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Systemic and topical drugs for the prevention of HIV infection: antiretroviral pre-exposure prophylaxis

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Abstract

Pre-exposure prophylaxis (PrEP), in which HIV uninfected persons use oral or topical antiretroviral medications to protect against HIV acquisition, is a promising new HIV prevention strategy. The biologic rationale for evaluation of PrEP for sexual HIV prevention included non-human primate models and antiretroviral prophylaxis for HIV-exposed infants. Proof-of-concept that PrEP protects against sexual HIV acquisition has been demonstrated in four clinical trials, which used the antiretroviral medication tenofovir, either as a vaginal gel or as daily oral tenofovir disoproxil fumarate, alone or co-formulated with emtricitabine. Importantly, however, two trials failed to demonstrate HIV protection with PrEP, with low adherence to daily use of PrEP the leading hypothesis for lack of efficacy. Next steps in the field include rigorous evaluation of uptake and adherence to PrEP in implementation settings and research into 'next-generation' PrEP agents with longer half-life and less user-dependence.

Introduction

The development and wide-scale roll-out of effective antiretroviral medications has revolutionized HIV treatment worldwide. Use of combination antiretroviral therapy by HIV infected persons is life-saving and these agents are the cornerstone of strategies to prevent HIV transmission from mother to child. During the past 10 years, a growing scientific and advocacy interest in antiretroviral-based strategies for prevention of sexual HIV transmission in adults has developed, and antiretroviral-based HIV prevention interventions are now among the most promising strategies for dramatically reducing HIV spread. For HIV-infected persons, observational data and one randomized trial have demonstrated that initiating combination antiretroviral therapy results in markedly reduced risk of HIV transmission to sexual partners (1–3). The clinical and prevention benefits of treating HIV infection with antiretroviral therapy, including earlier in the course of HIV infection, must become part of the lexicon for those who care for HIV-infected patients.

For HIV-uninfected persons with repeated and ongoing HIV exposures, primary prevention strategies remain urgently needed. Use of antiretrovirals as pre-exposure prophylaxis (PrEP) – specifically, in which HIV uninfected persons use oral or topical antiretroviral medications to protect against HIV acquisition – is a promising new primary HIV prevention strategy.

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The past two years have seen significant new advances in HIV prevention as a result of antiretroviral-based PrEP. This review will focus on the rationale and evidence for PrEP for HIV prevention, hypotheses to explain areas of uncertainty in the available data, and next steps for the field.

Rationale for evaluation of PrEP for HIV prevention

The concept of chemoprophylaxis against an infectious disease is an established one – for example, chemoprophylaxis against malaria is routinely done when non-immune individuals visit or live in endemic areas. The idea that antiretroviral medications, which had been developed for treatment of HIV infection, could be used by uninfected persons as chemoprophylaxis against virus acquisition was first considered approximately a decade ago (4). For individuals with a single, isolated HIV exposure (e.g., a needlestick occupational injury, sexual assault), post-exposure prophlyaxis (PEP), with generally a four-week course of antiretrovirals, is used to reduce risk of HIV infection after a high-risk exposure. Transitioning from PEP to PrEP involves, at minimum, extending antiretroviral use to initiate prior to HIV exposure, and ideally, for those with ongoing and repeated exposures, continuing use throughout the period of risk. HIV exposures may be unrecognized or unacknowledged by those with high-risk behaviors, and PrEP thus offers substantial advantages over PEP. Animal models of PEP and human cases of failure of PEP demonstrate the importance of prompt initiation of PEP after exposure, which canbe a major challenge; PEP is also impractical for repeated exposures.

While a number of antiretroviral medications could have been considered as potential first candidates for evaluation as PrEP agents, the greatest amount of data available is based on the nucleotide reverse transcriptase inhibitor tenofovir, as a topical microbicide gel, oral tenofovir disoproxil fumarate (TDF), and oral combination emtricitabine (FTC)/TDF. Tenofovir, which as TDF (as branded Viread®) and FTC/TDF (Truvada®) is licensed for treatment of HIV infection, has several qualities that made it a potentially important PrEP agent: potency with activity against all HIV subtypes, rapid onset of activity, and early action in HIV's lifecycle, which could be important for blocking initial infection. TDF is a recommended component of first-line combination antiretroviral therapy regimens for persons with HIV infection, and its widespread use as part of combination antiretroviral therapy meant that a substantial and reassuring safety and tolerability profile was available. TDF is administered once-daily for HIV treatment, at a dose of 300 mg (FTC/TDF also includes 200 mg of FTC); this same standard dose was chosen for studies of PrEP.

