WHO-UNAIDS brief on pre-exposure prophylaxis (PrEP)

Date: 20 September 2010

This brief is intended as an introduction to HIV pre-exposure prophylaxis (PrEP) for WHO and UNAIDS country and regional staff. If PrEP is shown to be effective in randomised controlled trials, countries need to be prepared to consider whether or not to include PrEP as part of combination prevention (behavioural, biomedical, and structural strategies). This document provides staff with the latest developments so they can brief stakeholders at country level on the progress of PrEP research and start discussions on the topic.

What is PrEP, and why do we need it?

PrEP is an experimental HIV prevention strategy that, if proven effective, would see HIV-negative people taking a single antiretroviral drug or combination of antiretroviral drugs to reduce their risk of HIV infection. Oral PrEP is not yet proven to work but one trial (CAPRISA 004) of topical PrEP in the form of 1% tenofovir vaginal microbicide reported promising results in July 2010.

Along with expanded scale-up of proven interventions, there is an urgent need for additional HIV prevention options. One of the potential advantages of PrEP is that an individual could use it without having to seek agreement from his or her sexual partner. In this way, those who are unable to negotiate condom use with their partners would still be able to reduce their risk of HIV infection.

Because PrEP is unlikely to be 100% effective, it will not replace other prevention strategies. It is anticipated that it will be most effective when used in combination with current HIV prevention methods, including male and female condom use, treatment of sexually transmitted infections, avoidance of penetrative sex, risk-reduction counselling, harm reduction for injecting drug users, and male circumcision. As a partially protective measure, it is important that PrEP not replace current effective strategies but rather be an additional tool in HIV prevention, expanding people's options.

What do we know about PrEP, and why might it work?

There is a strong scientific rationale for studying PrEP for HIV risk reduction. Studies of different PrEP dosing strategies in animal models (macaques) have shown high levels of protection when antiretroviral drugs are administered before HIV exposure. Other supporting evidence from humans includes:

- Preventing mother-to-child transmission of HIV through HIV-positive mothers and their infants taking antiretroviral drugs.
- Post-exposure prophylaxis (PEP) where people recently exposed to HIV (e.g. through a needle stick or an unprotected sex act) take antiretroviral drugs for 30 days to block acquisition.

Current state of the research

Current PrEP trials are enrolling more than 20,000 participants to test whether different oral PrEP formulations and combinations reduce the risk of HIV acquisition via different routes of transmission, in various populations, and in diverse epidemic settings (for trial details, see Appendix A). Oral PrEP trials are testing either tenofovir disoproxil fumarate (TDF), also known as tenofovir, or a combination of TDF plus emtricitabine (FTC). Gilead Sciences, Inc. markets TDF as Viread and

TDF/FTC as Truvada, but has licensed these drugs to generic manufacturers, mostly in India and South Africa. TDF and TDF/FTC were chosen for oral PrEP studies because they require only a single daily dose, have relatively low rates of side-effects, and have good long-term safety and resistance profiles in HIV-positive people on treatment. Positive or negative results from any one of the ongoing PrEP trials will not be the final answer on whether or not PrEP works. Each current trial is designed to answer a specific question, or set of questions, and the safety and effectiveness results from each trial will inform the broader field. While it is impossible to predict future results, it is highly likely—based on experience with male circumcision—that effectiveness trials will continue even if a single trial shows benefit. This is even more likely with PrEP because the study populations, settings, modes of transmission, and drug combinations being tested are different.

At the International AIDS Conference in Vienna, in July 2010, data from an extended safety trial of PrEP in men who have sex with men in the United States, revealed no safety concerns. CAPRISA 004, a phase IIB proof-of-concept trial of a 1% tenofovir gel used as a vaginal microbicide produced exciting results – the first signal that topical PrEP will work for women. Women had inserted the gel up to 12 hours prior to sex and a second time in the 12 hours following sex. Gel use blocked HIV infection in 39% of women over a 30-month period. As with condoms, the effectiveness increased with consistent use. Women who used the gel for more than 80% of their sex acts had a 54% reduced risk of HIV acquisition. The gel offers no direct protection to heterosexual men. Since 1% tenofovir gel is a new product, the findings require confirmation before a product is licensed and commercially available – a process that will likely take several years. In addition to planned confirmatory trials of the CAPRISA dosing (before and after sex), the safety of gel use in women aged 16 and 17 will be assessed, as will the effectiveness of a once-only dose strategy before sex. One trial, the VOICE trial, is already testing both daily oral PrEP and daily vaginal PrEP. Safety studies are underway testing tenofovir gel for prevention of HIV transmission among men who have sex with men.

