Review Article

Pre-exposure prophylaxis of HIV

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Abstract

Pre-exposure prophylaxis (PrEP) is an experimental approach to HIV prevention and consists of antiretroviral drugs to be taken before potential HIV exposure in order to reduce the risk of HIV infection and continued during periods of risk. An effective PrEP could provide an additional safety net to sexually active persons at risk, when combined with other prevention strategies. Women represent nearly 60% of adults infected with HIV and PrEP can be a female-controlled prevention method for women who are unable to negotiate condom use. Two antiretroviral nucleoside analog HIV-1 reverse transcriptase inhibitor drugs are currently under trial as PrEP drugs, namely tenofovirdisoproxilfumarate (TDF) alone and TDF in combination with emricitabine (FTC), to be taken as daily single dose oral drugs. There are 11 ongoing trials of ARV-based prevention in different at risk populations across the world. The iPrex trial showed that daily use of oral TDF/FTC by MSM resulted in 44% reduction in the incidence of HIV. This led to publication of interim guidance by CDC to use of PrEP by health providers for MSM. Few other trials are Bangkok Tenofovir Study, Partners PrEP Study, FEM-PrEP study, and VOICE (MTN-003) study. Future trials are being formulated for intermittent PrEP (iPrEP) where drugs are taken before and after sex, "stand-in dose" iPrEP, vaginal or rectal PrEP, etc. There are various issues/concerns with PrEP such as ADRs and resistance to TDF/FTC, adherence to drugs, acceptability, sexual disinhibition, use of PrEP as first line of defense for HIV without other prevention strategies, and cost. The PrEP has a potential to address unmet need in public health if delivered as a part of comprehensive toolkit of prevention services, including risk-reduction, correct and consistent use of condoms, and diagnosis and treatment of sexually transmitted infections.

Key words: HIV/AIDS, issues, pre exposure prophylaxis, trials

INTRODUCTION

There is a growing global access to antiretroviral drugs to HIV-positive patients including India. Still, approximately 7000 new infections occur daily globally; more than 50,000 new infections each week[1] and 2.7 million continue to get infected annually. Moreover, there is feminization of this HIV/AIDS pandemic with women and girls representing slightly more than half of all people living with HIV.[2] In subSaharan Africa, where the majority of new HIV infections continue to occur (1.8 million in 2009),[2] women represent nearly 60% of adults and in most cases, they acquire HIV through sexual intercourse with an infected male partner.[3] Hence, the need of the hour is to effectively prevent HIV transmission to uninfected individuals. Although behavior change programs have contributed to dramatic reductions in the number of annual infections, still at-risk population is enormous and more comprehensive strategies are needed.[4]

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CONSTRAINTS IN CURRENT PREVENTION STRATEGIES

Barriers against HIV/AIDS control

- Low condom acceptance in non-commercial sex
- Low acceptance of circumcision (provides only

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partial and no protection against penile and rectal transmission, respectively)[5]
- Low acceptance of testing
- Low awareness of vulnerability (youth and female)
- More emphasis on treatment

STRATEGIES FOR REDUCING ACQUISITION OF HIV INFECTION

Include (1) expanded HIV testing so that infected persons can be treated and their risk for transmitting infection minimized; (2) individual, small-group, and community-level behavioral interventions to reduce risk behaviors; (3) promotion of condom use; (4) detection and treatment of sexually transmitted infections; and (5) mental health and substance abuse counseling when needed.[4]

PRE-EXPOSURE PROPHYLAXIS OF HIV

Definition

PrEP is an experimental approach to HIV prevention and consists of antiretroviral drugs to be taken before potential HIV exposure in order to reduce the risk of HIV infection and continued during periods of risk. PrEP can be in the form of a pill taken by mouth or a gel applied in the vagina or rectum.[6,7]

Difference between pre-exposure prophylaxis and post-exposure prophylaxis

Post-exposure prophylaxis (PEP) is antiretroviral (ARV) drugs given to individuals within 3 days (72 hours) after possible exposure to HIV, to reduce risk of HIV infection.[1]

PrEP is the approach used in which uninfected individuals take an HIV treatment drug (ARV) in order to build a concentration of the medication in their bodies, so that if they are exposed to the virus, the medicine may reduce the chances of HIV acquisition.[1]