Animal model studies provided evidence in support of use of antiretrovirals for PrEP. Macaque SHIV challenge studies (5) have tested drug dosing to mimic oral dosing in humans and repeat low-dose mucosal virus challenges to mimic sexual exposure to HIV. Overall, these studies indicated high levels of protection from topical tenofovir gel (6) and daily oral dosing of TDF and FTC/TDF (5; 7), as well as FTC/TDF dosed intermittently (3 days before and 2 hours after rectal viral exposure) (8). Some evidence found greater HIV protection from combination FTC/TDF than TDF alone, suggesting that combination PrEP could provide greater benefit than from a single agent.

Additional rationale for PrEP for HIV prevention stems from efficacy of antiretrovirals for the prevention of mother-to-child transmission of HIV, which relies on a combination of maternal treatment and infant prophylaxis. Studies demonstrated that post-natal antiretrovirals, provided to infants who have ongoing exposure to HIV through breastmilk, can substantially reduce HIV risk (9). The analogy between infants with ongoing and repeated HIV exposure through breastmilk and adults with ongoing and repeated sexual HIV

exposure is compelling – indicating that antiretroviral prophylaxis could be highly efficacious for preventing infection as a result of sexual exposure (10).

Efficacy trials of topical and oral PrEP

Seven randomized, double-blind, placebo-controlled clinical trials of PrEP – using tenofovir gel or daily oral TDF or FTC/TDF – and involving >19,000 participants, from four continents and multiple risk groups, are completed or ongoing (Table 1, listed in chronological order of reporting of their results). Six trials included African women at risk of heterosexual HIV acquisition: 1) CAPRISA 004 (CAPRISA is the Center for AIDS Programme of Research in South Africa), 2) FEM-PrEP, 3) Partners PrEP, 4) TDF2, 5) VOICE (VOICE is the acronym for Vaginal and Oral Interventions to Control the Epidemic study), and 6) FACTS 001 (FACTS is the Follow-on African Consortium for Tenofovir Studies). Two of these studies also enrolled African heterosexual men (Partners PrEP, TDF2). One study -- iPrEx (the name represents the Spanish acronym for PrEP Initiative) – enrolled men who have sex with men (MSM) from the Americas, Thailand, and South Africa. Finally, one study enrolled injection drug users (Bangkok Tenofovir Study). Together, these trials provide a comprehensive picture of the global HIV epidemic and the potential for PrEP to reduce HIV incidence in key at-risk groups.

All trials included monthly study visits with HIV serologic testing (generally with point-of-care rapid tests), provision of study medication, and individualized adherence counseling. PrEP was delivered in a context of a package of HIV prevention services, including pre- and post-test HIV counseling, risk-reduction counseling, screening and treatment for sexually transmitted infections, free provision of condoms, and other services (e.g., access to PEP and referral for male circumcision for heterosexual men) according to availability and national standards. Thus, it is important to remember that randomized trials of PrEP assessed whether this intervention had efficacy for HIV prevention over and above standard HIV prevention services.

CAPRISA 004 enrolled 889 HIV uninfected women from Durban and rural KwaZulu-Natal, South Africa who were aged 18–40 years (mean age 24). Participants were randomized to receive 1% tenofovir gel or placebo. Unlikely other completed trials of PrEP, which recommended daily dosing, CAPRISA 004 dosed the study product using a strategy called BAT24 (for before and after sex, not to exceed two doses in 24 hours); this event-driven approach was developed to mimic dosing of peripartum nevirapine prophylaxis as used for prevention of mother-to-child HIV transmission and resulted in an average of 6 applications of gel per month. Overall, compared to those randomized to placebo, those receiving tenofovir gel had a reduced risk of HIV acquisition – by 39% (95% CI 6–60%, p=0.017) (11). In the subgroup of women who reported >80% adherence to gel use, efficacy was estimated to be 54% (p=0.025). Furthermore, in a case-control analysis of cervicovaginal fluid tenofovir levels among HIV seroconverters and matched controls, women with levels >1000 ng/mL had 74% lower risk of HIV infection than those with <1000 ng/mL (12). An unexpected additional result of CAPRISA 004 was a 51% reduction in HSV-2 incidence among women assigned to the tenofovir gel arm, which is consistent with subsequent *in vitro* studies that demonstrated direct anti-herpetic activity with high concentrations of tenofovir diphosphate, the active intracellular metabolite of tenofovir (13). Concentrations of tenofovir diphosphate in vaginal tissues are approximately 100-fold higher with 1% tenofovir gel dosing compared to oral dosing using TDF (14), and thus oral TDF PrEP theoretically will be less likely than vaginal application of tenofovir gel to provide protection against HSV-2. One important finding in CAPRISA 004 was the 9.1 per 100 women-years HIV incidence in the placebo arm, an extraordinarily high rate, emphasizing an incredible prevention need for young women in South Africa. The FACTS 001 study,

