e-ISSN 2249-7552
Print ISSN 2229-7502

International Journal of
Preclinical & Pharmaceutical Research

Journal homepage: www.preclinicaljournal.com

CONCEPT OF PrEP (PRE-EXPOSURE PROPHYLAXIS) AND ROLE OF ADHERENCE IN IT

Matin Ahmad Khan[1], Ramji Lal Agarwal[2], Arun Kumar[3], Lakshman Lal[4], Shubhshish Sircar[5], Binod Kumar[6], Uma Shankar Singh[7], Indrajeet Kumar[8], Asish Kumar Biswas[9]

[1]Associate Professor, Dept of Biochemistry, [3]Principal & Professor, Dept of PSM,
[9]Associate Professor, Dept of Pharmacology, Patliputra Medical College & Hospital, Dhanbad, Jharkhand, India.
[2]Associate Professor, Dept of Medicine, Rohilkhand Medical College, Bareilly, Uttar Pradesh, India.
[4]Professor & HOD, Dept of Biochemistry , [5]Associate Professor, Dept of PSM, [6]Assistant Professor, Dept of Pathology,
[7]Assistant Professor, Dept of Pathology, [8]Lecturer, Dept of PSM, MGM Medical College, Jamshedpur, India.

ABSTRACT

PrEP (Pre-Exposure Prophylaxis) has been used in diseases like Malaria and Rabies in the past Recent clinical trials have shown clearly that daily, oral pre-exposure prophylaxis (PrEP) using the antiretroviral drugs tenofovir (TDF) and emtricitabine (FTC) dramatically reduces the risk of HIV infection for HIV negative men and women who take it as directed in situations, when they have substantial higher-than –average risk of contracting an HIV infection. While PrEP won't be right for every individual at risk for HIV, untold numbers of men and women will benefit—if they can access this potentially life-saving option as directed .Adherence is essential .Each of the trials that found benefit also found that people who had high levels of adherence had high levels of protection. Lower adherence has been associated with low or no protection.

Key Words: PrEP, Tenofovir, Emtricitabine,

INTRODUCTION

PrEP, an acronym for Pre-Exposure Prophylaxis is nothing new in preventive medicine. Pre prophylaxis medication has been used in Malaria and Rabies prevention. In HIV dialect; it is the use of prescription drugs by people who do not have HIV/AIDS as a strategy for the prevention of HIV/AIDS. It is an optional treatment which may be taken by people who are HIV negative, but who have substantial, higher-than-average risk of contracting an HIV infection. This strategy involves use of antiretroviral medications (ARVs) to reduce the risk of HIV infection in only people who are HIV-negative. All of the current effectiveness and follow-on trials are testing tenofovir-based regimens—using either TDF/FTC (an antiretroviral containing tenofovir (TDF) and emtricitabine (FTC) that is sold under the brand name Truvada) or TDF (an antiretroviral pill marketed under the brand name Viread).

Based on the data that have been collected to date the US Food and Drug Administration (FDA) announced its approval of daily oral TDF/FTC for PrEP ON 16th. July 2012.

The Centers for Disease Control says that "PrEP is a powerful HIV prevention tool and can be combined with condoms and other prevention methods to provide even greater protection than when used alone. But people who use PrEP must commit to taking the drug every day and seeing their health care provider for follow-up every 3 months." Clearly there is a message of commitment and adherence, without which the whole ethos of PrEP would have no meaning. CDC announced its guidelines for HIV prevention recommending pre-exposure prophylaxis with Truvada to high infection risk populations on 14 May 2014, due to research indicating prophylactic effectivity

Corresponding Author

Matin Ahmad Khan
Email: mak5962@hotmail.com

preventing transmission from mother to child. In July 2014 the World Health Organization issued guidelines saying it "strongly recommends men who have sex with men consider taking antiretroviral medicines as an additional method of preventing HIV infection. PrEP is not to be confused with the similar sounding words like PEP (Occupational -Post Exposure Prophylaxis), nPEP (Non - Occupational Post Exposure Prophylaxis), Treat as Prevention (TasP) and HAART, because involvement of taking anti-AIDS drugs is there in all these modalities.

