



PRE-EXPOSURE PROPHYLAXIS (PrEP)

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Technical update on Pre-exposure Prophylaxis (PrEP), February 2015

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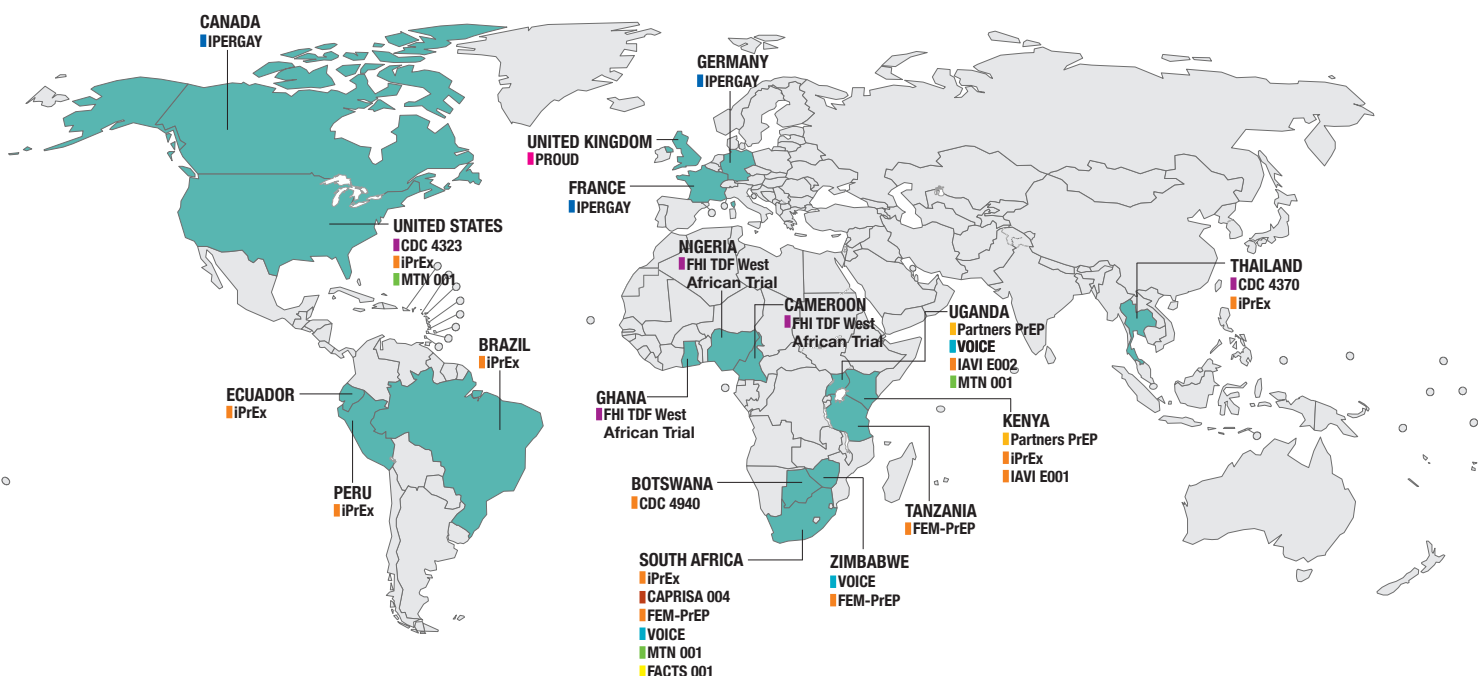
# WHO TECHNICAL UPDATE ON PRE-EXPOSURE PROPHYLAXIS (PrEP)

The development of oral pre-exposure prophylaxis began in the early part of the last decade. Proof of concept was suggested through comparisons with prevention of mother-to-child transmission and post-exposure prophylaxis and was supported by animal models, both in mice (1) and in macaques (2–5). Safety was demonstrated with a Phase II study conducted in west Africa (6). Soon after, enrollment in Phase III efficacy trials of both topical and oral PrEP among different groups began:

