforded by prevention. Attention, therefore, should be focused on ensuring access to a full range of ARVs for treatment and minimizing "overlap" of treatment and prevention medications.

In sum, the possibility of drug resistance should not be a roadblock to PrEP implementation, but the following issues should be addressed:

- Identify the testing interval that provides adequate protection; i.e., to minimize the threat of drug resistance, testing must be accurate and occur frequently[2]
- Identify the minimum dose exposure needed to prevent HIV acquisition
- Develop methods to assure that individuals are not acutely infected at the time of PrEP initiation
- Evaluate ARVs for PrEP that are non-overlapping with antiretroviral therapy

Drug-Drug Interactions

The scope of potential drug-drug interactions to be assessed in the prevention population overlaps, but is not necessarily the same as, the treatment population. Assessment of important drug-drug interactions requires an understanding of the likely targeted individual. For example, data on drug interactions with contraceptives would be important in this population. Depression is another example of a frequent concomitant illness that should be considered when identifying drug-drug interactions to investigate. In addition, assessing drug-drug interactions early is important to identify any potentially significant adverse reactions that may result, as these adverse events are less likely to be acceptable in the setting of PrEP than they would be for HIV treatment. Any emergent toxicity in a previously healthy individual is likelier to be perceived as more serious than the same event in a patient who must be on medication to control an otherwise fatal illness.

RISK MITIGATION STRATEGIES

In 2007, Congress enacted the Food and Drug Administration Amendments Act ("FDAAA") that provided the Food and Drug Administration ("FDA") with expanded authority over post-marketing safety of drugs. These include authorities to require sponsors to make safety-related labeling changes, conduct safety-related post-marketing studies and clinical trials, and implement Risk Evaluation and Mitigation Strategies (REMS). Elements of REMS may include communication and education programs directed to healthcare professionals or patients, such as a Medication Guide. If there are potential, significant safety risks, a REMS plan could also include such elements to assure safe use (ETASU) as restricted distribution programs or mandatory medical testing of individuals to document conditions of safe use. An integral part of any REMS is periodic evaluation by the sponsor of the impact of the REMS on risk mitigation.

FDA can implement these safety regulations in a number of ways to achieve risk mitigation in association with drug use. FDA could require restricted drug distribution in various ways, education and communication plans (directed to clinicians, patients, or other caregivers) or clinical studies such as drug-drug interaction trials, trials in relevant subpopulations, or implementation demonstration projects. These tools could be implemented by the pharmaceutical company under FDA direction or may be potentially implemented as wise public health activities outside the scope of REMS. To that end, some of these same tools are available to the medical profession, either individually or collectively, on a voluntary basis. In some settings, clinical trials may benefit from public health sponsorship to help persuade otherwise disenfranchised populations to participate. Education and communication plans could be crafted by the clinical and research community as clinical guidelines. Counterbalancing these external controls, respect for individual autonomy may dictate that individuals themselves should be assigned the responsibility for risk mitigation.

Restricted or controlled distribution

FDA could require the pharmaceutical sponsor to institute a REMS that includes a restricted or controlled distribution plan limiting the ability of prescribers to prescribe or of patients to fill prescriptions. Examples of existing REMS that control distribution include mandatory physician qualification, certification or registration; pharmacy certification and distribution limitations; and mandatory patient testing, e.g., to assure that patients on teratogenic drugs are not pregnant. Manufacturer-managed restricted distribution systems have proven effective in reducing the risks associated with potent teratogens, like thalidomide, and to ensure the appropriate use of narcotics. In the PrEP setting, similar restrictions might provide assurance of HIV negativity before a refill could be ordered or dispensed.

