Clinical guideline on the use of pre-exposure prophylaxis (PREP) for HIV in the context of sexual health in the Northern Macedonia

Република Северна Македонија
Министерство за здравство

MINISTRY OF HEALTHCAR

2450.

Врз основа на член 27 став (1) од Законот за здравствената заштита („Службен весник на Република Македонија“ бр. 43/12, 145/12, 87/13, 164/13, 39/14, 43/14, 132/14, 188/14, 10/15, 61/15, 154/15, 192/15, 17/16, 37/16 и 20/19 и „Службен весник на Република Северна Македонија“ бр.101/19, 153/19, 180/19, 275/19 и 77/21), министерот за здравство донесе

InP A T WT I O
FOR MEDICAL CARE WHEN USING PREESCPOSIC WANTS PROPHYLAXIS
(PREP) Against HIV infections

Член 1

Со ова упатство се утврдува медицинското згрижување при примена на постекспозициона медицинска профилакса против ХИВ инфекција.

Член 2

Начинот на медицинското згрижување при примена на постекспозициона медицинска профилакса против ХИВ инфекција е даден во прилог, кој е составен дел на ова упатство.

Член 3

Здравствените работници и здравствените соработници ја вршат здравствената дејност на медицинското згрижување при примена на постекспозициона медицинска профилакса против ХИВ инфекција по правило согласно ова упатство.

По исклучок од став 1 на овој член, во поединечни случаи по оценка на докторот може да се отстапи од одредбите на ова упатство, со соодветно писмено образложение за причините и потребата за отстапување и со проценка за натамошниот тек на згрижувањето, при што истото од страна на докторот соодветно се документира во писмена форма во медицинското досие на пациентот.

Член 4

Ова упатство влегува во сила наредниот ден од денот на објавувањето во „Службен весник на Република Северна Македонија“.

No.09-4575/1
2 Jumn2021 it di of
Skopjs

We wester health care,
e-r **Vefilipce,** p.r.

Clinical guideline on the use of pre-exposure prophylaxis (PREP) for HIV in the context of sexual health in the Northern Macedonia

Skopje, 2021

Working Party on Writing the PrEP Guidelines:

- Dr. Milena Stevanovic, specialist infectologist; national HIV coordinator
- Dr Biljana Petreska, specialist infectologist, University Clinic for Infectious Diseases and Febrile Conditions
- Dr Vladimir Mikic, Institute of Public Health

- Dr Velimir Saveski, University Clinic for Infectious Diseases and Febrile Conditions
- Marija Trajculeski, Medicines and Medical Devices Agency of the Republic of Northern Macedonia
- Irina Luceska, Health Insurance Fund of the Republic of Northern Macedonia
- Andrei Senih, Association for support of people living with HIV – TOGETHER STRONGER Skopje
- Zoran Yordanov, EGAL Association
- Borce Bozhinov, STAR-STAR Association

PrEP Guidance Consultant:

- Dr Ioanis Hodges-Mamelezis, World Health Organization

The development of the Clinical Guideline for Pre-Exposure Prophylaxis was a foreseen activity in the Hiv Infection Population Protection Programme 2019, and was implemented within the framework of the World Health Organisation's mission to technically support the national process for the introduction of pre-exposure prophylaxis as an additional tool and service in the context of combined HIV prevention. The process was helped by the regional project "Sustainability of services for key HIV-affected populations in Eastern Europe and Central Asia", with financial support from the Global Fund for Combating AIDS, tuberculosis and malaria, and logistical and additional technical support was provided by the Association for the Support of People Living with HIV – TOGETHER STRONGER Skopje. The need to expand the available HIV and HIV testing options is a priority set by the National HIV Commission of the Ministry of Health in 2018, preceded by a wide consultation process with all relevant institutions and civic sector organisations.

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

CONTENT

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

ABBREVIATIONS

AIDS immunodeficiency syndrome

ART antiretroviral therapy

BDT rapid diagnostic test **BMD** mineral bone density **eCrCl** estimated creatinine clearance **eGFR** estimated glomerular filtration

FTC emtricitabine

HBV hepatitis B virus

HCV hepatitis C virus

HIV human immunodeficiency virus **iPrEx** initiative for pre-exposure prophylaxis **MSM** men who have sex with men

nPEP non-occupational post-exposure prophylaxis

PEP post-exposure prophylaxis

PrEP pre-exposure prophylaxis

LID persons injecting drugs

SPI sexually transmitted infections

TD* thanofovir disoproxil maleate or fumarate or phosphate **TDF** thanofovir disoproxil fumarate (trade name *Viread* from the originator company) thanofovir dysoproxil fumarate in co-formulation with emtricitabine (trade name *Truvada* originator company). On **TDF/FTC** e.g., regulatory agencies around the world have approved a number of generic products of tenophovir dysoproxil maleate and emtricitabine in co-formulation; tanofovir dysoproxil phosphate and emtricitabine

TDF/3TC Tenofovir dysoproxil fumarate in co-formulation with lamivudine

TFV-DP thanofovir diphosphate

TRM transgender man

TRG transgender woman

WHO World Health Organization

EXECUTIVE SUMMARY

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

Oral preexposure prophylaxis (PrEP) is a powerful intervention that is highly effective in reducing the risk of HIV in adolescents and adults. PrEP can be useful for individuals (preventing HIV infection, which requires lifelong antiretroviral therapy); public health (reducing new HIV infections at population level); health care system (payable, and ultimately, if offered to the most at risk, leads to cost savings).

The first evidence of the effectiveness of PrEP in reducing HIV risk was recorded in 2010, based on the findings of a study conducted in several countries, iPrEx. In 2015, the World Health Organization (WHO) published a strong recommendation for PrEP for each person at significant RISK of HIV based on high-quality clinical research in different populations, and in 2017, three drugs with an indication of use such as PrEP (TDF/FTC; TDF/3TC; and TDF as monotherapy) were also included as essential drugs in the WHO's List of Essential Drugs.

