

UNAIDS 2015 | REFERENCE

ORAL PRE-EXPOSURE PROPHYLAXIS

QUESTIONS AND ANSWERS

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ORAL PRE-EXPOSURE PROPHYLAXIS—A NEW TOOL FOR HIV PREVENTION

QUESTIONS AND ANSWERS

UNAIDS welcomes the additional evidence released in February 2015 showing that pre-exposure prophylaxis using oral antiretroviral medication, PrEP, can contribute to preventing people from acquiring HIV.

The findings of PrEP trials showing its effectiveness for gay men and other men who have sex with men, heterosexual men and women, people who use drugs and transgender women confirm the usefulness of this approach as an additional HIV prevention tool.

Proposing PrEP to people at substantial risk of acquiring HIV can have particular benefits for those who are not able to consistently use other prevention methods, such as condoms and lubricants. Using PrEP during periods of higher risk of HIV responds to the reality of people's lives and strengthens a comprehensive HIV prevention and treatment service.

Expanding access to PrEP can encourage more people to consider their HIV risk and learn about their HIV status, offering further opportunities to provide expanded access to both HIV prevention services and, in the event that a person tests positive, treatment services.

Implementing PrEP poses new challenges in planning, managing and funding combination prevention. Realizing the promise of PrEP will require governments, funders, civil society and other stakeholders to join forces to systematically address them—licensing antiretroviral medicines for PrEP use, setting priorities for locations and populations for implementation, making services user-friendly and ensuring adherence. These efforts are worthwhile based on their contribution to achieving the global targets of less than 500 000 people annually acquiring HIV in 2020 and the end of AIDS as a public health threat by 2030.

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PrEP BASICS

What is PrEP?

PrEP is the use of antiretroviral medication to prevent people from acquiring HIV. PrEP adds an extra HIV prevention option to the use of condoms and lubricant, behavioural counselling, post-exposure prophylaxis, treatment for sexually transmitted infections, voluntary male medical circumcision and antiretroviral therapy for partners living with HIV. The PrEP medication most frequently used is a combination of tenofovir (TDF, 300 mg) and emtricitabine (FTC, 200 mg).¹

Why is another prevention tool needed?

PrEP provides one more effective prevention option for people to minimize the likelihood of HIV. The number of adults acquiring HIV is decreasing too slowly, and in some key populations it is still rising. Not everyone at risk of HIV can use condoms consistently nor can they choose their sexual partners independently. PrEP therefore responds to a prevention need that is not currently being met.

What is the evidence that PrEP works?

PrEP has been shown to prevent HIV in diverse groups: gay men and other men who have sex with men, transgender people, heterosexual men and women and people who inject drugs. PrEP reduces HIV by up to 90% compared with placebo when taken correctly; the actual efficacy achieved depends on adherence (Annex).

¹ PrEP trials using TDF alone also showed a preventive effect, but most providers recommend TDF + FTC.

What is the current guidance?

WHO anticipates issuing recommendations in 2015 to offer PrEP to all people at substantial risk of HIV, with relevant implementation guidelines.

The United States Food and Drug Administration has approved the use of TDF with FTC for preventing HIV, and the United States Centers for Disease Control and Prevention have developed PrEP guidelines for adults at higher risk of HIV exposure.²

UNAIDS advocates scaling up of PrEP as an additional effective HIV prevention intervention, and the Fast-Track approach includes PrEP as part of combination HIV prevention in populations at higher risk of HIV.

ELIGIBILITY FOR PrEP

Who is PrEP for?

PrEP is an additional prevention tool for HIV-negative people at substantial risk of HIV exposure who are not always able to have safer sex and who are ready to have ongoing follow-up with regular HIV testing. “Substantial risk” has no strict definition and depends on national epidemic priorities. Some groups of gay men, sex workers in higher-incidence locations, young women and girls and men in very-high-incidence settings and the sex partners of people living with HIV have exceptionally high incidence of HIV, such as 2–3%. For individuals within these populations, markers of substantial risk can include frequent condomless sex, repeat sexually transmitted infection and repeated use of post-exposure prophylaxis.

Can PrEP bring HIV prevention to people “left behind”?

Yes: PrEP is specifically relevant for groups and individuals who cannot control their risk of acquiring HIV with the currently available prevention approaches. PrEP is under individual control, it is invisible at the time of sex and the decision to take it is separate from the sex act. However, the structural barriers that block access to other HIV services (criminalization, discrimination, poor service coverage and low awareness of those who could provide PrEP) also need to be addressed to enhance HIV prevention for people “left behind”.

² Preexposure prophylaxis for the prevention of HIV infection in the United States – 2014 clinical practice guideline. Atlanta: United States Centers for Disease Control and Prevention; 2014 (<http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf>, accessed 14 July 2015).

What about people who are only at risk of acquiring HIV during certain periods?