Scope of pre-exposure prophylaxis

An effective PrEP could provide an additional safety net to sexually active persons at risk, when combined with reduction in the number of sex partners, HIV counseling and testing, consistent and correct condom use, and other prevention strategies. And hence, it could help address the urgent need for a female-controlled prevention method for women worldwide who are unable to negotiate condom use, because of cultural and other barriers.[4]

Statistics

Mathematical modeling suggests that approximately 2.7 to 3.2 million new HIV-1 infections could be averted in southern sub-Saharan Africa over 10 years by targeting PrEP (having 90% effectiveness) to those at the highest behavioral risk and by preventing sexual disinhibition. But this benefit could be reduced to ≤50% by sexual disinhibition and by high PrEP discontinuation and lower PrEP effectiveness.[8]

Rationale of pre-exposure prophylaxis

PrEP follows the concept of providing a preventive drug before exposure to the infectious agent. Similar concept holds true for travelers being given prophylactic drugs for malaria before going to endemic countries. Theoretically, if HIV replication can be inhibited from the moment the virus enters the body, it may not be able to establish a permanent infection.[4]

DATA SUPPORTING THIS APPROACH OF PRE-EXPOSURE PROPHYLAXIS

Prevention of mother to child transmission

Single dose of nevirapine to HIV-infected women during labor and to their newborns immediately after birth reduces the risk for MTCT of HIV by about 50%.[4]

Post exposure prophylaxis

Zidovudine taken few hours after an occupational exposure e.g. needle prick and taken for 28 days decreases the chances of HIV transmission by 80%.[4]

Animal studies

Several studies on monkeys have shown that tenofovir alone or in combination with emtricitabine given before exposure to simian HIV provides significant protection to the monkeys exposed repeatedly to the virus.[4]

Animal studies where combination of tenofovir and emtricitabine was tested on humanized BLT (bone marrow liver thymic) mice, having fully developed human immune systems, showed that the drugs provided 100% protection against vaginally introduced HIV to the mice. This led to the conclusion that PrEP could be a very effective method for preventing vaginal HIV-1 transmission.[6,9]

DRUGS FOR PRE-EXPOSURE PROPHYLAXIS

Two antiretroviral nucleoside analog HIV-1 reverse transcriptase inhibitor drugs are currently under trial as PrEP drugs, namely tenofovir disoproxil fumarate (TDF) alone and TDF in combination with

emricitabine (FTC).[10,11]

Mechanism of action and advantages of TDF

TDF, the orally bioavailable prodrug of tenofovir, is metabolized to a nucleotide analog HIV-1 reverse transcriptase inhibitor.[12,13]

Advantages for use as ARV and PrEP[13]

- Potency against wild-type HIV and some nucleoside-resistant strains of HIV
- Low potential of selecting for TDF-resistant mutants
- Low likelihood of metabolic/mitochondrial toxicity
- Pharmacologic profile supporting daily dosing

Dosage-1 tablet TDF [300 mg] alone or in combination with FTC [200 mg] daily with or without food[10]

ADR of TDF/FTC combination[10]

- Boxed warning: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases.
- Boxed warning: Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1. Hepatic function should thus be monitored closely.
- New onset or worsening renal impairment including acute renal failure and fanconi syndrome can occur. The combination should not be used if creatinine clearance is <30 mL/min or patient is on hemodialysis. Regular serum phosphorus monitoring is also advised.

Newer drugs under trial

Two drugs, raltegravir (integrase strand transfer inhibitor) and maraviroc (CCR5 inhibitor), have been tested on humanized RAG-hu mice and results show that oral administration of either of these drugs prevents vaginal HIV-1 infection.[14]

PRE-EXPOSURE PROPHYLAXIS TRIALS

There are 11 ongoing trials of ARV-based prevention in different at risk populations across the world [Figure 1].

The iPrex trial (The pre-exposure prophylaxis initiative trial)

The iPrex study was a phase 3 study conducted in 11 sites in six countries, namely Peru, Ecuador, United States, South Africa, Brazil, and Thailand[7] from July 2007 to December 2009. A total of 2499 HIV-uninfected men including 29 male-to-female transgender adults (aged ≥18 years) who reported sex with a man and reported engaging in high-risk sexual behaviors during the preceding 6 months, and had no clinical contraindication were enrolled and were given daily oral combined formulation of 300 mg TDF and 200 mg FTC (TDF/FTC). Four weekly follow up of participants for HIV testing,