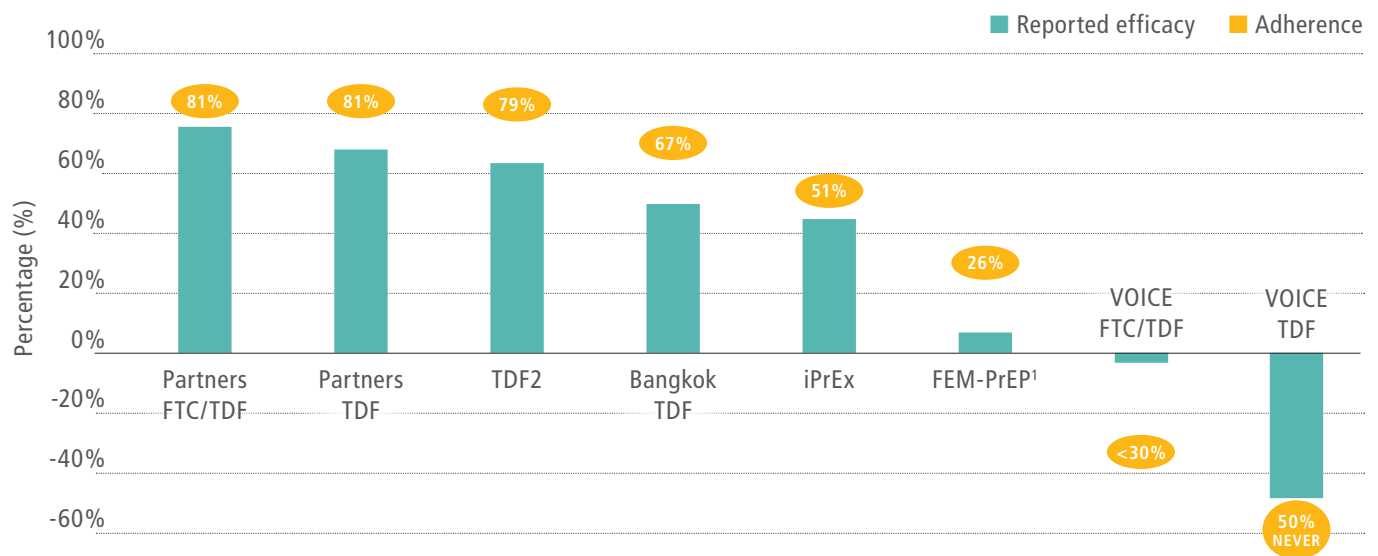
- Oral PrEP among persons who inject drugs in Bangkok, Thailand in 2005 (7);
- Oral PrEP among men and transgender women who have sex with men (MSM) in multiple countries (8) and among highly sexually active men and women in Botswana (9) and topical PrEP among young women at risk in South Africa (10) in 2007;
- Oral PrEP among serodiscordant heterosexual couples in Kenya and Uganda in 2008 (11); and among young women at high risk of HIV in 2009 (12);
- Oral and topical PrEP among women in Uganda, South Africa and Zimbabwe in 2009 (13).

The first evidence of effectiveness of 39% was found for tenofovir vaginal gel in 2010 among women age 18–40 years old in South Africa (10) and soon after for daily oral PrEP among men and transgender women who have sex with men (44%) (8). The efficacy of daily oral PrEP was found to be significantly higher in those more adherent to PrEP use. Subsequently, overall efficacy ranging from 62% to 75% was found in young heterosexuals and serodiscordant (SDC) couples respectively (81% and 79% among those more adherent) (9,11). In contrast, the FEMPrEP trial and the VOICE trial (which evaluated efficacy of topical as well as oral PrEP) demonstrated no effect. This was mainly explained by low levels of adherence with the recommended prevention regimen (14).

