

*#offerPrEP #PrEPworks*

# TDF/3TC for PrEP: the rationale and the evidence

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## DISCLAIMER

No conflicts of interest to declare

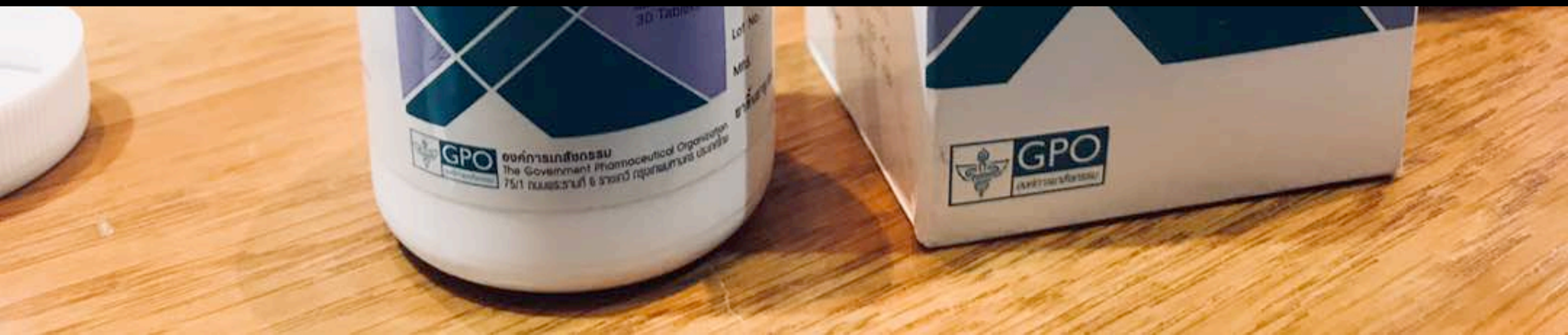
# OVERVIEW

- What is WHO's position on TDF/3TC?
  - Current oral PrEP recommendation
  - EML
  - Rationale for TDF/3TC
  - Evidence base
- What is happening in other countries with PrEP implementation, including TDF/3TC?





# What is PrEP?

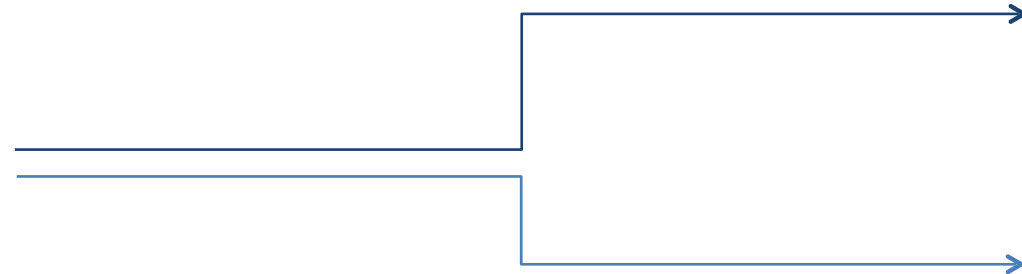


**NOT ONLY TRUVADA**

**Over 10 generic products (appropriate for PrEP) are  
WHO prequalified (TDF/FTC and TDF/3TC)**

# WHO RECOMMENDATION (2015)

PrEP trials  
considered



**TDF**



**TDF/FTC**

# WHO RECOMMENDATION (2015)

- PrEP is recommended for any person at *substantial* risk for HIV
- **TDF-containing**
  - TDF/FTC, TDF/3TC, or TDF monotherapy
- Daily dosing currently recommended for all populations
- Near future, event-driven PrEP ('on-demand') for MSM
  - 2 + 1 + 1 (Ipergay dosing)
- Not just a pill, but part of a **package** of combination HIV prevention and sexual health



WHO guidance documents available online at:  
<https://www.who.int/hiv/topics/prep/en/>