In the setting of PrEP, however, panelists concluded that a restricted distribution plan for an ARV drug could not be successfully introduced without also inhibiting access to the same drug for treatment, which would have a potentially devastating impact on HIV management. For example, a requirement for documentation of negative HIV testing for PrEP would inadvertently have the result of restricting access to treatment for HIV-infected individuals. Restricted-use programs through certified pharmacies, on the other hand, work well for drugs like lenalidemide, indicated for Hansen's disease, where the patient population is small and well-defined. A similar system, for buprenorphine/naloxone, has

[2] The Centers for Disease Control and Prevention has recommended a three month interval.

had the intended effect of limiting access. Restricted-use programs, however, would not be practical for ARVs due to their potential widespread use for PrEP and the need to not limit access to these same drugs for treatment. Even a system of pharmacy reminders – for refills or HIV testing – would be difficult to implement as PrEP users might only require drug for a limited period as compared to the HIV-infected population which needs life-long treatment. Finally, a restricted approach is unwieldy when the premise of PrEP is not simply a drug prescription and regular blood test but also routine counseling – most likely done by healthcare providers other than pharmacists. Options that target prescribers of PrEP, through registration or certification, or by limiting prescribers to clinicians trained in HIV medicine, would create additional burdens to the already overtaxed HIV healthcare workforce and might also limit access to care.

A representative from the insurance carrier Aetna noted that the insurer has no plans to implement utilization management controls, such as prior authorization, that would place limits on prevention or treatment of HIV. Aetna's view is that any restrictive plan for purposes of PrEP would spill over and be counter-productive to the needs of the HIV treatment community. Given PrEP's proven value, Aetna's current plan is to provide PrEP as off-label use of ARVs, regardless of whether a particular drug is approved by the FDA for a PrEP indication. Kaiser-Permanente has also developed a policy for implementation of PrEP and some of their clients have already initiated PrEP as the drugs used for prevention are readily available on the market for treatment.

Prevention should be seen as an opportunity to reach individuals most at-risk for HIV acquisition and restrictions to access may result in limiting that opportunity. Restricted distribution would impose substantial burdens on healthcare providers and patients and limit access to a needed prevention strategy and other services. Highly vulnerable individuals that represent the target population for PrEP are already disenfranchised and a restrictive access system would discourage rather than encourage participation in PrEP. Further, such a system could facilitate drug diversion or encourage clinicians to write prevention prescriptions outside the system since the drugs would still be unrestricted for treatment.

Participants agreed that the threat of drug resistance had not reached the threshold of a significant safety risk to justify controls such as utilization management or mandated restricted distribution. Indeed, the data regarding resistance from the initial trials do not implicate seroconversion between the first prescription and the refill as the cause, but rather the initiation of PrEP among individuals with undiagnosed acute infection. The panelists considered the risk of limited access for vulnerable populations more significant than the currently known risk of development of drug-resistant virus.

That said, many endorsed the concept that clinicians should not prescribe PrEP or refill prescriptions without initial and repeated HIV testing as necessary to provide assurance that individuals were not HIV-infected at PrEP initiation and to prevent the emergence of drug resistance. The system in place for smoking cessation products, where counseling is an important component of the therapeutic intervention, provides a good model. One recommendation was that short-term prescriptions should have refills predicated on completion of risk-reduction counseling, possibly including condom distribution.

Communication and educational programs

Gastrointestinal effects (nausea, diarrhea, and weight loss) did not appear to prevent participants in the clinical trials from continuing therapy, likely because the symptoms were mild, short-lived, or of little concern. That said, individuals should be counseled about potential gastrointestinal side-effects.

Clinicians must also be attentive for potential renal complications and bone mineral density loss. The panelists did not believe that bone mineral density should be measured in all persons on PrEP, but concern was expressed about the potential effects on bone mineral density in adolescents, especially young men whose long bones have not yet fused and young women on long acting contraceptives who may already have associated bone demineralization. A package of support services, training, and consensus guidelines to assist practitioners should be made available. Web-based strategies may also be useful for some healthcare providers.