## PrEP clinical trials geographical coverage



## PrEP adherence and PrEP efficacy in key studies



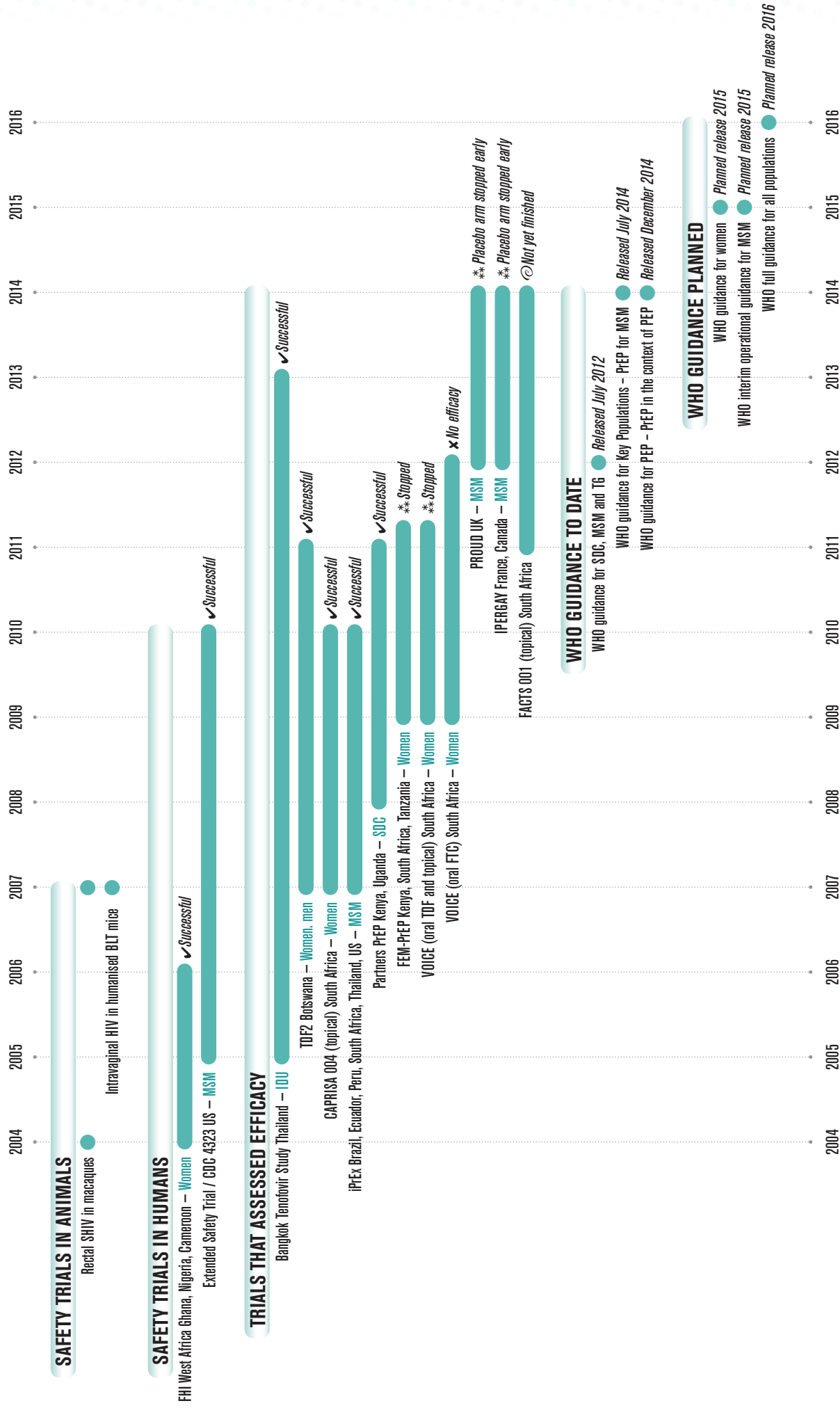
<sup>1</sup> 26% over two visits, 38% maximum at one visit.