PrEP (pre-exposure prophylaxis) is only for people who are at ongoing very high risk of HIV infection.

But PEP (post-exposure prophylaxis) is an option for someone who thinks they've recently been exposed to HIV during sex or through sharing needles and works to prepare drugs.

PEP means taking antiretroviral medicines after a potential exposure to HIV in occupational situations like needle stick injury to prevent becoming infected. PEP must be started within 72 hours of possible exposure to HIV. The prescribed HIV medicines ate to be taken twice daily for 28 days. Naturally adherence is again important issue.

nPEP means PEP following non-occupational exposure to HIV (nPEP). Addressing nPEP for significant risk exposures following sexual and needle-sharing activities, needle-sticks outside of occupational settings, and trauma, including human bites. Within the category of sexual exposure, sexual assault merits special focus.. nPEP too must be started within 72 hours of possible exposure to HIV. The prescribed HIV medicines ate to be taken twice daily for 28 days. Adherence is again important issue here.
TasP (Treatment as prevention) TasP is an HIV prevention intervention where treating an HIV-positive person with antiretroviral medication (ART) is used to reduce the risk of transmission of the virus to a negative partner. (Sero-discordant or magnetic couples) The primary purpose of antiretroviral treatment (ART) is to treat HIV disease in order to improve health and extend lifespan TasP is a secondary benefit of ART. CD4 cell count is not a criteria.

To differentiate it from HAART (Highly active Anti-Retroviral Therapy) , it is to be mentioned that HAART to is given to HIV positive persons too as in TasP but a CD4 count is a criteria here while in TasP , CD4 cell count cutoff value is not required. (As in our country to initiate HAART the cut off value for initiation HAART is < 350 CD4 cells/mm3)

INDICATIONS

PrEP is for people without HIV who are at very high risk for getting it from sex or injection drug use. The federal guidelines recommend that PrEP be considered for people who are HIV-negative and in an ongoing sexual relationship with an HIV-positive partner.
This recommendation also includes anyone who isn't in a mutually monogamous relationship with a partner who recently tested HIV-negative, and is a gay or bisexual man who has had anal sex without using a condom or been diagnosed with an STD in the past 6 months, or

- heterosexual man or woman who does not regularly use condoms during sex with partners of unknown HIV status who are at substantial risk of HIV infection (for example, people who inject drugs or women who have bisexual male partners).

- PrEP is also recommended for people who have injected drugs in the past 6 months and have shared needles or works or been in drug treatment in the past 6 months.

- If the partner who is HIV-positive and is considering getting pregnant, she will need to talk to her doctor about PrEP if she is not already taking it. PrEP may be an option to help protect her and her baby from getting HIV infection while she tries to get pregnant, during pregnancy, or while breastfeeding.
- Because PrEP involves daily medication and regular visits to a health care provider, it may not be right for everyone.
- And PrEP may cause side effects like nausea in some people, but these generally subside over time. These side effects aren't life threatening.

Mutually monogamous means that the partners (couple) only have sex with each other and do not have sex outside this relationship**.**

CONTRA-INDICATIONS

Reasons for not using PrEP include the following:

- Persons with HIV should never use PrEP, and an HIV test is necessary before starting to use PrEP.
- Persons with kidney problems, especially decreased renal functions, have increased safety problems with using PrEP
- Persons with hepatitis B have increased safety problems with using PrEP
- Women who are pregnant or breastfeeding should speak with their doctors about potential risk to their children
- Minors may not have access to services which complement the effective use of PrEP, and need extra attention from their doctor if they use PrEP

SCIENCE BEHIND PrEP

Initial studies of PrEP strategies in non-human primates showed a reduced risk of infection among animals that receive ARVs prior to exposure to a simian form of HIV. A 2007 study at UT-South western (Dallas) and the University of Minnesota showed PrEP to be effective

in "humanized" laboratory mice. In 2008, the iPrEx study demonstrated 42% reduction of HIV infection among men who have sex with men and subsequent analysis of the data has suggested that 99% protection is achievable if the drugs are taken every day.