As shown by the existing study data, detection of acute HIV infection is critical before PrEP initiation. In sites where available, HIV RNA or p24 antigen testing might be appropriate. Otherwise, clinical assessment of acute infection followed by an immunoassay test at one month should be sufficient. If clinical assessment suggests acute infection, PCR or other acute testing is advisable, if available. In settings where such testing is not available or feasible, PrEP could await two consecutive negative serologic tests. In any event, any individual with an acute viral infection syndrome should not be enrolled in PrEP. Conversely, providers must be mindful not to miss an opportunity to initiate PrEP in a high-risk individual when information about PrEP and risk behavior has prompted a first contact with the healthcare professional.

Ideally, healthcare providers for PrEP would include infectious disease specialists and specialists in HIV medicine, but workforce limitations among these specialists is a concern. Ryan White centers have limited resources and, moreover, their funding is limited to care of HIV-infected individuals. Thus, thought should be given to how best to reach, recruit, and educate primary-care givers. PrEP providers should also include gynecologists – many of whom

provide primary care for women. Other potential provider groups to target include internists with a predominantly gay male clientele (e.g., Gay and Lesbian Medical Association), family medicine practitioners, family-planning clinicians, substance abuse clinics, community-based organizations with visiting nurse practitioners, sexual-assault nurse examiners who may already be familiar with post-exposure prophylaxis, emergency room physicians, and clinicians who treat sexually transmitted infections. Many of the latter do not often engage in longitudinal care, but should be educated about PrEP. Community centers may be an ideal starting point for initiating PrEP discussions outside the medical environment, with sexual risk reduction counseling as a first step and referral for biomedical intervention as appropriate. Medical homes may be another model. Access to information for providers, given workforce issues, is critical and web-based strategies may have a role. Whatever the format, the education program must be targeted to clinicians with limited experience prescribing antiretroviral medications.

Educational materials for caregivers must also make clear that PrEP is part of a package and not just a biomedical intervention. Education in this setting should be about sustained sexual health programs. Education should also be directed to the proper care of other sexually transmitted infections and provision of sexual health services. For instance, providers should be encouraged to "Ask, Screen and Intervene" [7]:

- Elicit sexual exposure history and define exposed anatomic sites;
- Perform appropriate screening (testing for sexually transmitted infection);
- Provide sexual health education;
- Intervene (targeting risk reduction, treatment, and now biomedical intervention) and;
- Address potential risk compensation and the importance of adherence when biomedical intervention is provided.

Education and outreach programs created by the pharmaceutical industry or public health organizations must recognize that prescribers may not be located in the same office as counselors or community-based organizations that provide sexual health counseling. Important elements of sexual health counseling would include discussion about risk perception and reduction, condom use and condom distribution, and education about other preventative measures (e.g., male circumcision), but the overall content and best method of delivery should be a subject for further implementation research. Programs to educate providers on taking sexual health histories are also a necessity as most caregivers are not experienced in this area.

Clinicians should not be considered the only healthcare providers and are not the only responsible parties. Risk reduction counseling may best be provided by other health professionals such as pharmacists, social workers, clinical psychologists, and other psychosocial or behavioral health professionals. These individuals must also be educated about the use of PrEP.

Important populations to reach with educational programs include adolescents and young black MSM. Adolescents and young black MSM may be less knowledgeable about HIV and risk behavior. Educational or communication plans concerning PrEP provide an opportunity to target these populations to improve sexual health. Achieving health literacy including sexual negotiation strategies and partner selection would be an important goal of a patient-centered communication plan. Another target population would be individuals who present with a sexually transmitted disease other than HIV.

Knowledge of populations with high HIV incidence also suggests that individuals who present with a history of mental health diagnoses, sexual abuse, injection drug use, or sexually transmitted infections are populations that might benefit from education about PrEP. Public health surveillance methods may help to identify success in reaching these subpopulations. Pharmaceutical company support in terms of educational materials that are directed to these populations may be helpful. Although important target populations have been identified, an indication for PrEP could extend to any person who is at risk – for instance, the entire gay male population and individuals in high prevalence communities. How can sexual decision-making be improved best in a communication strategy for these subpopulations but also be conveyed to a more general population? Other key clinical questions to be answered include who decides to use PrEP and why.