## GUIDELINES



### CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION

RECOMMENDATIONS FOR A  
PUBLIC HEALTH APPROACH

SECOND EDITION  
2016

## MODULE 1 CLINICAL

### WHO IMPLEMENTATION TOOL FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) OF HIV INFECTION

JULY 2017



## MODULE 10 TESTING PROVIDERS

### WHO IMPLEMENTATION TOOL FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) OF HIV INFECTION

JULY 2017



## TECHNICAL BRIEF

### PREVENTING HIV DURING PREGNANCY AND BREASTFEEDING IN THE CONTEXT OF PREP

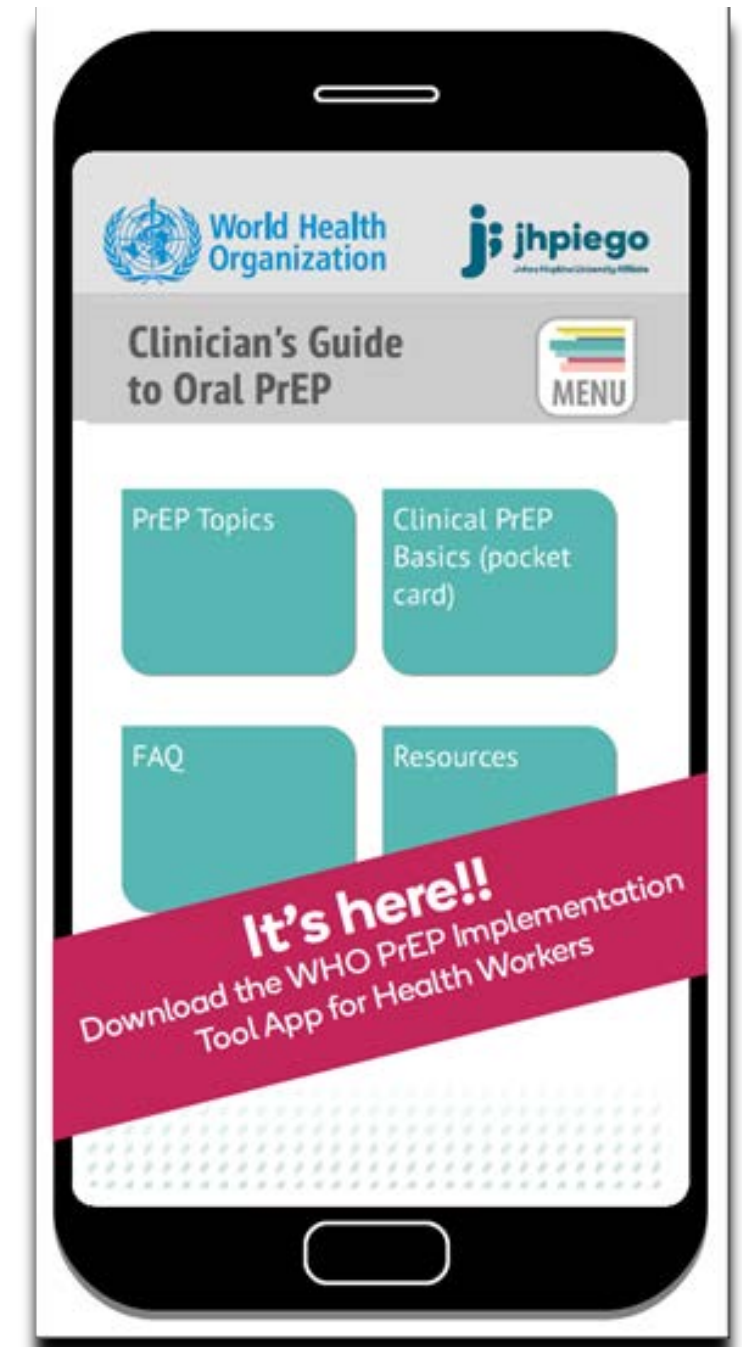
JULY 2017



# WHO PrEP Implementation Tool (2017)



<http://who.int/hiv/pub/prep/prep-implementation-tool>





- STI testing recommended during PrEP use



Also, PrEP always comes with a mandatory medical follow up every 3 months so you can get tested for other STDs and check on your sexual health in general!

The use of PrEP changes according to the country you live in. Some countries like France have universal healthcare so PrEP is totally free, and in other like the United States, it will depend on your insurance.

Good to know: there are also organizations that can help you pay for PrEP if you have no insurance!

# WHO MODEL LIST OF ESSENTIAL MEDICINES

- guide for development of national/institutional essential medicine lists
- updated/revised every two years by the WHO Expert Committee on Selection and Use of Medicines.
- 20th Essential Medicines List, published on 6 June 2017, marks the 40th anniversary of this flagship WHO tool to expand access to medicines.
- **433 drugs** deemed essential for addressing the most important public health needs globally.