Individuals who predictably and periodically have a higher risk of HIV exposure, such as migrant workers and their partners, prisoners or sex workers who travel for periods of work, might consider taking PrEP just to cover these periods. The effectiveness of PrEP in these situations depends on initiation that is early enough and taking the tablets consistently throughout the period of higher risk. People considering PrEP need to test negative for HIV antibodies, need to be assessed for the risk of recent HIV and need to be offered combination HIV prevention options as well.

USING PrEP

How does PrEP need to be taken?

PrEP can only be started once a person has tested HIV-negative. PrEP is a once-daily pill, and adherence is critical for effectiveness (Annex). People can only benefit from this if they are ready to have ongoing follow-up with regular HIV testing. PrEP should be combined with the promotion of other types of safer sex behaviour, including the use of condoms and lubricant.

Didn't some trials show effectiveness with fewer PrEP doses?

One trial among men who have sex with men showed good effectiveness of PrEP when doses were taken only before and after the time of sex. Nevertheless, the large majority of the studies have used daily dosages, and this is still the recommended approach. The adherence of men who have sex with men to PrEP does not have to be perfect, and even the men who missed two or three pills per week were still protected more than 80% of the time.

How long does it take for PrEP to become effective in different types of tissue, and how long does this last?

The length of daily dosing required to reach protective levels for rectal exposure has been estimated as five days. When PrEP is stopped, protection could still persist for seven days but it then drops dramatically. In contrast, up to an estimated three weeks of daily dosing for women is required before reaching protective levels for vaginal sex.

POTENTIAL RISK COMPENSATION

Is introducing PrEP leading to sexual behaviour that is less safe?

No evidence indicates that PrEP will undermine the use of condoms and other safer sex behaviour. For example, the PROUD study found no increase of sexually transmitted infections.³ These men seem to have used PrEP as an additional protection that reduced their anxiety about HIV and allowed them more ownership of their safer sex behaviour.

PrEP does not prevent pregnancy or other sexually transmitted infections.

Do third parties pose additional risk?

Male and female sex workers have expressed concerns in consultations that, if people know that they are taking PrEP, third parties (such as brothel owners, clients and managers) would pressure them to reduce condom use. Authorities seeking to persecute sex workers may also use the possession of PrEP pills as evidence of sex work.

Experience with PrEP use among sex workers remains limited, but involving third parties early in planning PrEP implementation programmes is important, as is continuing to promote condoms and lubrication as a critical component of combination prevention.

³ Behaviour change could not be assessed in double-blind trials. PrEP users need to know that they are taking PrEP and not placebo for any behaviour change to be evaluated. McCormack S, Dunn D. Pragmatic open-label randomised trial of preexposure prophylaxis: the PROUD Study. Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 23–26 February 2015 (<http://www.croiconference.org/sessions/pragmatic-open-label-randomised-trial-preexposure-prophylaxis-proud-study>, accessed 14 July 2015).

SIDE-EFFECTS AND RESISTANCE

Is PrEP safe?

PrEP is safe if there is appropriate HIV testing, assessment of the risk of recent infection and regular follow up with laboratory monitoring of kidney function. No serious toxicity has been seen during PrEP trials, and further monitoring of side-effects in diverse populations will be an important part of PrEP implementation. TDF and FTC are widely used for HIV treatment, but using medicines for prevention always requires higher safety standards, and ongoing surveillance for rare events is needed. The most common mild side-effects are nausea, headache and weight loss in the first month. Serious side-effects are rare but can affect the kidneys, liver and bones.

Congenital abnormalities have not increased significantly, but PrEP has not been formally researched among pregnant or breastfeeding women.

PrEP does not interact with alcohol or other drugs, nor does it interfere with the effectiveness of contraceptive medication. Doses of methadone and buprenorphine do not need to be adjusted.

Can PrEP cause resistance to antiretroviral medicines?

PrEP is only for people who are HIV-negative, and resistance cannot develop in HIV-negative people. This is why ongoing follow-up with regular HIV testing is required for PrEP. If people have undetected acute HIV when they start PrEP or if they acquire HIV while taking PrEP, there is a risk of drug resistance.

IMPLEMENTING PrEP

How can PrEP be delivered?

PrEP is synergistic with the accelerated scale up of HIV treatment to everyone living with HIV who wants treatment; with harm reduction services for people who inject drugs; and with other evidence-informed HIV interventions, including promoting condoms and lubricants.

