# Looking beyond TDF based Oral PrEP: Criteria for Identifying the Next PrEP Candidates

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## Introduction

Over the next few years, results from a number of effectiveness trials using antiretroviral (ARV) drugs as pre-exposure prophylaxis (PrEP) will be released. These trials test TDF (tenofovir disoproxil fumarate) and TDF/FTC (tenofovir disoproxil fumarate and emtricitabine) in oral and topical form in different populations and through different routes of HIV transmission. The iPrEx study, testing the safety and effectiveness of daily tenofovir/emtricitabine in preventing HIV transmission in 3000 HIV-negative men who have sex with men (MSM), is expecting to release results in early 2011. In addition, a study funded by the CDC testing daily dosage of tenofovir (CDC 4323) to prevent HIV infection in injection drug users in Bangkok, Thailand is xpecting to release results by early 2011. These trials will provide the first effectiveness results for daily oral use of ARVs for HIV prevention. Whatever the results of these ongoing trials, there will still be good reasons to test other ARVs as a PrEP agents.

A robust PrEP pipeline is important to ensure that the possible HIV prevention strategy PrEP is examined thoroughly, and if found to be safe and effective, can be implemented successfully. Although the currently studied PrEP candidates TDF and TDF/FTC might be found to be safe and effective, there may be other candidates or compounds that could be more effective, or have better safety profiles or fewer side effects. It would be advantageous to find a PrEP agent that is not currently a part of any ARV treatment regimen to address concerns about the effect of PrEP use on drug resistance to existing treatment regimens. It would also be useful to explore different types of PrEP delivery mechanisms to suit the needs of different people and different stages of peoples' lives. While the topical PrEP pipeline has multiple agents in development and being studied including combination products, the oral pipeline is currently examining too few candidates.

| | Pre-Clinical studies | Human Exploratory Studies | Safety Studies | Effectiveness Studies |
|---|---|---|---|---|
| Oral | | • Darunavir<br>• Etravirine<br>• Maraviroc | • Tenofovir<br>• Tenofovir and emtricitabine | • Tenofovir<br>• Tenofovir and emtricitabine |
| Topical | • Maraviroc<br>• MIV-150<br>• ML-644<br>• BMS793<br>• M167,M878, M882<br>• T1249<br>• S-DABO | | • UC-781<br>• TMC-120 (Dipivirine) | • Tenofovir |
| Injectable | | | • TMC-278LA (Rilpivirine) | |

## What Should the PrEP Pipeline Look like?

During 2009 and 2010, AVAC interviewed researchers, product developers, treatment implementers, treatment advocates, and regulators to describe the attributes of an optimal PrEP drug and to identify potential next-generation PrEP agents from the current licensed and experimental antiretroviral drugs.

## Results of interviews

### *List of ideal Attributes of an Oral PrEP agent*

- Safe (short term and long term) for intermittent and daily use in diverse HIV negative populations and pregnant women.
- Protection against HIV infection in tissue and in blood.
- Long lasting activity.
- A high genetic barrier to resistance.
- No clinically significant interactions with other drugs, including hormonal contraceptives.
- Minimal side effects for a healthy population of users.
- Acceptable to users.
- Stable without refrigeration, long shelf life.
- Not a part of any treatment regimen.
- If resistance develops, does not exclude other ARVs in the same drug class.
- Good penetration of drug into mucosal areas.

### *Possible Agents to be Studied for PrEP*

In our interviews we asked which licensed or experimental drugs might make good PrEP drugs because of their mechanism of action, patient acceptability, safety profiles and resistance profiles. There was no consensus in the responses we received, however, ARVs most often mentioned as drugs which could be considered as oral PrEP agents were:

- Lamivudine (3TC)
- Maraviroc (MVC)
- Rilpivirine (TMC278)
- Raltegravir (RAL)

Each drug had advantages and concerns, and all drugs had a number of areas where the lack of data made assessment difficult. Results from our interviews also indicated consensus on the need to identify ARVs that would be dedicated to a prevention-only use, so as to minimize the likelihood for resistance to develop. There are currently other ARVs which can be considered. These ARVs can be placed into three categories:

- ARVs previously in development for HIV treatment, but found not to be appropriate for treatment.
- ARVs which are used for treatment, but could be phased out and used for prevention only in the future.
- ARVs which could be developed for prevention use only.