# PrEP is an essential medicine as of 2017

- **TDF/3TC**
- **TDF/FTC**
- **TDF mono-therapy**
- Full report accessible here: <http://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf?sequence=1>



Essential medicines and health products

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WHO Model Lists of Essential Medicines

The WHO Model Lists of Essential Medicines has been updated every two years since 1977.

The current versions are the 20<sup>th</sup> WHO Essential Medicines List (EML) and the 6<sup>th</sup> WHO Essential Medicines List for Children (EMLc) updated in March 2017.

The 2017 Expert Committee on the Selection and Use of Essential Medicines

Executive Summary  
pdf, 723kb

Report of the 2017 Expert Committee

CURRENT LISTS

- EML – 20<sup>th</sup> edition (March 2017, amended August 2017)
- EMLc – 6<sup>th</sup> edition (March 2017, amended August 2017)

Meetings & events



40<sup>th</sup> ECDD Meeting on Cannabis and Cannabis-Related Substances

Training resources

## RATIONALE

- COST
- SUPPLY CHAIN

# MARCH 2016 CONSULTATION ON APPROPRIATE MEDICINES

- TDF/FTC as PrEP availability remains limited globally
  - Need to clarify use of TDF/3TC instead of TDF/FTC as PrEP
  - WHO Guidelines state that "Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches".
  - How should we interpret the guidelines?

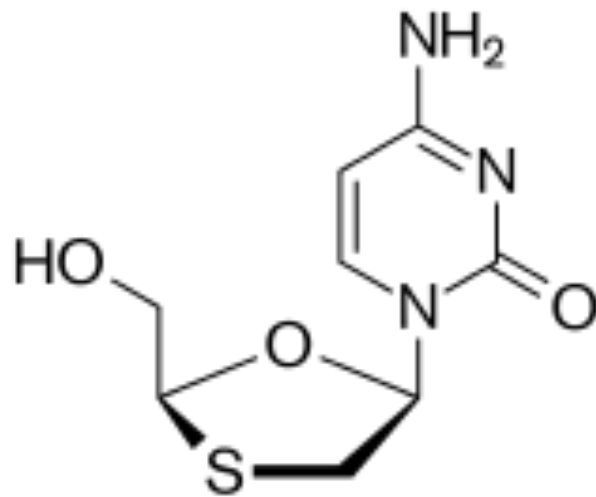


# Considerations

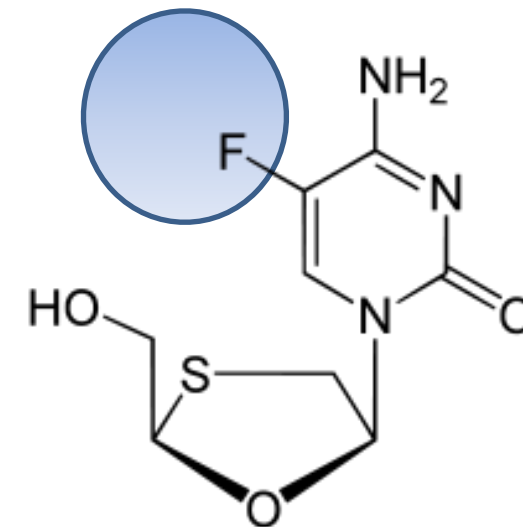
- What is the added-value (to public health and individual health) to undertake a non-inferiority PrEP RCT (TDF/FTC vs TDF/3TC)?
- What are the short-term and longer term benefits of implementing TDF/3TC within a health system (e.g. cost-saving in order to target resources to other services for key populations, e.g. optimised STI case management) ?

# Chemical structure: very similar

3TC



FTC



- The chemical structures of 3TC and FTC differ only by the presence in FTC of **fluorine** at the 5'-position of its cytosine ring
- 3TC and FTC are oxathiolane-cytosine analogs that selectively inhibit HIV replication.
- Like other NRTIs, 3TC and FTC must be triphosphorylated **intracellularly** before they can competitively inhibit endogenous deoxycytidine triphosphate (dCTP) and cause chain termination.