In December 2015, the IPERGAY study was published looking at an alternative strategy of "on-demand" PrEP where Truvada was taken 2–24 hours before sexual activity and only continued for 2 days afterwards. In a population of 400 gay men in France and Canada at high risk for HIV, this strategy led to an 86% drop in HIV infections over the average 9 month follow-up of the study. As of December 2015, non-continuous PrEP methods have not been endorsed by WHO or national guidelines. A number of RCTs have established the efficacy of PrEP with TDF/FTC or TDF alone to prevent HIV transmission among high-risk populations. PrEP has significantly reduced HIV transmission rates among sexually active men and women in Botswana, a country with a high HIV burden9; among serodiscordant heterosexual couples in eastern Africa8; among IDUs in Thailand ; and among a global sample of MSM that included participants in San Francisco and Boston A Cochrane meta-analysis of these studies found a relative risk of acquiring HIV infection of 0.49 (95% confidence interval, 0.28–0.85) for those taking TDF/FTC daily and 0.33 (95% confidence interval, 0.20–0.55) for those taking TDF alone. There was no statistically significant difference in HIV incidence between groups using TDF/FTC compared with TDF alone, and neither group had a significantly increased risk of adverse events. Early results from subsequent open-label studies suggest that PrEP is effective18 and adherence is high19 in real-world as well as investigational settings.

The benefits of PrEP for female patients who do not use intravenous drugs are less clear. Three randomized controlled trials conducted in Africa failed to show any statistically significant reduction in HIV incidence among heterosexual women using daily oral PrEP. Two studies also investigated the use of pre- and post-coital tenofovir vaginal gel, but only one of these found a statistically significant effect on HIV incidence. While non-adherence likely contributed to the lack of effect, the authors of one study noted that some HIV infections occurred in female study participants with detectable serum concentrations of tenofovir.

Trials published to date have investigated only the daily use of TDF or TDF/FTC among adults. Early results show that PrEP may also be effective as a “bridge” to antiretroviral therapy in sero-discordant African couples. RCTs are currently underway to investigate the use of PrEP with TDF/FTC in adolescents, I intermittent “on-demand” dosing with TDF/FTC in adults, and an injectable depot formulation in adults that would only require treatment once every 3 months. Early results from one trial of “on-demand” PrEP for MSM are encouraging.

Table 1. PrEP approaches with agents besides oral Truvada are currently in clinical trials not listed here

Study	Type of PrEP	Study Population	Efficacy	Percent of patients who took medication (adherence)
CAPRISA 004	Pericoital tenofovir gel	South African females	39% reduction of HIV infection[19]	72% by applicator count
iPrEx	Oral emtricitabine/tenofovir	Men who have sex with men and transgender women	42% reduction of HIV infection. 99% reduction estimated with daily adherence	54% detectable in blood
Partners PrEP	Oral emtricitabine/tenofovir; oral tenofovir	African heterosexual couples	Reduction of infection by 73% with Truvada and 62% with tenofovir	80% with Truvada and 83% with tenofovir] detectable in blood
TDF2	Oral emtricitabine/tenofovir	Botswana heterosexual couples	63% reduction of infection	84% by pill count
FEM-PrEP	Oral emtricitabine/tenofovir	African heterosexual females	No reduction (study halted due to low adherence)	<30% with detectable levels in blood
VOICE 003	Oral emtricitabine/tenofovir; oral tenofovir; vaginal tenofovir gel	African heterosexual females	No reduction in oral tenofovir or vaginal gel arms [oral emtricitabine/tenofovir arm ongoing]	<30% with detectable levels in blood
Bangkok Tenofovir Study	Oral tenofovir	Thai male injection drug users	48.9% reduction of infection[	84% by directly observed therapy and study diaries
ANRS - Ipergay	Oral emtricitabine/tenofovir	French gay males	86% reduction of infection	86% with detectable levels in blood

For those at very high risk for HIV, PrEP can significantly reduce their risk of HIV infection if taken daily. Daily PrEP use can lower the risk of getting HIV from sex by more than 90% and from injection drug use by more than 70%.

