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

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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.

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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 after PrEP had been stopped for one to three months. Based on the study protocol, if a break of more than a 1 week occurred since taking the last pill, re-initiation was with a double dose before sex; if less than a one-week break occurred, re-initiation was with one pill before sex. However, to simplify dosing recommendations among people who stop and restart PrEP, and to be more cautious, the ED-PrEP programme in France now suggests that all re-initiations start with a double dose (J.M. Molina, personal communication, May 2019).

The IPERGAY study population was at particularly high risk for HIV, having frequent unprotected sex acts. Participants reported taking a median of 15 pills of TDF/FTC or placebo per month, and analysis of plasma drug concentrations in a subset of those randomized to TDF/FTC indicated that 86% had tenofovir concentrations consistent with having taken the drug during the previous week. In contrast, in the iPrEx RCT, only 50% of participants in the active arm had such levels of drug detected after randomization to daily dosing *(9)*.

At the time of the initial IPERGAY findings in 2015, it was uncertain whether an event-driven dosing strategy would also work for men who have sex with men who had infrequent sex. In 2017 a follow-up (sub-group) analysis from the IPERGAY trial reported on 134 person-years of follow-up from 269 subjects who reported less frequent sex and event-driven PrEP use *(15)*. In this analysis participants reported having sex a median of five (IQR: 2 to 10) times per month, which translated into a median of 9.5 (IQR: 6 to 13) pills per month. All six reported infections occurred in the placebo arm of the study, with a relative reduction of HIV incidence of 100% in the active arm (95% CI: 20–100). This showed that ED-PrEP is effective among men who have sex with men even when sex is infrequent.

THE OPEN-LABEL EXTENSION STUDY OF IPERGAY

In 2017, findings from the open-label extension of IPERGAY were released. ED-PrEP again proved highly effective, with a reported reduction in HIV incidence of 97% (95% CI: 81–100) relative to the placebo group from the randomized phase *(16)*. A key lesson of this study, also seen in other open-label studies *(17)*, is that trial participants are more likely to continue with oral PrEP when they know that they are taking the active medicine rather than a placebo. No increase in the incidence of sexually transmitted infections (STIs) was seen in this study.

LARGE DEMONSTRATION PROJECT OF BOTH DAILY DOSING AND ED-PREP: PREVENIR

France, an early adopter of PrEP globally, currently has an estimated 10 400 PrEP users *(18)*, and its PrEP guidelines recommend both daily dosing and ED-PrEP for men who have sex with men *(19)*.

Prevenir, an ongoing observational study, sponsored by the French research agency l'Agence française de recherche sur le sida (ANRS) and launched in May 2017, is designed to demonstrate a 15% reduction in new HIV infections among study participants using daily or ED-PrEP. Prevenir aims to enrol 3000 HIV-negative individuals, largely men who have sex with men, but including transgender men and women, heterosexual men and women, sex workers and migrants, in Île-de-France (Paris region) *(20)*. Alongside the Impact trial in the United Kingdom and the EPIC-New South Wales study in Australia, Prevenir is one of the largest demonstration/implementation projects for oral PrEP since WHO recommended daily dosing of PrEP for any person at substantial risk of HIV *(21, 22)*.

Table 1. HIV incidence reported from interim analysis of Prevenir study, 2019

PrEP dosing regimen	Follow-up (person-years)	HIV incidence per 100 person-years (95% CI)
TDF/FTC (daily)	1073	0 (0–0.3)
TDF/FTC (ED-PrEP)	1133	0.18 (0.02-0.6)

Source: Molina et al., 2019 *(47)*.