# Evidence base for TDF/3TC as PrEP

1. Indirect evidence from systematic review of ART studies on interchangeability of 3TC and FTC (*WHO, 2012, 2016*)
2. Clinical trials of 3TC in prevention of mother-to-child transmission
3. WHO post-exposure prophylaxis guidelines
4. Animal and human pharmacokinetic studies
5. Direct evidence: phase I study of TDF/3TC as PrEP in MSM (ongoing Phase II) from Universidade Federal de Minas Gerais, Brazil (no HIV seroconversions)

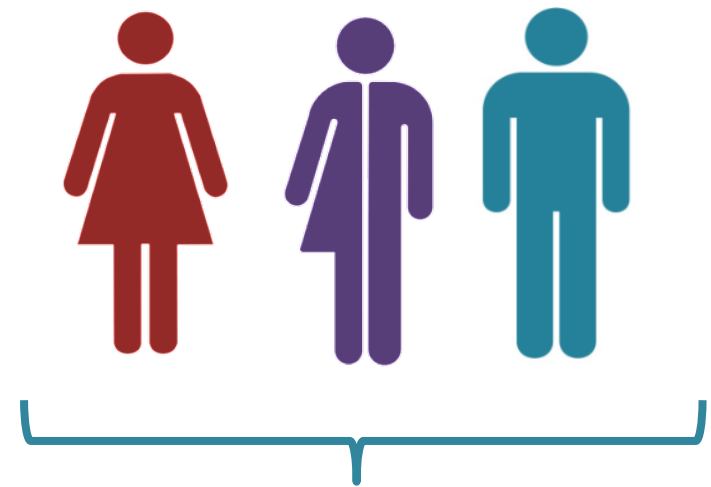
## Indirect evidence

- evidence on the safety and/or efficacy of (pre-exposure prophylaxis) drugs inferred from studies whose primary aim is not to directly assess these outcomes of interest

# Spectrum of evidence reviewed



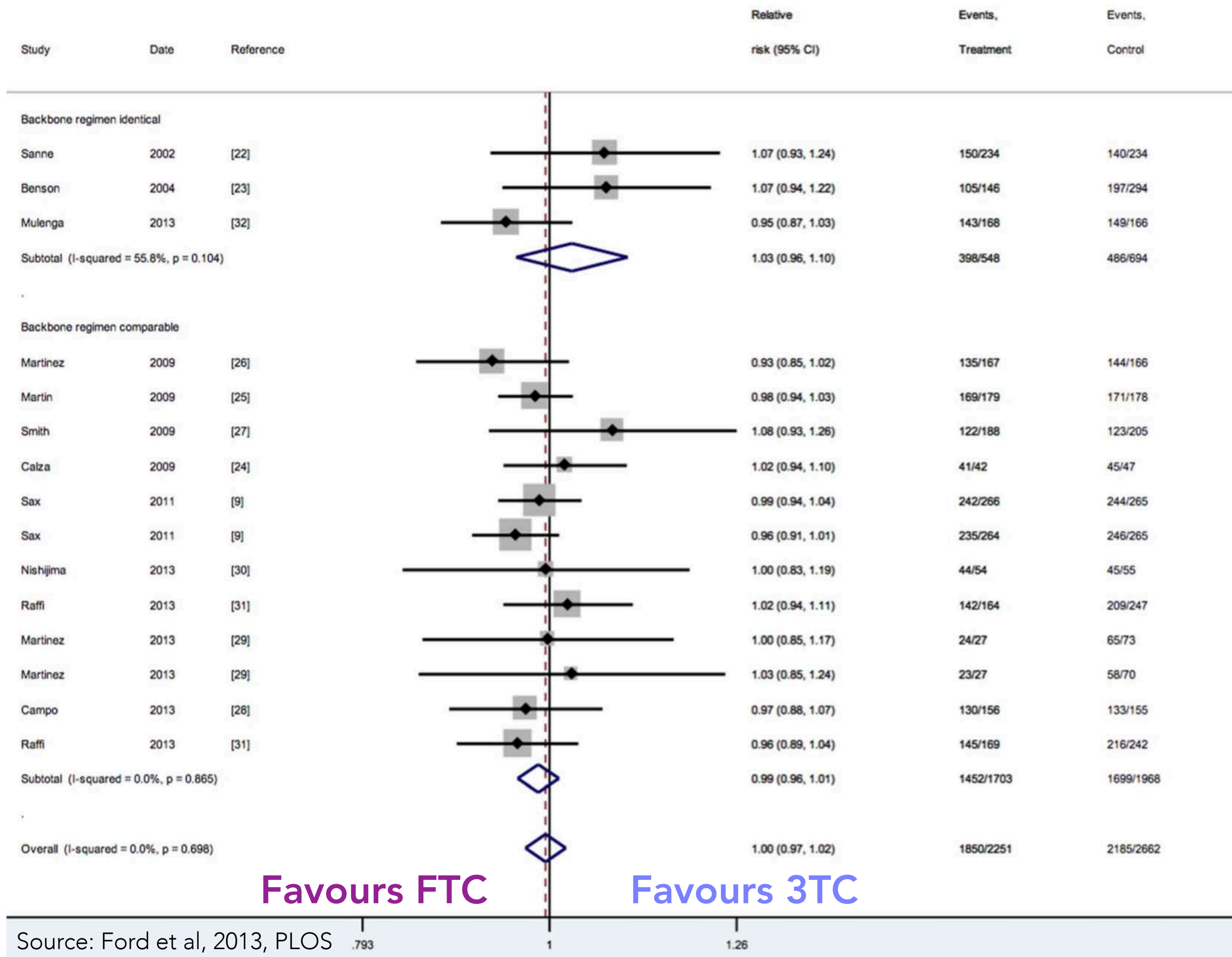
- Animal pharmacology
- Virus challenge studies
  - *Rhesus macaques (rectal transmission)*
  - *Pigtail macaques (vaginal transmission)*