PrEP does not work the same way as a vaccine. A vaccine teaches your body to fight off infection for several years. For PrEP, one will has to take a pill every day by mouth. The pill that was shown to be safe and to help block HIV infection is called "Truvada". Truvada is a combination of two drugs (tenofovir and emtricitabine). If PrEP is taken daily, the presence of the medicine in the bloodstream can often stop HIV from taking hold and spreading in the body.

If PrEP is not taken every day, there may not be enough medicine in the bloodstream to block the virus.

PrEP can cause side effects like nausea in some people, but these generally subside over time. No serious side effects have been observed, and these side effects aren't life threatening.

In people who are HIV-negative and have taken PrEP for up to 5 years, no significant health effects have been seen.

Also, while PrEP can significantly reduce one's risk of HIV infection if taken daily, one can combine additional strategies like condom use with PrEP to reduce one's risk even further. One should not stop using condoms because somebody is taking as PrEP doesn't give any protection against other STDs, like gonorrhea and chlamydia.

If used the right way every time you have sex, condoms are highly effective in preventing HIV and some STDs you can get through body fluids, like gonorrhea and chlamydia. However, they provide less protection against STDs spread through skin-to-skin contact, like human papillomavirus or HPV (genital warts), genital herpes, and syphilis.

Discontinuation of PrEP

One must take PrEP daily for it to work. But there are several reasons people stop taking PrEP. For example,

- If one' risk of getting HIV infection becomes low because of changes in one's life, then one may want to stop taking PrEP.
- If one find s one doesn't want to take a pill every day or often forgets to take one's r pills, other ways of protecting oneself from HIV infection may work better.
- If one develops side effects from the medicine that are interfering with one's r life, or if blood tests show that one's body is reacting to PrEP in unsafe ways, the provider may stop prescribing PrEP
- Scientists do not yet have an answer on how long it takes PrEP to become fully effective after one starts taking it. Some studies suggest that if one takes PrEP every day, it reaches its maximum protection in blood at 20 days, in rectal tissue at about 7 days, and in vaginal tissues at about 20 days.

STATUS OF ADHERENCE IN ANTI RETRO VIRAL THERAPY

The success of treatment as prevention is highly dependent upon people adhering to their treatment. It is widely agreed that once treatment is initiated it should not be interrupted, as incomplete viral suppression causes the more sensitive strains of HIV to be suppressed and the resistant strains to become dominant. Resistant strains are harder to treat. Adherence is an issue even where treatment is widely available. In 2011, one study from the United States of America (USA) reported that 15 years after the initiation of highly active antiretroviral therapy (HAART), and four years after the introduction of combination prevention, only 19% of 1.1 million people living with HIV in the country had an undetectable viral load. In South Africa which has the largest treatment program in the world, a study found that only 64% of people who were initiated on treatment between 2002 and 2007 were still in care three years on.

ADHERENCE IN INDIA

There are studies in India which have demonstrated the sub optimal adherence to ART. Basavaprabhu Achappa, etal has found- in one study that out of 116 participants, 63.7% reported adherence ≥ 95%, and mean adherence index was 91.25%. Financial constraints, forgetting to take medication, lack of family care, depression, alcohol use, social stigma and side effects to antiretroviral therapy were barriers for adherence in our study.

A**DHERENCE IN JHARKHAND**

There is only one study done before regarding adherence to ART by Sandeep Rai et al which examines the effect of optimal adherence to ART on survival status of HIV infected patients attending ART centers in Jharkhand, India. Optimal adherence was assessed using pill count methods; patients who took <95% of the specified regimens were identified as non-adherent. The mortality rate was higher among patients who were non-adherent to ART) than who were adherent. The risk of mortality was fourfold higher among individuals who were non-adherent to ART than who were adherent They conclude that Adherence to ART is associated with a higher chance of survival of HIV infected patients, ascertaining the need for interventions to improve the ART adherence and early initiation of ART.

