

Does PrEP need a Pipeline? Criteria for Identifying the Next PrEP Candidates

Kevin Fisher, Lori Miller, Mitchell Warren

AVAC: Global Advocacy for HIV Prevention

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. Despite the results of these ongoing trials, there are still good reasons to test other ARVs as a PrEP agent.

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, the oral pipeline is currently examining too few candidates.

PrEP Agents Being Studied Currently

	Pre-Clinical studies	Human Exploratory Studies	Safety Studies	Effectiveness Studies
Oral		<ul style="list-style-type: none"> Darunavir Etravirine Maraviroc 	<ul style="list-style-type: none"> Tenofovir Tenofovir and emtricitabine 	<ul style="list-style-type: none"> Tenofovir Tenofovir and emtricitabine
Topical	<ul style="list-style-type: none"> Maraviroc MIV-150 ML-644 BMS793 M167/M878, M882 TL249 S-DABO 		<ul style="list-style-type: none"> UC-781 TMC-120 (Dipivirine) 	<ul style="list-style-type: none"> Tenofovir
Injectable			<ul style="list-style-type: none"> TMC-278LA (Rilpivirine) 	

What Should the PrEP Pipeline Look Like?

During 2009, 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

Attributes of ideal PrEP agents

- 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.

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 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

Study Name	Location	Sponsor/Lead	Population (no. of participants)	Intervention arm(s)	Status / Results expected
US Extended Safety Trial (CDC 022) Phase II, safety	US	CDC	400 gay men and other men who have sex with men (mhw/mw)	Daily oral TDF/FTC	Completed / Q3 2010
iPrEx Phase II, safety and effectiveness	Brazil, Ecuador, Peru, South Africa, Thailand, US	NHLBI, BARCF	2,488 gay men and other men who have sex with men (mhw/mw)	Daily oral TDF/FTC	Fully enrolled / Q4 2010
Bangkok Tenofovir Study (CDC 070) Phase III, safety and effectiveness	Thailand	CDC	2,800 injecting drug users (IDUs)	Daily oral TDF	Enrolling / Q4 2010
TDF (CDC 048) Phase II, safety and effectiveness	Bhutan	CDC	1,200 heterosexual men and women (genital and vaginal)	Daily oral TDF/FTC, placebo from TDF Q1 2007	Fully enrolled / Q4 2010
Partners PrEP Phase II, safety and effectiveness	Kenya, Uganda	BARCF	4,700 heterosexual heterosexual couples (genital and vaginal)	Daily oral TDF-daily oral TDF/FTC	Enrolling / 2012
FEM-PrEP Phase II, safety and effectiveness	Kenya, Malawi, South Africa, Tanzania, Zambia	FHI, USAID, BARCF	3,800 heterosexual women (vaginal)	Daily oral TDF/FTC	Enrolling / 2013
VOICE (MTH 001) Phase II, safety and effectiveness	Malawi, South Africa, Zambia, Zimbabwe	MTH, NIH	6,000 heterosexual women (vaginal)	Daily oral TDF, daily oral TDF/FTC, daily topical tenofovir gel	Enrolling / 2013
IMPACT & ONO Phase I/II, safety, acceptability, adherence	Kenya, Uganda	MSF	150 men/consistent couples and men and women (genital and vaginal/rectal)	Daily oral TDF/FTC, placebo/oral TDF/FTC, placebo rectally + oral dosing	Fully enrolled / Q4 2010
PrEP in MSM (MTH 002) Phase II, safety, acceptability, feasibility	US	ATL, NCI/NIH	90 young men who have sex with men (MSM) (penile/rectal)	Daily oral TDF/FTC	Enrolling / 2011
CAPRISA 001 Phase II, safety and effectiveness	South Africa	CAPRISA, FHI, CONRAD, USAID, ICF/Abt	900 heterosexual women (vaginal)	Culturally dependent topical tenofovir gel	Completed / Q3 2010
PrEP Using TMC278LA Phase III, safety and pharmacokinetics	United Kingdom	St. Stephen's AIDS Trust	100 men and women (vaginal and penile)	TMC278LA injected intravenously	Enrolling / 2011

ATL - Adolescent Trial Network; BARCF - Bill & Melinda Gates Foundation; CAPRISA - Center for the AIDS Programme of Research in South Africa; CDC - US Centers for Disease Control and Prevention; FHI - Family Health International; FHI - International AIDS Technical Assistance Agency; ICF/Abt - International Country Support Group; MTH - National Institutes of Health; MSF - Médecins Sans Frontières; NCI/NIH - National Institutes of Health; NIH - US National Institutes of Health; Q1 - quarter 1; Q3 - quarter 3; Q4 - quarter 4; TDF - tenofovir disoproxil fumarate; TDF/FTC - tenofovir disoproxil fumarate and emtricitabine; 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.

About AVAC

Founded 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.