- Human pharmacology
- Clinical trials (men, women, and transgender persons)
  - *TDF alone*
  - *TDF/FTC*
- Systematic reviews/meta-analyses
  - *PrEP*
  - *ART*

Full report available here: [http://apps.who.int/iris/bitstream/handle/10665/70936/9789241503815\\_eng.pdf?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/70936/9789241503815_eng.pdf?sequence=1)

**TECHNICAL UPDATE ON TREATMENT OPTIMIZATION  
PHARMACOLOGICAL EQUIVALENCE  
AND CLINICAL INTERCHANGEABILITY OF LAMIVUDINE  
AND EMTRICITABINE: A REVIEW OF CURRENT LITERATURE**



MTCT data: 3TC has been studied as a component of combination therapy for its capacity to decrease the risk of MTCT and infant mortality.

- SIMBA study (Rwanda/Uganda)
  - IAS 2003
- Mitra study (Tanzania breastfeeding study)
  - JAIDS 2008
- Kesho Bara study reported that infants of mothers treated with 3TC-containing ART during pregnancy and breastfeeding had a decreased risk of HIV transmission (43% reduction,  $P = 0.029$ ), mortality, and HIV transmission or death (36% reduction,  $P = 0.017$ ) at 12 months compared with mothers treated with ART that did not include 3TC
  - Lancet ID, 2011
- Infant lopinavir/r versus 3TC to prevent postnatal HIV-1 transmission: the ANRS 12174 trial
  - Kankasa C et al, CROI 2014



# 3TC vs FTC half-life

**TABLE 1.** Virological, Biochemical, and Pharmacological Characteristics of NRTIs Used in Contemporary HIV Therapy

	3TC	ABC	FTC	ZDV	TDF*	TAF*
HIV-1 reverse transcriptase in MT-4 cells†, mean (SD, n), $\mu\text{M}^{104-106}$	2.1 (0.6, 7)	4.0 (1.6, 21)	0.5 (NA, 2–3)	0.040 (0.005, 51)	4.2 (0.8, 2)	0.005 (0.002, 2)
Intracellular half-life, $h^{75,107}$	10.5–15.5	3.3	>20	3–4	>60	NA <sup>108‡</sup>
Plasma or serum $T_{1/2}$ , $h^{75,107,109}$	5–7	1–2	7–10	0.8–1.9	17	0.4
Reverse transcriptase $K_i$ §  , mean (SE), $n\text{M}^{110-112}$	233 (28)	10 (1)¶	430 (60)	4.4 (2)	980 (NA)#	NA
Relative mtDNA content after 25 days of treatment, mean % vs untreated control cells** (SD) <sup>61,113</sup>	137 (7)	134 (27)	110 (15)	118 (24)	101 (20)	107 (16)

3TC, lamivudine; ABC, abacavir;  $EC_{50}$ , drug concentration needed to inhibit 50% of viral spread; FTC, emtricitabine;  $IC_{50}$ , half-maximal inhibitory concentration;  $K_i$ , apparent inhibitor dissociation constant; mtDNA, mitochondrial DNA; n, number of determinations; NA, not available; SD, standard deviation; SE, standard error of the mean; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

\*Active moiety is tenofovir diphosphate.