This document is the first national clinical guideline for PrEP in northern Macedonia, based on the current guidelines of the WHO and the European Clinical Association for AIDS (EACS). The target audience of this guideline is clinical staff as well as other parties involved working to provide PrEP in northern Macedonia, including doctors, nurses, pharmacists, counselors, peer navigation ists, as well as civic organisations and organisations based in the communities concerned. The document provides an overview of how to provide PREP safely and effectively, including: screening for significant HIV risk; appropriate testing in front of the person to start with prep and during the taking of the PrEP; and monitoring prep users and advising them on issues such as adherence (adherence).

Indications for PrEP:

Any adolescent and adult at risk of receiving HIV, who does not use condoms consistently (HIV-negative status must be confirmed before starting PrEP with 3rd or 4th generation HIV tests, including rapid tests at the place of service)

Recommended drugs:

Any of the three medicines recommended by the WHO on its List of Essential Drugs can be prescribed for PrEP, although the use of double combinations is preferred. (TDF/FTC and TDF/3TC)

Way of dosing:

Daily dosing is recommended for each person, regardless of gender; situational conditioned dosing ("2+1+1") is an additional dosing option in men who have sex with men

Giving the service:

When possible, starting prep should be practiced on the same day (when the potential user contacted the service), because people who seek PrEP or who are identified as persons at risk of HIV will benefit the most if they start immediately. The possibility of providing PrEP services within the community itself should also be considered.

In drafting this document, key parties concerned were actively involved, with extensive discussions, including representatives of institutions, health workers, and civil society representatives. The guidance

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

group included representatives from clinical experts on HIV, WHO and organisations of the affected communities. In order to expand the involvement of the parties concerned, a meeting of HIV-affected activists and organisations was also held in November 2019, with their fidget asked for how the PrEP could be introduced in northern Macedonia.

The guidance group agreed that although tenophovir dysoprockyl fumarate (TDF) was used in the PrEP trials, more and more other salts of tenophovir dysoproxil (including maleate, succinate and phosphate) would be used within generic formulations.

Finally, due to the COVID-19 pandemic, consultations on initial and consecutive visits to users could take place virtually (e.g. tele-PrEP) by telephone or video calls, and in order to facilitate access to PrEP.

General recommendation

Oral preexposure prophylaxis (PrEP) containing tenophovir dysoproxil should be offered to persons at significant risk of HIV infection, as part of a package of sexual and reproductive health services, tailored to the individual choice and risk profile, which is determined during the initial and consistent assessment and risk mitigation advice.

Given the COVID19 pandemic, the use of virtual consultations ("tele-PrEP") should be facilitated in order to allow access to PrEP, especially when the time to visit clinics is drastically limited due to the implementation of public health and social ("restrictive") measures.

1. INTRODUCTION TO PREP AS PART OF COMBINED PREVENTION REGARDING HIV AND SEXUAL HEALTH

The transfer of HIV continues to be a public health challenge in northern Macedonia and around the world. A person diagnosed with HIV needs lifelong treatment with a combination of antiretroviral (ARV) drugs. Currently, despite efforts in research, there is still no preventive vaccine or cure for a complete cure of HIV infection.

As a result of more than a decade of research, quality evidence has been obtained from clinical trials showing that the use of antiretroviral drugs to prevent HIV infection in HIV-negative persons is a fairly effective and safe option (1). This is called pre-exposure prophylaxis (PrEP). Currently, PrEP is identified with oral PrEP (namely, oral tablets containing tenofovir dysoproxil fumarate (TDF) as a key anti-HIV drug). However, clinical research also examines the use of several other products, including the vaginal ring with dapivirine and long-acting cabotegravir, which falls within the class of HIV drugs called inhibitors of

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

integration (2). However, what is currently available to national health systems to use in clinical practice is an oral tablet containing tenofovir dysoproxil.

The World Health Organisation prepared the first guidelines for PrEP intended for affected public health parties in 2012, specifically recommending daily oral PrEP in the context of demonstration projects for men and transgender women having sex with men, as well as for serodiscord heterosexual couples (3). The WHO further published an additional guideline in 2014, recommending the daily oral PrEP for MSM and outside demonstration projects and research (4). As the basis for the recommendation the WHO made in 2014, the iPrEx survey served, an examination of 3. phase, which assessed the safety and effectiveness of oral administration of TDF/FTC once a day compared to placebo, for HIV prevention in MSM. The survey was conducted with 2,499 participants from six countries: Peru, Ecuador, South Africa Brazil, Thailand and the United States (United States) (5).

In 2015, additional evidence from two decisive studies, PROUD and Ipergay, where both saw an 86% reduction in the risk of HIV in tdf/FTC, were analysed together with all other clinical trials and prolonged studies without placebo ('open-label') as part of who's meta-analysis (6). Fonner et al.'s systematic analysis served as the basis for the WHO's 2015 recommendation to open the door for PrEP to take an oversight for each person at risk of HIV, regardless of gender (7). This recommendation was also included in the Purified Guideline on the use of antiretroviral drugs to treat and prevent WHO HIV infection from 2016 (8).

Although epidemiological patterns and trends vary greatly from one European country to another, There have been continuous increases in the number of newly diagnosed infections in certain transmission groups in parts of the Region: MSM in the WHO's central and eastern European region, and heterosexual transmission to the eastern European region (9). Heterosexual transmission has decreased significantly in the EU/EEA and western Europe, especially among women, as well as the number of cases arising from sex between men in certain EU/EEA countries and western Europe, in recent years (as a result of extended prevention pledges). Drug injection transmission continued to decrease in a number of countries, although it still accounted for 37% of reported newly diagnosed cases with a known transmission method in the eastern European region in 2017.

