Title:

Standard procedure for preventing the spread of HIV infection at risk population in the Slovak Republic: Evaluation and selection of patients for prophylaxis prior to HIV exposure

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According to § 45 par. 1 letter c) of Act 576/2004 Coll. on health care, services related to the provision of health care and on amendments to certain acts, as amended, the Ministry of Health of the Slovak Republic issues a standard procedure:

Standard procedure for the performance of prevention of the spread of HIV infection in the at-risk population in the Slovak Republic: Evaluation and selection of patients for prophylaxis prior to HIV exposure

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Keywords

prevention, prevention procedure, standard procedure for HIV infection, PrEP, population at risk

List of abbreviations and definitions

DXA	two-energy X-ray absorptiometry
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration

FTC	emtricitabine
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human immunodeficiency virus
IZA	Institute of Health Analyses
MSM	Men who have sex with men
MSW	Men who only have sex with women
MZSR	Ministry of Health of the Slovak Republic
Prep	Pre-exposure prophylaxis
SOP	Standard operating processes
SOP	Standard operating process
STI	sexually transmitted infection
SP	Standard procedure
TAF - FTC	tenofovir - alafenamide - emtricitabine
TDF - FTC	tenofovir - disoproxil fumarate - emtricitabine
PHA SR	Public Health Authority of the Slovak Republic
VZSaP	Department of Public Health, Screening and Prevention

Competence

The implementation of this standard procedure shall be the responsibility of:

- infectiologist, doctor of tropical medicine, doctor without specialization **(in training) for management in an infectology clinic,** - Nurse providing nursing care for an HIV patient **and those seeking consultation before and during the use of PrEP,**
- **other healthcare professionals** (including laboratory diagnostics, clinical microbiologist, nephrologist, clinical pharmacist, pharmacist) involved in individual medical and support (diagnostic and therapeutic and other) procedures;
- **a clinical psychologist in preparing** (and, if indicated, diagnosing before and during PrEP use) the patient/person – ruling out depression, clarifying the motivation for taking PrEP,
- **Social worker** – in field social work, streetwork and harm reduction.

Introduction

Globally, there are up to two million new HIV infections annually. Since there is no effective vaccine to prevent HIV transmission, behavioral and biomedical HIV prevention strategies are needed to reduce HIV acquisition (Maartens, 2014; Jones
2014; Grossman, 2016). For patients not infected with HIV, pre-exposure prophylaxis is

(PrEP) by using antiretroviral drugs in an evidence-based manner to prevent new infections in those at highest risk.

The goal of this standard procedure is to identify candidates for PrEP. Discussion of antiviral therapy for PrEP.

Other strategies for preventing HIV infection (e.g. antiretroviral therapy for HIV-infected patients, post-exposure prophylaxis for non-HIV patients, and male circumcision) are discussed elsewhere (see *Standard Practice for the Management of an Adult Patient with HIV Infection*). Also, this procedure does not mention the use of PrEP in adolescents, despite the FDA having this option approved. This is related to risks, behavioral and cultural specifics, which in this context still need to be treated in the territory of the Slovak Republic and in accordance with its legislation.

This prevention procedure was developed to guide health professionals who put PrEP prevention into practice and for those responsible for consultation, education, evaluation of the effectiveness of the National Programme against HIV and AIDS in the Slovak Republic and preparing behavioral and medical interventions for at-risk population groups in SR. SP procedure is methodologically prepared in the form ***of adoption*** according to the preventive/public health procedure for the performance of prevention, prepared by the Working Group on Management of HIV Infection Prevention in the WHO and most of the interventions come from the authors Krakow D. and Kenneth H.M. from the preventive procedure entitled: *Evaluation and selection of patients for prophylaxis prior to HIV exposure* published on 9. January 2020. The proposal passed the opposition of the Slovak Infectological Society.