Where is PrEP research taking place and in which groups?

Oral PrEP clinical trials are currently underway in a number of countries in Africa, Asia, Latin America, and North America. The current PrEP trials are designed to produce results in the following populations:

- Heterosexual women in high-prevalence settings
- Serodiscordant heterosexual couples (one partner is HIV-positive and one is HIV-negative)
- People who inject drugs
- Men who have sex with men

When will we get results?

In addition to the results reported in Vienna on safety of oral PrEP in men who have sex with men and on effectiveness of tenofovir gel in women, results from a phase II PrEP safety study among women in Cameroon, Ghana and Nigeria found once-daily TDF was safe and well tolerated.

The first results from effectiveness trials of oral PrEP are expected in late 2010 or early 2011 from the iPrEX trial in 5 countries among men who have sex with men. Results from the other trials will follow in 2012 and 2013. In addition to providing data on safety and effectiveness, these trials will assess adherence, acceptability, and risk compensation. Seroconverter studies will determine resistance, viral load, antiretroviral treatment options, and clinical outcomes in trial participants who become infected while taking oral PrEP.

What questions are likely to remain, after the current PrEP trials are completed?

Even if several of the ongoing trials find that PrEP is safe and effective in reducing HIV risk, several important questions will remain unanswered. Additional research will be needed on long-term

safety; use in pregnant women, adolescents, and people with hepatitis B (groups not included in current effectiveness trials); and the potential effectiveness of other dosing and delivery strategies.

What if PrEP works? What are the possible implementation challenges?

Positive results from ongoing PrEP trials would be an exciting development for biomedical HIV prevention. However, even if PrEP is determined to be effective, the challenges in translating this benefit into an impact outside of the trial setting could be considerable. These include: communicating what the new tool does and does not do; ensuring adherence and correct use; determining the risk profiles and most appropriate populations for PrEP use, developing programmes that deliver it as part of a comprehensive prevention package; and ensuring adequate and sustained financing for new programmes. Given that PrEP involves antiretroviral drug use in HIV-negative people, its introduction—if the trials show benefit—would require careful consideration of HIV testing frequency, safety monitoring, integration with existing services, and implications for national antiretroviral treatment programmes.

How are WHO and UNAIDS involved in preparing for PrEP?

Under funding from the Bill and Melinda Gates Foundation, WHO and UNAIDS are working with other partners to address PrEP implementation challenges and assess its 'proof of deliverability'. Countries hosting PrEP trials are receiving support to hold stakeholder consultations to foster dialogue for future action on PrEP. Regional stakeholder consultations are permitting countries to share their experience and thinking about the potential for PrEP implementation, should the trials show sufficient effectiveness.

Conclusions and questions from these consultations are refining region-specific mathematical modelling presented at each of 5 regional consultations. A decision–makers' programme planning tool will allow countries individually to assess country-specific costs and benefits of PrEP and reach an informed decision on the place of PrEP in combination prevention.

When results from the PrEP trials become available, WHO will assess the sufficiency of the data for developing norms, standards, and guidelines for PrEP use. As well, WHO and UNAIDS will provide tools and guidance to countries to facilitate implementation of PrEP.

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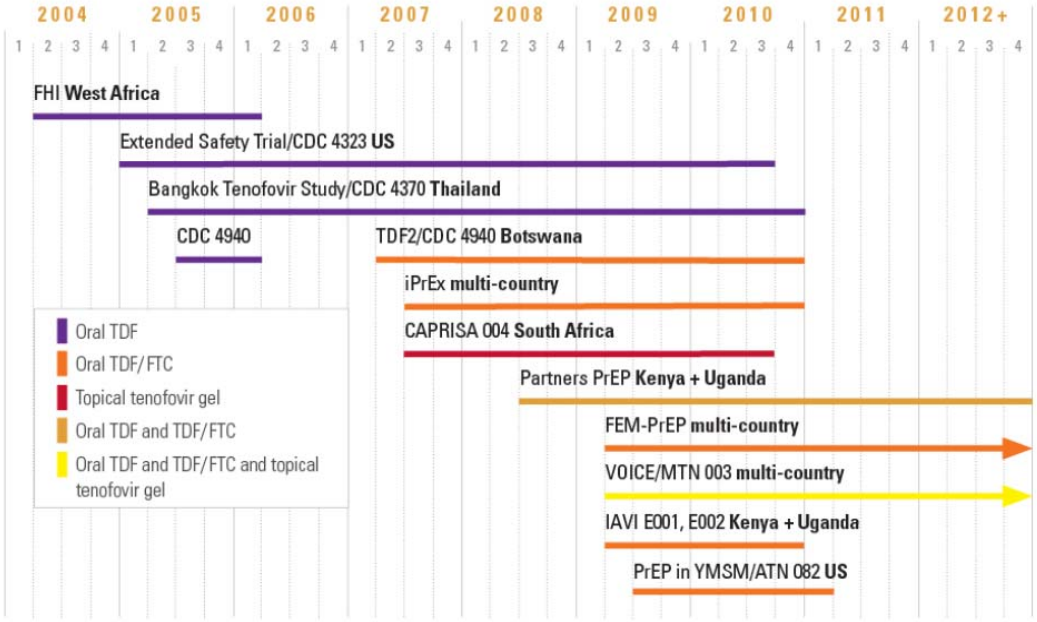
Appendix A*