Northern Macedonia has a concentrated HIV epidemic in key populations, with a growing trend in the number of new HIV infections, especially among men having sex with men (MSM) and transgender women (TRG) (10). PrEP should become a decisive element of the country's HIV response. Based on consultations and discussions over the past 12 months, the need for PrEP is visible to suppress the influx of new HIV infections.

2. EFFICIENCY OF PREP

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

PrEP is designed to be taken during an individual's "risk period", which could be an isolated sexual encounter (for example, over a weekend) or a longer exposure period (e.g., months/years). The majority of clinical studies among all populations have shown that daily use of PrEP is very effective in reducing the risk of hiv to 99% (6). For the greatest effectiveness of PrEP, sexual exposure requires sufficient (protective) levels of drugs in the genital tissue to be achieved before sexual exposure. For both men and women, the WHO recommends taking an initial concentration dose of one tablet per day for a week before having sex (Figure 1). For safe stopping with PrEP, the PrEP user should take one tablet a day for a week after the last risk exposure (11).

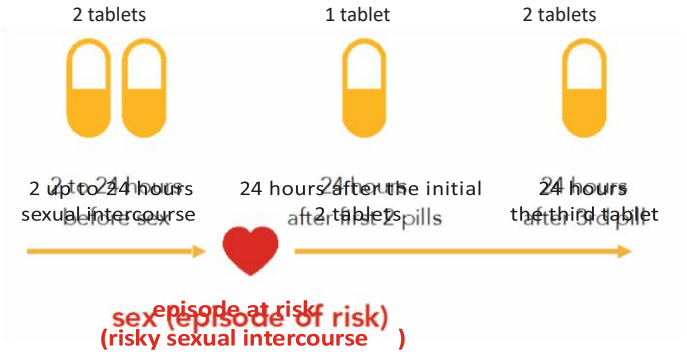
The efficacy of PrEP is directly related to adherence to the drug, with placebo-free trials showing high adherence and a greater reduction in the risk of hiv obtaining compared to previous blind trials (12–14). Although PrEP is very effective in reducing HIV transmission, it offers no protective effect against other bacterial and viral sexually transmitted infections (SPI), with the exception of HSV-2 infections (15–16).

There are studies that have also shown the high efficiency of what is called "situational PrEP" (SPREp, event-driven PrEP) in MSM (11). This dosing approach consists of taking a double dose (two pills, which serves as an initial concentration dose) of TDF/FTC (or TDF/3TC) between two and 24 hours before 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). SPREP is described as dosing "2+1+1", a term that can be of help to communicate this approach as an alternative to daily dosing for MSM. Such a dosage of 2+1+1 is the only SPREP regimen that has proved effective. Other regimens that include taking only one pill before and after sex, or taking PrEP four times a week, have been investigated, but their efficacy is unknown (17). Dosing 2+1+1 is a SPREP when it comes to an isolated sexual act. If more sexual acts occur over the coming days, one PrEP pill per day can continue as long as sexual acts last, with one pill taken every two days after the last sexual act.

Figure 1: Daily dosing of oral PrEP (applicable to each person, regardless of gender)

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

Figure 2: Dosage of SPREP (applies only to MSM and can be offered as an additional option in people looking for PrEP)



3. SAFETY OF PREP

Based on randomised clinical efficacy studies involving several countries (the gold standard of clinical trials) and the increasing amount of data from implementation in practice, the use of tdf-containing oral PREP is very safe, with minimal adversity in a minority of individuals (6, 18–20). TDF is widely used worldwide and is the most commonly prescribed antiretroviral drug to treat HIV infection (21). Extensive available data show that TDF-based PrEP is well tolerated and has a favorable security profile.

About 10% of people starting prep will receive some short-term, mild unwanted actions (20). Possible unwanted actions include:

- gastrointestinal symptoms (diarrhea, nausea, decreased appetite, stomach cramps or bloating) (39),
- dizziness or headaches have also been observed.
- Such unwanted actions are usually mild and resolved without stopping PrEP.
- Usually, these symptoms begin within the first few days or weeks of PrEP use and last several days, and almost always less than a month.

It is estimated that one in 200 PrEP users will receive an increase in serum creatinine during the use of PrEP (22). Therefore, the percentage of renal function is indicated as an important element in prescribing PrEP. The WHO recommends examining serum creatinine before starting PrEP and on consecutive visits every 6 months (20), but also notes that more frequent examination can be taken into account if there is a history of kidney-affecting conditions, including diabetes or hypertension.

Serological examination for viral hepatitis B and C is also important in the context of starting PrEP. If the hepatitis B screening test is negative, the person wishing to start PrEP could benefit from hepatitis B vaccination (20); if the test result is positive, the person may undergo further blood tests to determine

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

whether hbv infection (23,24) would be appropriate. Not everyone with detected antigens from hepatitis B virus (HBsAg) needs therapy. Indications of therapy can be assessed in several ways, depending on what laboratory tests are available. TDF is a recommended option for treating HBV (23); therefore, oral PrEP containing TDF can help those whose HBV infection requires therapy. People who stop hbv infection therapy are at risk of virological and clinical return to their HBV infection. This risk is higher in people who have liver fibrosis before starting therapy (25). The clinical return after stopping PrEP is not observed in the limited data available to people with HBV infection who have stopped oral PrEP containing TDF in the trials (26:27).

Evidence of HCV infection in MSM and people injecting drugs before starting PrEP and every 12 months thereafter may also be taken into account. Evidence testing for HCV infection is usually carried out using serological testing to detect HCV antibodies (anti-HCV) (28).