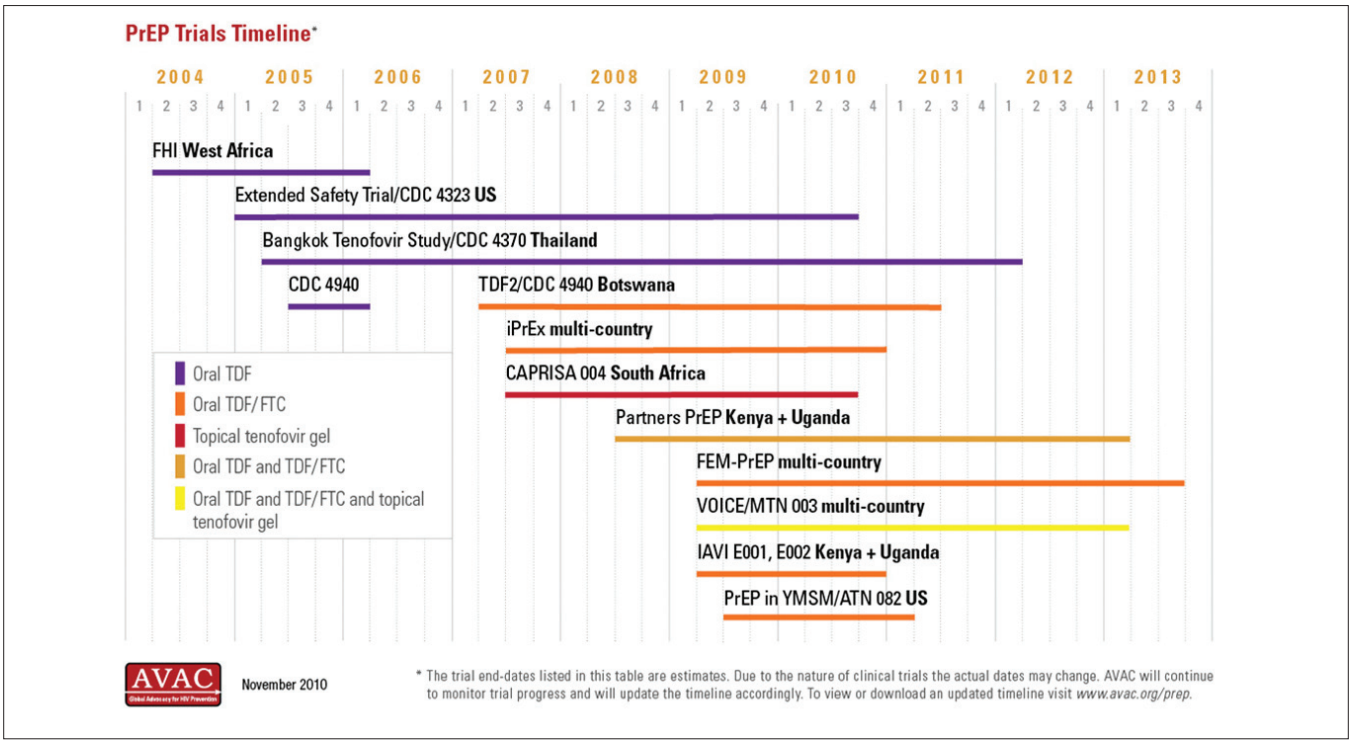

Figure 1: Timeline of PREP trials worldwide[15]

risk-reduction and PrEP medication adherence counseling, dispensing of condoms was done. The subjects were followed for median 1.2 to maximum 2.8 years.[5,7,16]

Results[5,7,16]

- Of these subjects, 10 were found to have been infected with HIV at enrollment, and 100 became infected during follow-up (36 in the FTC–TDF group and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV.
- Reduction in risk for HIV acquisition was 21% among participants with <90% adherence and 73% with ≥90% adherence, highlighting the importance of adherence to a prophylactic regimen.
- Drug level testing showed a 92% reduction in risk for HIV acquisition in participants with detectable levels of TDF/FTC versus those with no drug detected.
- TDF/FTC generally was well tolerated, except nausea in the first month; raised serum creatinine levels (which reversed within 4 weeks of discontinuation of drug); and unintentional weight loss.
- No drug-resistant virus was found in the 100 participants infected after enrollment.
- Among 10 participants who were seronegative at enrollment but later found to have been infected before enrollment, 2 cases of FTC resistance occurred; posing an important question of drug resistance in those who seroconvert.
- Participants in both TDF/FTC and placebo arms reported lower total numbers of sex partners and higher percentages of partners who used condoms than reported at baseline- highlighting the importance of behavior counseling.