Attention must also be paid to education of insurers and government about the need for funding PrEP implementation and including not just pharmaceutical coverage but a complete PrEP package. For instance, the Public Health and Wellness program under the newly enacted Affordable Care Act should include sexual health support. Ultimately, there is a need for an infrastructure for PrEP implementation.

In summary, PrEP should be considered as a package of prevention modalities, including adherence counseling, risk reduction, condom use, better risk perception and understanding, and biomedical intervention when appropriate. PrEP is not just a prescription; it is a comprehensive program of HIV risk management.

CLINICAL STUDIES OR DEMONSTRATION PROJECTS

Many questions remain to be addressed and could best be evaluated by future studies. Partnership with the pharmaceutical industry may be helpful in some instances. In some settings, however, direct pharmaceutical company involvement may be counterproductive because of the perception of commercial motivation.

Knowledge about the risk of renal impairment in HIV-uninfected individuals with hypertension or existing renal disease would be valuable in the prevention setting. Individuals with HIV have options with regard to alternative ARVs that may avoid the toxicities associated with TDF or FTC. Individuals with renal impairment and hypertension have not been studied in the pre-market evaluations done so far. Further study is also needed about the clinical impact of bone mineral loss in adolescents – especially males whose long bones have not yet fused and young women on long-acting contraceptives who may be at higher risk of bone related complications. Other questions to be answered include whether biological differences exist in bone demineralization for adolescents compared to adults and long-term consequences of bone demineralization for adolescents. Given the growing epidemic in the young black MSM population, and the absence of specific data on safety of PrEP in this group, specific studies in this population are needed.

To date, the area of greatest demand for PrEP in the community appears to be among serodiscordant couples and one potential value of PrEP is the opportunity it affords them to conceive. However, more information about the safety of PrEP during pregnancy and lactation, including neonatal development and infant outcomes, is needed.

Another active area of proposed research is periodic or intermittent drug dosing related to periods of vulnerability. For instance, what is the duration of the protective benefit of PrEP after drug administration? What is the optimal timing of PrEP initiation before sexual contact to provide maximal preventative benefit? This information may be crucial in assessing the degree of adherence necessary to ensure PrEP effectiveness and to advising individuals on proper use. Further studies on methods to increase adherence, especially in low-income or underserved populations, must be addressed.

Related to this issue is our lack of current knowledge about the appropriate interval for repeat HIV testing that will minimize the development of resistance and ensure that infection is caught early while resistance may be readily managed. The potential for drug resistance in real-world settings must be evaluated and quantified. To date, resistance has not been an issue but clinical studies are conducted under different conditions than those expected in implementation. The capacity to deliver resistance testing in a real-world setting should be evaluated in demonstration projects that follow a cohort of individuals in community-based settings carefully and longitudinally.

Long-term follow-up safety data are necessary. The introduction of PrEP necessitates better understanding of the long-term (or intermittent short-term) safety of drugs where current data are otherwise confounded by chronic HIV infection itself. An important goal of both short and long-term safety evaluation is that physicians and other healthcare providers are able to advise individuals on the proper monitoring for adverse effects and the duration of PrEP that is both safe and beneficial.

Content and delivery of risk counseling is another area in need of public health study. Who best can perform this activity? What strategies are most effective in changing behavior among those at highest risk? Many of the most vulnerable persons have poor risk perception. How can the use of PrEP be leveraged to improve sexual health? Various strategies to reach the most vulnerable populations, such as those living in poor but high prevalence areas, adolescents, and young black MSM, should be formally studied to identify those strategies that are most successful.