In clinical trials, it was observed statistically significant, albeit a small, decrease in bone mineral density in people taking PrEP. PrEP is associated with a slight decrease in bone mineral density (0.5–1.5%) in the spinal cord and hip in the first six months, which further does not progress (29.30). The research found no increase in bone fractures (29). Bone mineral density returns to normal as soon as the use of PrEP (29) is complete. Persons with a history of pathological bone fractures were excluded from the PrEP trials; people with such a history who are thinking about PrEP should also take into account and receive low mineral bone density therapy.

The WHO also recommends the use of PrEP during pregnancy and breast-smoking, although this is more significant in environments with higher HIV incidence, especially in East and South Africa. The risk of transmitting HIV infection to the baby is higher if the mother becomes infected while pregnant. Existing safety data support the use of PREP in pregnant women and breastfeeding women at constant and significant risk of HIV infection (31,32).

The doctor who prescribes the therapy is responsible for taking into account the active monitoring of safety problems that could arise, as well as for reporting any more serious harmful consequences to the relevant health authorities.

4. INDICATIONS

PrEP is indicated for persons (adults and adolescents) who may be at increased risk of HIV infection due to inconsistent use or non-use of condoms (Table 1). The pilot project currently planned aims to include people aged 18 and older who mainly come from key populations in northern Macedonia and at significant risk of hiv. Given the country's current HIV epidemiology, MSM and transgender women will take priority in this pilot project.

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

However, other people may be at significant risk of HIV, e.g., drug use (LKD) / drug injectors (LID) and HIV-negative people who have HIV-positive partners in whom the virus is not suppressed. This pilot project will not include adolescents. However, adolescents may be particularly vulnerable to HIV infection (33), so PrEP services in Northern Macedonia should include them.

Table 1: Populations (including criteria for behavioral risks) that will qualify/be suitable for PrEP in this pilot project. The priority will be given to MSMs, transgender people and sex workers (belonging to MSM, transgender and heterosexual populations).

Men who have sex with men (MSM)	Transgender faces	Heterosexual faces	Persons who inject / use drugs
The appropriateness for prep can be based on the following:			
• condomless sex (ASBC) with any irregular male partner. • Rectal gonorrhea, rectal chlamydia or infectious syphilis. • Use of methamphetamine. • ASBC with a regular HIV+ partner who does not receive therapy and/or has detectable viral load.	• ASBC with any irregular male partner. • Rectal or vaginal gonorrhea, chlamydia or infectious syphilis. • Use of methamphetamine. • ASBC with a regular HIV+ partner who does not receive therapy and/or has detectable viral load.	• ASBC with any irregular MSM partner. • A woman in a serodiscord heterosexual relationship, who plans to conceive naturally within the next 3 months. • ASBC with a regular HIV+ partner who does not receive therapy and/or has detectable viral load.	• Sharing injection equipment with an HIV+ individual or with MSM with unknown HIV status.

5. RISK ASSESSMENT: HOW TO IDENTIFY PEOPLE AT RISK OF HIV

People who come to request PrEP are usually at high risk of HIV infection and should not be dissuaded from using PrEP. This would deny the person access to one of the most effective HIV prevention tools available at the moment. Doctors who do not feel comfortable prescribing PrEP should immediately refer the person to a colleague or other service offering PrEP (e.g., in the pilot project planned in Skopje).

It should also be stressed that taking a history of sexual behavior is a necessary and routine part of medical practice, and when such a process determines that the person may be at risk of HIV, clinical staff should proactively offer PrEP to these patients. In addition, clinical staff should be encouraged to start a

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

conversation about PREP as an HIV prevention strategy in people who consider themselves at risk of becoming infected with HIV, even when the purpose of the patient's visit is not related to sexual health, SPI or drug use.

PrEP service providers should take a history of sexual behaviour and a history of drug use to see the situation, when determining whether the person is appropriate for PrEP, and their ongoing need for PrEP to revise it on each consecutive visit. It is important to recognise that a person's behaviour can change over time, and that the person may wish to continue with PrEP even if his/her immediate risk of contracting HIV is not considered "high".

This guideline recognises that PREP should be recommended as a strategy for HIV prevention in those at risk of HIV infection over the previous 3 months and who expect similar risks over the next 3 months. This guideline also recommends PrEP for those who were not at risk of HIV during the previous 3 months, but whose circumstances have changed, and now predict the occurrence of HIV risk over the next 3 months. Even in the context of COVID-19 and the recommendations of public health authorities for physical distance, people should have access to PrEP and, consequently, the stigma and discrimination of such persons should be a topic of conversation during the interaction between the user and the PrEP provider.

Table 1 compliance criteria may help structure a discussion with the person regarding his sexual health and behaviour. Clinical staff with limited experience in prescribing PrEP are encouraged to talk to colleagues who have experience with PrEP (e.g., those colleagues who will be part of the pilot project in Skopje) about those cases where the person's suitability for PrEP is not clear.

6. CONTRAINDICATIONS TO PREP

PrEP should not be used in case:

- The person is infected with HIV-1 or HIV-2
- There are signs and symptoms indicating acute HIV infection with probable exposure
- There is an estimated creatinine clearance (glomerular filtration rate [GFR]) <60ml/ min
- He has a history of chronic kidney disease, osteoporosis or osteophenia
- Allergy or contraindication to any remedy of the PrEP regimen (based on personal statement or on the basis of records)

If HIV status is indefinite on a registration visit, the start of TDF/FTC is postponed by at least 1 month to confirm negative HIV status.