Methodology and methodological approaches used to develop and evaluate this procedure

The methodological team evaluated the available procedures for the performance of prevention in this area with the AGREE II tool according to the unified methodology for creating procedures for the performance of prevention developed by the Ministry of Health of the Slovak Republic (2017). According to the critical evaluation, the above-cited preventive - clinical procedure was selected as suitable for the adoption method. The Slovak version of the adopted prevention procedure was evaluated by the AGREE II tool by members of the methodological team of the ŠDTP project and further evaluation was carried out by members of expert working groups (OPS) from representatives of the Slovak Infectological Society and representatives of public health.

PICO Public Health/Clinical Question: *Does PrEP use affect the incidence of new HIV infections in adults in individuals at increased risk and with reduced or no behavioral measures (safe sex practices)?* The panel's compilers and authors conducted a systematic review of the best available evidence according to the PICO classification. They then used a modification of the Recommendation Classification Method (GRADE) to assess the quality of available evidence, determine the strength of recommendations, and demonstrate the

relationship between evidence and recommendations. Disagreements were resolved through discussion and consensus.

The system of grading recommendations on the basis of weights of evidence in this procedure is as follows:

Category IA. It is highly recommended for implementation and strongly relies on well-designed experimental, clinical or epidemiological studies as well as systematic reviews.

Category IB. It is highly recommended for implementation and supported by some experimental, clinical or epidemiological studies and a strong theoretical a justification, or Accepted practice with limited evidence.

Category IC. It is required under state laws, regulations, rules, or standards.

Category II. Designed for implementation and supported by suggestive clinical or epidemiological studies or theoretical justification. This includes expert consensus on a given clinical/preventive issue.

Unresolved clinical or public/preventive question. It represents an unresolved issue in relation to prevention, for which there is insufficient evidence or there is no consensus on efficacy.

Epidemiological studies

Currently, there are no epidemiological studies in this area in the Slovak Republic. The introduction of monitoring is highly recommended *(Weight of Evidence Level, IA).*

Key Risk Assessment Recommendations for Choosing a Person for PrEP

For non-HIV patients who are at high risk of contracting HIV and are willing to adhere to prescribed medications, PrEP is very effective. Among adherents, PrEP can reduce the risk of HIV transmission by more than 90% (Andreson, 2012), although rare infections can still occur (Knox, 2017; Grossman, 2016; Hoornenborg, 2017).

The main option for PrEP in all patients is *tenofovir-disoproxil fumarate-emtricitabine* (TDF-FTC). For men who have sex with men (MSM) and transgender women at risk for sexual exposure to HIV, another option is *tenofovir-alafenamide-emtricitabine* (TAF-FTC). In order to determine who should receive PrEP and what drug should be used, physicians should assess the potential benefits and risks of treatment during the initial interview (the so-called consultation initial examination when applying for PrEP) (Table 1) (CDC, 2017; Marrazzo, 2014; WHO, 2014):

- A detailed history of sexual relations and drug use should be taken to determine if the patient is at high risk of developing HIV and therefore likely to benefit from taking PrEP (see below).
- The person seeking PreP should be screened for situations that could put the person at risk of developing PrEP-related adverse reactions (e.g., decreased kidney function and osteoporosis associated with TDF-FTC use, weight gain, and TAF-FTC-related

dyslipidemia). Other risks and benefits include the possibility of infection with hepatitis B virus and in women of pregnancy.

- It should also be ascertained if the person has potential barriers that would prevent him/her from adhering to a daily treatment regimen of taking PrEP. *(Weight of Evidence level, IA).*

Table 1: Patient evaluation prior to initiation of preexposure prophylaxis (PrEP) against HIV

