APPROPRIATE MEDICINES: OPTIONS FOR PRE-EXPOSURE PROPHYLAXIS

MEETING REPORT
21-22 March 2016
<table>
<thead>
<tr>
<th>CONTENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>3</td>
</tr>
<tr>
<td>ACRONYMS AND ABBREVIATIONS</td>
<td>4</td>
</tr>
<tr>
<td>DEFINITION OF KEY TERMS</td>
<td>5</td>
</tr>
<tr>
<td>EXECUTIVE SUMMARY</td>
<td>7</td>
</tr>
<tr>
<td>INTRODUCTION: MEETING OBJECTIVES AND METHODOLOGY</td>
<td>9</td>
</tr>
<tr>
<td>RATIONALE FOR REVIEW</td>
<td>10</td>
</tr>
<tr>
<td>WHAT DO WE KNOW ABOUT USE OF TDF/3TC?</td>
<td>11</td>
</tr>
<tr>
<td>WHAT DO WE KNOW ABOUT USE OF TDF ALONE?</td>
<td>19</td>
</tr>
<tr>
<td>USE OF PREP IN PREGNANCY AND BREASTFEEDING</td>
<td>22</td>
</tr>
<tr>
<td>FLEXIBILITY FOR COUNTRIES</td>
<td>24</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>25</td>
</tr>
<tr>
<td>RESEARCH GAPS</td>
<td>27</td>
</tr>
<tr>
<td>ANNEX I. MEETING AGENDA</td>
<td>31</td>
</tr>
<tr>
<td>ANNEX 2. LIST OF PARTICIPANTS</td>
<td>35</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>39</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

The contents of this technical report reflect the dedicated efforts of many experts who contributed their time, insight, and expertise before and during the WHO/UNAIDS Technical Consultation on Alternative Drug Options for HIV Pre-Exposure Prophylaxis which took place in Geneva, Switzerland on 21-22 March 2016.

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<table>
<thead>
<tr>
<th>ACRONYM/ABBREVIATION</th>
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<tr>
<td>3TC</td>
<td>lamivudine</td>
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<tr>
<td>3TC-TP</td>
<td>lamivudine-triphosphate</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<td>ART</td>
<td>antiretroviral therapy</td>
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<td>ARV</td>
<td>antiretroviral</td>
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<td>AZT</td>
<td>zidovudine</td>
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<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>dATP</td>
<td>deoxyadenosine triphosphate</td>
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<td>dCTP</td>
<td>deoxycytidine triphosphate</td>
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<tr>
<td>DXA</td>
<td>dual energy x ray absorptiometry</td>
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<tr>
<td>EC90</td>
<td>drug concentration associated with a 90% reduction in HIV acquisition</td>
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<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>FTC</td>
<td>emtricitabine</td>
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<tr>
<td>FTC-TP</td>
<td>emtricitabine-triphosphate</td>
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<td>HBV</td>
<td>hepatitis B virus</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>LBW</td>
<td>low birth weight</td>
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<td>LPV/r</td>
<td>lopinavir/ritonavir</td>
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<td>MR</td>
<td>meta-regression</td>
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<td>NMRA</td>
<td>national medicines regulatory authority</td>
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<td>PBMC</td>
<td>peripheral blood mononuclear cell</td>
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<td>PD</td>
<td>pharmacodynamics</td>
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<td>PEP</td>
<td>post-exposure prophylaxis</td>
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<tr>
<td>PEPFAR</td>
<td>United States President’s Emergency Plan for AIDS Relief</td>
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<tr>
<td>PK</td>
<td>pharmacokinetics</td>
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<tr>
<td>PMTCT</td>
<td>prevention of mother-to-child HIV transmission</td>
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<td>PrEP</td>
<td>pre-exposure prophylaxis</td>
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<tr>
<td>PTD</td>
<td>preterm delivery</td>
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<td>RCT</td>
<td>randomized clinical trial</td>
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<tr>
<td>RR</td>
<td>relative risk or risk ratio</td>
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<tr>
<td>RF</td>
<td>rectal fluid</td>
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<tr>
<td>sdNVP</td>
<td>single-dose nevirapine</td>
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<td>SHIV</td>
<td>simian/human immunodeficiency virus</td>
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<tr>
<td>SIV</td>
<td>simian immunodeficiency virus</td>
</tr>
<tr>
<td>SRA</td>
<td>stringent regulatory authority</td>
</tr>
<tr>
<td>TAF</td>
<td>tenofovir alafenamide</td>
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<td>TDF</td>
<td>tenofovir disoproxil fumarate</td>
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<td>TFV</td>
<td>tenofovir</td>
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<td>TFV-DP</td>
<td>TFV-diphosphate</td>
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<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<td>VF</td>
<td>vaginal fluid</td>
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<td>VPTD</td>
<td>very preterm delivery</td>
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<td>WHO</td>
<td>World Health Organization</td>
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DEFINITION OF KEY TERMS

**Age brackets:** The following definitions for adults, adolescents, children and infants are used to ensure consistency within these guidelines. Other agencies may use different definitions.

- **An adult** is a person older than 18 years.
- **An adolescent** is a person 10–19 years old inclusive.
- **A child** is a person younger than 10 years old.
- **An infant** is a child younger than 1 year old.

**AUC (area-under-the-curve)** refers to the systemic exposure to a drug following dosing by a route of administration, used as a measure of the quantity of drug in the body.

**Breakthrough infection:** refers to HIV infection occurring in an individual who is taking pre-exposure prophylaxis (PrEP). Note: Most infections occurring in persons who have been prescribed PrEP appear to be related to lack of adherence to the PrEP regimen and are not explicitly breakthrough infections.

**Combination HIV prevention:** a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

**Direct evidence:** evidence on the safety and/or efficacy of (pre-exposure prophylaxis) drugs generated from studies whose aim is to directly assess these outcomes of interest. This includes randomized clinical trials and meta-analyses of studies. For example, the United States Centers for Disease Control and Prevention study of TDF provides direct evidence of the safety of TDF alone in men who have sex with men and indirect evidence on efficacy (see “Indirect evidence” below).

**Elimination half-life:** the amount of time it takes for a drug concentration in the blood to decline by half. The half-life can be a critical pharmacokinetic parameter for how often a drug should be dosed (for example, once a day or twice a day).

**HIV:** human immunodeficiency virus, of which there are two types: **HIV-1** and **HIV-2**. **HIV-1** is responsible for the majority of HIV infections globally.

**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.

**Interchangeability:** refers to when a biological product, in addition to meeting the bio similarity standard, has the same clinical result as the reference product in any given patient.

**Public health approach:** addresses the health needs or collective health status of a population, rather than focusing primarily on individual case management. This approach aims to ensure the widest possible access to high quality services at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings. For HIV key elements of a public health approach include simplified treatment algorithms; large-scale use of fixed-dose combinations for first-line treatment for adults, adolescents and children; care and treatment provided free at the point of service delivery; decentralization and integration of services, including task shifting; and simplified approaches to clinical monitoring.

**Pre-exposure prophylaxis (PrEP):** oral pre-exposure prophylaxis for HIV infection is the use of antiretroviral drugs by HIV-uninfected people before potential exposure to block the acquisition of HIV.
**Serodiscordant couple:** a couple in which one partner is living with HIV and the other is HIV-negative. A couple refers to two people in an ongoing sexual relationship; each of these persons is referred to as a partner in the relationship. How individuals define their relationships will vary according to their cultural and social context.

**Substantial risk of HIV infection:** defined, based on the WHO 2015 recommendation on PrEP, by an incidence of HIV infection in the absence of PrEP that is sufficiently high (>3% incidence) to make offering PrEP potentially cost-saving (or cost-effective). Offering PrEP to people at substantial risk of HIV infection maximizes the benefits relative to the risks and costs. People at substantial risk of HIV infection are present in most countries, including some (but not all) people identified within key and vulnerable populations.

**Technical Group:** the group of scientific, technical and programmatic experts convened by WHO and UNAIDS for this review of PrEP drug regimens, whose contribution, insight and expertise contributed to decision-making, including decisions on this technical report. The term “technical group” does not include observers at the March 2016 meeting in Geneva, who had a very limited role observing specific discussion points.
EXECUTIVE SUMMARY

In March 2016, WHO and UNAIDS jointly convened a technical group of experts in antiretroviral (ARV) pharmacology and HIV pre-exposure prophylaxis (PrEP) clinical research to provide clarifications related to three specific implementation concerns for countries regarding the appropriate use of PrEP drug regimens:

1. possible use of lamivudine (3TC) as an alternative to emtricitabine (FTC) for oral PrEP containing tenofovir disoproxil fumarate (TDF),
2. possible use of TDF alone for oral PrEP, and
3. safety of PrEP during pregnancy and breastfeeding, in terms of both maternal and fetal/newborn outcomes.

The technical consultation reviewed a spectrum of evidence, including animal studies, human pharmacology and randomized clinical trials (RCTs) on PrEP as well as indirect evidence from HIV treatment studies.

In 2015 WHO recommended 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 HIV prevention approaches. This recommendation was based on a systematic review and meta-analysis of the clinical trial evidence available at the time. All these trials investigated either TDF/FTC and/or TDF alone. Since the release of that recommendation, countries and civil society have requested that WHO provide additional clarification on the safety and efficacy of PrEP drugs, including the potential role of TDF/3TC. Country ownership is a guiding principle for WHO, for the uptake of new recommendations. WHO recognizes that countries face many practical considerations with regards to PrEP implementation, including cost and feasibility.