As for the SPP, however, it should be offered as an additional option for dosing only to MSM; not indicated for: (a) cisgender women or transgender women

b) transgender men having vaginal/frontal sex

c) men who have vaginal or sex with women

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

(d) persons with chronic hepatitis B infection

7. START WITH PREP

For someone to be given PrEP, there is a minimum set of testing procedures for safe start, which include tests for rapid diagnosis of HIV from 3. or 4. generation, which will exclude the possibility that the person is already infected with HIV, a creatinine test, and an HBsAg test. Table 2 shows the tests and procedures to be carried out before the start of PrEP, as well as within a year of the use of PrEP. PrEP is also a great opportunity to test other bacterial and viral SPI, although this is not a prerequisite for the use of PrEP. Under the proposed pilot project in Skopje, molecular testing for gonorrhea and chlamydia will be provided, at the starting level, at 6. month, and at 12. month, depending on resources. If this cannot be implemented when prep users are included in the pilot program, spi syndrome management will be used as a standard of care offered to them. The initial consultation should contain confirmation of bihayvioral qualification (meeting table 1 risk criteria), clinical assessment (history), education (counselling), and laboratory assessment. In the first meeting, it is common for users to be given a supply of PrEP sufficient for 1 month, provided a normal kidney function and a negative HIV test. After the start, successive meetings are scheduled on 1st, 3rd, 6th and 6th. and 12. Month. There are also cases where a quantity can be prescribed early on in 3 months.

Time needed to achieve and maintain protection

When starting, it is important to talk to first-time prep people about how important the level of the drug is to enable high efficiency of PrEP. Particular attention should be paid to the time it takes to achieve protection (the 7-day rule for men and women, including transgender people; an initial dose of two tablets taken together as part of the SPREP).

The pharmacokinetics of TD* and FTC vary from tissue to another (34). Data from exploitative pharmacokinetic studies conducted in men and women who do not have HIV indicate that the maximum intracellular concentration of tenophosphate is achieved in the blood after approximately 20 days of daily oral dosing (35,36). Current evidence suggests that for both rectal and vaginal exposure, a high level of protection is achieved after 7 days of daily dosing (37), and this is the basis for who's recommendation. Women should maintain a high degree of adherence to daily dosing with TD*/FTC to maintain the appropriate level of the drug in vaginal and cervical tissues (37). Data on the inner cell concentration of the drug in penis tissues susceptible to HIV infection are not yet available, on which observations on the protection of male insertsexual partners would be formed. There are limited data on transgender and gender different persons, so it is recommended to pay additional attention to daily dosing.

Table 2 Successive tests and procedures during the PrEP pilot project

	/when	switching on consistently

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

Test/procedure	-1. or 0. Sunday	1. month	3. month	6. month	9. month	12. month
3. or 4. generation bdt for HIV	I do	I do	I do	I do	I do	I do
Creatinine clearance (kidney function)*	I do			I do		I do
HBsAg ** (anti-HBs, if on the disposal)	I do					
Syphilis serologically	I do			I do		I do
N. gonorrhea PCR	I do			I do		I do
H. trachomatis PCR	I do			I do		I do
HCV*	I do					I do
HBV vaccination**	I do					
HPV vaccination	I do					
Check for serious unwanted phenomena		I do	I do	I do	I do	I do
Qualification check	I do	I do	I do	I do	I do	
Check adherence	I do	I do	I do	I do	I do	
Issuing the drug	I do	I do	I do	I do	I do	

*Creatinine clearance is examined at the starting level, at 6 months, at 12 months.

** HBV vaccination should be offered to anyone without HBV infection who does not have immunity.

HCV testing for anyone at risk due to drug injection.

8. CLINICAL MONITORING AND OBSERVATION OF PERSONS USING PREP

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

Successive meetings usually consist of 15–20 minutes of consultation with clinical staff (doctor/nurse) (unless longer consultation is required to discuss an additional clinical problem). The consultation assesses adherence, unwanted actions, current other medicines and ongoing behavioral risk, laboratory testing, SPI prevention advice, and supply of medicines for PrEP for up to 3 months (after a visit after 1 month, a quantity of PrEP will be offered for 2 months).

All prescriptions should be approved by an authorized doctor of medicine in Northern Macedonia.

Interrupted or stopped PrEP

People who start prep have the autonomy to continue, stop and restart the PrEP.

On each consecutive visit, participants will be educated on the importance of safe start and stop with PrEP. Persons who will come to the clinic again after a certain pause of PrEP will need to be re-evaluated (to remove the possibility of HIV infection) and re-placed on PrEP, with a recommendation for hiv testing after the window period, and additional screening or management, depending on the risk.

9. SPECIAL CLINICAL OBSERVATIONS

Coping with raised creatinine

Due to the possible harmful effects of TDF/FTC on the kidneys, the increase in serum creatinine (38) should be observed closely. TDF/FTC as PrEP is interrupted when creatinine clearance is below 60 mL/min/1.73 m^2, and stops completely if the clearance is retained below 50 mL/min/1.73 m^2 after retesting.

Those who test will be shown to be positive for HIV or other infection, as well as persons with abnormal renal function, are recorded and will urgently call for further evaluation in consultation with a doctor. The results for HIV and renal function will be announced in principle on the same day (or the next day).

People with impaired renal function, suspected HIV infection/seroconversion or harmful phenomena will be referred and prioritized for medical examination and monitoring. Additional support will be made available to people with chronic viral hepatitis and other medical or psychosocial problems.

PrEP during pregnancy and breast-feeding

HIV infection can occur with high incidence during pregnancy and breast-smoking. The risk of transmitting HIV infection to the baby is higher if the mother becomes infected while pregnant. Existing safety data support the use of PREP in pregnant women and breastfeeding women at constant and significant risk of HIV infection (32).

Mineral bone density

In people taking PrEP containing TDF, a slight decrease in bone strength is recorded. PrEP is associated with a slight decrease in bone mineral density (0.51.5%) in the vertebrae and hip in the first six months,

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

which further does not progress (39.40). The research found no increase in bone fractures (39). Bone mineral density returns to normal as soon as the use of PrEP (39) is complete. Persons with a history of pathological bone fractures were excluded from the PrEP trials; people with such a history who are thinking about PrEP should also take into account and receive low mineral bone density therapy.