An interim analysis presented in July 2019 at the International AIDS Conference reported only two HIV infections among 3,057 Prevenir participants taking either ED-PrEP or daily dosing (Table 1) (*47*). Among the participants, 51% took PrEP on a daily basis and 49% chose ED-PrEP. There were two HIV infections in the ED-PrEP group in participants who had discontinued PrEP, and no HIV infections in the daily group. Only 3 participants discontinued PrEP due to drug-related adverse events, thus supporting the safety of this dosing strategy. Among those on ED-PrEP, 18% did not use ED-PrEP at their last sexual intercourse, but when PrEP was used adherence was high (79%), and reflected that participants were able to predict when they would have sex and use ED-PrEP. An important observation in Prevenir interim analysis was that **20% of participants overall also used condoms, irrespective of the dosing strategy.**

Based on the available evidence, this technical brief updates the current WHO recommendation on oral PrEP to **include an option of event-driven dosing for men who have sex with men**. Since ED-PrEP data are limited in other populations, such as transgender women and people having heterosexual sex, and for women showed lower coverage of sex acts than daily dosing, event-driven dosing is not currently recommended for other population groups. Daily oral PrEP is still recommended for all people at risk of HIV, including men who have sex with men. Table 2 outlines when ED-PrEP could be considered as an alternative to daily PrEP.

Table 2. When ED-PrEP could be considered

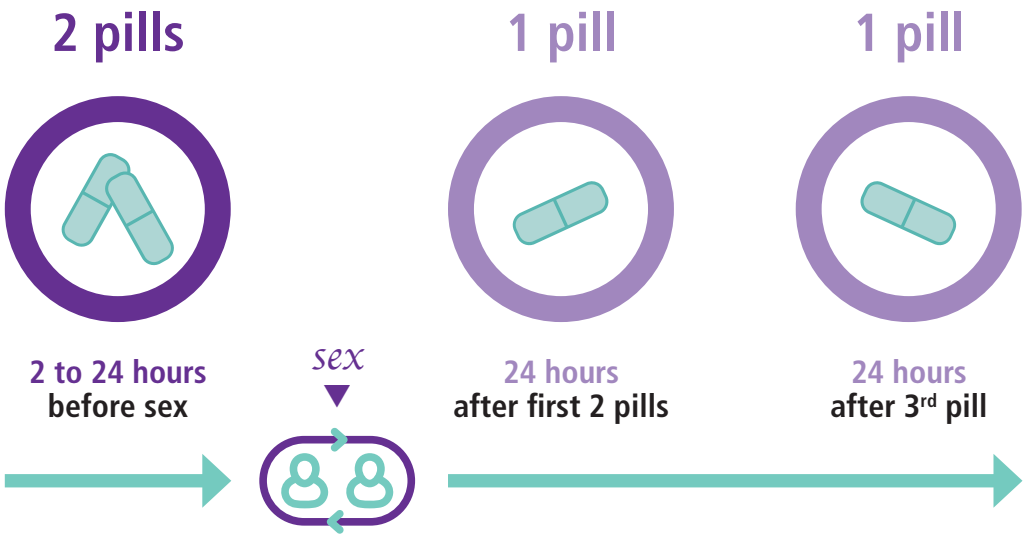
For whom is ED-PrEP appropriate?	For whom is ED-PrEP NOT appropriate?
• a man who has sex with another man: – who would find ED-PrEP more effective and convenient – who has infrequent sex (for example, sex less than 2 times per week on average) – who is able to plan for sex at least 2 hours in advance, or who can delay sex for at least 2 hours	• cisgender women or transgender women • transgender men having vaginal/frontal sex • men having vaginal or anal sex with women • people with chronic hepatitis B infection.

WHAT IS 2+1+1 ED-PREP, AND HOW SHOULD MEN WHO HAVE SEX WITH MEN USE IT?

Event-driven PrEP (ED-PrEP) for men who have sex with men consists of the use of a double dose (two pills, which serves as the loading dose) of TDF/FTC (or TDF/3TC) between two and 24 hours in advance of sex; then, a third pill 24 hours after the first two pills, and a fourth pill 48 hours after the first two pills (Fig. 1). ED-PrEP has been described as "2+1+1" dosing, a term that can be helpful to communicate this approach as an alternative to daily dosing for men who have sex with men. This 2+1+1 dosing is the only ED-PrEP regimen that has been demonstrated to be effective. Other regimens, involving use of only a single pill before and after sex, or taking PrEP four times per week, have been studied, but their efficacy is not known *(14, 23)*.