This report presents direct and indirect evidence for each of the three regimens (TDF alone, TDF/FTC, TDF/3TC), which can be considered by countries as they look towards adopting WHO guidelines on PrEP and introducing PrEP as a service to individuals at substantial risk of HIV acquisition. Most clinical trial evidence on the safety and efficacy of oral PrEP has been generated by studies that examined TDF/FTC in men who have sex with men, and heterosexual populations. Two major RCTs (Partners PrEP and Bangkok Tenofovir Study) looked at the efficacy of TDF alone in heterosexual and drug-using populations. There are some limited data for TDF alone in men who have sex with men, from one small safety study. No clinical trials have been conducted to assess the safety and efficacy of TDF/3TC for PrEP in any of the population groups, although there have been two clinical studies on TDF/3TC for prevention of mother-to-child transmission (PMTCT), which provide indirect evidence for the use of TDF/3TC and serve as proof of principle. The expert group suggested that off-label use of TDF/3TC could be appropriate in countries where TDF/FTC is not available or accessible.

Approval by a national medicines regulatory authority for a prevention indication for a suitable TDF-containing product is preferred but not necessary to prescribe ARVs for HIV prevention. Previous WHO recommendations have supported countries using ARV drugs and regimens off-label for post-exposure prophylaxis (PEP) and PMTCT indications, even in the absence of supporting RCT data, given the programmatic and public health advantages of such an approach. Despite the paucity of data on TDF/3TC’s efficacy as PrEP in humans, the Technical Group concluded that indirect evidence of its efficacy from studies on antiretroviral therapy (ART), coupled with preliminary pharmacokinetic data, is sufficient for countries to consider TDF/3TC for use as PrEP if TDF/FTC is not available or accessible. At the time of the March 2016 consultation, Brazil was conducting a pilot PrEP study of TDF/3TC among men who have sex with men (n=40), in the state of Minas Gerais. The Technical Group emphasized the need for active follow-up of PrEP users on TDF/3TC and monitoring for breakthrough infections. The group also suggested the need to generate data from additional pharmacology studies, although it was emphasized that implementation of TDF/3TC for PrEP should not be postponed awaiting the results.
The Technical Group also considered the use of TDF-containing PrEP during pregnancy and breastfeeding. Currently, in some countries where PrEP is offered to women at substantial HIV risk, PrEP is discontinued if a woman becomes pregnant and only restarted once the breastfeeding period has ended, even though this may be a time of ongoing high HIV acquisition risk for the woman. If HIV is acquired during pregnancy or the breastfeeding period, HIV could be transmitted to the infant. In high HIV prevalence settings, PrEP can be considered for women wishing to conceive and who have partners with HIV not virally suppressed (or whose status is unknown).

Three primary sources of safety data were reviewed for pregnant and breastfeeding populations (TDF-based regimens for HIV treatment, TDF for treatment of chronic hepatitis B virus infection, and TDF-based regimens in PrEP trials). The Technical Group concluded that, although additional surveillance is important, given the available data there does not currently appear to be a safety-related rationale for discontinuing PrEP during pregnancy or breastfeeding for HIV-uninfected women who become pregnant and remain at continuing risk of HIV acquisition. In such situations the risk of HIV acquisition and accompanying increased risk of mother-to-child HIV transmission appear to far outweigh the potential risk of fetal and infant exposure to TDF used for PrEP. The IMPAACT 2009 parallel, observational cohort study of HIV-uninfected pregnant adolescents and young women (ages 16–24) will evaluate adherence over time among women who initiate once-daily oral PrEP during pregnancy and continue in the first six months following delivery. The study will compare pregnancy outcomes among women who take PrEP and those who decline PrEP during the antenatal period.

Irrespective of which drugs countries use in their PrEP services, including in the private sector, mechanisms for effective monitoring and evaluation must be developed during the initial stages of PrEP policy formulation and service development. Adequate resources should be allocated for monitoring and evaluation activities, which must be in place prior to PrEP policy or service implementation.

Further review of the safety and efficacy of PrEP drugs will be conducted as part of a future WHO guidance update.

**Box 1. Data reviewed by Technical Group, March 2016**

| Pregnancy and breastfeeding | • Direct and indirect evidence, HIV treatment data, hepatitis B virus treatment data, and limited PrEP clinical trial data  
|                           | • Data indicate negligible levels of tenofovir in breast milk (based on a prospective short-term, open-label study of daily oral TDF/FTC PrEP among 50 HIV-uninfected breastfeeding African mother–infant pairs 1–24 weeks postpartum) (1). |
| TDF alone                 | • Direct evidence from trials, but limited data on use in men who have sex with men (one small pilot study)  
|                           | • WHO systematic review and meta-analysis showed no statistically significant difference between TDF/FTC and TDF alone in heterosexual populations |
| TDF/3TC                   | • Indirect evidence from systematic review of ART studies on interchangeability of 3TC and FTC  
|                           | • Clinical trials of TDF/3TC in prevention of mother-to-child transmission  
|                           | • WHO post-exposure prophylaxis guidelines  
|                           | • Animal and human pharmacokinetic studies |
| TDF/FTC                   | • Direct evidence from randomized clinical trials  
|                           | • WHO systematic review and meta-analysis  
|                           | • Open-label extension studies |
INTRODUCTION: MEETING OBJECTIVES AND METHODOLOGY

In March 2016 WHO and UNAIDS jointly convened a group of scientific experts in antiretroviral (ARV) pharmacology and HIV pre-exposure prophylaxis (PrEP) in animal and human clinical research to address specific concerns on the use of PrEP drugs. The group of experts assessed the evidence on three issues that have implications for countries as they consider implementation of PrEP as part of their HIV response:

1. Possible use of lamivudine (3TC) or emtricitabine (FTC) for oral PrEP containing tenofovir disoproxil fumarate (TDF).
2. Possible use of TDF alone for oral PrEP.

The full spectrum of existing data (see Figure 1), ranging from animal studies to human pharmacology to randomized clinical trials (RCTs) on PrEP, and indirect evidence from HIV treatment studies were reviewed. Pharmacokinetic (PK) data was also generated by the Centers for Disease Control and Prevention (CDC) and academic laboratories in the United States as part of this consultation.

Figure 1. Evidence reviewed to address appropriate use of TDF/3TC, and TDF alone, for PrEP (A) and safety of PrEP during pregnancy and breastfeeding (B)
RATIONALE FOR REVIEW

What is the current WHO recommendation on PrEP?

Oral PrEP is the use of ARV drugs by people who do not have HIV infection to prevent HIV acquisition. WHO currently recommends that any person at substantial risk of HIV should be offered PrEP as an additional prevention choice, as part of combination HIV prevention approaches (2). In 2014, WHO recommended offering oral PrEP containing TDF to men who have sex with men (3). Based on further evidence of the effectiveness and acceptability of PrEP, WHO has now broadened the recommendation to include all population groups at substantial risk of HIV infection. This recommendation is rated as strong, based on high-quality evidence (see Table 1).

Table 1. WHO 2015 recommendation on the use of oral PrEP

<table>
<thead>
<tr>
<th>Target population</th>
<th>Specific recommendation</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
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<tr>
<td>HIV-negative individuals at substantial risk of HIV infection</td>
<td>Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches</td>
<td>Strong</td>
<td>High</td>
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Although most PrEP users are in the United States, where regulatory approval for PrEP was first granted, other countries are beginning to consider how PrEP can be effectively introduced into their settings. Since the release of WHO’s 2015 recommendation on PrEP, national medicines regulatory authorities (NMRAs) in France, South Africa, Kenya, Australia, Peru, Thailand, and Tanzania, as well as the European Medicines Agency have officially approved the use of TDF/FTC for PrEP. Many activities to prioritize PrEP for adolescent girls and young women have also been integrated into the President’s Emergency Plan for AIDS Relief (PEPFAR) DREAMS initiative. The 2016 United Nations Political Declaration on Ending AIDS includes the ambitious global target of reaching 3 million people at higher risk of HIV infection with PrEP by 2020.

What is the key issue?

Considering the 2015 WHO recommendation on PrEP, countries are beginning to consider how best to implement PrEP, which requires strategic planning from a public health perspective. It is important to underscore that the WHO 2015 recommendation calls specifically for ‘oral PrEP containing TDF’, which should provide flexibility for countries in deciding which drugs to consider. Although the body of evidence from clinical trial research rests with the use of TDF/FTC and TDF alone, WHO has been asked to provide clarity and guidance on whether 3TC is interchangeable with FTC for prevention. More countries globally, including Kenya and Uganda, procure TDF/3TC for their treatment programmes than TDF/FTC. TDF/3TC represents 60-70% of the global adult market share, whereas only an estimated 100,000 people living with HIV receive TDF alone as part of their triple antiretroviral therapy (ART) regimen (4). Therefore, current demand for stand-alone TDF is low.