PrEP IN INDIA

Currently, there is one Indian PrEP demonstration project focusing on female sex workers, led by The Sonagachi Project in Kolkata Since that trial is designed to

assess PrEP feasibility in one population, the study will not provide sufficient evidence to recommend that PrEP be made routinely available by the National or State AIDS Control Programmes for high risk individuals. Thus, other Indian demonstration projects are needed to provide sufficient evidence to support wider implementation. Prior socio-behavioural studies have found that Indian women and MSM indicated a willingness to use oral or topical PrEP, if proven to be effective, but now the challenge is to determine feasibility and impact in all key populations.

ROLE OF ADHERENCE IN PRE-EXPOSURE PROPHYLAXIS:

Adherence is a key issue in ensuring PrEP effectiveness. Adherence to study product varied widely across randomized control clinical trials, and clear evidence emerged from those trials that higher adherence is directly correlated to higher HIV prevention effectiveness.
Treatment adherence differs from PrEP adherence in the following key ways:

- Treatment, once started, must be taken for life. PrEP can be selected for periods of high risk and stopped at other times.
- Treatment requires high consistent rates of adherence to be effective (although newer regimens appear to afford similar benefits with lower adherence). PrEP (using tenofovir [TDF] or emtricitabine/tenofovir [FTC/TDF]) may still provide protection if taken less than daily, depending on overall adherence patterns and route and timing of exposure to HIV.
- People on treatment have no alternatives available that provide the treatment benefit. PrEP users may choose other means to prevent HIV acquisition, especially in periods when HIV risk is lower.
- People on treatment are under known, constant threat of viral replication- they have a known condition with known outcomes if non-adherent. PrEP protects against a possible exposure and possible infection –odds of exposure per event are not known and are often underappreciated

The standards for successful ART adherence have changed with time and are often dependent on the treatment regimen and time on treatment. Now modern potent ART regimens (e.g., NNRTI or boosted PI-based regimens) allow for treatment success at lower levels of adherence (i.e., a greater degree of forgiveness). For example, if a person living with HIV is taking 80% of their antiretroviral medications, then he/she will have a high chance of viral suppression; prior standards dictated 95% adherence. Treatment success also depends on time—if a person living with HIV has been taking ARVs for long periods of time, even lower levels of ART adherence may be sufficient to maintain viral suppression. Patterns of adherence have also proved to be important. Treatment interruptions, when ARVs are not taken for 1 or 2 weeks perhaps because the person does not make it to the clinic, often lead to viral rebounds. Despite nuances that continue to emerge with newer regimens, the current ART adherence message still emphasizes that people on ART should maintain 95% adherence indefinitely. The expectation with treatment is that every person with HIV should be on ART and he/she should take antiretrovirals consistently for the rest of their lives. ARV use is very different in the context of PrEP. Little is known about how people will use PrEP outside of clinical trials or what their patterns of adherence may be.

As an HIV prevention intervention, PrEP may be best suited for use during periods of high risk of HIV infection, not for a lifetime. In addition, though it is recommended for daily use, "nearly daily use" of oral PrEP may afford sufficient protection from HIV once levels of TDF-FTC have reached effective concentrations in target tissues (see 3.2 below). Moreover, the public health strategies differ between PrEP and ART. PrEP use is an individual choice, an opt-in strategy, while ART is increasingly becoming an opt-out strategy. Public health programs can also potentially offer PrEP as part of combination prevention to specific groups of people who may not be ideal users of other prevention methods and are at high risk of HIV (e.g. people in high incidence cohorts who have difficulty using condoms consistently). Since adherence to a daily regimen of TDF/FTC is clearly associated with a reduced risk of HIV seroconversion, clinicians should consider using motivational interviewing and other techniques shown to improve adherence to PrEP. an evaluation of interventions to promote adherence to PrEP recommended participant-centered approaches, including addressing the specific context in which an individual incorporates and negotiates PrEP use. While complex, resource-intensive interventions are most effective for improving adherence to medical interventions in general, a systematic review also found evidence to support low-cost, low-intensity interventions that provided education or telephone calls. CDC guidelines recommend that clinicians incorporate motivational interviewing into their visits for prescribing PrEP with 4 simple items:
(i) When you have taken medications previously? (ii) How did you remember to take them? (iii) Please tell me about any problems you had taking your pills. (iv) What was most helpful in remembering to take them?