The 2+1+1 dosing describes ED-PrEP when an isolated act of sex is involved. If more sex acts take place over the following days, a single PrEP pill can be continued daily for as long as sex continues, with a single daily pill taken for each of two days after the last sex act.

Fig. 1. Schematic of how to take ED PrEP (the 2+1+1)



There have been no trials of ED-PrEP among adolescent men who have sex with men, apart from youth over 18 years who participated in the ADAPT/HPTN 067 trial, where it was found that daily dosing had better coverage than non-daily PrEP. Since youth may require more active support for continuation and in understanding how to safely start and stop PrEP, along with how and when to shift back and forth between daily dosing and ED-PrEP), some may find a daily oral schedule easier to follow. Module 12 of the WHO PrEP Implementation Tool *(24)* offers more information on special considerations for provision of oral daily PrEP to adolescents and young adults.

Adolescents may need more active support for use and adherence.

HOW CAN USERS CHANGE BETWEEN ORAL DAILY AND ED-PREP?

For all people at risk for HIV, daily oral PrEP should be used once daily during periods of frequent sex or when sex is unpredictable. PrEP can be stopped when no sex occurs. Frequency of sex will vary from person to person, based on several factors, including sexual practices, lifestyle, relationship status, sexual dynamics, age, and risk of HIV is affected by the background community prevalence of HIV.

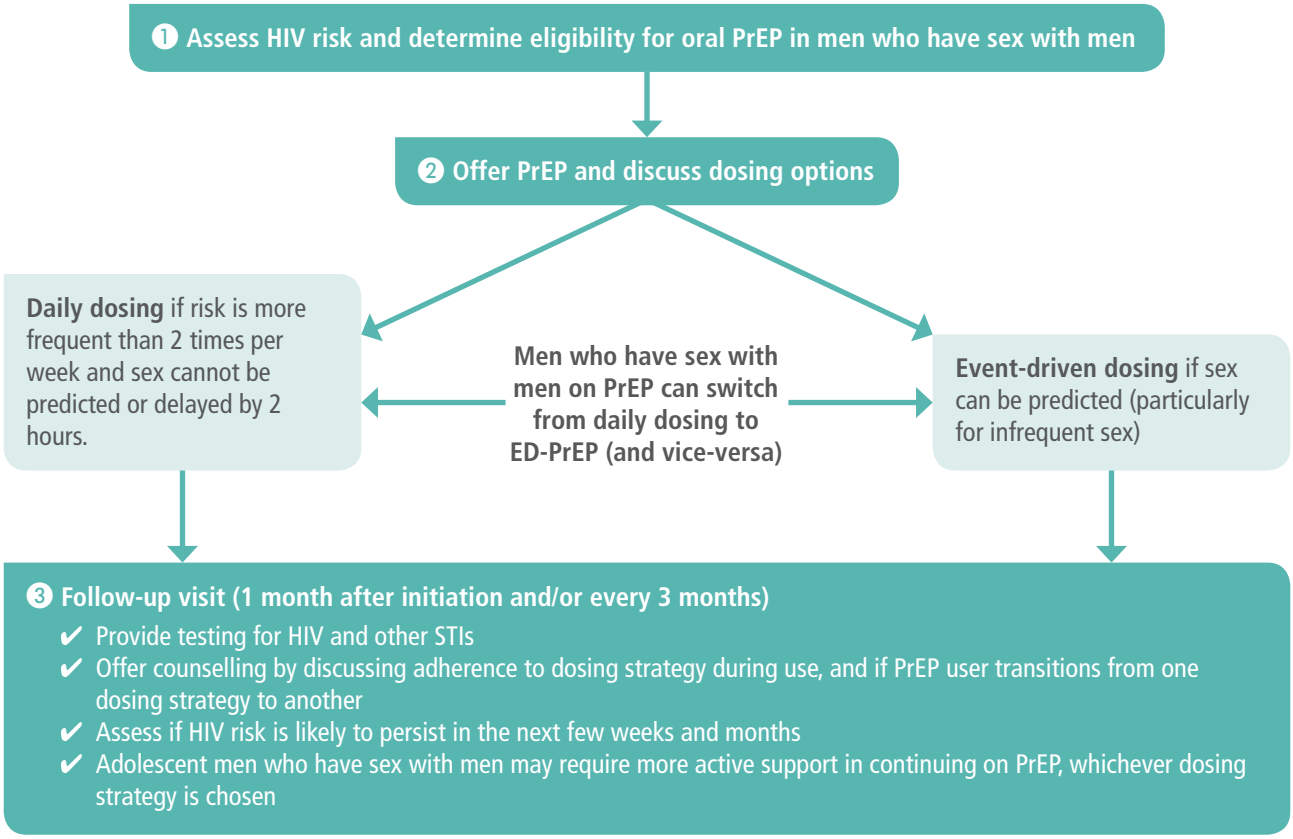
For men who have sex with men oral daily PrEP and ED-PrEP can be offered as options, and the choice can be based on a person's circumstances and preferences, as determined by what best fits their lifestyle, including the frequency and predictability of sex and whether sex is anticipated. Fig. 2 proposes an algorithm that PrEP providers might follow with clients eligible for PrEP, including key considerations during follow-up visits. Daily dosing is appropriate for clients where the occurrence of sex cannot be predicted and for those whose potential exposures to HIV are more frequent than 2 times per week, such that ED-PrEP would be taken so frequently that it would effectively resemble daily PrEP.