Preventívne postupy	**Hodnotenie pacientov pred začatím preexpozičnej profylaxie (PrEP) proti HIV**
Pred začatím PrEP	
Určiť oprávnenosť iniciácie PrEP	
	Negatívne testy na HIV zdokumentujte bezprostredne pred začatím liečby PrEP.
	Test na akútnu infekciu HIV pomocou HIV RNA, ak má pacient príznaky zodpovedajúce akútnej infekcii HIV alebo bol v posledných štyroch týždňoch vystavený vysokému riziku.
	Na základe podrobnej anamnézy sexuálnych a drogových závislostí, a výsledkov testovania STI potvrďte, že u pacienta je vysoké resp. pretrvávajúce vysoké riziko vzniku infekcie HIV.
	Potvrďte, že vypočítaná odhadovaná rýchlosť glomerulárnej filtrácie je ≥30 ml / min / 1,73 m. ¶Δ
Ďalšie odporúčané testy na stanovenie rizík PrEP	
	Skríning HBV ◊ a HCV. §
	Získajte rozbor moču u pacientov s rizikovými faktormi pre ochorenie obličiek. ¥
	Vykonajte skenovanie DXA u pacientov s alebo s vysokým rizikom osteoporózy. ‡
	Vykonajte tehotenské testy u pacientok, ktoré by mohli otehotnieť.
Počiatočný liečebný režim PrEP	
	Predpíšte 1 tabletu TDF-FTC alebo TAF-FTC denne. Δ
	Všeobecne predpisujte maximálne 90-dennú zásobu obnoviteľnú až po potvrdení HIV, že pacient zostáva HIV negatívny (a má adherenciu).
	Poskytujte poradenstvo týkajúce sa kondómov a bezpečného pohlavného styku, † znižovania rizika a dodržiavania užívania PrEP.

DXA: dvojenergetická röntgenová absorpciometria; eGFR: odhadovaná rýchlosť glomerulárnej filtrácie; FTC: emtricitabín; HBV: vírus hepatitídy B; HCV: vírus hepatitídy C; HIV: vírus ľudskej imunodeficiencie; PrEP: pred-expozičná profylaxia; STI: sexuálne prenosná infekcia; TDF: tenofovir-dizoproxilfumarát; TAF: tenofovir alafenamid.

¶ Jednotlivci s eGFR <30 ml / min / 1,73 m 2 nie sú kandidátmi na PrEP s TDF-FTC alebo TAF-FTC. Jedinci s EGFR <60 ml / min / 1,73 m 2, nie sú kandidátmi pre PrEP s TDF-FTC.

Δ TDF-FTC je náš preferovaný režim pre väčšinu pacientov. TAF-FTC je alternatívna terapia pre PrEP pre mužov, ktorí majú sex s mužmi a transrodové ženy s ochorením obličiek a kostí. Ďalšie informácie o výbere režimu nájdete v téme, ktorá pojednáva o podaní PrEP.

◊ Ak je to možné, očkujte proti hepatitíde B. Ak je diagnostikovaná chronická HBV, môžu sa na liečbu chronickej HBV aj na prevenciu HIV použiť TDF-FTC alebo TAF-FTC; existuje však teoretické riziko, že prerušenie liečby môže viesť k vzplanutiu HBV. Pacienti s chronickou HBV by preto mali byť tiež odoslaní k špecialistovi so skúsenosťami v liečbe HBV.

§ Osoby, ktoré injekčne podávajú drogy, a muži, ktorí majú sex s mužmi, ktorí sa podieľajú na vysokorizikovom sexuálnom správaní, sú vystavení riziku infekcie HCV. Pacienti, ktorí majú pozitívny test, by mali byť odkázaní na liečbu.

¥ Medzi rizikové faktory pre ochorenie obličiek patrí hypertenzia, cukrovka, proteinúria a anamnéza renálnej insuficiencie.

‡ Pozrite si tému v rámci UpToDate, ktorá pojednáva o rizikových faktoroch pre osteoporózu.

† Okrem prevencie sexuálne prenosných infekcií je potrebné podporovať kondómy, kým sa nedosiahne adekvátna hladina tenofoviru v rektálnom a cervikovaginálnom tkanive (7 dní u pacientov s análnym sexom a 21 dní u žien s vnímavým vaginálnym sexom).

Populations known from other studies to be particularly limited in use and adherence to PrEP should be evaluated in particular detail while posing the highest risk of HIV infection (e.g., African Americans) (Laufer, 2015; Misra, 2017) *(Weight of Evidence level, IB).*

HIV Acquisition Risk Assessment

Before deciding to start PrEP, it is important to obtain a detailed history of sexual relations and drug use in order to evaluate a patient's risk for acquiring HIV (Mayer, 2016). The risk of acquiring HIV depends on the type of exposure (Table 2) (Weight of Evidence level, IA). A more detailed discussion of risk factors for HIV infection is discussed in various studies that are not part of this procedure.

