TECHNICAL BRIEF

WHAT'S THE 2+1+1?

EVENT-DRIVEN ORAL PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV FOR MEN WHO HAVE SEX WITH MEN: UPDATE TO WHO'S RECOMMENDATION ON ORAL PREP

JULY 2019

World Health Organization

WHO/CDS/HIV/19.8

Suggested citation. What's the 2+1+1? Event-driven oral pre-exposure prophylaxis to prevent HIV for men who have sex with men: Update to WHO's recommendation on oral PrEP. Geneva: World Health Organization; 2019 (WHO/CDS/HIV/19.8). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Design and layout by L'IV Com Sàrl

Printed in Mexico

World Health Organization

WHAT'S THE 2+1+1?

EVENT-DRIVEN ORAL PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV FOR MEN WHO HAVE SEX WITH MEN: UPDATE TO WHO'S RECOMMENDATION ON ORAL PREP

JULY 2019

CONTENTS

ACKNOWLEDGEMENTS

Mary Aikenhead (The Bill and Melinda Gates Foundation, USA), **George Ayala** (MPact Global Action for Gay Men's Health and Rights, USA), **Ruanne V Barnabas** (University of Washington, USA), **Benjamin Bavinton** (University of New South Wales, Australia), **Irene Benech** (CDC, USA), **Carlos Caceres** (Cayetano Heredia University, Peru), **Delivette Castor** (USAID, USA), **Connie Celum** (University of Washington, USA), **Ines Dourado** (Universidade Federal da Bahia, Brazil), **Robyn Eakle** (USAID, USA), **Ade Fakoya** (The Global Fund, Switzerland), **Robert Grant** (University of California at San Francisco, USA), **Andrew Grulich** (University of New South Wales, Australia), **Rena Janamnuaysook** (Thai Red Cross, Thailand), **Bill G. Kapogiannis** (National Institutes of Health, USA), **Kenneth Mayer** (Fenway Community Health Center, USA), **Sheena McCormack** (University College London, UK), **Jean-Michel Molina** (University Paris Diderot, Sorbonne Paris Cité, Saint-Louis Hospital, Assistance Publique Hôpitaux de Paris, France), **Irene Mukui** (NASCOP, Kenya), **Will Nutland** (PrEPster, UK), **Pragna Patel** (CDC, USA), **Nittaya Phanuphak** (Thai Red Cross, Thailand), **Midnight Poonkasetwattana** (APCOM), **Kevin Rebe** (ANOVA, USA), **Jason Reed** (Jhpiego, USA), **Pich Seekaew** (Thai Red Cross, Thailand), **Dawn Smith** (CDC, USA), **Hasina Subedar** (National Department of Health, South Africa), **Valdiléa Veloso** (FIOCRUZ, Brazil), **Mitchell Warren** (AVAC, USA), **Vincent Wong** (USAID, USA).

Representatives of UN agencies and other partners

UNAIDS: **Rosalind Coleman, Peter Godfrey-Faussett, and Heather-Marie Schmidt**
UNICEF: **Chewe Luo and Damilola Walker**
UNFPA: **Elizabeth Benomar**
UNITAID: **Carmen Perez Casas, Heather Ingold, Charlotte Kristiansson**

WHO: The following WHO staff contributed to developing this technical brief: **Rachel Baggaley, Andrew Ball, Silvia Bertagnolio, Shona Dalal, Joumana Hermez, Naoko Ishikawa, Virginia Macdonald, Antons Mozalevskis, Busisiwe Msimanga–Radebe, Van Thi Thuy Nguyen, Giovanni Ravasi, Michelle Rodolph,** and **Annette Verster**.

WHO administrative support was provided by **Valerie Amiel-Fourtas** and **Veronique Millot**; and communication support was provided by **Tunga Namjilsuren**. **Ward Rinehart** and **Sarah Johnson** (Jura Editorial Services) edited the document.

WHO also thanks external contributors to the development of the technical brief including **Ioannis Hodges-Mameletzis, Robert Grant, and Jean-Michel Molina**.

Overall coordination

Rachel Baggaley coordinated the overall technical brief development process with **Shona Dalal** and **Michelle Rodolph** under the supervision of **Andrew Ball** (Department of HIV).

OVERVIEW

What's in this technical brief?

This technical update by the World Health Organization (WHO) aims to:

- update the dosing considerations for oral pre-exposure prophylaxis (PrEP) containing TDF for men who have sex with men
- summarize current evidence on the safety and efficacy of event-driven PrEP (ED-PrEP)
- describe the rationale for offering ED-PrEP as an alternative to daily oral PrEP to men who have sex with men as part of comprehensive HIV prevention and sexual health services
- discuss considerations for offering ED PrEP to men who have sex with men, including clear messaging on how men who have sex with men can switch from ED-PrEP to daily dosing (and vice-versa).

Terms and definitions used in this brief

In this brief the following terms are used:

- **PrEP, or pre-exposure prophylaxis** refers to a pill containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), unless otherwise specified.
  - Daily Oral PrEP is relevant for all people, irrespective of gender, sexual orientation, or sexual behavior.
  - Event-Driven PrEP is recommended ONLY for men who have sex with men, based on this technical update.
- **Men who have sex with men** includes gay and bisexual men and other men who have sex with men.
- **Transgender** refers to people whose gender identity is different from the one they were assigned at birth (for example, an individual who was considered to be male as a child but who now identifies as female).
- **Cis, or cisgender** refers to people whose gender identity matches the one they were assigned at birth.

There are a range of terms in the literature used to describe event-driven (ED-PrEP), including "2+1+1", "on-demand", "non-daily", "event-based", "pericoital" and "intermittent" PrEP. This can be confusing for both health-care providers offering PrEP and for individuals seeking PrEP services. In this technical brief, we employ the term "**ED-PrEP**".