Men who have sex with men can choose whether daily PrEP or ED-PrEP better suits them.

If sex continues beyond one day, a user of ED-PrEP can stay protected by taking another pill each day as long as sex continues and stopping 2 days after the last sex act. Conversely, if an individual starts daily oral PrEP, but then sex becomes infrequent and predictable, ED-PrEP can be used instead.

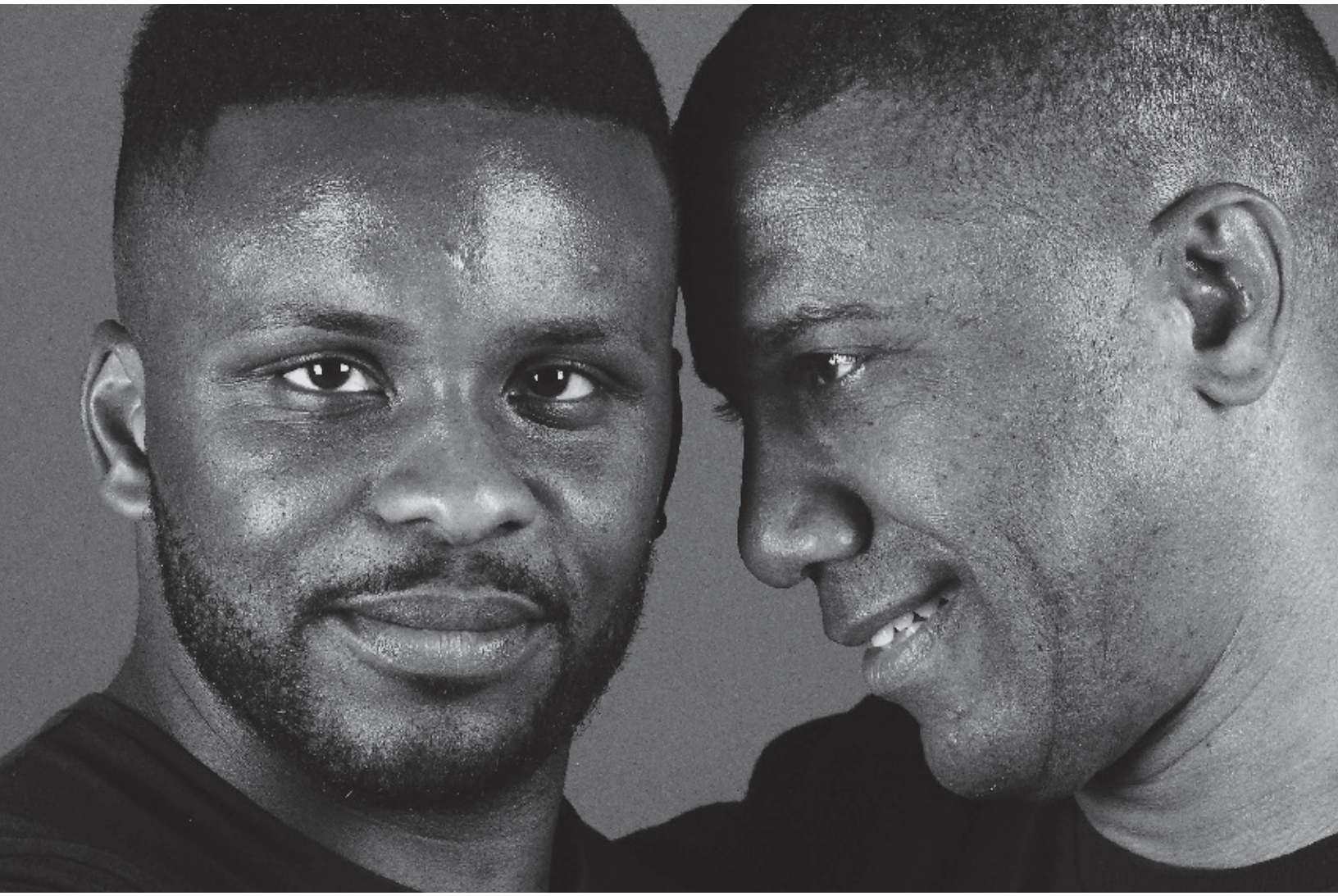
To stay protected, a user of ED-PrEP can take another pill each day as long as sex continues. .

Fig. 2. Proposed algorithm for PrEP providers when considering how to offer ED-PrEP



Monitoring visits and HIV testing and other laboratory testing for people taking PrEP should be the same whether they take oral daily PrEP or event-driven PrEP. See the clinical module (Module 1) in the WHO PrEP Implementation Tool *(7)*. However, a man taking ED-PrEP infrequently may not always need a new PrEP prescription as often as every three months, or may be prescribed fewer bottles of PrEP. If that might be the case, counselling should specifically emphasize testing for HIV every three months.

An advantage of ED-PrEP is that guidance about how and when to start and stop PrEP are built into the regimen, that is, "2+1+1". With daily PrEP, various experts make different recommendations regarding the minimum number of days of daily dosing required to achieve protection before sex. Prior recommendations were intended to be conservative and were based on pharmacological models for TDF alone. More recent modelling of observed pharmacokinetics with both FTC and TDF is consistent with the observed high efficacy of ED-PrEP among men who have sex with men *(25, 26)*. Given the clinical evidence for the efficacy of ED-PrEP among men who have sex with men and this recent pharmacological modelling, it is suggested that men who have sex with men starting PrEP begin with a single loading dose of two tablets of FTC/TDF (or 3TC/TDF) taken two to 24 hours before sex, whether the intention is to use daily PrEP or ED-PrEP. PrEP programmes for men who have sex with men that offer both the event-driven and daily approaches usually advise that PrEP can be stopped after two daily doses following the last sexual exposure.



WHY IS WHO NOT RECOMMENDING ED-PREP FOR OTHER POPULATIONS?

At this time there is evidence on safety and efficacy/effectiveness for ED-PrEP only for men who have sex with men (men exposed through receptive or insertive anal sex with other men) *(26–28)*. There is insufficient evidence for ED-PrEP to be considered as a dosing strategy for women, transgender women and men who have vaginal and/or anal sex with women. PrEP providers should ensure that these populations are offered daily dosing.