Timeline for Ongoing PrEP Trials* (May 2010)



* The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor trial progress and will update the timeline accordingly. To view or download an updated timeline visit *www.prepwatch.org*.

Pre-Exposure Prophylaxis Trials (June 2010)					
Study; Study phase	**Location**	**Sponsor; Funder**	**Population** (*mode of exposure*)	**Intervention arm(s)**	**Status/ Results expected**
US Extended Safety Trial (CDC 4323) Phase II, safety	United States	CDC	400 gay men and other men who have sex with men (*penile/rectal*)	Daily oral TDF	Completed / Q3 2010
Bangkok Tenofovir Study (CDC 4370) Phase II/III, safety and efficacy	Thailand	CDC	2,400 injecting drug users (*parenteral*)	Daily oral TDF	Enrolling / Q4 2011
iPrEx Phase III, safety and efficacy	Brazil, Ecuador, Peru, South Africa, Thailand, US	NIH, BMGF	2,499 gay men and other men who have sex with men (*penile/rectal*)	Daily oral TDF/FTC	Fully enrolled / Q4 2011
TDF2 (CDC 4940) *Phase II, safety and adherence*	Botswana	CDC	1,200 heterosexual men and women (*penile and vaginal*)	Daily oral TDF/FTC; *switched from TDF Q1 2007*	Fully enrolled / Q4 2010
Partners PrEP Phase III, safety and efficacy	Kenya, Uganda	BMGF	4,700 serodiscordant heterosexual couples (*penile and vaginal*)	Daily oral TDF; daily oral TDF/FTC	Enrolling / 2012
FEM-PrEP Phase III, safety and effectiveness	Kenya, Malawi, South Africa, Tanzania	FHI, USAID, BMGF	3,900 heterosexual women (*vaginal*)	Daily oral TDF/FTC	Enrolling / 2013
VOICE (MTN 003) Phase IIb, safety and effectiveness	Malawi, South Africa, Uganda, Zimbabwe	MTN, NIH	5,000 heterosexual women (*vaginal*)	Daily oral TDF; daily oral TDF/FTC; daily topical tenofovir gel	Enrolling / 2013
IAVI E001 & E002 Phase I/II, safety, acceptability, adherence	Kenya, Uganda	IAVI	150 serodiscordant couples and men and women (*vaginal and penile/rectal*)	Daily oral TDF/FTC; intermittent oral TDF/FTC (twice weekly + coital dosing)	Fully enrolled / Q4 2010
PrEP in YMSM (ATN 082) Phase II, safety, acceptability, feasibility	United States	ATN, NICHD	99 young men who have sex with men (YMSM) (*penile/rectal*)	Daily oral TDF/FTC	Enrolling / 2011
PrEP Using TMC278LA Phase I/II, safety and pharmacokinetics	United Kingdom	St. Stephens AIDS Trust	100 men and women (*vaginal and penile/rectal*)	TMC278LA injected intramuscularly	Enrolling / 2011

ATN – Adolescent Trial Network; BMGF – Bill & Melinda Gates Foundation; CDC – US Centers for Disease Control and Prevention; FHI – Family Health International; FTC – emtricitabine; IAVI – International AIDS Vaccine Initiative; MTN – Microbicide Trials Network; NICHD – National Institute of Child Health and Human Development; NIH – US National Institutes of Health; Q1-4 – quarters 1-4; TDF – tenofovir disoproxil fumarate; USAID – United States Agency for International Development

* ***Source of Appendix A: AVAC http://www.avac.org/***