PrEP is already being delivered through sexual health clinics and HIV services. Locally trusted providers are working with communities to respond to early demand for PrEP. Potential PrEP users should be involved in developing the service to support access, adherence and demand. A PrEP service needs trained, non-stigmatizing staff to provide high-quality HIV testing in order to identify people who are HIV-negative, at substantial risk of HIV and ready to have ongoing follow-up and regular HIV testing. Other needs include: reliable systems for prescribing and dispensing medicines; linkage to HIV treatment services for those found to be HIV-positive; appropriate laboratory facilities (or referral systems) for monitoring renal function; and other HIV prevention services, including the provision of condoms and appropriate lubricants. Many PrEP services will be integrated within broader sexual and reproductive health services, including managing sexually transmitted infections and providing contraceptives to women who need them. Good referral pathways or integration with social and legal support, counselling and harm-reduction services are also important for many people who might benefit from PrEP.

How does PrEP fit within national HIV programmes?

PrEP should become a core part of combination HIV prevention programmes as a choice for people at substantial risk of acquiring HIV. By increasing the relevance of HIV services to populations at higher risk, PrEP is synergistic with other prevention options and HIV treatment in addressing the HIV epidemic. Since PrEP is intended to serve populations that often have difficulty accessing health services, it must be provided in as user-friendly a service as possible.

What authorization is needed to implement PrEP?

Each country's medicines regulatory agency is responsible for authorizing the use of these antiretroviral medicines as prevention. So far, only the United States Food and Drug Administration has approved TDF + FTC for prevention; the manufacturer has also been filed for licensing for this indication in Australia, Brazil, France, South Africa and Thailand.

THE COST AND COST-EFFECTIVENESS OF PREP

What do PrEP programmes cost?

PrEP should not be expensive. Many programmes are already using TDF as part of their HIV treatment programme. Generic manufacture can bring the price of PrEP to less than US\$ 70 per person per year. The cost of a prevention programme that includes PrEP depends on the other elements in the HIV prevention package, tailored to local prevention needs, including the costs of staff. Just as treatment prices have been lowered, low-cost PrEP can be achieved through price negotiations with the manufacturers or management of intellectual property rights⁴ to secure a generic supply.

Opportunity costs can be minimized by integration with HIV treatment and prevention services and by appropriate task shifting away from specialist delivery.

Cost-effectiveness is not the only consideration when starting a new health programme. PrEP could contribute wider benefits beyond HIV prevention, including through increased engagement with health services (such as sexual and reproductive health or mental health services) by marginalized populations, that would otherwise not access health services at all.

⁴ For example, by using the flexibilities contained in the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property such as parallel import or compulsory licensing.

THE ROLE OF UNAIDS

How can UNAIDS facilitate the roll-out of PrEP?

UNAIDS advocates for scaling up PrEP as an additional effective intervention for HIV prevention. Priority actions for UNAIDS in the next three years include:

- Increasing public demand by engaging civil society.
- Promoting the inclusion of PrEP in national HIV strategies and making the case for funding.
- Supporting countries in licensing the use of appropriate antiretroviral medicines for prevention.
- Advocating for affordable PrEP and regulated generic manufacturing.
- Convening the required technical expertise for estimating costs and HIV incidence.
- Working with national programmes to define eligibility for PrEP and set priorities for PrEP appropriately.
- Promoting access and adherence to PrEP based on best practices.

THE FUTURE BEYOND ORAL PrEP

What new drugs are being tested for PrEP?

Topical and longer-acting preparations currently being investigated could provide more choice and improve long-term adherence. These include slow-release dapivirine in vaginal rings, long-acting PrEP injections (cabotegravir and rilpivirine) and subcutaneous implants with TDF derivatives. If they are effective, they can also be tested in combination with contraception.

Annex | Oral PrEP: protective effect and adherence in various studies

STUDY AND POPULATION	PROTECTIVE EFFECT OF PREP—ALL STUDY PARTICIPANTS	PROTECTIVE EFFECT AMONG PARTICIPANTS WITH HIGHER ADHERENCE
Heterosexual men and women (Partners PrEP ⁵ ; TDF-2 study ⁶): Botswana, Kenya and Uganda	62% – 76%	Up to 90%
Gay men and other men who have sex with men (iPrEX study ⁷): Brazil, Ecuador, Peru, South Africa, Thailand and the United States	44%	90%
People who inject drugs (Bangkok Tenofovir Study ⁸)	49%	75%
FEM-PrEP ⁹ : heterosexual women in Kenya, South Africa and the United Republic of Tanzania	<30% adherence, no effect	<30% adherence, no effect
VOICE ¹⁰ heterosexual women in South Africa, Uganda and Zimbabwe	<30% adherence, no effect	<30% adherence, no effect

- 5 Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* 2012;367:399–410.
- 6 Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med.* 2012;367:423–34.
- 7 Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; 363: 2587-2599. PubMed
- 8 Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2013;381:2083–90.
- 9 Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* 2012;367:411–22.
- 10 Marrazzo JM, Ramjee G, Nair G, Palanee T, Mkhize B, Nakabiito C et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections, 3–6 March 2013, Atlanta, GA, USA (Abstract 26LB).



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