There is evidence on the efficacy and safety of ED-PrEP only for men who have sex with men.

The pharmacology of tenofovir, particularly in the female genital tract, suggests that the original ED-PrEP dosing strategy may not confer sufficient protection for women *(25, 29, 30)*. WHO has addressed this specific issue previously, as part of a technical consultation on the pharmacology of PrEP medicines in 2016 *(31)*. Additional research in women is needed to evaluate the safety and efficacy of different ED-PrEP regimens for vaginal exposure to HIV. Investigational regimens for women could include higher loading doses or co-formulation with additional medications (such as integrase inhibitors) that have good ability to penetrate into vaginal tissues.

Transgender women can safely take daily oral PrEP. Recent pharmacology data on the interaction of PrEP and feminizing hormone therapy in transgender women suggests caution with considering ED-PrEP as an additional choice *(32, 33)*. Data presented at the 2018 International AIDS Conference in Amsterdam indicated that in 20 Thai HIV-negative transgender women on feminizing hormones (iFACT study), daily oral PrEP did not alter feminizing hormone levels *(33)*. However, it was observed that plasma levels of tenofovir (TFV) decreased by 13%. This decrease in tenofovir concentration is small and not expected to decrease the effectiveness of daily PrEP dosing in transgender women, but it could affect the efficacy of ED-PrEP.

Similarly, a study in the United States of America observed changes in the TDF/FTC pharmacology in four transgender women receiving ART containing TDF *(32)*. Unlike the Thai study, which examined plasma levels, this study looked at tenofovir rectal concentrations in transgender women on feminizing hormone therapy. Active anabolite tenofovir-diphosphate levels relative to dATP (the natural substrate of HIV-1 reverse transcriptase) were significantly lower in these transgender women than in cisgender women and decreased with increasing concentrations of estrogen from injectable feminizing hormone therapy. This pilot study was very small and the laboratory methods were challenging; more research is needed to confirm the results.

WHO recognizes the urgent need for health care systems to be more inclusive of transgender populations, especially transgender women, across the spectrum of prevention/PrEP research, from pharmacology to implementation science. In addition, public health authorities should prioritize increasing awareness of and access to PrEP for transgender women.

WHAT ARE USERS' PREFERENCES FOR ED-PREP VERSUS DAILY PREP?

Preference for ED-PrEP in some settings is high among men who have sex with men. The strength of preference appears to depend on men's risk profiles and whether ED-PrEP and daily PrEP are offered as equal options or ED-PrEP is offered only if a client refuses daily PrEP. A survey in France before initiation of ED-PrEP trials indicated a high level of interest for event-driven dosing among men who have sex with men. Approximately 40% of 443 men who have sex with men reported interest in participating in an ED-PrEP trial *(34)*. In China, after publication of these ED-PrEP results, 100 of 292 survey respondents (34.2%) in Shanyeng City had heard of PrEP, and 170 (58.2%) were interested in participating in a demonstration project using ED-PrEP, while 140 (48.3%) were interested in daily use *(35)*.

In the Prevenir study, 53% of men who have sex with men preferred ED-PrEP when both were offered in a manner that encouraged the PrEP user to make his own informed decision *(8)*. In another hospital in Paris where men who have sex with men were offered both options, 75.6% of men who have sex with men opted for ED-PrEP *(36)*. In contrast, in a clinic cohort in Montreal where daily PrEP was offered as the medically preferred regimen, and ED-PrEP was offered as an alternative to men who have sex with men hesitant to start daily dosing, 22% selected ED-PrEP *(37)*. Clinicians with more than 10 years of clinical experience were more likely to write prescriptions for ED-PrEP *(38)*.