## Current Ongoing PrEP Trials

**Ongoing PrEP Trials (May 2010)**

| Study<br>Study phase | Location | Sponsor<br>Vendor | Population<br>(mode of exposure) | Intervention arm(s) | Status /<br>Results expected |
|---|---|---|---|---|---|
| ***US Extended Safety Trial (CDC 4323)***<br>Phase II, safety | US | CDC | 400 gay men and other men who have sex with men (penile/rectal) | Daily oral TDF | Completed / Q3 2010 |
| ***iPrEx***<br>Phase III, safety and effectiveness | 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 2010 |
| ***Bangkok Tenofovir Study (CDC 4370)***<br>Phase II/III, safety and effectiveness | Thailand | CDC | 2,400 injecting drug users (parenteral) | Daily oral TDF | Enrolling / Q4 2010 |
| ***TDF2 (CDC 4940)***<br>*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***<br>Phase III, safety and effectiveness | Kenya, Uganda | BMGF | 4,700 serodiscordant heterosexual couples (penile and vaginal) | Daily oral TDF; daily oral TDF/FTC | Enrolling / 2012 |
| ***FEM-PrEP***<br>Phase III, safety and effectiveness | Kenya, Malawi, South Africa, Tanzania, Zambia | FHI, USAID, BMGF | 3,900 heterosexual women (vaginal) | Daily oral TDF/FTC | Enrolling / 2013 |
| ***VOICE (MTN 003)***<br>Phase IIb, safety and effectiveness | Malawi, South Africa, Uganda, Zambia, Zimbabwe | MTN, NIH | 5,000 heterosexual women (vaginal) | Daily oral TDF; daily oral TDF/FTC; daily topical tenofovir gel | Enrolling / 2013 |
| ***IAVI E001 & E002***<br>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)***<br>Phase II, safety, acceptability, feasibility | US | ATN, NICHD | 99 young men who have sex with men (YMSM) (penile/rectal) | Daily oral TDF/FTC | Enrolling / 2011 |
| ***CAPRISA 004***<br>Phase II, safety and effectiveness | South Africa | CAPRISA, FHI, CONRAD, USAID, LIFElab | 900 heterosexual women (vaginal) | Coitally dependent topical tenofovir gel | Completed / Q3 2010 |
| ***PrEP Using TMC278LA***<br>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; CAPRISA – Centre for the AIDS Programme of Research in South Africa; 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; US – United States; USAID – United States Agency for International Development

## Conclusion

While the microbicides field is actively ensuring there is a healthy pipeline of agents to consider, the oral PrEP pipeline in clinical testing is heavily based on only two drugs, both containing Tenofovir. Regardless of the results of the trials currently ongoing, the biomedical HIV prevention field will need to consider other oral PrEP agents besides TDF and TDF/FTC. There is great concern in the field about resistance, as the current oral PrEP pipeline relies on drugs that are recommended as first-line therapy for HIV. Having ARVs for prevention-only use would help minimize this risk. Although TDF and TDF/FTC seem promising as PrEP agents, there may be other candidates or compounds that could be more effective, or have better safety profiles or fewer side effects. Finally, as with any public health approach, it would also be useful to have different options. There may be different types of PrEP delivery mechanisms to suit the needs of different people and different stages of peoples' lives.

If new ARVs for oral PrEP are to be successfully developed and successfully rolled out in populations, the PrEP field needs to develop a structure for analyzing comprehensive and multidisciplinary issues, and making decisions on next steps. Drug developers, researchers (preclinical and clinical), funders (public and private), regulatory bodies, treatment advocates, prevention specialists, policy makers, HIV treatment implementers, WHO, community members and public health stakeholders must come together to build a PrEP pipeline, consider long term issues, and make decisions about the most appropriate way forward. While there are significant obstacles to testing another PrEP candidate, it is critical to bring together multidisciplinary HIV prevention research stakeholders along with treatment advocates and providers in the planning of next steps results in the CDC4323, CAPRISA004 and iPrEx trials.

### About AVAC

Funded in 1995, AVAC is a non-profit, community- and consumer-based organization that uses public education, policy analysis, advocacy, and community mobilization to accelerate the ethical development and global delivery of new HIV prevention options as part of a comprehensive response to the global pandemic.

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