initiated in 2011, is replicating the CAPRISA 004 BAT24 intervention in a randomized, placebo-controlled trial among a larger population of women from diverse sites across South Africa (15). Tenofovir vaginal gel is not currently licensed in any country and continued accumulation of efficacy (and safety) data for this novel product makes FACTS 001 important for determining whether tenofovir gel will one day be available for HIV (and possibly HSV-2) prevention.

The iPrEx study enrolled 2499 HIV seronegative MSM and transgender women from North and South America, South Africa and Thailand in a randomized placebo-controlled trial of daily oral FTC/TDF. The majority of men were enrolled from the South American sites; 9% were from the US. Eligible men had behavioral characteristics defining higher risk for HIV acquisition: anal sex with 4 or more male partners, a diagnosis of a sexually transmitted infection, transactional sex activity, or condomless anal sex with a partner who was HIV infected or of unknown infection status in the prior 6 months. Overall, the iPrEx study demonstrated that FTC/TDF reduced HIV acquisition risk by 44% (95% CI 15–63%, p=0.005). Like CAPRISA 004, additional analyses indicated higher efficacy among those measured to have higher adherence: 73% among those with ≥90% adherence as measured by pill counts of returned, unused study product (16). Adherence was assessed by a strongly objective measure of pill-taking – plasma and intracellular drug levels, measured in at the visit closest to seroconversion in those who seroconverted as well as a matched visits in a subset of non-seroconverters. Only 8% of seroconverters and 54% non-seroconverters had detectable tenofovir or emtricitabine; having detectable drug was strongly associated with substantially lower risk of acquiring HIV (relative reduction in risk 92%, 95% CI 40–99%, p<0.001). The low level of detection of drug in the non-seroconverters indicates that overall adherence in the study population was only moderate; correlates of higher adherence included age >25 years, participants from US sites, and recent unprotected anal receptive sex – the last reassuring that those at highest risk of HIV were more, and not less, likely to use the medication (17).

The FEM-PrEP study enrolled 2021 high-risk HIV uninfected women from Kenya, South Africa, and Tanzania into a placebo-controlled trial of daily oral FTC/TDF – thus, an identical design to iPrEx. The mean age of study participants was 24 years. The study was stopped by its Independent Data Monitoring Committee in April 2011 due to futility when equal numbers of infections were seen in each of the two study arms. Final results of the trial were presented in March 2012: a total of 68 infections were observed – 35 among those randomized to placebo and 33 among those randomized to FTC/TDF (efficacy estimate of 6%, not statistically significant). Follow-up assessments demonstrate that adherence was very low in FEM-PrEP: in a matched case-control analysis, only 26% of non-seroconverters had consistent tenofovir levels detected in plasma (and only 15% of seroconverters as well) (18). The study team concluded that study drug adherence was too low to assess the efficacy of FTC/TDF PrEP for HIV prevention in the study population – with estimated overall adherence in the study <30%, the statistical ability to demonstrate any HIV protection was irrevocably compromised. Notably, in standardized surveys, most subjects in FEM-PrEP (70%) reported they perceived themselves to have little or no chance of acquiring HIV. Low risk perception (in spite of HIV incidence of 5.0 per 100 person-years in the placebo arm) may be an explanation for low product use in the FEM-PrEP trial.

The TDF2 study enrolled 1200 heterosexual HIV uninfected men and women between the ages of 18 and 39 in Botswana into a placebo-controlled trial of daily oral FTC/TDF. The study reported results in July 2011: 63% efficacy (95% CI 22–83%, p=0.01) for HIV protection among those randomized to FTC/TDF PrEP compared to placebo (19). Among those known to be receiving study product at the time of seroconversion (i.e., censoring follow-up time for those who had been lost to follow-up or had study product held for other

reasons), efficacy was 78% (95% CI 41–94, p=0.005). The trial was relatively small – only 33 seroconversions were observed overall and only 29 during time periods when subjects were receiving study product – and thus the ability to demonstrate differences by gender was somewhat limited. Nonetheless, efficacy estimates suggested protection for both men (overall: 80%, p=0.03; subgroup receiving medication: 82%, p=0.06) and women (overall: 49%, p=0.1; subgroup receiving medication: 76%, p=0.02).