3TC is structurally related to FTC (see Figure 2). From a treatment perspective, 3TC has been critical for all first-line ARV regimens in high-income as well as resource-limited settings since the advent of

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2 Switzerland issued a recommendation in 2016 on the off-label use of TDF/FTC for PrEP. Other countries, including Botswana, Kenya and Thailand, have guidelines for PrEP use.
ART. It is a core component of the dual nucleoside reverse transcriptase inhibitor backbone in all currently preferred first-line ARV combinations. It is safe, has an excellent toxicity profile, is non-teratogenic and is effective against hepatitis B virus (HBV) (5,6). It is widely available in fixed-dose combinations. However, 3TC’s low genetic barrier to resistance is a major weakness: specific resistance to 3TC evolves frequently (7,8).

Figure 2. Molecular structures of lamivudine (3TC) and emtricitabine (FTC) (9)

WHAT DO WE KNOW ABOUT USE OF TDF/3TC?

Can TDF/3TC be used for PrEP?

WHO currently recommends TDF/XTC for HIV treatment, prevention of mother-to-child HIV transmission (PMTCT) (10) and post-exposure prophylaxis (PEP) (11) but not explicitly for PrEP. (“XTC” is used to designate either FTC or 3TC.) The treatment recommendation is based on a systematic review undertaken by Ford et al. (12), which examined the pharmacological equivalence and clinical interchangeability of FTC and 3TC based on the evidence generated by 12 clinical trials among people living with HIV.

For the technical consultation, the Ford et al. systematic review was updated with an end date of 20 March 2016. This update resulted in the screening of an additional 130 titles. However, no additional eligible studies were identified. Treatment success was not significantly different among any of the 12 trials conducted in 2013 (see Figure 3). In the three trials that directly compared 3TC and FTC, the relative risk (RR) of achieving treatment success (as defined by each study) was non-significant (RR 1.03, 95% CI 0.96–1.10; p=0.3). The pooled RR for treatment success was also non-significant (RR 1.00, 95% CI 0.97–1.02).
The Dutch ATHENA cohort study (13) assessed observational data in Western Europe and suggested better virological responses to FTC than to 3TC as part of first-line ART. However, the comparison groups in the ATHENA cohort study were unbalanced both geographically, between Western European and sub-Saharan settings, and temporally, with the median ART initiation year at 2004 for 3TC and 2009 for FTC. A commentary (14) by WHO highlighted the methodological limitations and the large discrepancy between the results reported in the ATHENA cohort study and those provided by prospective RCTs, the “gold standard” for assessment of efficacy. Consequently, WHO did not revise its recommendation on the interchangeability of 3TC and FTC based on the ATHENA study.

In 2015 PEPFAR’s Scientific Advisory Board recommended flexibility in drug selection at the country level to support implementation of PrEP. Given the limited availability of TDF alone or of co-formulated TDF/FTC in many countries where PEPFAR operates, the availability of TDF/3TC for PMTCT, treatment and PEP, and the “similar pharmacovailability of 3TC and FTC in heterosexual populations”, the Scientific Advisory Board declared TDF/3TC to be an acceptable alternative to TDF/FTC for PrEP. The PEPFAR recommendation does not specify whether TDF/3TC is acceptable for use by heterosexual users or men who have sex with men.

WHO has published four documents on the interchangeability of 3TC and FTC (see Table 2).
Table 2. Summary of WHO position on interchangeability of 3TC and FTC according to guidance and technical updates

<table>
<thead>
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<th>WHO document</th>
<th>WHO position</th>
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<tr>
<td>WHO Technical Update 3TC FTC, 2012</td>
<td>- Clinical and virological efficacy and safety of 3TC and FTC are comparable.</td>
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<td></td>
<td>- Development of the M184V/I mutation associated with 3TC</td>
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<tr>
<td>WHO ART Guidelines, 2013</td>
<td>- 3TC and FTC are pharmacologically comparable</td>
</tr>
<tr>
<td>WHO PEP Guidelines, 2014</td>
<td>- TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for adults and adolescents.</td>
</tr>
<tr>
<td>WHO ART Guidelines, 2015</td>
<td>- TDF + 3TC (or FTC) is recommended.</td>
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The evolution of evidence on PrEP from animal models

In preclinical PrEP research, animal studies, particularly those using macaque models or humanized mice models, have been essential in providing proof of concept of efficacy, informing dose selection, defining pharmacologic correlates of protection, and assessing biological factors that can modulate PrEP efficacy (15).

Macaque models of mucosal simian immunodeficiency virus (SIV) or simian/human immunodeficiency virus (SHIV) transmission have generated data on efficacy against both rectal and vaginal infection. A range of oral and topical PrEP regimens including drugs such as tenofovir (TFV), TDF and FTC have been tested against both wild-type and drug-resistant viruses. These models have helped define prophylactic windows of protection of nondaily dosing and are being used increasingly to study PK and pharmacodynamic (PD) parameters.

Derdelinckx et al. outlined some basic criteria for drugs intended for use in PrEP and pointed to 3TC as a potential PrEP candidate that met most of these criteria (see Box 2) (16). TDF also met these criteria. Despite these findings, 3TC did not progress to human clinical trials.

Box 2. 3TC characteristics relative to PrEP drug criteria16

1. **Safety profile**: 3TC is well tolerated and with minimal toxicity.
2. **Ease of use**: 3TC, like FTC, can be taken once daily without food restrictions.
3. **Mode of action and pharmacology**: 3TC acts early in the HIV replication cycle, before the integration of viral DNA into host cell DNA.
4. **Antiviral profile**: 3TC has been successfully used as PrEP in HIV-negative infants during a six-month period where they were breastfed by their HIV-positive mothers (SIMBA study (17) and MITRA study (18)).
5. **Cost-effectiveness**: 3TC is associated with lower costs than FTC.

The Derdelinckx study noted the impact of 3TC resistance in people with HBV. In its 2015 guidelines for HBV treatment, WHO does not recommend 3TC as a first-line treatment for chronic hepatitis B, given its low barrier to resistance.

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16 TDF and FTC were developed by Gilead Sciences.
The initial macaque study conducted by Tsai et al. in 1995 provided the first proof of concept that was fundamental in shaping clinical trial research on PrEP. In that study subcutaneous TFV protected all macaques from intravenous SIV challenge (both PrEP and PEP) (19). Animal models have since improved, notably the CDC repeat-exposure macaque models, which have included more clinically relevant PrEP dosing based on PK. Pigtail macaques are appropriate for studying vaginal efficacy of PrEP drugs, as they have normal lunar menstrual cycles and changes in hormone levels similar to women's. Rhesus macaques, being more widely available, serve as the rectal model.

In 2006, Subbarao et al. (20) demonstrated partial protection against infection from rectal SHIV exposure in rhesus macaques using oral TDF, although no statistical significance was reported due to the small study groups.

In 2008, daily and intermittent PrEP regimens, using FTC/TDF, FTC/TFV and FTC alone, were evaluated in a repeat-exposure macaque model with 14 weekly rectal virus challenges (see Figure 4) (21). These three drug regimens were given once daily, each to a different group of six rhesus macaques. Group 1 was treated subcutaneously with a human-equivalent dose of daily FTC; group 2 received the human-equivalent oral dosing of both FTC and TDF daily; and group 3 received subcutaneously a similar dosing of FTC and a higher dose of TFV daily. A fourth group of six rhesus macaques received an intermittent PrEP regimen similar to group 3 except that this was administered two hours before and 24 hours after each weekly virus challenge. Results were compared with 18 control macaques that did not receive any drug treatment. The risk of infection in macaques treated in groups 1 and 2 was 3.8- and 7.8-fold lower, respectively, than in untreated macaques (p=0.02, p=0.008, respectively). All six macaques in group 3 were protected. All six animals in group 4 that received intermittent PrEP were also protected. This study demonstrated the high efficacy of TDF/FTC and suggested that a combination of ARVs would increase the level of protection provided by daily PrEP.

**Figure 4. Daily and intermittent PrEP regimens in a macaque model**

Source: Garcia-Lerma et al., (22).

A subsequent paper by Garcia-Lerma et al. (22), in 2010, describing the high rectal efficacy of intermittent PrEP modalities based on FTC/TDF. This informed the IPERGAY study that tested on-demand PrEP. A study by Radzio et al. also showed high protection from vaginal SHIV challenges by TDF/FTC despite lower TFV-diphosphate (TFV-DP) levels in peripheral blood mononuclear cells (PBMCs) in vaginal tissues when compared with rectal tissues (23). Anderson et al. estimated the mean steady-state TFV-DP concentrations and determined the prophylactic EC90 (drug concentration associated with a 90% reduction in infection rate) for PrEP with FTC/tenofovir.

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* Clinically relevant regimens: oral TDF (22 mg/kg), oral FTC (20 mg/kg).
* Of the 12 macaques, 4 received oral TDF daily, 4 received oral TDF once weekly, and 4 (control animals) received no TDF.
with a 90% reduction in HIV acquisition) for TFV-DP in macaques exposed rectally, which compared well with the EC\(_{90}\) previously identified in men who have sex with men (24). In sum, these studies reflect the relevance of the macaque model in informing human PrEP studies.

**Generating PK data on 3TC in macaque models: informing interchangeability of 3TC and FTC for oral PrEP**

For the technical consultation, the CDC, in collaboration with the University of North Carolina, conducted a single-dose PK study with 3TC in rhesus macaques, with the aim of defining clinically relevant macaque doses and better understanding mucosal penetration of 3TC. Three different doses (10, 20 and 30 mg/kg) of 3TC were administered orally by gavage under anaesthesia based on body weight (four macaques per dose). 3TC levels were measured in plasma and rectal/vaginal fluids. 3TC-triphosphate (3TC-TP) concentrations were measured in PBMCs and vaginal biopsies by the laboratory of Angela Kashuba.