† $IC_{50}$  for 3TC, ABC, FTC, and ZDV;  $EC_{50}$  for TDF and TAF.

‡Could not be estimated.

§Inhibition constants for the triphosphate analogs of 3TC, ABC, FTC, and ZDV.

||Values were generated using a homopolymeric RNA/DNA template for 3TC; DNA template for TDF, FTC, and ZDV; and RNA template for ABC.

¶In the form of carbovir, the active metabolite of ABC.

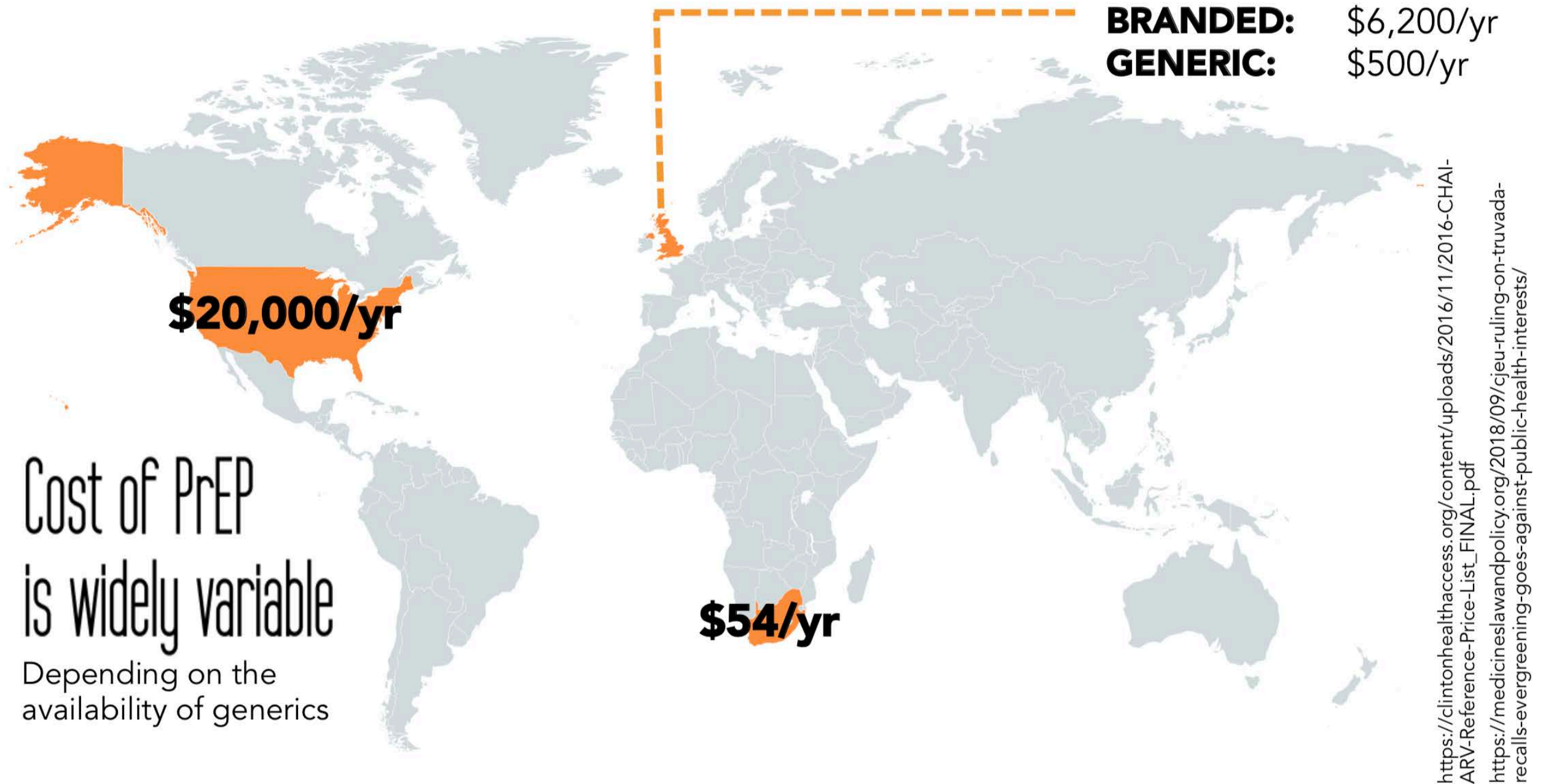
#Average standard error for  $K_i$  values for TDF and its analogs was 16%.