Status assessment for hepatitis A, B and C

Patients appropriate for PrEP may also be at risk of hepatitis A, hepatitis B virus infection (HBV) (25), and hepatitis C virus (HCV) infection (26). When it begins with PrEP, infectious status in relation to hepatitis A, B and C is required by serological screening.

Hepatitis A and B vaccination is recommended in all susceptible priority populations, including MSM, sex workers, people from countries with high prevalence of HIV, HBV or HCV, their sexual partners, as well as those injecting drugs (41, 42). Persons who, at the starting level, will be found to have undiagnosed chronic hepatitis B should be referred to clinical staff with experience in dealing with hepatitis B for assessment of possible treatment. Persons infected with chronic hepatitis B should only be offered daily PrEP, not situational PrEP. They should also be advised on the importance of strict adherence to PrEP to prevent and inflame their hepatitis B infection as well as develop hepatitis B virus resistance to TD*/FTC.

Persons who, at the later level, will be found to have an undiagnosed hepatitis C infection should be referred to clinical staff with experience in dealing with hepatitis C for his treatment. Diagnosing hepatitis B or hepatitis C is not an obstacle to starting PREP for HIV.

Interaction of PrEP drugs with other medicines

In addition to safety data obtained by clinical trials of PrEP, data on drug interaction and longer-term toxicity were obtained through the study of constituent drugs individually in their use in the treatment of people with HIV infection. Studies have also been carried out on fewer healthy adults without HIV infection. No significant effect was observed, and no dose adjustment of TD*was required, but there is no data for the FTC (43, 44).

The excretion of FTC and TD* is primarily done through the kidneys, as a combination of glomerular filtration and active tubular secretion. Since both drugs are primarily eliminated through the kidneys, co-administration of TD*/FTC with drugs that reduce renal function or are competitive for active tubular secretion can lead to an increase in serum Concentrations of TD*, FTC and other drugs that are eliminated renally, including (among others) cidofovir, acyclovir, valaciclovir, gancyclovir, valgancyclovir, aminoglycosides and in a high or multiple dose of nonsteroidal anti-inflammatory drugs (41).

Cocaine, methamphetamine and alcohol have not been observed to affect the concentration of PrEP drugs (45), but their use may affect the person's ability to maintain his adherence to PrEP.

Dealing with HIV infection

If a person becomes infected with HIV during the use of PREP, they should immediately stop PrEP. In this case, if the necessary resources are available, genotype resistance testing should be approached in

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

accordance with WHO guidelines, as well as viral load testing, and the person should be immediately referred for immediate start of ART.

10. PRIVATE PROCUREMENT OF PREP MEDICINES IN OTHER COUNTRIES OR OVER THE INTERNET

In the past few years, the emergence of private procurement of generic drugs containing TD*/FTC from different manufacturers has spread in several European countries, especially in countries where people have had no other way of accessing PrEP (for example through the health system or through a study). In addition, the emergence of ordering drugs over the Internet at prices significantly lower than the retail price in the home country was particularly present. In northern Macedonia, the Law on Medicines and Medical Devices prohibits internet traffic with prescription drugs. If a medicine is necessary that does not have sales approval for a particular group of patients, imports may be approved.

In relation to possible cases of procurement of medicines from individuals from other countries, it should be stressed that medicines should be stored in their original packaging, and transported in accordance with the storage instructions as stated by the manufacturer, as this not only allows the drug to be identified, but also contributes to maintaining its stability.

There have been cases in different countries where drugs supplied over the Internet have been seized by border control authorities, with customs duties charged. There are also reports of delays in delivery of TD*/FTC purchased over the Internet due to the COVID-19 pandemic, as well as occasional problems with depletion of supplies. This should be taken into account if PREP drugs are ordered over the Internet.

Situations may occur when the person has already supplied PrEP drugs in one of these ways; these persons should be encouraged to join the PrEP system – and to undergo initial and consistent procedures, as set out in this guideline.

Authenticity of tenofovir/emtricitabine purchased over the Internet

There are several manufacturers of generic TD*/FTC whose products are imported into European countries at affordable prices, although they are not registered by the European Medicines Agency or by national regulatory agencies. Some of these generic drug manufacturers have their own quality control system and meet the standards according to the expectations of the WHO and the United States Food and Drug Administration. However, there are concerns that PrEP purchased over the Internet may be substandard (contain a smaller or variable amount of active ingredients) or be a forgery.

11. KEY MESSAGES FOR COUNSELLING

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

Potential risks

People should always be informed not only of the effectiveness of PrEP, but also of the potential risks of more commonly reported unwanted actions by TDF and FTC when given as PrEP (e.g., headache, back pain, abdominal pain, unwanted weight loss, nausea, bloating). They should also be told that and, after the start of PrEP, in most PrEP users, symptoms disappear within 4 weeks. As has been said, clinical trials have seen a slight decrease in kidney function, but such a reduction is unlikely to be clinically significant. Deterioration of kidney health is more likely to occur in older people and people with elevated blood pressure, or diabetes, or in people who already have some mild form of kidney disease. Studies have shown that as soon as it stops with PrEP, the kidneys return to normal.

PrEP is also associated with a slight decrease in bone mineral density, according to clinical trials, but such a decrease is unlikely to be clinically significant. The doctor prescribing PrEP may suggest that the person take additional tests (serological examination of calcium concentration) before starting PrEP, especially in the elderly, in people with diabetes, or people taking steroid tablets, or having chronic heart disease. Studies have shown that as soon as it stops with PrEP, bone mineral density returns to normal.