An initial PK assessment by the CDC (25) suggests that 30 mg/kg of 3TC achieves plasma drug exposure in macaques comparable to 300 mg of 3TC in humans and can be used to design proof-of-concept PrEP efficacy studies in macaques (see Figure 5). The bioequivalence of plasma 3TC and intracellular 3TC-TP concentrations after administration of two different 3TC doses was determined in the ENCORE2 study (n=24 human subjects) (26).

Relative penetration and drug exposure in rectal fluid (RF) and vaginal fluid (VF) following 30 mg/kg 3TC dosing indicates that 3TC penetrates VF at higher concentrations than it does RF (see Figure 5). The half-life of 3TC in blood plasma, RF, and VF has yet to be estimated. Intracellular concentrations of 3TC-TP in PBMCs were determined across each of the three doses (10, 20 and 30 mg/kg). With the 30 mg/kg dose, peak 3TC-TP levels were 1.8 (1.4–1.9) pmols/10\(^6\) cells, well within the range seen in humans. 3TC-TP concentrations in vaginal biopsies were similar across the three doses and highest at 6 hours after administration (see Figure 6).

**Figure 5. Penetration of 3TC in rectal and vaginal fluids in a macaque model**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0</th>
<th>6</th>
<th>12</th>
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<tbody>
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<td>10000</td>
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</table>

**Figure 5.**

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>AUC(_{0-24h}) (ug<em>h/ml)</em></th>
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</thead>
<tbody>
<tr>
<td>Blood plasma (BP)</td>
<td>16.8 (13.2-31.7)</td>
</tr>
<tr>
<td>Rectal fluids (RF)</td>
<td>101.2 (10.8-814.5)</td>
</tr>
<tr>
<td>Vaginal fluids (VF)</td>
<td>335.9 (75.7-643.6)</td>
</tr>
</tbody>
</table>

*VF:RF 3.3
VF:BP 20
RF:BP 6

*median (range)
Group suggestion: The Technical Group discussed the possibility of conducting a virus challenge study in monkeys using 3TC to determine similarity to FTC. The study of FTC alone and TDF/FTC could be mimicked with 3TC (for example, TDF compared with TDF/3TC).

Human pharmacology of 3TC versus FTC

There are limited data from human pharmacology studies comparing 3TC and FTC, particularly in plasma, PBMCs, and for genital/rectal distribution. What is known is that 3TC and FTC are structurally similar, are anabolized and phosphorylated by the same enzymes, and both are effective in treatment with daily dosing (27, 28). There is evidence that 3TC has a slightly shorter half-life (6–8 hours) than FTC (8–10 hours). Both drugs accumulate in PBMCs, with FTC-triphosphate (FTC-TP) and 3TC-TP having a similar accumulation half-life (29, 30, 31, 32, 33, 34, 35, 36) (see Figure 7), whereas the elimination half-life appears to be longer for FTC-TP. There is similar distribution of 3TC and FTC in cervicovaginal fluid and in semen (37, 38, 39, 40, 41). However, no information is available on 3TC rectal concentrations in humans.

Given the lack of 3TC rectal data in humans, Peter Anderson made a presentation to the Technical Group on the relevance of rectal efficacy and “PK forgiveness” for current TDF/FTC as PrEP in men who have sex with men. The IPERGAY strategy of on-demand dosing among men who have sex with 

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* Elimination half-life for 3TC is 6.1–7.9 hours. The mean plasma elimination half-life of FTC after a single dose is approx. 8–10 hours in HIV-infected patients.
men at high risk of HIV demonstrated an 86% reduction in HIV acquisition, with an average of 3.75 doses per week (42). As to levels of adherence, only 43% of study participants took the regimen according to protocol, suggesting that, despite the variability in PrEP use, this TDF/FTC dosing strategy was particularly forgiving in this study population. The mechanism for “PK forgiveness” in men who have sex with men may be related to high concentrations of TFV-DP in rectal tissues (43, 44). Levels of TFV-DP are higher in rectal tissue cells relative to PBMCs than are FTC-TP levels. The main message is that TDF may be providing the “PK forgiveness” observed in men who have sex with men, giving some level of reassurance with regards 3TC if it were to be used in a co-formulation with TDF for PrEP among this population group.

How are in vitro and phase I PK data used to generate an estimate of efficacy of TDF/FTC as PrEP, with different dosing schedules?

A review by Thompson et al. (45) highlights the need to better understand ARV PK-PD within mucosal tissues to characterize the related correlates of efficacy and the implications for PrEP. Colorectal levels of ARV drugs, in general, tend to be higher than those in the female genital tract (see Figure 8).

**Figure 8. ARV exposure at mucosal surfaces (female genital tract and colorectal tissue exposure) relative to blood plasma**

![Figure 8](image)

Source: Angela Kashuba presentation

Data from the CAPRISA 004 trial showed that women randomized to receive TFV vaginal gel and who had genital TFV concentrations greater than 1000 ng/mL had a significantly reduced risk of HIV acquisition compared with women whose genital tract concentrations were less than 1000 ng/mL. HIV risk in women with genital TFV concentrations less than 1000 ng/mL was similar to that for women receiving a placebo gel (46).

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vi WHO does not currently recommend event-driven PrEP, based on its latest guidelines, since there is only one clinical trial for a single population (men who have sex with men) that demonstrates the efficacy of this strategy. WHO is actively monitoring the planned/ongoing research related to event-driven PrEP in additional populations, particularly women.
A recently developed predictive model suggests that rectal tissue contains significantly less deoxyadenosine triphosphate (dATP) and deoxycytidine triphosphate (dCTP) than vaginal or cervical tissue (47). Endogenous factors such as dATP and dCTP compete with the active intracellular phosphorylated metabolites of TFV and FTC for incorporation into the proviral DNA strand to terminate chain elongation (48). In sum, the female genital tract is associated with higher dATP concentrations and lower TFV-DP concentrations than colorectal tissue, constituting a “double strike” against the female genital tract, with lower forgiveness for fluctuating doses.

PK-PD modelling has also been an informative tool in estimating PrEP efficacy by looking at healthy volunteer women. It has been demonstrated that two doses of TDF/FTC per week can achieve target drug exposure in colorectal tissue, while seven doses are required to achieve target drug exposure in the female genital tract. PK-PD modelling using IPERGAY dosing indicates that TDF and TDF/FTC concentrations are maintained for up to 10 days in men who have sex with men. A similar dosing strategy in women has different results, with concentrations of TDF/FTC dropping off after 3–4 days. This difference should be considered when selecting an event-driven dosing approach with TDF/FTC for women. Animal data are available for one event-driven dosing in which TDF/FTC was given 24 hours before and 2 hours after a vaginal SHIV challenge in fully protected macaques (25). Importantly, this type of PK-PD modelling exercise is not meant to be used in place of clinical trials but rather to enhance them. The United States Food and Drug Administration (FDA) is currently utilizing PK-PD modelling approaches to inform or define study design and dosing for certain populations such as infants and pregnant women.

There are limited PK dataviii for 3TC in the female genital tract (49, 50). Fletcher et al. report efficacious extracellular target concentrations for 3TC (51). The lack of rectal tissue data for 3TC is a current gap in knowledge for this drug compared with FTC.

**Summary**

The Technical Group considered that the indirect evidence from the WHO systematic review on the interchangeability of FTC and 3TC for treatment indicated TDF/3TC to be an appropriate option for PrEP. However, the group also recognized that there are no clinical data for HIV-uninfected persons using TDF/3TC for PrEP. A pilot study of 40 men who have sex with men using TDF/3TC for oral PrEP was completed in Brazil with zero breakthrough infections reported by completion of the study (4 months, with 33 individuals completing the study)x (52).

From a pharmacological perspective:

- Initial human PK data for 3TC in the female genital tract is promising. However, there is a need for higher quality PK evidence for 3TC and 3TC-TP, equivalent to that available for FTC in the female genital tract and colorectal tissue.
  - PK studies for PrEP are typically conducted among healthy volunteers, but HIV-infected individuals currently taking a 3TC-containing regimen could be studied.
- A study on protection with 3TC in monkeys would determine similarity to FTC. Studies conducted on FTC alone and TDF/FTC could be mimicked with 3TC.
- There are several clinical study options for estimating the efficacy of TDF/3TC, including demonstration projects and cluster RCTs, without having to do a formal Phase III investigation (while still allowing for an HIV incidence endpoint).

**WHAT DO WE KNOW ABOUT USE OF TDF alone?**

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viii Experts attending the March 2016 technical consultation recognized the need to generate data for the active metabolite of 3TC in vaginal and colorectal tissue.

x Study led by Marise Fonseca, University of Minas Gerais.
Is TDF alone appropriate for PrEP?

The systematic review and meta-analysis conducted in 2015 that served as the evidence base for the latest WHO PrEP recommendation showed that both TDF alone and TDF/FTC were effective, with broad confidence intervals (see Table 3). The 2015 review was updated for the March 2016 expert consultation. No new studies comparing oral PrEP containing TDF alone to placebo were identified. Therefore, the sub-group analysis comparing TDF alone to TDF/FTC regimens remained unchanged. New data from one existing study (VOICE) related to pregnancy outcomes was included (53). In the meta-analysis, when the VOICE and FEM-PrEP studies were removed (the two trials where female participants had low adherence), the risk ratios indicated increased efficacy for both TDF alone and TDF/FTC, with tighter confidence intervals.