Table 2*:* Estimated risk of HIV transmission by exposure situation

Preventívne postupy — **Odhadované riziko prenosu HIV podľa jednotlivých expozičných situácií**		
Cesta expozície		**Riziko na 10 000 expozícií infikovaným zdrojom (riziko)**
Prenos krvnou cestou	Krvná transfúzia	9000 (9/10)
	Injekčné užívanie drog - zdieľané ihly	67 (1/150)
	Perkutánna ihla	23 (1/435)
	Vystavenie sliznici krvi (napr. postriekanie do očí)	10 (1/1 000)
Sexuálne pôsobenie	Receptívny análny styk	138 (1/72)
	Zavádzací análny styk	11 (1/900)
	Receptívny pohlavný styk (penis – vagína)	8 (1/1250)
	Zavádzajúci penis-vaginálny styk	4 (1/2500)
	Styk typu: penis-orál	0-4
Iné	Hryzenie, pľuvanie, narábanie s telesnými tekutinami (vrátane semena a slín), zdieľanie sexuálnych hračiek	Zanedbateľné

O riziku expozície na jeden kontakt nie sú k dispozícii dostatočné empirické údaje. Táto tabuľka uvádza odhadované riziko podľa typu expozície pri absencii antiretrovírusovej liečby zdroja infikovaného HIV a pri absencii zosilňujúcich faktorov. Väčšina z týchto odhadov je odvodená z modelových štúdií rôznych kohort. Lekári si musia byť vedomí, že odhady sexuálneho rizika sú často založené na štúdiách monogamných párov, medzi ktorými boli facilitačné faktory a opakovaná expozícia môže poskytnúť zatiaľ nevysvetlenú ochranu pred infekciou. Použitie jednej premennej na posúdenie rizika prenosu HIV na základe spôsobu sexuálnej expozície neodráža variácie spojené s dôležitými kofaktormi. Boli identifikované aj rôzne facilitačné faktory a podmienky, a dá sa očakávať, že tieto faktory zvyšujú v praxi pravdepodobnosť prenosu.

Sexually risky behavior

Sexual history – To determine if a patient is at risk of acquiring HIV through sexual transmission, we recommend doctors evaluate sexually risky behaviors within the past six months. We obtain information regarding the patient's sexual behavior as well as HIV status and the risky behavior of the patient's sexual partners. This includes:

- If a person had a so-called penis - or so-called penis - vaginal intercourse without a condom with partners other than their permanent partner.

- If a person is in a monogamous relationship, he has HIV serostatus and a state of viral suppression of the partner.
- If a person has a history of drug use during sex (called chems).
- If the person has had any sexually transmitted infections (STIs).
- Number of sexual partners (Weight of Evidence level, IA).

It is important for the doctor to ask about the sexual behavior of a person with both a permanent (formal) partner and informal partners. Although some studies report a higher number of transmissions from informal partners, one study estimated that 68% of HIV transmission in men who have sex with men (MSM) comes from the main partner (Sulliva, 2009) (so-called open relationships) *(Weight of Evidence level, IA).*

When discussing the level of risk, it is also important to understand the context of various social and situational factors. Doctors and patients/individuals requesting PrEP can make more informed decisions if an individual's behavior patterns can be clarified. For example, a person discusses HIV status with their partners or has anonymous partners with unknown HIV status.

Some CS providers may not feel comfortable talking about detailed sexual history. For such doctors, an online or printed questionnaire can be prepared that can be used to be completed before meeting with a PrEP applicant (we recommend that at least one be part of local SOPs) to assist in HIV risk assessment.