## WHO WORK ON PrEP TO DATE

The WHO HIV Department began its work on PrEP in 2009 to help countries prepare for potential implementation of PrEP, should the trials show sufficient safety and effectiveness. With its partner UNAIDS, and in partnership with Georgetown University School of Law, WHO convened a number of country and regional consultations to address issues of PrEP implementation and to help countries think through the process and the implications.

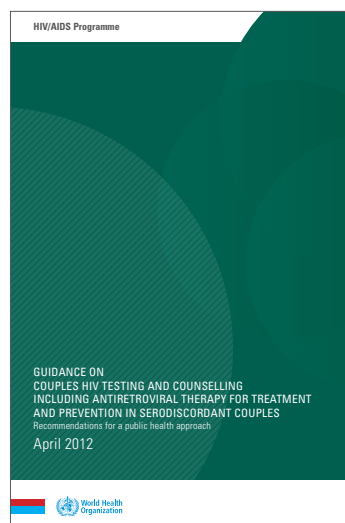
This work with key international partners and stakeholders continues as a consortium that aims to exchange information on the evidence and experience on PrEP use and prioritise future research questions. In a similar fashion, WHO's Reproductive Health Department worked with countries to develop support and acceptance for the possible future implementation of topical vaginal tenofovir gel.

# Timeline of PrEP scientific progress and guidance – past, present and future

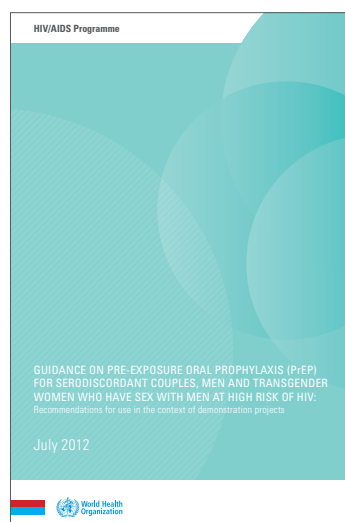


# 2012 GUIDANCE

PrEP first appeared in WHO's 2012 guidance on couples HIV testing and counselling in the context of antiretroviral therapy for treatment and prevention in serodiscordant couples. The possibility of PrEP as an additional option for the HIV negative partner of an HIV positive person on treatment was introduced. Reference was made to the 2012 guidance on PrEP that was under development and planned for publication later that year.



Following the first evidence of effectiveness of oral PrEP in the iPrEx trial in 2010, and subsequently the Partners PrEP and the TDF2 trials in 2012 (8,11), WHO started the formal review and analysis required for the generation of guidance. This resulted in PrEP guidance for MSM and SDC in 2012. Given the numerous uncertainties around how best to deliver oral PrEP safely to achieve similar effectiveness to that found in the trials, the guidance recommended undertaking demonstration projects in countries where additional prevention was needed and where capacity existed. Recommendations for other groups were not included at that time, as further specific trial evidence was anticipated from the FEM-PrEP and VOICE trials for young women and from the Bangkok IDU trial for people who inject drugs. It was seen as more desirable to have those results before proceeding with additional recommendations.



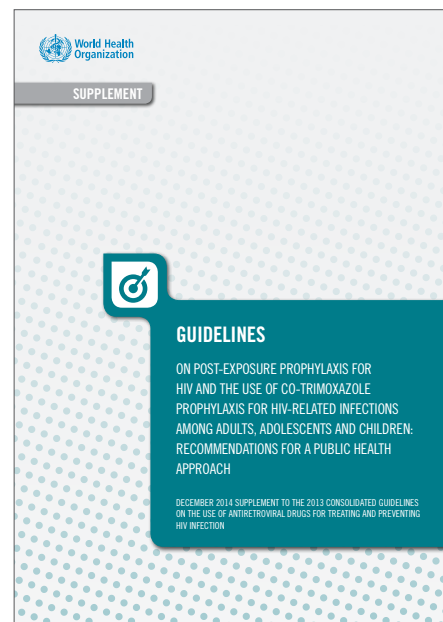
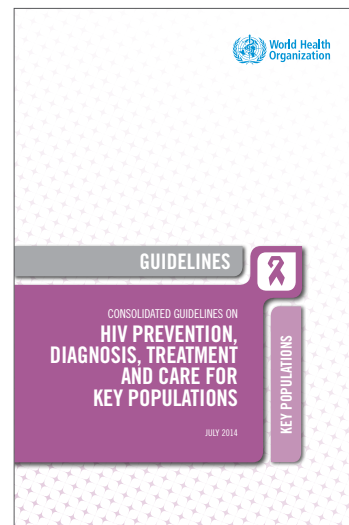