The Partners PrEP Study (for which we are the lead investigators) is a three-arm placebo-controlled trial of daily oral TDF and FTC/TDF among 4758 HIV serodiscordant couples from Kenya and Uganda in which the HIV-infected partner was not eligible for ART according to national guidelines at the time of enrollment; the HIV uninfected partners are randomized to receive PrEP or placebo (20). On July 10, 2011, the study's Data Safety Monitoring Board recommended that the placebo arm be discontinued due to meeting pre-determined stopping guidelines for efficacy. The Partners PrEP Study demonstrated 67% efficacy of TDF (95% CI 44–81, p<0.001) and 75% efficacy of FTC/TDF (95% CI 55–87, p<0.001) compared to placebo; the difference between TDF and FTC/TDF was not statistically significant (p=0.23). Both TDF and FTC/TDF significantly reduced HIV risk for both men and women (21) – for TDF 63% (p=0.01) for men and 71% (p=0.002) for women and for FTC/TDF 84% (p<0.001) for men and 66% (p=0.005) for women – the differences in efficacy for men versus women for both TDF and FTC/TDF were not statistically different (p=0.65 and p=0.24, respectively, for the interaction p-value, indicating that the degree of HIV protection for both medications was similar across genders). Adherence to study drug was very high based on clinic-based pill counts of unreturned study medication as well as electronic monitoring and home visits for unannounced pill counts done at 3 of the 9 study sites (22). Like iPrEx, tenofovir measurement in blood samples was done to further explore use of study product and its association with HIV protection. Tenofovir was detected in plasma in 82% of samples from a randomly-selected subpopulation of non-seroconverters (confirming high adherence to PrEP in the trial); detection was less frequent (31%) in those who acquired HIV. Detection of tenofovir was associated with substantial HIV protection (86%, p<0.001 for the TDF arm and 90%, p=0.002 for the FTC/TDF arm) (23).

The VOICE trial is an ongoing five-arm study among 5021 HIV uninfected women from South Africa, Uganda, and Zimbabwe in which daily 1% tenofovir gel, daily oral TDF, and daily oral FTC/TDF are being evaluated for safety and effectiveness compared to respective gel/oral placebos. The Data Safety Monitoring Board for the VOICE trial recommended discontinuation of the oral TDF arm in September 2011 (24) and the daily vaginal 1% tenofovir gel arm in November 2011 due to inability to demonstrate efficacy (25). Further information – including objective measures of adherence – is not yet available from the trial as the FTC/TDF and oral placebo arms remain ongoing. The VOICE trial will complete follow-up by mid-2012, with results expected in 2013.

Lastly, the Bangkok Tenofovir Study trial of daily oral TDF among HIV uninfected injection drug users compared to placebo is fully enrolled with 2413 participants and is anticipated to have efficacy results in 2012. A majority of the participants are enrolled in methadone replacement programs, where they receive their study medication, essentially as directly-observed PrEP (26).

Understanding the divergent results of PrEP efficacy trials

Evidence from four randomized clinical trials – CAPRISA 004, iPrEx, TDF2, and Partners PrEP – provide clear evidence of HIV protection due to PrEP, with efficacy estimates ranging from 39–75% in the intention-to-treat comparisons and 90–92% among those using

the study medication, as measured by levels of drug in blood. Thus, it is clear that tenofovir-based PrEP protects against HIV, in both MSM and heterosexual populations at high risk for acquiring the virus. The lack of efficacy in two trials – FEM-PrEP (testing FTC/TDF) and VOICE (testing TDF and daily tenofovir gel) – as well as the range of efficacy estimates in the other trials indicates that there are important factors that influence PrEP efficacy. Statistical, biologic, and behavioral hypotheses have been offered.