Interim guidance for use of pre-exposure prophylaxis

The U. S. Centers for Disease Control and Prevention (CDC) on the January 28, 2011, in Morbidity and Mortality Weekly Report published interim guidance regarding the use of tenofovir/emtricitabine for PrEP against HIV infection based on the iPrEx trial.[16-18] [Table 1].

Other current trials

In all the trials it has been ensured that all subjects receive HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections before starting with the oral preventive drug regimens [Table 2].

Table 1: CDC interim guidance for health-care providers electing to provide pre-exposure prophylaxis for the prevention of HIV infection in adult men who have sex with men (MSM) and who are at high risk for sexual acquisition of HIV[16-18]

Before initiating pre-exposure prophylaxis
Determine eligibility
Document negative HIV antibody test(s) immediately before starting PrEP medication.
Test for acute HIV infection if patient has symptoms consistent with acute HIV infection.
Confirm that patient is at substantial, ongoing, high risk for acquiring HIV infection.
Confirm that calculated creatinine clearance is ≥60 mL per minute (via Cockcroft-Gault formula).
Other recommended actions
Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision about prescribing PrEP.
Screen and treat as needed for STIs.
Beginning pre-exposure prophylaxis medication regimen
Prescribe 1 tablet of (TDF [300 mg] plus FTC [200 mg]) daily*.
In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected.
If active hepatitis B infection is diagnosed, consider using TDF/FTC for both treatment of active hepatitis B infection and HIV prevention.
Provide risk-reduction and PrEP medication adherence counseling and condoms.
Follow-up while pre-exposure prophylaxis medication is being taken
Every 2--3 months, perform an HIV antibody test; document negative result.
Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
Every 2--3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STI as needed.
Every 6 months, test for STI even if patient is asymptomatic, and treat as needed.
3 months after initiation, then yearly while on PrEP medication, check blood urea nitrogen, and serum creatinine.
On discontinuing pre-exposure prophylaxis (at patient request, for safety concerns, or if HIV infection is acquired)
Perform HIV test(s) to confirm whether HIV infection has occurred.
If HIV positive, order and document results of resistance testing and establish linkage to HIV care.
If HIV negative, establish linkage to risk-reduction support services as indicated.
If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B.

HIV = Human immunodeficiency virus; STI = Sexually transmitted infection; TDF = Tenofovirdisoproxilfumarate; FTC = Emtricitabine.

*These recommendations do not reflect current Food and Drug Administration approved labeling for TDF/FTC

Table 2: Current ongoing trials of pre exposure prophylaxis of HIV

Name of study	Phase	Drugs evaluated	Objectives of study	Population groups studied	Study duration
CDC sponsored trials[4,6,19-21]					
Bangkok Tenofovir Study-Thailand	II/III	Tenofovir (TDF)®	Safety and effectiveness	2400 injection drug users (IDUs)	2005 to early 2012
TDF2/ CDC 4940-Botswana	II	Tenofovir plus emtricitabine (TDF/FTC)®®	Behavioral and clinical safety and adherence	1200 heterosexual men and women	Early 2007 to mid 2011
Partners PrEP Study[21] Kenya and Uganda	III	TDF TDF/FTC regimens	Safety and efficacy	3900 heterosexual serodiscordant couples	Mid 2008 to Early 2013
CDC U.S. Tenofovir Extended Safety Trial[21]	II	TDF	Clinical and behavioral safety and adherence	400 HIV-negative MSM	Preliminary analysis in July 2010 suggested no serious safety concerns and no increased risk in men taking a study pill compared to those not taking it
VOICE - (Vaginal And Oral Interventions To Control The Epidemic)- MTN-003-Africa[3,22,23]	IIb	Vaginal microbicide containing 1% tenofovir gel oral TDF oral TDF/FTC	Safety and efficacy	5,000 sexually active, HIV-uninfected women (18 to 45 years)	Early 2013(duration of study 22.5 months)
MTN-001 - US and Africa[23-26]	II	3 daily regimens - tenofovir gel, tenofovir tablet and the two together	Women's acceptability and adherence and the pharmacokinetics of each approach	Sexually active, HIV uninfected women	2008 to 2010*
FEM-PrEP study[20]Kenya, South Africa, Tanzania and Zimbabwe	III	TDF/FTC		3,900 high-risk heterosexual women	
FHI- West Africa Study[13]	II	TDF		936 high risk HIV-negative women	June 2004 to March 2006#