Table 3. Meta-analysis and meta-regression results for PrEP efficacy (10 studies)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of studies</th>
<th>Risk ratio (95% CI)</th>
<th>p-value</th>
<th>I²</th>
<th>Meta-regression (MR) coefficient</th>
<th>MR standard error</th>
<th>MR p-value</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>5</td>
<td>0.49 (0.28–0.86)</td>
<td>0.001</td>
<td>63.9</td>
<td>ref</td>
<td>0.06</td>
<td>0.40</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>7</td>
<td>0.51 (0.31–0.83)</td>
<td>0.0007</td>
<td>77.2</td>
<td></td>
<td>0.40</td>
<td>0.88</td>
</tr>
</tbody>
</table>

The evidence for TDF’s efficacy when used alone is based on RCTs among serodiscordant heterosexual couples (54, 55) and people who inject drugs (56). For men who have sex with men, one safety study (57) investigated TDF alone in 400 subjects. Although all seven HIV seroconversions occurred in the deferred/placebo phase of the study, this trial was too underpowered to evaluate efficacy. Box 3 highlights the three studies that reported on head-to-head comparisons of TDF and TDF/FTC. Figure 9 presents a graphic on meta-regression for all 10 studies.

Box 3. Studies making head-to-head comparisons of TDF and TDF/FTC

**Partners PrEP Study (Baeten et al., 2012)**

- TDF: 67% relative reduction in HIV acquisition (95% CI, 44–81; p<0.001)
- TDF/FTC: 75% relative reduction in HIV acquisition (95% CI, 55–87; p<0.001)
- No significant difference in protective effects of TDF/FTC and TDF (p=0.23)

**Partners PrEP Study Continuation (Baeten et al., 2014)**

- No significant difference in protective effects of TDF/FTC and TDF

**VOICE (Marrazzo et al., 2015)**

- TDF: ~49.0% effectiveness (hazard ratio (HR): 1.49; 95% CI, 0.97–2.29)
- TDF/FTC: ~4.4% effectiveness (HR: 1.04; 95% CI, 0.73–1.49)
- No evidence of effectiveness of either PrEP drug (but note that adherence was inadequate in this study)

**Figure 9. Regression of log RR of PrEP effectiveness by regimen** (meta-regression coefficient: 0.06, p=0.88)

* Studies comparing more than one PrEP regimen contributed to both TDF and TDF/FTC groups (data were disaggregated by regimen).

* Study conducted by the United States Centers for Disease Control.
A case study report by Fox et al. provided evidence on the potential limitations of TDF for preventing HIV in men who have sex with men (58). The paper described two reported cases of TDF PrEP failure in men who have sex with men who were receiving long-term TDF treatment for HBV. In both cases therapeutic plasma levels of TDF were detected immediately after HIV was diagnosed.

**Partners PrEP update**

For heterosexual transmission the Partners PrEP study provides evidence of the efficacy of TDF as a single drug to reduce HIV acquisition (59). *This* was a Phase III, randomized, double-blind, placebo-controlled, three-arm trial of daily oral TDF and TDF/FTC PrEP to prevent HIV-1 acquisition by HIV-1 seronegative partners in heterosexual HIV-1 serodiscordant partnerships. A total of 4747 couples was enrolled from nine sites in Kenya and Uganda. Both TDF and TDF/FTC PrEP provided significant protection against HIV-1 acquisition compared with placebo in this population group. Both TDF alone and TDF/FTC provided significant protection for both men and women (see Figure 10).

The Technical Group was presented with updated findings that included an additional 3569 person-years of follow-up, re-randomization of the placebo arm to TDF or TDF/FTC, and 26 additional HIV-1 infection endpoints. The analysis still suggests similar HIV-1 protective efficacy and safety for once daily oral TDF and TDF/FTC. HIV-1 incidence, after July 2011, in both the TDF and TDF/FTC arms were similar (<1% per year). Before July 2011, HIV-1 incidence in the placebo arm was 2 per 100 person-years. Subgroup analyses, defined by sex, age, country, male circumcision status, sexual behaviour, and CD4 and plasma HIV-1 RNA levels among HIV-1 infected partners, did not demonstrate significant differences in HIV-1 protection between TDF alone and TDF/FTC.

As for adherence, detection of TFV in plasma samples, compared with no detection, and as measured in seroconverters and a subset of non-seroconverters, was associated with an 85% RR reduction in HIV-1 acquisition for the TDF arm and 93% reduction for the TDF/FTC arm (both p<0.0001) (see Figure 10).
Figure 10. Tenofovir in plasma comparison

Note: Case-cohort analysis: plasma TFV detection (>0.3 ng/mL). Cases = HIV-1 seroconverters (n=31 TDF, n=20 TDF/FTC).

Table 4. Key studies showing efficacy of TDF alone for PrEP

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Key finding</th>
</tr>
</thead>
</table>
| Men who have sex with men                       | US CDC Safety Study (Grohskopf et al., 2013) | (n=400) HIV infections:  
  - 0 infections after active TDF PrEP administered  
  - 7 infections in the deferred/placebo phase |
| People who inject drugs (parenteral and sexual transmission not differentiated) | Bangkok Tenofovir Study (Choopanya et al., 2013) | (n=2413, 1204 in TDF arm; n=1209 in placebo arm) HIV infections:  
  - 17 in TDF group (incidence of 0.35 per 100 person-years)  
  - 33 in placebo group (incidence of 0.68 per 100 person-years)  
A 48.9% reduction in HIV incidence in intervention arm (95% CI, 9.6–72.2; p=0.01). Intention to treat analysis not controlled for adherence. |
| Heterosexual men and women                      | Partners PrEP (Baeten et al., 2012, 2014) | 2012 analysis  
3163 couples received either TDF or TDF/FTC HIV infections:  
  - 17 in the TDF group (incidence of 0.65 per 100 person-years)  
  - 13 in TDF/FTC group (incidence of 0.50 per 100 person-years)  
A relative reduction of 67% in the incidence of HIV-1 with TDF (95% CI, 44–81; p<0.001) and of 75% with TDF/FTC (95% CI, 55–87; p<0.001). Intention to treat analysis not controlled for adherence. Protective effects of TDF/FTC and of TDF alone against HIV-1 were not demonstrated to be significantly different (p=0.23). |
2014 analysis
4410 (99.6%) of 4427 couples received TDF or TDF/FTC HIV infections:
- 31 in TDF group (incidence of 0.71 per 100 person-years)
- 21 in TDF/FTC group (incidence of 0.48 per 100 person-years)
HIV-1 incidence in the placebo group until discontinuation was 2 cases per 100 person-years.
HIV-1 prevention efficacy with TDF/FTC was not demonstrated to be significantly different from that of TDF alone (HR=0.67, 95% CI, 0.39–1.17; p=0.16).

USE OF PREP IN PREGNANCY AND BREASTFEEDING

A systematic review commissioned for the March 2016 technical consultation examined the available data on adverse outcomes related to the use of TDF in pregnancy and breastfeeding in HIV-infected and HIV-uninfected women and their infants (60).

PK studies reviewed indicated that there is substantial fetal exposure to TFV, as demonstrated by TFV levels observed in amniotic fluid and cord blood (61, 62, 63, 64). In contrast, studies in breastfeeding women and their infants indicate that there is limited to no exposure to TFV from breast milk (65, 66, 67). Despite extensive in utero exposure to TFV, safety data from this review and previous reviews are generally reassuring regarding any specific adverse effects of TDF exposure on pregnancy outcomes and infant growth.

Most studies on the use of TDF-containing regimens have been conducted among HIV-infected women receiving ART. Additional studies have demonstrated higher rates of adverse pregnancy outcomes than HIV-uninfected women even in the presence of ART, which also was observed in this review (68). Furthermore, studies comparing ART (TDF ART or non-TDF ART) with single drug in utero exposure to zidovudine (AZT)/single-dose nevirapine (sdNVP) generally report lower rates of adverse outcomes with AZT/sdNVP than with ART regimens (69, 70). Therefore, studies involving TDF ART among HIV-infected women, when seen as a model for what might be expected with TDF or TDF/FTC exposure in HIV-uninfected women, likely provide a worst-case scenario in terms of adverse outcomes. The majority of studies in HIV-infected women on ART show no increased risk of adverse pregnancy outcomes associated with TDF ART exposure, as suggested by the primary outcomes evaluated in this review.

There are fewer studies of TDF in HIV-uninfected women. The studies in HBV mono-infected women have demonstrated adverse outcome rates much lower than seen in HIV-infected women. In these studies, no significant differences in any outcome were observed between TDF, 3TC, and no drug exposure (71, 72, 73, 74, 75). The data from the two PrEP studies (VOICE and Partners PrEP) on TDF and TDF/FTC in HIV-uninfected women are similarly reassuring. Although the VOICE study is confounded by poor adherence to PrEP (hence true TDF and TDF/FTC exposures were lower than the number of persons randomized to receive these medicines would suggest), in Partners PrEP adherence was excellent, particularly in women around the periconception period (76,77, 55).