While statistical chance could explain divergent PrEP efficacy findings, the strength of evidence when trials are taken together argues against this hypothesis. For example, the FTC/TDF efficacy estimate for Partners PrEP was 75%, with a p-value of <0.0001 – indicating a less than 1 in 10,000 chance that this result would be observed if FTC/TDF truly has no protection against HIV, as was found in the FEM-PrEP trial. Moreover, the TDF2 findings, consistent with Partners PrEP, would be even more unlikely. Consistent, replicated findings are critically important to the scientific process, as such results are expected to occur when an intervention is equivalently implemented in different populations – for example, the three trials of male circumcision for prevention of HIV acquisition in men (27–29). Thus, different results in different PrEP trials most plausibly reflects important differences in the study populations or delivery of or uptake of the intervention, rather than statistical chance.

Biological hypotheses to explain divergent PrEP trial results have generally focused on trying to explain why PrEP would not work in higher-risk women, like those enrolled in FEM-PrEP and VOICE. Intensive PK studies indicate that oral dosing of TDF achieves higher concentrations (by a factor of 10-fold) in rectal tissue compared to cervicovaginal tissue (30; 31), suggesting a hypothesis that oral PrEP could be less effective in women, whose primary exposure is through vaginal sex, compared to MSM whose primary risk is through receptive anal sex. However, gender-specific subgroup results from Partners PrEP and TDF2 suggest high efficacy in women – with equivalent protection to that found in men – providing objective evidence that PrEP does provide protection in women. Important co-factors for HIV acquisition – including genital tract infections and mucosal inflammation, contact with partners with high viral loads including during acute HIV infection, and potentially other factors such as intravaginal practices and use of hormonal contraception (32; 33) – are potentially key risk factors in the FEM-PrEP and VOICE populations. However, for these factors to result in null efficacy for PrEP among women would require that they not only increase the baseline HIV risk in the population (which would elevate risk in both the placebo and active arms, without necessarily diminishing the relative protection provided by PrEP) but that they negate PrEP protection. Subgroup analyses from Partners PrEP – including among women and among subjects whose HIV-infected partners were known to have higher plasma viral loads – suggests that PrEP efficacy was not diminished in higher-incidence subgroups. Understanding the interplay of biologic risk and HIV protection for PrEP is a clear priority.

One specific biologic consideration is the difference in efficacy results for tenofovir gel seen in the CAPRISA 004 and VOICE trials. While statistical chance could explain the findings (the lower limit of the 95% confidence interval for efficacy for CAPRISA 004 was 6%), one important consideration between the two trials is the dosing schedule – used with coitus only for CAPRISA 004 versus daily for VOICE. While pre-clinical and early safety studies suggested daily use of tenofovir gel posed no obvious safety concerns, the hypothesis that daily use of a hyperosmolar product on a mucosal surface results in a different benefit/toxicity balance will be a focus of ongoing investigation. Lower adherence to gel used daily versus with sex is an alternative consideration.

The strongest hypothesis to explain differential results across PrEP trials is differences in adherence. Inarguably, PrEP cannot work if it is not taken. Missed doses and missed visits to collect PrEP study medication diminish benefit – an effect that might be particularly profound if PrEP is not missed at random with those at greater HIV risk or periods of highest risk uncovered by PrEP. Thus, efficacy estimates from the clinical trials are underestimates of the true biologic efficacy of the products for preventing HIV infection – as evidenced by the gaps between efficacy estimates and protection estimates when tenofovir was present in blood seen in iPrEx and Partners PrEP. Objective adherence measures show that PrEP use was high, modest, and low in Partners PrEP, iPrEx, and FEM-PrEP, respectively, and that HIV protection followed this overall degree of use (Table 2). Importantly, some HIV seroconverters in PrEP trials had some study medication detected at the time seroconversion was measured – understanding whether these are truly breakthrough infections or instead reflect PrEP reinitiation after a high-risk exposure is a priority. Differential penetration of the metabolites of TDF and FTC in cervical, vaginal, and rectal tissues could theoretically make oral TDF-based PrEP more vulnerable to non-adherence in women than men, and analyses of the relationship between adherence and efficacy will likely be a priority for analyses from the still-ongoing VOICE trial.

Additional outcomes from PrEP clinical trials: safety, resistance, sexual behavior

Completed clinical trials of PrEP included a number of outcomes in addition to efficacy for HIV prevention, with the goal of better understanding the risks and benefits related to PrEP. Among these additional outcomes, three have been raised most commonly: clinical safety, antiretroviral resistance, and sexual behavior.