*Result of MTN-001 study = Daily use of the vaginal gel achieved a more than 100-times higher concentration of active drug in vaginal tissue than did the oral tablet, while, compared to the gel, the tablet used daily was associated with a 20-times higher active drug concentration in blood. Acceptability was > 80% to all the three regimens and they were well tolerated (nausea with oral and vaginal itching and irritation with gel formulation).[23-26] #Result of FHI- West Africa Study = Daily oral use of TDF in HIV-uninfected women was not associated with increased clinical or laboratory adverse events (in terms of renal and hepatic functions and serum phosphorus levels). Effectiveness as PrEP to HIV could not be conclusively evaluated because of the small number of HIV infections observed during the study; and because the study in Cameroon and Nigeria were prematurely halted due to protests.[13,27] MTN = Microbicides trial network; FHI-Family Health International, ®-TDF = Tablet tenofovir (300 mg) orally once daily, ®®-TDF/FTC = Combination of oral tenofovir (300 mg) + emtricitabine (200 mg) orally once daily

Intermittent pre-exposure prophylaxis[28,29]

This study investigated the efficacy of PrEP drugs when taken before and after sex, hence named intermittent PrEP (iPrEP).

The efficacy of a two-dose oral iPrEP regimen with Truvada was evaluated in 24 male rhesus macaques (6 in each of the four groups) by exposing them with simian HIV rectally and repeating the exposure weekly for 14 weeks. The two doses were given at different time schedules, and the results are as follows [Table 3].

It was concluded that effective PrEP with TDF/FTC does not require daily dosing in repeat-exposure macaque model, and support the (formulation of next generation) iPrEP efficacy trials in humans.[29,30]

Future trials

- Intermittent PrEP with dosing that is not exposure driven (independent of the time of exposure), known as "stand-in dose", which is one or two doses of TDF/FTC in a week, followed by a second dose after exposure.
- iPrEP trial has suggested that the modalities that are independent of the time of exposure appear to be more protective than if the doses are given right around the time of exposure.[29]
- iPrEP in the macaques/ animals in vaginal

Table 3: Intermittent pre-exposure prophylaxis dosage and results[28,29]

Group*	Timings of dosage of TDF/FTC with reference to virus exposure	Protection after 14 exposures (risk of infection reduced by____ folds)
I	2 hours before and 22 hours after virus exposure	3.9 fold (3 of 6 macaques protected)
II	22 hours before and 2 hours after exposure	15.9 fold (5 of 6 protected)
III	3 days before and 2 hours after exposure	14.5-fold (5 of 6 protected)
IV	2 hours and 26 hours after exposure	3.8-fold (3 of 6 protected)

*Control group- 27 macaques, out of which 26 seroconverted after 2 exposures with simian HIV

transmission model to evaluate the efficacy of oral drugs in preventing vaginal transmission.[29]
- Efficacy of single drug as iPrEP.[29]
- Vaginal or rectal PrEP.[29]

PRE-EXPOSURE PROPHYLAXIS AND MICROBICIDES

PrEP is an oral prophylaxis for HIV. Microbicides are now referred to as "topical" PrEP.[29]

CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 study

A phase II b (proof of concept) trial in which 889 women at high risk of acquiring HIV through sexual intercourse from South Africa were enrolled and there were 39% fewer HIV infections among women who used 1% tenofovir gel within 12 h prior to sex and as soon as possible within 12 h after sex than among those who used the placebo gel.[30-32] The reduction in HIV acquisition was 54% in women with high gel adherence.[32]

ISSUES RELATED TO PRE-EXPOSURE PROPHYLAXIS

There are various issues that have cropped up with the ongoing trials for PrEP and several concerns have emerged especially with issuing of interim guidance for PrEP for MSM by CDC