ED-PrEP can be an attractive choice for men who have sex with men who decline daily oral PrEP. In a survey in the USA, 74.3% of men who have sex with men who were hesitant to start daily PrEP indicated that they would be more willing to try ED-PrEP *(39)*. Greater interest in ED-PrEP was expressed by men who have sex with men who reported non-black race, were students or fully employed, had some college schooling, were currently insured and were concerned about being infected with HIV.

User preferences, barriers and facilitators to PrEP regimens have been explored among men who have sex with men in Thailand, Canada and the United States. In Thailand some PrEP users considered daily regimens the easiest to use, as it could be incorporated into daily routines and did not require planning for sex. These men expressed concerns, however, about the long-term safety and affordability of daily oral dosing *(40)*. Study participants appreciated ED-PrEP for minimizing drug exposure and potential adverse events. They considered ED-PrEP an attractive choice for men who have sex with men who had infrequent sex, had the capacity to plan for sex, and had the ability to take the post-sex dose *(40)*. In the Canadian study, men who have sex with men who reported less frequent sex with "occasional" partners or who were older greatly preferred ED-PrEP, while men who have sex with men in HIV serodiscordant partnerships were more likely to prefer daily dosing *(37)*. Similarly, among ADAPT trial participants in the United States, ED-PrEP was valued as "congruent with the episodic nature of HIV risk", allowing users to stop PrEP as they moved out of high-risk situations and time periods *(41)*. Such strategic dosing of PrEP, emphasizing greater PrEP use during periods of greatest potential exposure to HIV, was valued by PrEP users and is correlated with PrEP efficacy in trials *(42, 43)*.

In the HPTN 067 ADAPT trial conducted among men who have sex with men in Thailand and the United States, people randomized to take PrEP once before and once after sex were more likely to miss the post-sex doses *(23)*. Barriers to post-sex dosing identified by PrEP users included being away from home after sex, fear of PrEP use being discovered by a partner, and disrupted routines following sex *(44)*. Participants were more likely to take the post-sex dose if PrEP use was accepted in the community or already known to the sex partner *(40)*.

WHAT ARE THE POTENTIAL BENEFITS OF ED-PREP IN MEN WHO HAVE SEX WITH MEN?

ED-PrEP is highly effective in reducing the risk of HIV acquisition in men who have sex with men, and it has the following additional benefits *(31–35)*:

- Provides choice and convenience for men who have sex with men who may be at high HIV risk for brief periods or have sex less than 2 times per week on average;
- Serves as an option for men who have sex with men who can anticipate, plan, or delay their sex events;
- Reduces pill burden;
- Saves costs, since fewer pills may be needed, including costs to the user if he buys PrEP.

WHAT ARE THE POTENTIAL RISKS OF ED-PREP IN MEN WHO HAVE SEX WITH MEN?

There are concerns that using ED-PrEP, and consistently taking the correct regimen, may be difficult for some people. Where ED-PrEP and daily PrEP are offered to men who have sex with men they can be supported to choose the option they prefer. However it is recognized that in some settings where clinics offer PrEP services to a range of populations including men who have sex with men (both those who identify as such and those do not), a single option of daily PrEP may be preferred. Further, daily dosing should be offered as an alternative that may be easier to use and is preferable when sex events are frequent and/or unplanned.

HIV drug resistance could emerge as a result of exposure of the HIV virus to antiretroviral drugs during suboptimal adherence to a PrEP regimen and consequent breakthrough infection. Resistance to FTC and/or TDF was infrequently reported in randomised controlled trials owing largely to the low incidence of HIV infection if PrEP is taken and the lack of drug exposure if adherence to PrEP is low *(10)*. Participants in the active arm of the Ipergay trial demonstrated high levels of adherence to PrEP, and no HIV infections occurred in people using ED-PrEP *(45)*.In the Prevenir study, two HIV infections occurred among ED-PrEP participants after they had discontinued PrEP; neither was drug resistant (*47*).