TDF is also active against HBV infection at the same dose used for PrEP. The WHO recommends TDF for the treatment of HBV infection in persons for whom therapy is indicated (23). There are no indications of therapy in all people with chronic HBV infection. Indications for HBV therapy can be assessed in various ways, depending on what laboratory tests are available. When HBV therapy is stopped, there may occasionally be a flare-up of HBV infection in the next one to three months. The risk of hepatitis inflammation after stopping HBV therapy is higher in people with liver fibrosis. Additional assessments may be taken into account for people with HBV infection thinking about PrEP. Situational conditional dosage (21–1) is also not recommended in people with HBV, and will not be offered under this project (11). Participants with HBV will only be offered daily dosing.

There are very few reported cases worldwide when a person has become infected with HIV, despite the existence of evidence that they took PrEP during the risk period. This is often described as a "failure of prep". It is believed that the reason the PrEP failed is that the person was infected with an HIV strain that was resistant to TDF/FTC.
The risk of TDF and FTC-resistant soy bean infection is very low but not zero.

Adherenza

Adherence, whether the PrEP user is administering daily dosing or SPREP dosing, is decisive for the effectiveness of PrEP (20). Different strategies can be applied to effectively support adherence to medicines. These include:

- educate people (including groups of non-MSM populations, especially women who may be thinking about PrEP) about medicines
- to help people expect and manage side effects
- to help people establish a routine dosage that will fit into their work and social schedule
- provide reminder systems and tools, for example, tablet boxes or electronic reminders
- address substance abuse or mental health problems that may prevent adherence

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

- to arrange more frequent clinical visits for adolescents to strengthen their adherence (or to use virtual services, such as WhatsApp, etc.)
- facilitate social and peer support, especially for specific groups, such as sex workers.

When the PrEP regime begins, clinical staff must educate people about the schedule of medicines (for daily or SPP, i.e. for the use of PREP before and after potential EXPOSURE to HIV), how to start taking PREP and how to stop taking PrEP, and what to do if they run into problems, such as unwanted actions or dropped doses.

Adherence to medicines should be discussed every time the PrEP prescription is issued, in order to identify obstacles to optimal adherence to PrEP and to develop appropriate management plans.

REFERENCES

1. World Health Organization PrEP website: https://www.who.int/hiv/topics/prep/en/
2. Coelho LE et al. Pre-exposure Prophylaxis 2.0: New Drugs and Technologies in the Pipeline. Lancet HIV. 2019 Nov;6(11):e788-e799. doi: 10.1016/S2352-3018(19)30238-3. Epub 2019 Sep 23.
3. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/bitstream/handle/10665/75188/9789241503884_eng.pdf?sequence=1)\
4. 2014 WHO MSM Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. https://apps.who.int/iris/bitstream/handle/10665/128048/9789241507431_eng.pdf?sequence=1
5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. (2010) 363:2587–99. doi: 10.1056/ NEJMoa1011205
6. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly KR, Koechlin FM, Rodolph M, Hodges-Mameletzis I, Gran RM. Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis. AIDS. 2016;30:1973–83.
7. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).
8. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV. Recommendations for a public health approach. Second edition. Geneva: World Health Organization; 2016 (https://www.who.int/hiv/pub/arv/arv-2016/en/).
9. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2019 - 2018 data. Stockholm: ECDC; 2019. https://www.ecdc.europa.eu/en/ publications-data/hivaids-surveillance-europe-2019-2018-data

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

10. Overview of the epidemiological situation with HIV in North Macedonia and the results achieved under the 2019 HIV Population Protection Program (up to December 1). Institute of Public Health of Republic of North Macedonia; 2019.: https://www.iph.mk/en/overview-of-the-epidemiological-situation-with-hivin-north-macedonia-and-the-results-achieved-under-the-2019-hiv-population-protection-program-up-todecember-1/

11. 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 (https://apps.who.int/iris/bitstream/handle/10665/325955/WHO-CDS-HIV-19.8-eng.pdf?ua=1)

12. Molina JM et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV. 2017 Sep;4(9):e402-e410.

13. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-Tenofovir Concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. (2012) 4:151ra125. doi: 10.1126/scitranslmed.3004006

14. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. (2014) 14:820–9. doi: 10.1016/S1473-3099(14)70847-3

15. Celum C, Morrow RA, Donnell D, Hong T, Hendrix CW, Thomas KK, et al. Daily oral tenofovir and emtricitabine-tenofovir preexposure prophylaxis reduces herpes simplex virus type 2 acquisition among heterosexual HIV-1-uninfected men and women: a subgroup analysis of a randomized trial. Ann Intern Med. (2014) 161:11–9. doi: 10.7326/M13-2471

16. Marcus JL, Glidden D V., McMahan V, Lama JR, Mayer KH, Liu AY, et al. Daily oral emtricitabine/tenofovir preexposure prophylaxis and herpes simplex virus type 2 among men who have sex with men. PLoS ONE (2014) 9:e91513. doi: 10.1371/journal.pone.0091513

17. Desai M, Field N, Grant R, McCormack S. Recent advances in pre-exposure prophylaxis for HIV. BMJ 2017;359:j5011

18. Solomon MM, Schechter M, Liu AY, McMahan VM, Guanira JV, Hance RJ, Chariyalertsak S, Mayer KH, Grant RM; iPrEx Study Team. The Safety of Tenofovir-Emtricitabine for HIV Pre-Exposure Prophylaxis (PrEP) in Individuals With Active Hepatitis B. J Acquir Immune Defic Syndr. 2016 Mar 1;71(3):281-6. doi:

19. Pilkington V, Hill A, Hughes S, Nwokolo N, Pozniak A. How safe is TDF/FTC as PrEP? A systematic review and meta-analysis of the risk of adverse events in 13 randomised trials of PrEP. J Virus Erad. 2018 Oct 1;4(4):215-224.

20. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Clinical module. Geneva: World Health Organization; 2017.

21. Hodges-Mameletzis I, Dalal S, Msimanga-Radebe B, Rodolph M, Baggaley R. Going global: the adoption of the World Health Organization's enabling recommendation on oral pre-exposure prophylaxis for HIV. Sex Health. 2018;15(6):489-500.

22. Mugwanya K et al. Brief Report: Frequency of Monitoring Kidney Function in HIV-Uninfected Persons Using Daily Oral Tenofovir Disoproxil Fumarate Pre-exposure Prophylaxis. JAIDS. 2018 Feb 1;77(2):206-211.

23. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf

24. Guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 http://apps.who.int/ iris/bitstream/10665/254621/1/9789241549981-eng.pdf?ua=1.

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

25. Mondou E, Sorbel J, Anderson J, Mommeja-Marin H, Rigney A, Rousseau F. Posttreatment exacerbation of hepatitis B virus (HBV) infection in long-term HBV trials of emtricitabine. Clin Infect Dis. 2005;41(5):e45-7.

26. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials. 2007;2(5):e27.

27. Solomon MM, Schechter M, Liu AY, McMahan VM, Guanira JV, Hance RJ, et al. The safety of tenofoviremtricitabine for HIV pre-exposure prophylaxis (PrEP) in individuals with active hepatitis B. J Acquir Immune Defic Syndr. 2015.

28. Hoornenborg E, Achterbergh RCA, Schim van der Loeff MF, Davidovich U, Hogewoning A, de Vries HJC, Schinkel J, Prins M, van de Laar TJW; Amsterdam PrEP Project team in the HIV Transmission Elimination Amsterdam Initiative, MOSAIC study group. MSM starting preexposure prophylaxis are at risk of hepatitis C virus infection. AIDS. 2017 Jul 17;31(11):1603-1610.

29. Mulligan K, Glidden DV, Anderson PL, Liu A, McMahan V, Gonzales P, et al. Effects of Emtricitabine/ Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, PlaceboControlled Trial. Clin Infect Dis. 2015;61(4):572-80.

30. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PloS one. 2011;6(8):e23688.

31. WHO Technical brief: Preventing HIV during pregnancy and breastfeeding in the context of pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2017.

32. Mofenson et al. Tenofovir Disoproxil Fumarate Safety for Women and Their Infants During Pregnancy and Breastfeeding. AIDS. 2017 Jan 14;31(2):213-232.

33. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 12: Adolescents and young adults. Geneva: World Health Organization; 2018.

34. Patterson KB, Prince HA, Kraft E, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med 2011;3:112re4.

35. Anderson PL. Pharmacology considerations for HIV prevention [presentation]. 13th International Workshop on Clinical Pharmacology of HIV. Barcelona, Spain; April 2012. Available at: http://regist2. virology-education.com/2012/13hivpk/docs/16_Anderson.pdf

36. Anderson PL, Kiser JJ, Gardner EM, et al. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. J Antimicrob Chemother 2011;66:240-50.

37. Cottrell ML, Yang KH, Prince HM, et al. A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against HIV in men and women using tenofovir disoproxil fumarate with or without emtricitabine. J Infect Dis 2016;214:55-64.

38. Cottrell L, Yang KH, Prince HMA, et al; A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. The Journal of Infectious Diseases 2016;214:55–64

39. Mulligan K, Glidden DV, Anderson PL, Liu A, McMahan V, Gonzales P, et al. Effects of Emtricitabine/ Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, PlaceboControlled Trial. Clin Infect Dis. 2015;61(4):572-80.

(Official Gazette of RSM, no. 148, from 2 July 2021, pp. 4-25)

40. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PloS one. 2011;6(8):e23688.

41. Australian Government Department of Health. Third national hepatitis B strategy 2018–2022. 2018. Available at: https://www.ashm.org.au/HBV/strategies-hepb/

42. Australian Government Department of Health. The Australian Immunisation Handbook. Updated 12 April 2019. Available at: https://immunisationhandbook.health.gov.au

43. Gilead Sciences. Full prescribing information. Issued June 2013. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2013/021752s035lbl.pdf

44. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Last updated 10 July 2019. Available at: http://www.aidsinfo.nih.gov/ContentFiles/ AdultandAdolescentGL.pdf

45. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014; 14:820–9.

Publisher: Ministry of Health of the Republic of Northern Macedonia

Graphic processing: Emilia Tashkova

Skopje, 2021

The publication is available under the regional project "Sustainability of Services for Key Populations in the Eastern Europe and Central Asia Region" (#SoS_project, 2019-2021) implemented with financial support from the Global Fund for combating AIDS, tuberculosis and malaria. Technical support for the publication was provided by the Association for the Support of People Living with HIV – TOGETHER STRONGER Skopje as a partner in the regional project from the Republic of Northern Macedonia. The views expressed in the publication are the views of the publisher and may not reflect the views of the Global Fund or other organisations partners in the project. The Global Fund did not participate in the coordination and approval of the issued material.

CIP - Catalogue in publication
National and University Library "St. Constantine and Helena" Kliment Ohridski", Skopje

616.98:578.828.7]-084:613.88(497.7)(035)

CLINICAL GUIDELINE on the use of pre-exposure prophylaxis (PREP) for HIV in the context of sexual health in northern Macedonia.
- Skopje: Ministry of Health of the Republic of Northern Macedonia, 2021 - 30 pp. : tables ; 21 cm

Bibliography: p. 1. 27-30

ISBN 978-608-4518-61-7

a) AIDS -- Pre-exposure prophylaxis -- Sexual health -Macedonia -- Manuals

COBISS. MK-ID 55974917

Република Северна Македонија

Министерство за здравство

#SOS_PROJECT

ЗАЕДНО ПОСИЛНИ