Only the PROMISE trial, which enrolled HIV-infected women (n=341) with CD4 cell count greater than 350 cells/mm³ randomized to TDF ART (TDF/FTC + lopinavir/ritonavir (LPV/r)), non-TDF ART (AZT/3TC/LPV/r) or AZT/sdNVP, suggested TDF ART was associated with a significant increase in pre-term delivery (PTD) (<37 weeks), particularly very preterm delivery (VPTD) (<34 weeks), and low birth weight (LBW) compared with AZT/sdNVP, and higher rates of early neonatal death compared with
non-TDF ART (AZT/3TC-based) \textsuperscript{(78)}. However, whether this is a TDF-specific effect remains unclear, as women randomized to non-TDF ART (AZT/3TC-based) had similarly elevated rates of PTD (<37 weeks) and LBW compared with AZT/sdNVP as those randomized to TDF ART. In addition, the rate of VPTD and early neonatal death observed with TDF ART, although higher than with non-TDF ART, was not significantly different from that with AZT/sdNVP. The similarity in VPTD and neonatal death rates between TDF ART and AZT/sdNVP, and the fact that most neonatal deaths occurred in preterm infants, suggests that the VPTD and subsequent neonatal death rates may be artificially lower in the non-TDF ART (AZT/3TC-based) group rather than abnormally high in the TDF ART group. In contrast to the PROMISE data, higher PTD rates were not observed in 4307 other TDF exposures (4083 in HIV-infected women and 224 in uninfected women), and higher rates of LBW were not observed in 3827 other TDF exposures (3725 in HIV-infected women and 102 in uninfected women) \textsuperscript{(79, 80, 81, 82, 83, 84, 85)}. Very few studies evaluated neonatal mortality. In contrast to the PROMISE trial, the one other study evaluating neonatal mortality did not show higher rates with TDF ART compared with non-TDF ART \textsuperscript{(86)}.

In addition, the WHO 2015 guidelines on ART indicate that the LPV/r-based regimen used in the PROMISE trial is distinct from the WHO-recommended first-line regimen for HIV-infected pregnant women, namely, TDF/3TC or FTC/efavirenz. The results from other studies have not suggested that TDF alone, TDF/FTC or 3TC are associated with increased risk of adverse pregnancy outcomes. By contrast, protease inhibitors, including LPV/r, are reported to be associated with prematurity and LBW. Given that a LPV/r-based regimen is recommended in second-line treatment, the WHO guidelines call for further research on toxicities associated with these regimens.

The increasingly available data on infant growth, bone development and renal function are similarly reassuring. The most recent dual energy X-ray absorptiometry (DXA) study from PROMISE suggests that ART itself may be associated with some decrement in neonatal bone mineral content, but this was not specific for TDF, as non-TDF ART showed a similar decrement \textsuperscript{(87)}. The investigators are conducting continued DXA evaluations in both the infants as they age and the mothers during the breastfeeding period; it is hoped that the results will become available within the next year.

Only three studies provide detailed reports on maternal adverse reactions; these were conducted in HIV-infected women on ART, which may not be reflective of the use of TDF or TDF/FTC by uninfected women \textsuperscript{(88, 89, 90)}. The PROMISE data did not find an increase in overall adverse maternal outcomes with TDF, but it did observe an increase in chemistry (primarily liver function) associated with both TDF ART and non-TDF ART; thus, this was not a TDF-specific effect. No significant effects of TDF ART on renal function were noted in studies that reported on this.

In conclusion, in the HIV-infected population, TDF ART-related maternal, pregnancy and growth outcomes appear to be generally similar to those for other ART regimens. These data, combined with the data from pregnant women receiving TDF for HBV treatment and the limited data in HIV-uninfected women, appear reassuring in terms of use of PrEP by HIV-uninfected women who conceive while receiving PrEP and continue PrEP during pregnancy and breastfeeding.

In assessing the data, the Technical Group noted that, as PrEP in women of childbearing age is being implemented, it will be critical to continue active surveillance of maternal, pregnancy and infant outcomes to confirm the safety that reviews to date, including that commissioned for this consultation, suggest.
FLEXIBILITY FOR COUNTRIES

Access and programmatic advantage for implementation

The Technical Group recognized the need for funding to expand access to PrEP. UNITAID, PEPFAR, the Bill and Melinda Gates Foundation and the Global Fund are actively exploring how to support PrEP access among populations at substantial risk of HIV. The Technical Group emphasized the role that PrEP can have in addressing the plateau of HIV incidence in most countries (for example, in Botswana, where there has been major scale-up of ART). Treatment and prevention modalities such as PrEP should be complementary in a country’s HIV response.

The patent status of TDF, 3TC and FTC (and the fixed-dose combinations) are relevant to PrEP access for individuals in all countries. Access to patent information in relation to medical products has a major, and growing, importance for public health, and is particularly relevant for PrEP. The Medicines Patent Pool’s Patent Status Database for Selected HIV Medicines provides information on the patent status of selected ARVs in many low- and middle-income countries.

Currently, the international patent for TDF expires in 2017/2018 in most countries. TDF/FTC is already licensed for use in prevention by some stringent regulatory authorities (SRAs), including those in, Australia, Canada, France and the United States (FDA), and by some NMRA, for example in South Africa. As described in this report, the evidence for the use of TDF/3TC as PrEP is indirect, with no direct clinical data on safety or efficacy. Therefore, the Technical Group recognized that it is unlikely that TDF/3TC will be registered for prevention by NMRA or SRA in the next few years. Nonetheless, it would still be possible for countries to authorize the use of TDF/3TC based on off-label prescription, as they do with many other prevention medicines, including those for PEP and PMTCT.

From an implementation perspective, countries can consider the off-label prescription of TDF/3TC or TDF alone if these drugs are readily available in country and/or registered for use, and depending on the priority populations for PrEP. The Technical Group recognized the following in terms of flexibility around PrEP drug choice:

- Allowing for flexibility in drug selection can foster PrEP access and allow public health officials to recognize that TDF/FTC may not be the only drug regimen of choice for initiating PrEP.
- Choice of TDF, TDF/FTC, or TDF/3TC for PrEP should be guided by the drugs approved for HIV treatment in each country and the populations prioritized for PrEP.
- Given the very limited availability of TDF alone or co-formulated TDF/FTC in many PEPFAR-supported countries, the availability of TDF/3TC for PMTCT treatment and PEP, and the similar pharmacoadvailability of 3TC and FTC in heterosexual populations, TDF/3TC can be considered as an acceptable alternative to TDF/FTC for PrEP in situations where access (including affordability) or availability of TDF/FTC is limited.
- Given the limited data on the efficacy of TDF alone for men who have sex with men, as well as the limited availability of TDF as a single drug within some national ART programmes, the use of TDF alone for PrEP may offer little advantage in some settings.
- Offering both generic and originators’ drugs could lead to lower costs, particularly beyond the duration of originator donations or in settings where the originator’s products are not available or available only at higher prices.
- Messaging and promotional materials need to accurately reflect the drugs that are being utilized at a country level to minimize confusion.
Supply chain systems need to be in place to ensure the continuity of drug access and the link, where possible, to ARV treatment.

CONCLUSIONS

PrEP trials and demonstration projects to date have used TDF/FTC in all populations and TDF alone in only heterosexual populations, with the exception of one safety study in men who have sex with men. However, given both the cost of the originator’s TDF/FTC product, particularly in countries where its patent is extended to 2024, and supply chain issues, any country that considers only TDF/FTC for PrEP could prevent or limit its ability to initiate strategic implementation of PrEP to address ongoing HIV incidence, particularly in key populations.

There are large potential gains in rolling out PrEP in key populations, including among pregnant women who remain at substantial risk of HIV. Significant roll-out delays would translate into new HIV infections and eventually increased morbidity. There are significant opportunity costs in delaying implementation of PrEP.

- The Technical Group advised that countries can consider all three drug regimens for PrEP (TDF alone, TDF/FTC and TDF/3TC) depending on their populations at risk, available TDF-containing products and other considerations.

- TDF/FTC has been more widely used in clinical trials, open-label extensions and demonstration projects than TDF alone or TDF/3TC, and, therefore, most evidence on the safety and efficacy for PrEP is based on the use of this product.

- Indirect evidence suggests that TDF/3TC could be an option for use as PrEP by countries, especially in instances when restricting the drug regimen choice to TDF/FTC would limit or prevent PrEP implementation.

- TDF only. The WHO meta-analysis does not demonstrate a statistically significant difference in effectiveness between TDF only PrEP and TDF/FTC PrEP in reducing the risk of heterosexual HIV acquisition; there were insufficient data for analysis among other populations, including men who have sex with men. These results are similar to those found by the Partners PrEP Continuation Study, which randomized participants to TDF or TDF/FTC PrEP. This study did not demonstrate a significant difference in effectiveness. Using TDF alone as oral PrEP for prevention of heterosexual HIV transmission could have the advantage of lower costs. However, few countries include TDF alone as part of their current ARV drug procurement. Further, providing different PrEP drug regimens for different populations (men who have sex with men, and women, for example) could pose complications for drug procurement, supply chains and training of providers.