Projects to assess feasibility (i.e., demonstration projects) should include multidisciplinary support services and be coordinated to facilitate collaboration and avoid duplication. For instance, communication and collaboration between CDC and HRSA will permit leveraging of scarce resources.

In sum, important issues about PrEP that should be addressed include:

- Safety and tolerability profiles in different subpopulations and during differing lengths of follow-up, including long-term follow-up in patients using PrEP for extended periods of time.
- The impact of social determinants, stigma, gender, age, socioeconomic status, ethnicity/race, on adherence.
- The impact of different patterns of use on efficacy
- The role of risk compensation
- Resistance profile, based on length of use and adherence to guidelines once established
- Best practices in terms of HIV test methodology (e.g., home testing), mix of providers, physician and patient education, type of counseling, monitoring (HIV testing, kidney functioning, bone health, sexual health) and best practices for provider training

Table 1: Summary of Available PrEP Safety Data (a)

	iPrEX		Partners PrEP			US-TDF		TDF-2		FEM-PREP
Randomized Arm	TDF/FTC	Placebo	TDF	TDF/FTC	Placebo	TDF	Placebo	TDF/FTC	Placebo	Combined
N	1251	1248	1584	1579	1585	205	199	601	599	2020
	%	%	%	%	%	%(c)	%(c)	%	%	%
Any adverse AE	NR (b)	NR	NR	NR	NR	NR	NR	89%	85.6%	63.2%
Grade 3 or 4 AE	12%	13%	NR	NR	NR	13.2%	9.9%	NR	NR	NR
Serious AE	5%	5%	6.8%	6.8%	6.6%	NR	NR	9.2%	8.5%	NR
Death	<1%	<1%	0.5%	0.4%	0.6%	NR	NR	0.3%	0.7%	NR
Creatinine Elevation (Grades 1-4)	2%	1%	NR	NR	NR	NR	NR	0.0%	0.0%	3.4%
Confirmed Creatinine Elevation	0.4%	0%	1.1%	1.3%	0.8%	NR	NR	NR	NR	NR
Creatinine Elevation (Grade 1)	NR	NR	NR	NR	NR	0.5%	0.0%	NR	NR	NR
Creatinine Elevation (Grade 2)	NR	NR	NR	NR	NR	0.5%	1.1%	NR	NR	NR
Creatinine Elevation (Grade 2+)	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.3%
Hypophosphatemia	NR	NR	NR	NR	NR	NR	NR	36.3%	40.1%	15.6%
Confirmed Hypophosphatemia	NR	NR	8.7%	8.4%	8.3%	NR	NR	NR	NR	NR
Hypophosphatemia (Grade 3+)	NR	NR	NR	NR	NR	0.5%	2.6%	3.5%	4.0%	3.6%
Depression	3%	5%	NR	NR	NR	9.2%	12.2%	NR	NR	NR
Headache	4%	3%	NR	NR	NR	9.9%	12.6%	37.8%	37.4%	13.6%
Diarrhea (month 1)	4%	4%	1.6% (4.1%)	1.8% (4.5%)	1.4% (2.8%)	15.4%	21.2%	12.6%	10.9%	1.2%
Nausea (month 1)	2%	<1%	1.6% (6.3%)	1.7% (5.9%)	1.5% (4.5%)	9.9%	5.0%	18.8%	7.2%	4.1%
Vomiting	NR	NR	NR	NR	NR	NR	NR	11.5%	6.8%	2.2%
Dizziness	NR	NR	NR	NR	NR	6.2%	3.4%	15.3%	10.7%	NR
Weight Decreased	2%	1%	NR	NR	NR	NR	NR	NR	NR	NR
BMD Decrease	1.0%	0.0%	NR	NR	NR	6.3%	3.7%	NR	NR	NR
Fractures	1.2%	0.8%	NR	NR	NR	5.5%	1.9%	0.8%	0.7%	NR

(a) Adapted from materials presented on August 19, 2011
(b) NR = not reported on August 19, 2011
(c) Rate per 100 person year

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