Across the major PrEP RCTs (below Table) , the association between efficacy and estimated adherence (detectable drug) is clear and approximates a sigmoid dose-response curve. Larger effects were reported by trials with higher proportions of participants with drug detected, leading many to conclude that the drugs work if taken . Reports to date from these trials suggest multiple levels of ecologic influences on adherence to study product.

Table 2. Major Pre exposure Prophylaxis Trials

Study	Efficacy	Estimated Adherence by Drug Concentration
PP-TDF/FTC [10]	75%	75%–80%
PP-TDF [10]	67%	67%–80%
TDF2 –TDF/FTC [14]	62%	80%
BKK-TDF [11]	49%	67%
iPrEX –TDF/FTC [12]	44%	51%
CAPRISA–TDF Gel BAT24 [9]	39%	38%–98%
VOICE-TDF Gel Daily [13]	14.7%	22%
FemPrEP–TDF/FTC [15]	6%	37%
VOICE-TDF/FTC [13]	−4%	29%
VOICE-TDF [13]	−49%	28%

ABBREVIATIONS

BKK, Bangkok Tenofovir Study; CAPRISA, Centre for the AIDS Programme of Research in South Africa; FTC, Emtricitabine; iPrEx, Iniciativa Profilaxis Pre-Exposición; PP, Partners PrEP; TDF, Tenofovir disoproxil fumarate; TDF2, Botswana TDF/FTC Oral HIV Prophylaxis Trial; VOICE, Vaginal and Oral Interventions to Control the Epidemic. It should come as no surprise that new data from the iPrEx open label extension shows that 100% of people taking the drug four or more times per week were protected, whereas the efficacy rate was much less when people took PrEP less often. The group of gay men and transgender women in this study who elected to take a daily tenofovir/emtricitabine (Truvada) pill had half as many HIV infections (relative risk = 0.51) compared with a comparator group of people who elected to stay in the study but not to take PrEP. They also had half the HIV infection rate (relative risk = 0.49) of people in the placebo arm of the original iPrEx randomized controlled trial (RCT).As has been seen in other studies of pre-exposure prophylaxis (PrEP), as well as in the original iPrEx, the primary determining factor when it came to the efficacy of PrEP was adherence.

All participants in iPrEx OLE had their level of adherence calculated from drug levels observed in blood samples. PrEP had no significant efficacy in people who took fewer than two doses a week. However, the efficacy of PrEP was 84% in people who took 2-3 doses a week – there was only one infection in this group – and no infections at all were seen in people taking at least four doses a week. This 100% efficacy translates into a minimum efficacy of 86% if the statistical uncertainty of the result is taken into account. If people were at higher risk they took more PrEP and adhered to it better...it shows that people who are at risk can take reasonable and appropriate decisions on their own behalf. It should come as no surprise that new data from the iPrEx open label extension shows that 100% of people taking the drug four or more times per week were protected, whereas the efficacy rate was much less when people took PrEP less often.

CONCLUSIONS

PrEP with daily oral TDF /FTC reduces the risk of HIV infection among high-risk MSM and transgender women who have sex with men, IDUs, and high-risk heterosexual men and possibly women. As the reduction in HIV incidence plateaus, and with a lack of better office-based strategies for preventing HIV transmission, it is important that all primary care clinicians be aware of PrEP and considers ways to safely implement this effective strategy for reducing HIV risk.

Discussion regarding the cost-effectiveness and opportunity costs will continue, and researchers will explore different delivery methods and dosing. In the meantime, there is widespread consensus that many more people could benefit from PrEP than are currently taking it. Primary care providers are at the front line of PrEP implementation and should embrace this opportunity to increase awareness of PrEP and to prevent HIV infection among those at risk. PrEP access varies worldwide.