For all PrEP clinical trials, safety has been a co-primary endpoint along with HIV prevention efficacy. For a preventive intervention, safety may be particularly important, arguably even more so than for a therapeutic intervention; more specifically, individuals taking PrEP to prevent an infection they do not have and may have only a fractional chance of acquiring must be assured a high degree of safety, while HIV-infected persons taking antiretrovirals for treatment reasons certainly face a different risk-benefit calculus, since treatment is life-saving. Reassuringly, completed PrEP clinical trials (CAPRISA 004, iPrEx, FEM-PrEP, TDF2, Partners PrEP) have shown that oral and topical tenofovir-based therapy appears to be well-tolerated among HIV-uninfected persons, with the rate of both serious and mild adverse events generally balanced between those receiving PrEP and those receiving placebo. For trials with modest or low adherence to PrEP (e.g., iPrEx, FEM-PrEP), there is the caveat that safety cannot be fully assessed in the absence of drug; however, side effect and adverse event rates were also reassuring in the Partners PrEP Study, where adherence was high. In both iPrEx and Partners PrEP, gastrointestinal side effects (e.g., nausea, diarrhea) occurred more commonly in those assigned active PrEP, although these symptoms were present only in a minority of subjects (~10% or less), were mild in severity, and were generally limited to the first month after initiation of the medication; this observation suggests that targeted counseling to anticipate time-limited side effects might help improve long-term adherence. A modest but statistically significant 1% reduction in bone mineral density was observed in the FTC/TDF arm in the iPrEx study and in an earlier phase II study of TDF PrEP in MSM (34), compared to placebo; this decline in bone mineral density is a known effect of tenofovir in studies of HIV treatment – the effect appears to be early then stabilizes, was not associated with increased risk of bone fracture, and was partially reversed after PrEP discontinuation. Oral TDF has been associated with renal complications in HIV-infected persons, particularly proximal tubular dysfunction with or without reduced glomerular filtration; however, renal complications are rare and have frequently occurred in persons with coexistent risk factors, such as pre-existing renal disease, advanced HIV

infection, and use of nephrotoxic medications. PrEP clinical trials have not found increased risk of renal complications associated with PrEP, but ongoing safety monitoring will be an essential component of PrEP roll-out. Finally, data from Partners PrEP (35), from clinical studies of women using TDF-containing combination antiretroviral therapy for HIV treatment, and from the Antiretroviral Pregnancy Registry (36) suggest that use of TDF and FTC/TDF in early pregnancy is not associated with increased rates of birth defects and adverse pregnancy outcomes, although more data are needed to fully assess the safety of these medications through pregnancy.

Antiretroviral resistance is a concern for PrEP, because individuals who become infected with HIV in spite of PrEP use will have weeks or even months of mono- or dual-agent antiretroviral therapy before seroconversion is detected and PrEP discontinued, which could select for resistant variants. In PrEP clinical trials, resistance has been rare to date. In CAPRISA 004, no antiretroviral resistance to tenofovir (i.e., the K65R mutation) was detected using standard population sequencing in HIV samples obtained from HIV seroconverters. In iPrEx, resistance to emtricitabine (i.e., M184I/V mutations) was detected in two participants randomized to FTC/TDF who had seronegative acute HIV infection at the time of randomization. For these two individuals, emtricitabine resistance was no longer detectable, even by ultrasensitive resistance testing, six months after PrEP discontinuation (37). In Partners PrEP, 2 of 8 individuals who were randomized to PrEP during seronegative acute HIV infection developed resistance mutations (one K65R and one M184V mutation) (21). However, in both iPrEx and Partners PrEP, no subjects who acquired HIV after PrEP initiation acquired mutations conferring resistance to TDF or FTC, consistent with low PrEP use among those who acquired HIV. Thus, a model of resistance risk related to PrEP is emerging: in the presence of high PrEP adherence infection is largely prevented and resistance thus cannot occur, in the absence of PrEP use infection may occur but drug pressure is absent and resistance does not develop. Whether there is a more dangerous middle-ground – i.e., modest PrEP use, conferring diminished HIV protection but sufficient drug pressure to select for resistance – is a key question for ongoing studies of PrEP but it appears this concern is theoretical at this time. Clearly, HIV testing to prevent PrEP initiation by those already infected, including those recently infected, is a high priority.