Conversely, HIV drug resistance was more commonly reported if oral TDF/FTC PrEP was inadvertently initiated during undiagnosed HIV infection *(10)*. As exposure to antiretroviral drugs in individuals with undiagnosed HIV represents the main risk for drug resistance acquisition associated with PrEP, it is imperative to take all reasonable steps to exclude HIV infections before PrEP initiation or reinitiation and to ensure consistent and frequent HIV testing while PrEP is administered.

HIV testing is recommended every three months both for people taking daily oral and for those taking ED-PrEP, usually coinciding with clients collecting their next prescription for PrEP drugs. Some clinicians have raised concerns that drug resistance risk may be higher with ED-PrEP because drug exposure is episodic and HIV testing may not occur before PrEP use. People taking ED-PrEP infrequently may theoretically become HIV infected in periods where they are off PrEP, with subsequent increased risk of resistance if ED-PrEP is taken without prior HIV testing ruling out HIV infection.

Monitoring ED-PrEP implementation and ensuring that follow-up monitoring every three months for HIV testing is an important component of PrEP interventions.

While it is informative for routine monitoring to disaggregate PrEP use by daily oral and ED-PrEP, a potential unintended consequence of monitoring ED-PrEP may be that it identifies men who have sex with men in recording and reporting systems since ED-PrEP is a dosing option only for men who have sex with men. Another is that undeclared men who have sex with men may have daily PrEP prescribed to avoid this identification but may decide on their own to use event-driven dosing. Monitoring may identify these users as apparently non-continuous if continuation is measured by number of pills taken. Furthermore, such users will not receive instructions for how to use ED-PrEP safely. Confidentiality and protection of health data are critical, and especially so in settings where men who have sex with men are marginalized and same-sex activity is criminalized. Establishing data systems with in-built protections, particularly for electronic records and reporting forms containing potentially identifying information, will be important both to ensure data security and to foster trust among PrEP users.

CONCLUSIONS AND CONSIDERATIONS FOR IMPLEMENTING ED-PREP FOR MEN WHO HAVE SEX WITH MEN

- **ED-PrEP is safe and highly effective** in reducing risk of HIV acquisition through receptive and/or insertive sex between men. It can be offered as an alternative to daily PrEP dosing for men who have sex with men. Data from available trials and open label extension studies and a recently completed two year demonstration study in Amsterdam *(46)* show that ED-PrEP is as effective in preventing HIV infection as daily PrEP in men who have sex with men.

- Countries with existing PrEP guidelines, but where ED-PrEP is not recommended, can **consider including the option of ED-PrEP** (TDF/FTC or TDF/3TC) in the "2+1+1" dose schedule for men who have sex with men when updating national guidelines and protocols.

- Countries with no guidelines on oral PrEP could consider adopting WHO's recommendation of oral PrEP for any person at substantial risk for HIV and, in the process of developing their national guidelines, **include options for both daily dosing and ED-PrEP for men who have sex with men**.

- **Education and support** for both ED-PrEP and daily dosing are necessary to aid people's choice between the two dosing strategies and their understanding of the requirements to maintain protection against HIV.

- **HIV testing is recommended every three months** whether a person is using daily oral PrEP or ED-PrEP. People taking ED-PrEP infrequently may not need prescriptions filled as often, or may have fewer bottles of PrEP prescribed, and so specific counselling to test for HIV every three months should be emphasized.

- **Caution should be taken when documenting ED-PrEP use** in settings where same-sex activity is criminalized. Although it is helpful to understand patterns of ED-PrEP use in men who have sex with men, monitoring and evaluation activities should protect the confidentiality of health data and the autonomy of individuals. For additional information on monitoring and evaluation in the context of PrEP, please refer to WHO's PrEP Implementation Tool Module 5 on Monitoring and Evaluation, which will be updated to include considerations for ED-PrEP *(7)*.

- Oral PrEP, irrespective of the dosing strategy, is **an opportunity to engage with individuals around sexual health**, particularly the management of bacterial and viral STIs. WHO will be providing additional guidance in STI management for PrEP users later in 2019.

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For more information, contact:

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

E-mail: hiv-aids@who.int

www.who.int/hiv