National factors include whether governmental regulatory agencies have approved PrEP and/or developed policies; whether Gilead Sciences (the manufacturer of Truvada) have registered TDF/FTC for treatment and prevention in country; and, whether governments or donors have incorporated PrEP into national plans and programs and/or whether there are demonstration projects happening in the country. The Southern African HIV Clinicians Society issued guidance in June 2012 for use of TDF/FTC as PrEP in gay men and other MSM. In July 2012, the US FDA approved daily oral TDF/FTC as PrEP. Gilead subsequently filed for approvals in Australia, Brazil, South Africa and Thailand; these approvals are still pending. In July 2012, WHO released guidance on PrEP for serodiscordant couples, MSM and transgender women in the context of demonstration projects. The US CDC

released US Public Health Service (PHS) guidelines for the use of TDF/FTC as PrEP in May 2014. These updated the interim guidance documents on PrEP in gay men and other MSM, heterosexual adults at risk via sexual exposure and injecting drug users. In 2014, Kenya incorporated PrEP for key populations into its Prevention Revolution Road Map. In July 2014, WHO released consolidated guidelines for HIV prevention, treatment and care for key populations, which include a recommendation that PrEP should be part of a comprehensive prevention package available to men who have sex with men. The European Medicines Agency (Europe's regulatory body) is updating its concept paper on the development of medicines to prevent HIV infection

TAKE HOME MESSAGE

- There were no significant side effects observed in trials of tenofovir-based PrEP in any of the trials.
- Adherence is essential. Each of the trials that found benefit also found that people who had high levels of adherence had high levels of protection. Lower adherence was associated with low or no protection.
- PrEP is highly protective in both men and women.
- People with high rates of HIV risk behaviors can also be highly adherent to PrEP.
- Serodiscordant couples—one HIV-positive individual and one HIV-negative individual—can use PrEP as a "bridge" during the period when the HIV-positive individual begins ART, or during the period when he or she chooses not to take ART. PrEP can also be used by serodiscordant couples for safer conception.
- Individual cases of HIV drug resistance (which could emerge if a person acquired HIV while on PrEP and went on taking the single drug during the time before diagnosis) have been observed in trials to date. These appear to have occurred in participants who were HIV-positive and in the "window period" of early infection when they began taking PrEP. These individuals tested HIV-negative on the trials' screening tests. This reinforces the importance of regular testing for anyone initiating or taking PrEP.
- TDF/FTC and TDF are both key drugs for treating HIV in HIV-positive people. Access to tenofovir-based PrEP can only be explored in the context of sustained ART access for HIV-positive people worldwide.
- Most of what is known about oral PrEP relates to daily use of oral TDF/FTC, and thus far this dosing is the only form approved and recommended for use by regulatory bodies. In February 2015, new data from a trial of an "event-driven" dosing schedule with four pills over three days was also shown to be effective in the context of penile-anal sex, but this is not yet being recommended for regular use. It is important to note that differences in drug absorption in vaginal and rectal tissue mean that data from gay men and MSM cannot be extrapolated to women whose primary exposure is via vaginal sex—and vice versa.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

REFERENCES

1. iPrEX, Grant RM, Lama JR, Anderson PL, et al, iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*, 363(27), 2010, 2587-99.
2. TDF2, Thigpen MC, Kebaabetswe PM, Paxton LA, et al, TDF2 Study Group. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med, 367(5), 2012, 423-34.
3. Partners PrEP, Baeten JM, Donnell D, Ndase P, et al, Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*, 367(5), 2012, 399-410.
4. Bangkok Tenofovir Study, Choopanya K, Martin M, Suntharasamai P et al. Bangkok Tenofovir Study Group. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study), a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*, 381(9883), 2013, 2083-90.
5. Grant RM et al. Results of the iPrEx open-label extension (iPrEx OLE) in men and transgender women who have sex with men, PrEP uptake, sexual practices, and HIV incidence. 20th International AIDS Conference, Melbourne, abstract TUAC0105LB, 2014.
6. The Economic Times. Anti-AIDS medicine project likely to take off at Sonagachi. 2015. Available from, http, //articles .economictimes.indiatimes.com/2015-01-01/news/57581530_ 1_hiv-infection-hiv-virus-aids-society, accessed on May 18, 2016.