- Monitoring and evaluation is an important part of PrEP implementation. Generating data on HIV drug resistance and drug levels in HIV seroconverters on PrEP can help public health authorities, particularly in settings that have resources. Since the number of seroconverters on PrEP is expected to be small, assays could, in most settings, be performed either locally or by referral to centres of excellence on venous blood plasma or dried blood spots. There are practical considerations in sample processing, however, including the storage of dried blood spots and the overall cost of generating data. Nevertheless, this should not hinder initial PrEP roll-out in settings where individuals and populations can benefit from access to PrEP.
• Given the lack of existing clinical trials in services that use TDF among men who have sex with men, or TDF/3TC among any populations, consideration should be given to setting up detailed clinical cohorts through research collaborations to understand the context of as many seroconversions as possible and to document any adverse events that might be caused by TDF used alone and TDF/3TC, including development of drug resistance.

• PrEP use during pregnancy and breastfeeding. Direct and indirect evidence shows that all three PrEP regimens (TDF alone, TDF/FTC and TDF/3TC) are safe in pregnancy and breastfeeding. Although additional surveillance is important, given the available data there does not currently appear to be a safety-related rationale for discontinuing PrEP during pregnancy and breastfeeding for HIV-uninfected women who become pregnant and remain at continuing risk of HIV acquisition. If pregnant and breastfeeding women taking PrEP are at substantial risk of HIV infection, the evidence suggests that the risk of HIV acquisition and accompanying increased risk of mother-to-child HIV transmission far outweigh the potential risk of fetal and infant exposure to TDF used for PrEP.

The Technical Group recognized the need to move beyond previous WHO recommendations, accelerating PrEP implementation whilst at the same time acknowledging uncertainty. As countries begin implementation, there will be a need for further updates of global guidance as well as efforts to address knowledge gaps, with a clear plan for national programmes to collect data to address uncertainty.

RESEARCH GAPS

The Technical Group identified a set of research gaps and proposed the type of study that could be designed and conducted for each drug considered during the consultation. The Group also discussed future PrEP drug candidates (see Table 5).

Table 5. Research gaps in current PrEP regimens and future PrEP candidates

<table>
<thead>
<tr>
<th>Product</th>
<th>Gaps in animal studies</th>
<th>Gaps in human studies</th>
<th>Remarks and potential added value</th>
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<tbody>
<tr>
<td>TDF</td>
<td></td>
<td>Need for more studies (with high adherence) in pregnant women, including close surveillance in pregnant women after PrEP implementation. [Note: pregnant women have lower TFV concentrations; hence this may be a population where two drugs, such as TDF/FTC or TDF/3TC, are more appropriate than TDF alone.]</td>
<td>Very few countries procure TDF alone. Therefore, there is no direct procurement advantage. Not ethically justifiable to have placebo-controlled arms in a PrEP study.</td>
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<tr>
<td></td>
<td></td>
<td>Event-driven dosing (IPERGAY) or averaged dosing. [Note: same comment is relevant as</td>
<td>UK, Switzerland and other countries are considering intermittent PrEP regimens due to drug costs.</td>
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</tbody>
</table>

27
<table>
<thead>
<tr>
<th>Product</th>
<th>Gaps in animal studies</th>
<th>Gaps in human studies</th>
<th>Remarks and potential added value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>above re: pregnant women. Event-driven dosing may have less PK forgiveness, especially where the frequency of sex is low. Therefore, two drugs, such as TDF/FTC or TDF/3TC, are likely to be preferable.]</td>
<td>More demonstration projects with women are required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of data for adolescents and transgender people. [Note: This is also true with regards to other PrEP drugs.] Some demonstration projects are in the pipeline.</td>
<td>Differences in efficacy and virological failure between FTC and 3TC are insignificant in HIV treatment.</td>
</tr>
<tr>
<td>FTC</td>
<td>Need for rectal concentrations for parent and metabolite. (The Technical Group noted that PK forgiveness from TDF/FTC provides some level of reassurance.) To determine rectal concentrations for protection, criteria that will satisfy ‘sufficient’ effectiveness and equivalence to FTC need to be defined. Need for macaque challenge study after rectal concentrations are determined.</td>
<td>Need for colorectal and vaginal tissue PK followed by animal challenge study. (The Technical Group recognized the data gap is larger for rectal concentrations than for female genital tract concentrations.)</td>
<td>There is a wide interquartile range in animal studies. Continue with the current 300 mg daily dose.</td>
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<tr>
<td>3TC</td>
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<tr>
<td>TDF/FTC</td>
<td>More event-driven PrEP data in different populations are needed.</td>
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</tr>
<tr>
<td>Product</td>
<td>Gaps in animal studies</td>
<td>Gaps in human studies</td>
<td>Remarks and potential added value</td>
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<tr>
<td>TDF/3TC</td>
<td></td>
<td>It is important to demonstrate that TDF/3TC is not inferior to TDF/FTC (in order to seek regulatory approval). A cluster randomized design could be appropriate, in which, for instance, some randomly selected districts use TDF/3TC and others use TDF/FTC. An open-label single arm study is needed. Given the very high efficacy expected in people who adhere, it would be possible to evaluate the incidence of seroconversion and explore resistance in seroconverters. If seroconversion happens in people who are adherent (as measured by blood levels) and the virus is not resistant, it would suggest that the regimen is not as effective as expected. An open-label cohort study with adherence monitoring by pharmacologic measures (for example, dried blood spots) may enable an “adherence-response” relationship similar to that observed for TDF/FTC.</td>
<td>High quality evidence from randomized trials. (However, the quality of evidence is reduced if participants are not blinded.) Recruitment of participants to a randomized trial may take too long. Manufacturers want Phase III efficacy studies. (Note: This was not applicable to PEP.)</td>
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<tr>
<td>Tenofovir alafenamide (TAF)/FTC</td>
<td>No clinical trial data available. Although efficacy against rectal infection demonstrated, there is no data on vaginal efficacy.</td>
<td>More studies are needed.</td>
<td>Mucosal PK in female genital tract and rectal cells not as good as TDF. Potential alternative to TDF/FTC for PrEP due to potentially less adverse effects on kidneys and bones; however, more studies are needed.</td>
</tr>
<tr>
<td>Product</td>
<td>Gaps in animal studies</td>
<td>Gaps in human studies</td>
<td>Remarks and potential added value</td>
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<tr>
<td>Non-oral PrEP (for example, vaginal rings, long acting injections)</td>
<td></td>
<td>Studies are needed on supporting adherence by younger women.</td>
<td>Advantages would be safety and lower dose and cost.</td>
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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the United States Centers for Disease Control and Prevention.
# ANNEX II. MEETING AGENDA

## WHO/UNAIDS Technical Consultation on Alternative Drug Options for Pre-Exposure Prophylaxis

**WHO-UNAIDS**  
Avenue Appia 20 (D Building, Kofi Annan Room)  
Geneva, Switzerland  
21-22 March 2016

### Day 1: Monday, 21 March 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda Item</th>
<th>Speakers/Facilitators</th>
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<tbody>
<tr>
<td>08:30 – 09:00</td>
<td>Registration</td>
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</table>
| 09:00 – 09:25   | Opening, welcome and introductions by WHO-UNAIDS and co-chairs (15’)       | Opening remarks:  
Gottfried Hirnschall  
WHO  
Peter Godfrey-Faussett  
UNAIDS  
Co-chairs:  
Jared Baeten  
University of Washington  
Mitchell Warren  
AVAC  
Rosalind Coleman  
UNAIDS |
|                 | Meeting objectives, expected meeting outcomes, working methods (10’)         |                                                            |
| 09:25 – 10:00   | Overview of evidence for existing WHO recommendation on oral PrEP: a meta-analytic approach  
Questions/Answers (5’) | Rachel Baggaley  
WHO  
Robert Grant  
WHO Consultant/University of California, San Francisco |
| 10:00 – 10:20   | Why flexibility of PrEP drugs globally matters:  
The technical and programmatic implications interchangability of 3TC and FTC for oral PrEP containing TDF, and for the use of TDF alone as PrEP  
Discussion (10’) | Ioannis Hodges-Mameletzis  
WHO Consultant |
| 10:30 – 11:00   | Break                                                                      |                                                            |