\*\*Changes were observed after 25 days of treatment in HepG2 cells for 3TC, ABC, FTC, and ZDV; changes were observed after 10 days of treatment in MT-2 cells for TDF and TAF.

## TDF/3TC conclusions from consultation

- There is indirect evidence that shows that TDF-3TC could be considered an option for countries to use for PrEP, especially where restricting PrEP drug choice to TDF/FTC would limit or prevent implementation
- Molecular structures of 3TC and FTC: Structurally related
- Mucosal PK profile suggests pharmacological equivalence of FTC and 3TC for PrEP (CDC data)
  - High concentrations in vaginal and rectal fluids with levels that are within the range seen in humans

# TD\*/FTC costs



# Prices vary considerably in Europe with generic TD\*/FTC

- IRELAND: MYLAN/TEVA (50-75 euros/month in retail pharmacies)
- SWEDEN: ACCORD (18 euros/month, covered by Swedish health system)
- GERMANY: HEXAL, RATIOPHARM (40-70 euros/month in select pharmacies)
- CROATIA: 75 euros/month, soon to drop down to 25/month (retail pharmacies)
- SWITZERLAND: RATIOPHARM (127 CHF/month in 3 pharmacies)
- ITALY: DOC 98.70 euros/month (no indication), TEVA similar price (has an indication)
- FRANCE: 5 generics in national procurement
- BELGIUM: Truvada (423 euro/month in pharmacies, while in national reimbursement individuals pay 11 euros/month). KrKA (245 euros/month) just became available

**Are countries putting PrEP into their guidelines?**



## Going global: the adoption of the World Health Organization's enabling recommendation on oral pre-exposure prophylaxis for HIV