# 2014 GUIDANCE

In 2014, WHO convened a group to develop consolidated guidelines on key populations. Given the growing evidence of need for additional prevention approaches for MSM and the increasing evidence of support for oral PrEP from this group, a strengthened recommendation was issued, despite the absence of any additional trial evidence of effectiveness since the previous 2012 recommendation. (Evidence from four additional observational studies was considered.) Increasingly supportive evidence was available from implementation and values and preferences studies among MSM. The guideline development group considered but did not make a PrEP recommendation for people who inject drugs as lack of support from the affected communities, coupled with existing highly effective needle syringe programmes and opiate substitution therapy, made this recommendation less crucial and feasible.

The Key Populations guidelines group also made no recommendation for oral PrEP among sex workers or transgender women due to a lack of implementation experience and evidence of supportive values and preferences for these groups. Support for work to fill these data gaps was recommended.

PrEP was then also discussed in the post-exposure prophylaxis (PEP) 2014 supplement to the 2013 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection. In certain situations where people are taking repeat PEP, it was recommended that consideration could be given to offering PrEP. In all cases the full range of prevention strategies was also to be considered and discussed. This provided an opportunity to integrate PrEP into the continuum of ARV-based prevention between PrEP and PEP.



## Status of WHO PrEP recommendations by population

Current WHO Recommendations	Population	WHO decision	Year
Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: Recommendations for use in the context of demonstration projects	MSM SDC	Yes Yes	2012
HIV prevention, diagnosis, treatment and care for key populations	MSM	Yes	2014
Guidelines on post-exposure prophylaxis for HIV: recommendations for a public health approach	Continuum of PEP – All at high risk	Yes	2014
<b>No current WHO recommendations</b>			
HIV prevention, diagnosis, treatment and care for key populations	IDUs	Not rec	2014
HIV prevention, diagnosis, treatment and care for key populations	Sex Workers (SW)	Further work required	2014
<b>Possible future WHO recommendations</b>			
Women/young women/sex workers, at high risk recommendations	Women, YW, SW	For consideration	2015
<b>Future implementation guidance</b>			
Operational guidance for MSM	MSM	Soon	2015
Full recommendations and guidance for all populations	All		2016

# WHO's FUTURE DIRECTIONS ON PrEP

## 1. PrEP for women at high risk of HIV infection – increasing prevention options for women

More prevention options are needed, especially for young women in high incidence settings. Some women face difficulties using existing prevention methods and the search for effective HIV prevention for women continues. Oral PrEP can offer high levels of protection to women if they use it consistently. It can complement condom use that women cannot always demand from their partners.

WHO will focus its attention in the coming months on considering a new recommendation for oral PrEP for women. This effort may be expanded to include topical PrEP as well if soon-to-be-released data from the FACTS study shows evidence of sufficient effectiveness for tenofovir gel. With continuing high incidence in many places, mounting evidence of acceptability of PrEP and the evidence of oral PrEP effectiveness among women, a strong rationale exists for a new PrEP recommendation. The WHO process of assessing the strength of these elements in guideline development will be followed.

The timeliness of this effort is important. Defining a comprehensive package of prevention options that meets the needs of women at particularly high risk is becoming an increasingly high priority. The GFATM has emphasized the

importance of including specific targets and comprehensive packages of care for high-risk women in country proposals, and this should be supported. The new PEPFAR coordinated DREAM initiative<sup>1</sup> for adolescent and young women in hyperendemic settings is a potentially powerful initiative to address the continued needs of young women at high risk of HIV. The role of PrEP as part of a comprehensive HIV prevention package for young women needs urgent consideration and WHO plans to develop this guidance in the first half of 2015. Modelling of cost effectiveness may help identify optimal settings and population groups where PrEP, either oral PrEP alone or in combination with topical PrEP, could be considered.