**SESSION 1**  
Assessing PrEP evidence: Animal studies for ARVs

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<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Description</th>
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<tbody>
<tr>
<td>11:00 – 12:00</td>
<td>Overview of the evidence (30’):</td>
<td>Walid Heneine&lt;br&gt;US Centers for Disease Control and Prevention (CDC) Gerardo Garcia-Lerma&lt;br&gt;US CDC</td>
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<tr>
<td>12:00 – 13:00</td>
<td>Lunch</td>
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<tr>
<td>SESSION 2</td>
<td>Assessing PrEP evidence: Human pharmacology studies</td>
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<td>13:00 – 13:30</td>
<td>Overview of the evidence from PK studies (30’)</td>
<td>Angela Kashuba&lt;br&gt;University of North Carolina Peter Anderson&lt;br&gt;University of Colorado</td>
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<td>13:30 – 14:00</td>
<td>Discussion (30’)</td>
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<td>14:00 – 14:30</td>
<td>Break</td>
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<tr>
<td>14:30-14:50</td>
<td>Do we have pharmacological equivalence and clinical interchangeability of 3TC and FTC for oral PrEP containing TDF? (15’)</td>
<td>Nathan Ford&lt;br&gt;WHO Marco Vitoria&lt;br&gt;WHO</td>
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<td></td>
<td>Questions/Answers (5’)</td>
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<tr>
<td>14:50- 15:10</td>
<td>Use of ARV drugs for PrEP in pregnancy (15’)</td>
<td>Lynne Mofenson&lt;br&gt;Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)</td>
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<td></td>
<td>Questions/Answers (5’)</td>
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<tr>
<td>15:10 – 17:00</td>
<td>Group Discussion: Framing the evidence from animals and humans for decision making on 3TC vs. FTC.</td>
<td>Moderator: Andy Gray&lt;br&gt;University of Kwazulu-Natal</td>
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<td>• What clarification on the use of TDF/3TC do we provide to countries and programmes?</td>
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<td>• What are the research gaps?</td>
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<tr>
<td>Time</td>
<td>Agenda Item</td>
<td>Speakers/Facilitators</td>
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<tr>
<td>09:00 – 09:30</td>
<td>Rapporteur update from Day 1</td>
<td>Rapporteur: Jared Baeten University of Washington</td>
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<td>Introduction to Day 2</td>
<td>Rosalind Coleman UNAIDS</td>
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<tr>
<td>09:30 – 09:50</td>
<td>Comparison of efficacy of TDF/FTC vs. TDF alone in Partners PrEP (15’)</td>
<td>Jared Baeten University of Washington</td>
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<td>Questions/Answers (5’)</td>
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<tr>
<td>09:50-10:10</td>
<td>Use of TDF in US PrEP Safety Study (15’)</td>
<td>Albert Liu San Francisco Department of Health</td>
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<td>Questions/Answers (5’)</td>
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<tr>
<td>10:10-10:30</td>
<td>PrEP failing in HBV-treated individuals: case report (15’)</td>
<td>Julie Fox Guys and St Thomas’ NHS Foundation Trust, London</td>
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<td></td>
<td>Questions/Answers (5’)</td>
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<td>10:30 – 10:50</td>
<td>Break</td>
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<tr>
<td>10:50 – 11:10</td>
<td>Update on WHO 2015 systematic review: analysis on TDF vs TDF-FTC (15’)</td>
<td>Ginny Fonner Medical University of South Carolina Caitlin Kennedy Johns Hopkins University</td>
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<tr>
<td></td>
<td>Questions/Answers (5’)</td>
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<tr>
<td>11:10 – 11:30</td>
<td>HIV drug resistance in the context of PrEP (15’)</td>
<td>Robert Grant WHO Consultant/University of California, San Francisco</td>
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<td></td>
<td>Questions/Answers (5’)</td>
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<tr>
<td>11:30-12:30</td>
<td><strong>Group Discussion:</strong> <strong>Is TDF alone as safe and efficacious as any dual combo?</strong></td>
<td>Moderator: Nikos Dedes EATG, Positive Voice</td>
</tr>
<tr>
<td></td>
<td>• What clarification on the use of TDF alone do we provide to countries and programmes?</td>
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<tr>
<td>12:30 – 13:30</td>
<td>Lunch</td>
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<tr>
<td>SESSION 2</td>
<td>Community, programmatic, and country-level input</td>
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| **13:30 – 15:00** | Panel Discussion: *Implications of PrEP drug flexibility*  
  - Midnight Poonkasetwattana (APCOM): Mobilizing community in PrEP implementation  
  - Marcelo Freitas (National HIV and Hepatitis Programme, Brazil): Brazil’s trial on TDF/3TC  
| **15:00 – 15:30** | Break |
| **15:30-17:00** | *Group discussion and next steps*  
  - Group consensus on the use of TDF-3TC and TDF alone in national PrEP programmes  
  - Research gaps identification |
| **17:00** | Coffee – End of Consultation |
Annex III.   LIST OF PARTICIPANTS

WHO/UNAIDS Technical Consultation on Alternative Drug Options for Pre-Exposure Prophylaxis

Geneva, Switzerland
21-22 March 2016

External Participants:

Peter Anderson
University of Colorado
USA
Peter.Anderson@ucdenver.edu

Gerardo Garcia-Lerma
Centers for Disease Control and Prevention
USA
jng5@cdc.gov

Marcelo Araujo de Freitas
National HIV and Hepatitis Programme
Brazil
marcelo.freitas@aids.gov.br

Tanuja Gengiah
CAPRISA
South Africa
tanuja.gengiah@caprisa.org

Jared Baeten
University of Washington
USA
jbaeten@uw.edu

Andy Gray
University of KwaZulu-Natal
South Africa
graya1@ukzn.ac.za

Gerard Belimac
National AIDS/STD Prevention and Control Program
Philippines
naspcp@yahoo.com

Walid Heneine
Centers for Disease Control and Prevention
USA
wheneine@cdc.gov

Nikos Dedes
European AIDS Treatment Group/Positive Voice
Greece
nikos.dedes@me.com

Andrew Hill
University of Liverpool
United Kingdom
microhaart@aol.com

Julie Fox
King’s College, London
United Kingdom
julie.fox@kcl.ac.uk

Angela Kashuba
University of North Carolina
USA
akashuba@unc.edu

Albert Liu
University of California, San Francisco
USA
albert.liu@sfdph.org

Mitchell Warren
AVAC
USA
mitchell@avac.org
**Midnight Poonkasetwattana**  
Asia-Pacific Coalition for Male Sexual Health  
Thailand  
[ midnightp@apcom.org ]

<table>
<thead>
<tr>
<th><strong>Observers:</strong></th>
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</table>
| **Esteban Burrone**  
Medicines Patent Pool  
Switzerland  
[ eburrone@medicinespatentpool.org ] | **Gina Dalabetta**  
Bill and Melinda Gates Foundation  
USA  
[ gina.dallabetta@gatesfoundation.org ] |
| **Yao Cheng**  
Medicines Patent Pool  
Switzerland  
[ ycheng@medicinespatentpool.org ] | **Lut Van Damme**  
Bill and Melinda Gates Foundation  
USA  
[ Lut.VanDamme@gatesfoundation.org ] |
| **Jennifer Cohn**  
Elizabeth Glaser Pediatric AIDS Foundation  
Switzerland  
[ Jcohn@pedaids.org ] | **Heather Watts**  
Office of the U.S. Global AIDS Coordinator and Health Diplomacy  
USA  
[ WattsDH@state.gov ] |

<table>
<thead>
<tr>
<th><strong>UNAIDS:</strong></th>
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</table>
| **Rosalind Coleman**  
Consultant, Office of the UNAIDS Science Panel  
Switzerland  
[ colemanr@unaids.org ] | **Carlos Passarelli**  
Country Programme Gap Analysis and Accountability  
Switzerland  
[ passarellic@unaids.org ] |
| **Peter Godfrey-Faussett**  
Office of the UNAIDS Science Panel  
Switzerland  
[ faussettp@unaids.org ] |  |

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<tr>
<th><strong>UNITAID:</strong></th>
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</table>
| **Carmen Perez Casas**  
UNITAID  
Switzerland  
[ perezcasasc@unitaid.who.int ] |  |
WHO:

WHO Headquarters Secretariat

Gottfried Hirnschall
HIV Department
hirnschallg@who.int

Nicola Magrini
Essential Medicines and Health Products Department
magrinin@who.int

Rachel Baggaley
Key Populations and Innovative Prevention
HIV/AIDS Department
baggaleyrg@who.int

Francoise Renaud
Strategic Information
HIV/AIDS Department
reaudf@who.int

Silvia Bertagnolio
Treatment and Care
HIV/AIDS Department
bertagnolios@who.int

Manjulaa Narasimhan
Department of Reproductive Health and Research
narasimhanm@who.int

Shaffiq Essajee
PMTCT and Maternal Child Health
HIV/AIDS Department
essajees@who.int

Marco Vitoria
HIV Treatment and Care
HIV/AIDS Department
vitoriam@who.int

Nathan Ford
Treatment and Care
HIV/AIDS Department
fordn@who.int

WHO/AFRO

Busisiwe Radebe
WHO South Africa Country Office
msimangaradebeb@who.int

WHO/WPRO

Ying-Ru Lo
WHO Western Pacific Regional Office
loy@wpro.who.int

WHO Consultants/Interns

Robert Grant
Consultant, Key Populations and Innovative Prevention
HIV/AIDS Department
grantro@who.int

Eshun Nwoza
Intern, Pandemic and Epidemic Diseases Department
nwozae@who.int
Ioannis Hodges-Mameletzis  
Consultant, Key Populations and Innovative Prevention 
HIV/AIDS Department  
mameletzisi@who.int

Michelle Rodolph  
Consultant, Key Populations and Innovative Prevention  
HIV/AIDS Department  
rodolphm@who.int

Praneel Kumar  
Intern, Key Populations and Innovative Prevention  
HIV/AIDS Department  
praneel.kumar@griffithuni.edu.au

**External virtual participants:**

Caitlin Kennedy  
Johns Hopkins Bloomberg School of Public Health  
USA  
caitlinkennedy@jhu.edu

Virginia Fonner  
Medical University of South Carolina  
USA  
fonnaer@musc.edu

Lynne Mofenson  
Elizabeth Glaser Pediatric AIDS Foundation  
USA  
mofensol@gmail.com


52. Mancuzo AV, Carvalho LV, Carvalho GC et al. Evaluation of the acceptability, feasibility, safety and adherence to pre-exposure prophylaxis (PrEP) for HIV prevention in men who have sex with men (MSM): Phase 1 study (submitted abstract).