Finally, the question of sexual risk compensation – i.e., increased sexual risk-taking accompanying PrEP use – has been explored in all PrEP trials. The question is not specific to PrEP – indeed, whether individuals will change their behavior in a way that might undermine the HIV protective effects of partially-protective biomedical prevention strategies (e.g., male circumcision, antiretroviral treatment) has been raised for a number of years (38). In iPrEx and Partners PrEP, there was no evidence of behavioral risk compensation – more specifically, self-reported condom use increased during the studies, to an equivalent degree across both active PrEP and placebo arms.

Current understanding and future directions for PrEP

Efficacy trials have demonstrated safety and efficacy of topical and oral PrEP among MSM and heterosexual populations from diverse settings, with the degree of HIV protection strongly tied to adherence. Simply put: if taken, PrEP works. The available data on PrEP safety and efficacy from the completed trials in MSM and heterosexual populations led the Antiviral Drugs Advisory Committee to the US Food and Drug Administration to recommend recently that a formal label indication for HIV prevention be made for branded FTC/TDF (Truvada®) – a landmark for HIV prevention.

In addition to important follow-up investigations related to safety, antiretroviral resistance, and sexual behavior, next step questions for PrEP will assess whether implementation

outside of rigorous clinical trials can achieve the high adherence necessary for HIV protection. PrEP trials showing efficacy for HIV protection have converted to open-label studies, to fulfill promises of access to effective products for study participants and to understand adherence and sexual behavior in the absence of placebo. The iPrEx Open Label Extension study (iPrEx OLE) is assessing adherence behaviors and appropriate counseling to motivate adherence among MSM now that PrEP protection is known. Ongoing follow-up in Partners PrEP is assessing similar questions, and an open-label provision of PrEP to participants in the TDF2 study is expected. A number of additional demonstration projects of PrEP are planned, in diverse populations and geographic settings.

The Partners PrEP and TDF2 trials provide strong evidence for PrEP efficacy among African heterosexual populations, who make up the largest portion of the global epidemic. Partners PrEP enrolled HIV serodiscordant couples who recognized their risk of HIV (39), and achieved high adherence to daily oral PrEP; serodiscordant couples in Africa account for a substantial proportion of new HIV infections in Africa, and are an increasing focus of HIV prevention efforts (40). New strategies for HIV prevention for serodiscordant couples could involve a staged approach, with PrEP for the HIV uninfected partner until the infected partner becomes eligible for and successfully initiates antiretroviral therapy, including achieving viral suppression (41). A follow-on study to Partners PrEP will evaluate this staged approach in Kenyan and Ugandan HIV serodiscordant couples, an important next step after the HPTN 052 and Partners PrEP efficacy results.

Additional analyses – particularly examining adherence – in the FEM-PrEP and VOICE studies will be necessary to understand fully what those trials mean for PrEP use in high-risk women in some African settings. At the same time, much more needs to be understood about targeting of PrEP to those at highest risk in order to be a cost-effective intervention (41–43), evaluating delivery models to optimize PrEP roll-out, and motivating and monitoring adherence to PrEP. Longer-term safety, adherence, and HIV acquisition risk need to be assessed in the context of less frequent visits and briefer counseling than was provided in the intensive proof-of-concept trials; most demonstration projects are planning less-intensive visits, spaced less often (e.g., quarterly).

Some persons at risk of HIV would prefer to use PrEP intermittently, which requires greater understanding of the pharmacokinetics and adherence to intermittent dosing of tenofovir-based PrEP. The potential for intermittent dosing of oral FTC/TDF is being evaluated in HPTN 067 with a focus on pharmacokinetics, adherence and risk behaviors (44) and in a recently-initiated trial among MSM in France and Canada (IPERGAY) (45). While macaque studies demonstrate biologic feasibility of intermittent oral PrEP dosing, human studies are needed to determine the extent to which individuals at high risk of HIV are able to anticipate sexual activity and achieve sufficient pre-exposure and post-exposure dosing to confer protection. For some individuals, periodic use of PrEP – for example during periods when attempting to conceive – could be envisioned (46). For the vast majority of individuals, PrEP should be envisioned as a time-limited prevention strategy, for periods (months to a few years) of highest behavioral risk – indeed, time-limited PrEP is an important contrast to use of antiretrovirals as treatment, which is necessarily life-long. Guidelines from WHO and CDC are in development and will help guide use of PrEP in clinical settings.

Next-generation PrEP

The PrEP field is also evaluating new candidate products, including new classes of antiretrovirals (non-nucleoside reverse transcriptase inhibitors [dapivirine and rilpivirine] and CCR5 coreceptor antagonists [maraviroc]), as well as sustained release delivery systems to provide more options with less dependence on coitally-dependent or daily dosing.