For other groups at high risk of HIV infection, WHO will continue to assess the suitability of PrEP as a potential additional prevention method. Specifically, WHO will monitor the need and the values and preferences about PrEP among members of the people who inject drugs (PWID) and transgender communities. In the latter group, potential toxicity issues stemming from the use of hormonal products will be further assessed before safety can be assured.

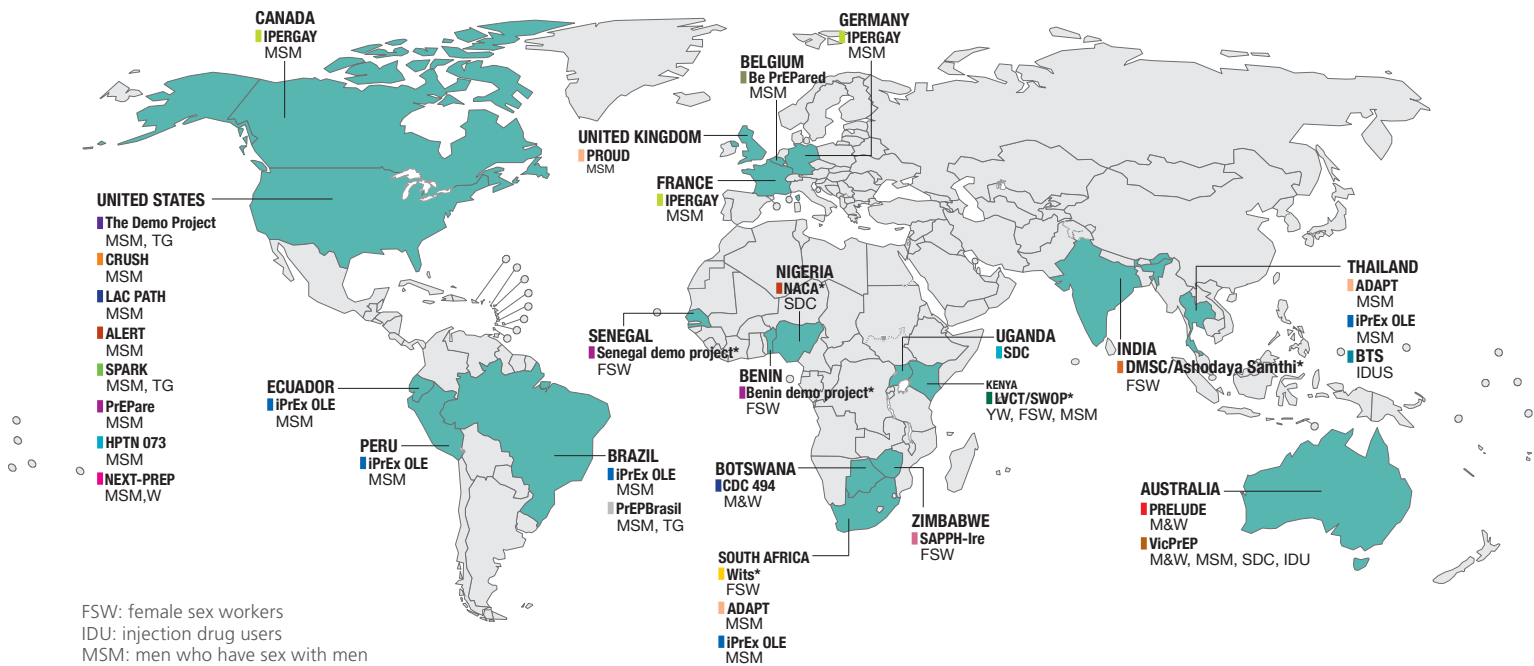
<sup>1</sup> <http://www.pepfar.gov/partnerships/ppp/dreams/index.htm>