- The individuals becoming HIV positive later on the trials are thus providing testing for viral load, CD4 count, and HIV resistance mutations, and infected participants are followed up for an additional six months, to help guide treatment decisions and to determine whether prior exposure to tenofovir or tenofovir plus emtricitabine affects the course of disease, testing is provided[4] (CDC)
- Sexual disinhibition/"risk compensation" after PrEP promoting riskier sexual behavior.[33]
- What if PrEP becomes a morning after pill
- ADRs of TDF/FTC because HIV prevention is not a FDA approved indication of TDF/FTC, its long-term safety in HIV-uninfected persons is not yet known.[16]
- Adherence taking PrEP daily is critical, as efficacy is strongly associated with medication adherence as highlighted by iPrex study.[5,33,34]
- Acceptability of a daily oral drug with various ADRs and potential for resistance.
- Use of other antiretrovirals which have not proven safe for uninfected persons (e.g., more than two drugs or protease inhibitors)[16]
- Use of PrEP by at risk population groups other than MSM[7,16]
- Use of dosing schedules of unproven efficacy (e.g., "intermittent" dosing just before and/or after sex).[7,35]
- PrEP should only be used among individuals who have been confirmed to be HIV negative. Not screening for acute infection before beginning PrEP or long intervals without retesting for HIV infection may have negative implications.[16,33]
- Duration of PrEP the drugs will have to be continued till high risk sexual activity is continued.
- The medication is costly, hence it is very important for the patients to understand the financial implications of starting PrEP.[7,16]
- PrEP should never be seen as the first line of defense against HIV. It was only shown to be partially effective when used in combination with regular HIV testing, condoms, and other proven prevention methods. Men who have sex with men should still:
  - ♦ Use condoms correctly and consistently
  - ♦ Get tested to know their status and that of their partner(s) for certain
  - ♦ Get tested — and treated if needed — for other sexually transmitted infections that can facilitate HIV transmission, such as syphilis and gonorrhea
  - ♦ Get information and support to reduce drug use and sexual risk behavior
  - ♦ Reduce their number of sexual partners[33]
- PrEP must be obtained and used in close collaboration with healthcare providers to ensure regular HIV testing, risk reduction and adherence counseling, and careful safety monitoring.[33]

CONCLUSION

"Female empowerment is a distant dream. Behavioral change is not yet on the horizon. Vaccines and microbicides need more encouraging trials. Till that time, pre and post-sexual exposure prophylaxis remain important armamentaria for females."

CDC states that "no single prevention strategy will be 100% effective against HIV transmission, abstinence and mutual monogamy with an HIV-negative partner will remain the only 100% effective ways to prevent infection." Hence, reducing transmission will require determining how best to integrate all available prevention strategies—both biomedical and behavioral.[4,22]

PrEP has the potential to address unmet need in public health[7] and contribute to effective and safe HIV prevention, if (1) it is targeted to population groupsat high risk for HIV acquisition; (2) it is delivered as part of a comprehensive toolkit of prevention services, including risk-reduction and PrEP medication adherence counseling, correct, and consistent use of condoms, and diagnosis and treatment of sexually transmitted infections; and (3) it is accompanied by monitoring of HIV status, side effects, adherence, and risk behaviors at regular intervals.[16]

DISCLAIMER

This review article is just to introduce the readers with the concept of PrEP. Prescribing PrEP is a very sensitive issue because of obvious reasons. If at all such need arises, please refer latest guidelines available at standard sites like CDC, WHO, and UNAIDS.

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Multiple Choice Questions

Q.1. How many individuals annually get infected with HIV globally?
a. 2.5 million
b. 3.3 million
c. 2.7 million
d. 4.8 million

Q.2. What is the mechanism of action of raltegravir?
a. Nucleotide reverse transcriptase inhibitor
b. Integrase strand transfer inhibitor
c. CCR5 inhibitor
d. Nucleoside reverse transcriptase inhibitor

Q.3. In the iPrex trial (the pre-exposure prophylaxis initiative trial), daily use of TDF/FTC resulted in overall reduction of HIV in MSM by _____ %
a. 33%
b. 73%
c. 44%
d. 92%

Q.4. Oral tenofovir cannot be prescribed in all cases except
a. Creatinine clearance is <30 mL/min
b. Patient is on hemodialysis
c. Active Hepatitis B infection is present

Q.5. Intermittent PrEP (iPrEP) stands for
a. Taking daily oral PrEP drug
b. Daily application of vaginal/ topical PrEP (microbicide)
c. Taking oral PrEP drug, one tablet before sexual exposure and one tablet after exposure
d. Taking one or two doses of oral PrEP drug in a week (independent of time of sexual exposure), followed by a second dose after exposure.

Answers
Q.1. c. 2.7 million
Q.2. b. Integrase strand transfer inhibitor
Q.3. c. 44%
Q.4. b. Active hepatitis B infection is present
Q.5. c. Taking oral PrEP drug, one tablet before sexual exposure and one tablet after exposure