Dapivirine has excellent safety and sustained dispersion in a vaginal ring formulation developed by the International Partnership for Microbicides (47), and will be studied for efficacy in collaboration with the US Microbicides Trials Network (MTN 020, ASPIRE trial), beginning in 2012. Oral maraviroc will be evaluated in a comparative safety and tolerability study in MSM (HPTN 069). Dapivirine and maraviroc are being co-formulated in a vaginal ring formulation. Animal studies also are being used to identify potential new PrEP candidates, including topical maraviroc (48) and raltegravir (49). Rilpivirine, a NNRTI recently-licensed for treatment, has been formulated into a parenteral formulation for prolonged plasma exposure, and is being evaluated for pharmacokinetics and dose ranging in early clinical trials (50). Tenofovir is being developed for a vaginal ring formulation and is currently in pre-clinical evaluation; tenofovir gel has recently been reformulated in an isoosmolar formulation for rectal application, which will be evaluated for safety and pharmacokinetics among MSM in a Microbicide Trials Network study that will be initiated in 2012.

Conclusions

Proof-of-concept has been demonstrated for tenofovir-based topical PrEP for primary prevention of HIV infection. Analyses from ongoing and completed PrEP trials will provide a more complete understanding of effectiveness in different populations, particularly the relationship between adherence and efficacy. Demonstration projects in populations where PrEP has been found to be effective are initiating this year, evaluating targeted implementation and cost-effectiveness of PrEP in different populations around the world. Effective HIV prevention requires choices of primary prevention strategies, such as PrEP, in synergy with other established prevention strategies (behavior change, HIV testing, male circumcision) and scale-up of secondary prevention activities, particularly ART for HIV-infected persons. While the public health impact of PrEP is anticipated to be greater as products and delivery systems with sustained coverage are identified, studies evaluating new products will take several years to complete. In the meantime, targeted provision of daily oral tenofovir-based PrEP to populations at high-risk of HIV acquisition should be evaluated for including as part of combination HIV prevention programs. Implementation of PrEP will face logistical, cost, and commitment hurdles but the scientific evidence to support this new HIV prevention strategy is strong, opening up a new avenue for prevention that could alter the course of the HIV epidemic.

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Table 1

Efficacy trials of topical and oral PrEP

Study (location)	Population	N	PrEP Agent	Status	References
CAPRISA 004 (South Africa)	Women	889	Tenofovir vaginal gel (coitally-associated use)	39% reduction in HIV incidence	(11)
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, US)	Men who have sex with men and transgender women	2499	FTC/TDF	44% reduction in HIV incidence	(16)
FEM-PrEP (Kenya, South Africa, Tanzania)	Higher-risk women	2120	FTC/TDF	Trial stopped early for lack of efficacy	(18)
TDF2 Study (Botswana)	Young heterosexual men and women	1200	FTC/TDF	62% reduction in HIV incidence	(19)
Partners PrEP Study (Kenya, Uganda)	Heterosexual HIV Serodiscordant couples	4758	TDF, FTC/TDF	67% reduction in HIV incidence for TDF 75% reduction in HIV incidence for FTC/TDF	(21)
VOICE (South Africa, Uganda, Zimbabwe)	Women	5021	TDF, FTC/TDF, Vaginal tenofovir gel (daily use)	Oral TDF and vaginal tenofovir gel arms stopped early for lack of efficacy, FTC/TDF arm results expected early 2013	(24; 25)
Bangkok Tenofovir Study (Thailand)	Injection drug users	2400	TDF	Ongoing, results expected late 2012	(26)
FACTS 001 (South Africa)	Women	2600	Vaginal tenofovir gel (coitally-associated use)	Initiated October 2011	(15)

Table 2

Efficacy estimates and PrEP adherence in four trials of oral FTC/TDF PrEP

Study	Population	HIV protection estimate (randomized comparison versus placebo)	HIV protection estimate (as related to high adherence)
iPrEx	Men who have sex with men and transgender women	44%	92% in subjects with detectable tenofovir levels
FEM-PrEP	Higher-risk women	6%	<30% of non-seroconverters with detectable tenofovir levels
TDF2	Young heterosexual men and women	62%	78% excluding follow-up periods when subjects had no PrEP refills for >30 days
Partners PrEP Study	Heterosexual HIV Serodiscordant couples	75%	90% in subjects with detectable tenofovir levels