## 2. Document evidence from ongoing demonstration projects

WHO will produce updated implementation guidance for the roll out and implementation of PrEP. To accomplish this, WHO will continue to support a number of PrEP demonstration projects that will provide information to inform this implementation guidance. These projects are taking place among young women at high risk of HIV (Kenya), sex workers (South Africa, India, Kenya, Benin and Senegal), serodiscordant couples (Nigeria) and men who have sex with men (Kenya). They are exploring the

best strategies for safe and effective implementation of oral PrEP and as such, will make important contributions to the guidance needed by health systems for broader PrEP implementation. In addition, WHO gather evidence and experience from other implementation projects through NEMUS, the network established to foster and support such research. Full guidance based on results from the demonstration projects for all groups is not likely to be available before mid-2016.

### Ongoing demonstration projects map



### 3. Implementation guidance for MSM

Guidance for implementing PrEP for MSM is needed now. Following the new recommendation for MSM issued in 2014, support has been growing from community networks, countries and regions to start implementing PrEP for MSM. To aid in this process, WHO will develop PrEP implementation guidance for this group.

This guidance may be adapted to support PrEP implementation for other populations if additional recommendations are developed. This guidance will be based on the best currently available information. It will be refined and updated as additional information from the demonstration projects and elsewhere becomes available.

This guidance will include:

- Possible target groups where offering PrEP could be cost effective and acceptable as an additional prevention choice in the context of combination prevention
- Quantification of adverse events and associated monitoring for these, including assessment of FTC-TDF toxicity risk by population (MSM, women, adolescent women, pregnant and breast feeding women) and recommended toxicity monitoring e.g. creatinine clearance monitoring
- Discussion of potential drug interactions including hormonal contraception, other hormones used by MSM, recreational drugs, drugs used for treatment of common co-morbidities including TB and hepatitis B and C
- Considerations regarding drug resistance
- Understanding and supporting adherence in the context of PrEP
- Issues relating to re-testing frequency and testing methods
- The 'package' of services, including the schedule and modes of re-testing
- Assessment of and support for adherence to the recommended PrEP regimen
- Potential models and sites where PrEP delivery and repeat-provision could be considered.

## WHO GOALS, 2015 AND BEYOND

### 1. Updating guidance in response to new evidence

**Research on PrEP continues. As new evidence on oral PrEP and its use develop, WHO will update its guidance to reflect this.** Data from two additional trials (PROUD and IPERGAY) will become available in early 2015. These data may affect the specific interim guidance proposed for MSM. The results from these two studies will be reviewed and considered when developing interim guidance.

**If evidence of effectiveness of topical PrEP is forthcoming from the FACTS 001 topical tenofovir study, WHO will expand its assessment of prevention options for women to include this.** The potential for further integration of topical and oral PrEP options for women will be influenced by these results that will be carefully monitored.

Other research efforts will also be tracked for their future implications. Long-acting formulations of PrEP are soon entering Phase III trials, with results possible in the next 3 years, especially for rilpivirine (TMC278) and GSK744, the two most advanced formulations. The results of these important trials may well affect PrEP use in the next five years.

The **RING study** and **ASPIRE study**, both trials of the dapivirine ring, may produce results in late 2015/early 2016. WHO will respond quickly to positive results to assure that its guidance can be updated to facilitate bringing new prevention products into use as quickly as possible.

### 2. Ongoing support for PrEP demonstration projects

WHO will continue to support demonstration projects, using that evidence and other implementation experience from a number of other pilot and implementation programmes to develop final guidance for effective PrEP implementation with least possible burden on the health system.

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**For more information, contact:**

World Health Organization  
Department of HIV/AIDS  
20, avenue Appia  
1211 Geneva 27  
Switzerland

E-mail: [hiv-aids@who.int](mailto:hiv-aids@who.int)

[www.who.int/hiv](http://www.who.int/hiv)