STI screening – Patients considering PrEP should be screened for common bacterial STIs. While HIV-related risk behaviors are likely to be reliable and truthful, some patients may not be comfortable sharing sensitive information with a healthcare professional. Thus, the mere reliance on risk communication by the applicant alone may not be sufficient to make an informed decision to start PrEP treatment, and necessary additional risk indicators (e.g. syphilis, anogenital gonorrhea or chlamydia) that are highly associated with HIV acquisition must be taken into account *(Weight of Evidence Level, IA).*

STI screening should include serological tests for syphilis and nucleic acid amplification tests for gonorrhea and chlamydia from relevant mucous membranes (Table 3). STI testing should also be done in the absence of symptoms. A more detailed discussion of JTI testing can be found elsewhere (microbiological standard procedures).

Screening for bacterial vaginosis and trichomonads is not routinely done as part of an examination before starting PrEP treatment, as these infections did not have such a strong association with HIV in the evidence evaluation. However, their presence indicates that there has been recent unprotected sex, and this should lead the clinic to questions about the number of partners and their possible risks.

Table 3: Recommendations for STI screening by sex and population

Odporúčania pre skríning STI podľa pohlavia a populácie				
Rod	**Populácia**	**Rutinné odporúčanie pre skríning**	**Frekvencia skríningu**	**Ďalšie skríningové odporúčania a komentáre**
Žena	Vek <25 rokov	Genitálne chlamýdie	Ročne	Vyšetrite na výskyt syfilisu, trichomoniázy, HBV a HCV, ak má osoba zvýšené riziko. *
		Genitálna kvapavka	Ročne	
		HIV	Aspoň raz za 6 m	
	Vek ≥ 25 rokov	HIV	Aspoň raz za 6 m	Vyšetrenie kvapavky, chlamýdie, syfilisu, trichomoniázu, HBV a HCV - ak má osoba zvýšené riziko. *
	Tehotná	Genitálne chlamýdie	Prvý trimester (ak <25 rokov alebo so zvýšeným rizikom *)	Ak je zvýšené riziko, opakujte skríning týchto infekcií v treťom trimestri. Všetky tehotné ženy s rizikom infekcie HCV by mali byť vyšetrené pri prvej prenatálnej návšteve. Tehotné ženy infikované HIV sú pri prvej prenatálnej návšteve vyšetrené aj na trichomoniázu.
		Genitálna kvapavka	Prvý trimester (ak <25 rokov alebo so zvýšeným rizikom *)	
		Syfilis	Prvý trimester	
		HIV	Prvý trimester	
		HBV a HCV	Prvý trimester	
	Infikovaná HIV	Genitálne chlamýdie	Ročne	
		Genitálna kvapavka	Ročne	
		Genitálna trichomoniáza	Ročne	
		Syfilis	Ročne	
		HBV	Prvá návšteva	
		HCV	Prvá návšteva	

Muž	TKO neinfikovaný HIV	HIV	Aspoň raz	Ak je zvýšené riziko, urobte skríning na kvapavku, chlamýdie, syfilis, HBV a HCV. ¶ Cielený skríning na chlamýdie sa odporúča u adolescentov, najmä v nápravných zariadeniach ev. podľa odporúčania sociálneho pracovníka.
	HIV neinfikovaný MSM	Genitálne chlamýdie	Minimálne ročne	U osôb s rizikovými faktormi sa odporúča častejšie skríning (každé tri mesiace) na chlamýdie, kvapavku a syfilis. Môže byť tiež oprávnený častejší skríning na HIV a HCV. Δ
		Rektálne chlamýdie (ak sú vystavené)	Minimálne ročne	
		Genitálna kvapavka	Minimálne ročne	
		Rektálna kvapavka (ak je vystavená)	Minimálne ročne	
		Hltanová kvapavka (ak je vystavená)	Minimálne ročne	
		Syfilis	Minimálne ročne	
		HIV	Minimálne ročne	
		HAV	Prvá návšteva	
		HBV	Prvá návšteva	
		HCV	Aspoň raz	
	TKO infikovaným HIV	Genitálne chlamýdie	Ročne	
		Genitálna kvapavka	Ročne	
		Syfilis	Ročne	
		HBV	Prvá návšteva	
		HCV	Prvá návšteva	
	HIV infikovaným MSM	Genitálne chlamýdie	Minimálne ročne	U osôb s rizikovými faktormi sa odporúča častejšie skríning (každé tri mesiace) na chlamýdie, kvapavku a syfilis. Môže byť tiež oprávnený častejší skríning na HCV. Δ
		Rektálne chlamýdie (ak sú vystavené)	Minimálne ročne	
		Genitálna kvapavka	Minimálne ročne	
		Rektálna kvapavka (ak je vystavená)	Minimálne ročne	