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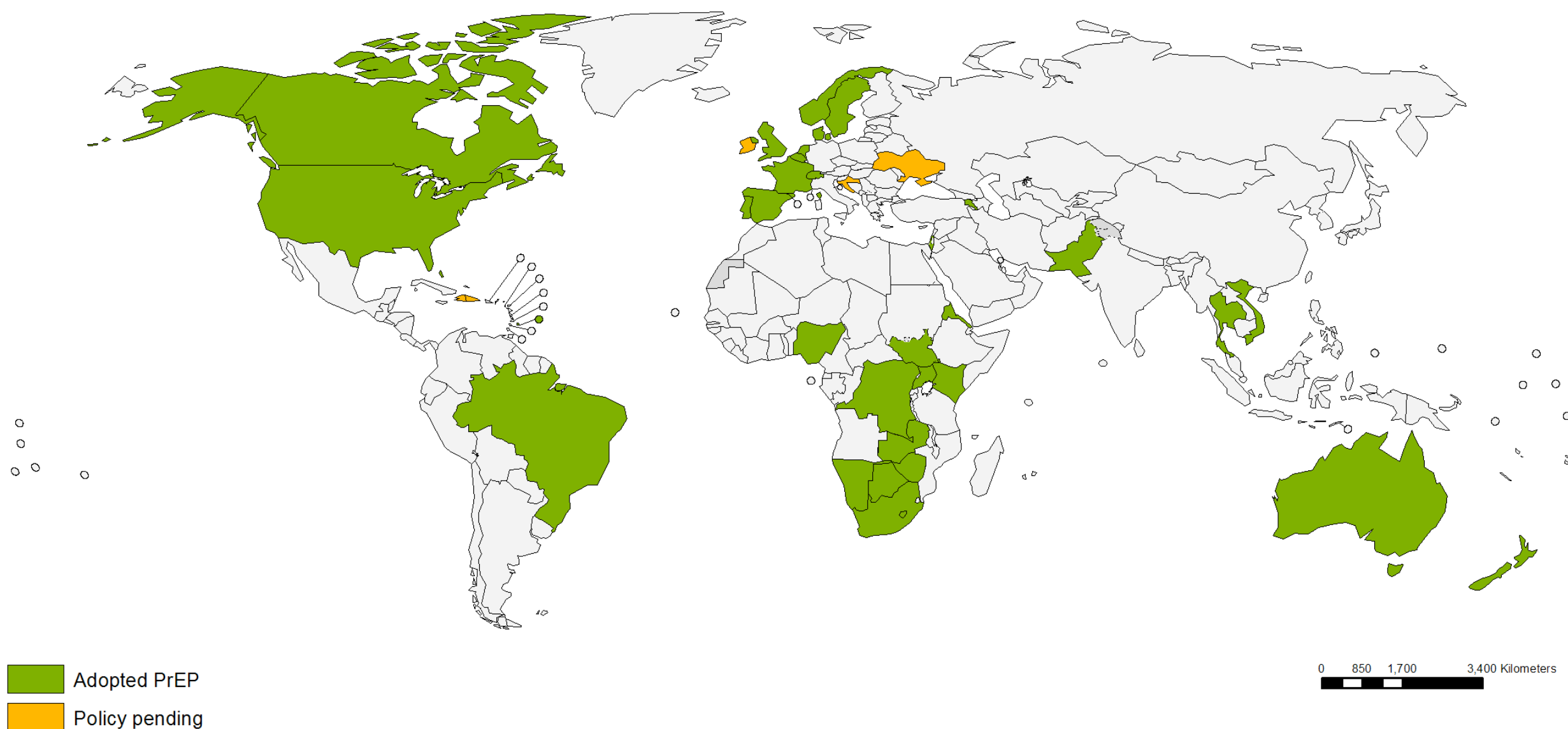
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**Abstract.** In September 2015, the World Health Organization (WHO) launched evidence-based guidelines by recommending that any person at substantial HIV risk should be offered oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) as an additional prevention choice. Since 2017, PrEP medicines have also been listed in the WHO's Essential Medicines List, including TDF/emtricitabine (FTC) and TDF in combination with lamivudine (3TC). A descriptive policy review and analysis of countries adopting WHO's 2015 recommendation on oral PrEP was conducted. As of June 2018, we identified 35 countries that had some type of policy on oral PrEP, and an additional five countries where a specific policy on PrEP is currently pending. A total of 19 high-income countries (HICs) and 21 low- and middle-income countries (LMICs) have adopted or have a pending policy.

## Status of adoption of WHO's oral PrEP recommendation (situation as of June 2018)



Data Source: World Health Organization  
Map Production: Information Evidence and Research (IER)  
World Health Organization



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# COUNTRIES RECOMMENDING TDF/3TC

- 6 countries recommended TDF/3TC for PrEP in addition to TDF/FTC (Pakistan, South Sudan, Namibia, Kenya, Zambia, and Zimbabwe)
- Lesotho's guidelines currently recommend exclusively TDF/3TC
- Asia/Pacific countries addressing TDF/3TC (given cost/supply chain)
- Europe: discussion on TDF/3TC next week at WHO EURO meeting



# KEY MESSAGES

- TDF/FTC has been used most widely in clinical trials, open label extension and demonstration projects, and therefore most evidence on the safety and efficacy for PrEP is based on the use of this drug (studied across all populations, MSM, women, SDC)
- TDF/3TC can be considered as an acceptable option for PrEP in situations where access (including affordability) or availability of TDF/FTC is limited.
  - Large potential gains in rolling out PrEP, including in populations including certain pregnant women who remain at substantial risk for HIV.
  - Significant delays to such a roll out will translate into new HIV infections and loss of life.
  - **There are significant opportunity costs in delaying implementation of PrEP.**

# CONCLUSIONS

- PrEP is highly effective, and should enhance our prevention efforts for STIs, including HIV.
- Public health argument for implementing PrEP medicines that could potentially be cost-saving to an HIV programme
- 3TC and FTC are interchangeable (for HIV treatment, PEP, and PrEP)
-



THANK YOU

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