INTRODUCTION

WHO recommends offering oral pre-exposure prophylaxis (PrEP) to people at substantial risk of HIV as part of comprehensive HIV prevention *(1)*. PrEP is the use of oral tenofovir disoproxil fumarate (TDF) or co-formulated TDF/emtricitabine (TDF/FTC) or co-formulated TDF/lamivudine (TDF/3TC) by HIV-negative people to prevent HIV acquisition. PrEP has been shown to be effective in a wide range of HIV-negative populations. WHO considers FTC and 3TC interchangeable, both for treatment and for prevention of HIV infection *(2–4)*.

An increasing number of countries are adopting policies endorsing PrEP for HIV prevention. A global review found that 40 countries had incorporated oral PrEP into their policies or guidelines by the end of 2018 *(5)*. The use of PrEP has grown substantially over time, particularly among men who have sex with men in high-income settings, where PrEP was introduced early on, as well as among other priority populations in low- and middle-income settings.

Emerging evidence from clinical research that different dosing strategies can be effective provides an opportunity to offer flexibility, choice and convenience to individuals who can benefit from PrEP and is considered by WHO in updating its guidance to countries. WHO also promotes the use of differentiated approaches for reaching men who have sex with men and other key populations[1] across the HIV services continuum, including for PrEP *(6)*. These new strategies have the potential to reduce the cost of drugs, to reduce pill burden and toxicity and to improve continuation among those who find daily pill-taking challenging.

Evidence that different dosing strategies can be effective offers users of PrEP flexibility, choice and convenience.

In 2016 WHO published the *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed*. This publication described the high efficacy of PrEP dosing both before and after sex among men who have sex with men who reported frequent sexual activity in the IPERGAY trial – a regimen now called event-driven PrEP (ED-PrEP) *(1)*. In those guidelines WHO noted that how best to adapt the PrEP recommendations to diverse and changing sexual practices would be an important focus for further implementation research.

WHO RECOMMENDATION ON PREP, 2015

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.

High quality evidence, strong recommendation

In 2017 WHO provided additional guidance to countries by releasing a modular PrEP implementation tool *(7)*. The clinical module in that tool noted that, while comparisons of daily and ED-PrEP regimens were limited by the size and diversity of the studies, the high effectiveness and acceptability of ED-PrEP among men who have sex with men in high-income settings was clear, as the 2016 consolidated ARV guidelines also had noted. However, research was lacking on the effectiveness of ED-PrEP during heterosexual sex and among transgender people, and the data then available came from only a single trial, IPERGAY. For these reasons daily dosing remained the only WHO-recommended option. Then, in 2018 an interim analysis from a large implementation study of ED-PrEP in France *(8)* led WHO to recognize the need to consider ED-PrEP as an additional option for men who have sex with men.

WHAT IS THE EVIDENCE THAT ED-PREP FOR MEN WHO HAVE SEX WITH MEN IS HIGHLY EFFECTIVE?

The first randomized, placebo-controlled trial (RCT) to report the efficacy of oral PrEP was iPrEx, a six-country study that randomized 2499 HIV-negative men and transgender women having sex with men to a daily dose of TDF/FTC or placebo *(9)*. A 44% reduction in HIV incidence (intention to treat; 95% confidence interval [CI] 15–63) was seen in the group randomized to daily oral PrEP compared with the placebo group. Detectable drug in the blood was strongly correlated with the prophylactic effect of PrEP.

Since iPrEx, most RCTs and open-label extension studies have examined the daily dosing regimen *(10)*. WHO recommended daily oral PrEP dosing in 2015–2016 based on a systematic review of 18 studies and a meta-analysis that also included the limited evidence available on ED-PrEP (10). WHO's literature search for the 2015 systematic review identified three RCTs that had evaluated "intermittent PrEP": the IAVI Uganda Study, the IAVI Kenya Study and IPERGAY *(11–13)*. The two IAVI studies were limited in sample size (both studies had 72 participants) and had some methodological uncertainty. Therefore, they were not included in WHO's meta-analysis for assessing HIV infection rates by dosing strategy – daily versus "intermittent". The WHO meta-analysis found a suggestion of higher efficacy rate for ED-PrEP than for daily dosing among men who have sex with men – 86% versus 50%. This difference did not reach statistical significance, however *(10)*.

As for women, the ADAPT study, published in 2018, compared daily and two types of non-daily PrEP dosing among women in Cape Town, South Africa. The study found that daily PrEP dosing resulted in more frequent PrEP use before and after sex events (defined as "PrEP coverage" in that study) among the participants than in the time- or event-driven arms (75% versus 56% and 52%, respectively) *(14)*. The event-driven dosing consisted of a single pill taken before sex and another single pill taken after sex. Daily PrEP showed better adherence to the regimen and higher drug concentrations in blood than either time-driven or event-driven dosing. These findings support recommendations that woman using oral PrEP take it daily.

THE INITIAL RCT DEMONSTRATING THAT ED-PREP WORKS FOR MEN WHO HAVE SEX WITH MEN

In the initial IPERGAY trial, ED-PrEP reduced risk of HIV infection by 86%.

In 2015 Molina and colleagues published the initial findings from the RCT known as IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays), which was conducted in France and Canada *(12)*. The IPERGAY trial (n=400) reported that use of ED-PrEP consisting of a double dose of two TDF/FTC pills taken between two and 24 hours in advance of anticipated sex; then, a third pill 24 hours after the first two pills and a fourth pill 48 hours after the first two pills by high risk men who have sex with men was associated with a relative reduction of 86% in the risk of HIV infection compared with those taking a placebo (intention to treat: 95% CI: 40–98%, P=0.002). Only two HIV infections occurred in the active arm, both