		Hltanová kvapavka (ak je vystavená)	Minimálne ročne	
		Syfilis	Minimálne ročne	
		HAV	Prvá návšteva	
		HBV	Prvá návšteva	
		HCV	Minimálne ročne	

STI: sexuálne prenosná infekcia; HBV: vírus hepatitídy B; HCV: vírus hepatitídy C; MSW: muži, ktorí majú sex iba so ženami; MSM: muži, ktorí majú sex s mužmi; HAV: vírus hepatitídy A.

* Medzi zvýšené rizikové faktory pre kvapavku, chlamýdie a trichomoniázu u žien patrí predchádzajúca infekcia, najmä za posledných 24 mesiacov; viac sexuálnych partnerov za posledný rok; podozrenie, že nedávny partner mohol mať súbežných partnerov; nový sexuálny partner za posledné tri mesiace; výmena sexu za drogy alebo peniaze za posledný rok; a bývajú v oblasti vysokej prevalencie STI.

¶ Medzi zvýšené rizikové faktory pre kvapavku a chlamýdie v MSW patrí infekcia za posledných 24 mesiacov.

Δ Medzi rizikové faktory pre kvapavku, chlamýdie, syfilis a HIV medzi MSM patria viacerí alebo anonymní partneri; intravenózne užívanie drog; pohlavie v súvislosti s nezákonným užívaním drog vrátane metamfetamínov; a sexuálnych partnerov, ktorí sa venujú týmto aktivitám. Medzi zvýšené rizikové faktory pre infekciu hepatitídou C medzi MSM patrí infekcia HIV, vysoká prevalencia a incidencia HCV v komunite, vysokorizikové sexuálne správanie a sprievodná ulcerózna pohlavná choroba alebo proktitída súvisiaca so sexuálnou infekciou.

Behavior in drug use – to evaluate a patient's risk of acquiring HIV through parenteral and other drug use, doctors should ask about the history of drug use in the past six months (Smith, 2015).

Factors associated with increased risk include:

- Injecting use of heroin, cocaine or methamphetamine (Nerlander, 2018)
- Sharing of needles or preparation and application equipment
- Use of nonparenteral drugs during intercourse (especially methamphetamine), which may reduce the likelihood of using condoms (Halkitis, 2016) (***Weight of Evidence Level, IA).***

Treatment risk assessment

To assess the potential risks of tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) therapy, the HCP provider should assess previously undetected or acute HIV infection, decreased kidney function, chronic hepatitis B, C infection, osteoporosis, and pregnancy (*weight of evidence level, IA).*

HIV testing – all patients should undergo HIV serological tests before receiving PrEP to be sure they do not have an undiagnosed HIV infection (CDC, 2016; Marazzo, 2014)). HIV-infected patients should be treated with a combination antiretroviral regimen (see Standard Procedure for the Management of HIV Infection in an Adult Patient), which typically consists of 3 antiretroviral agents, and use of TDF-FTC or tenofovir-alafenamide-emtricitabine (TAF-FTC) for PrEP would put them at risk of developing resistance to treatment of the virus *(Weight of Evidence Level, IA).*

An advantageous HIV screening test is a 4th generation antigen/antibody test called RDTs (rapid diagnostic test) (***weight of evidence level, IA).***

A third-generation test is acceptable if a combined antigen-antibody test is not available, and clinical history indicates that acute HIV infection is unlikely ***(weight of evidence level, IB).***

Rapid tests that use oral fluid should not be used (CDC, 2020) (Weight of Evidence Level, IA). A detailed discussion of diagnosis is in the relevant SDTP for HIV.

Before starting PrEP therapy, additional HIV RNA tests should be performed on the following groups of patients (regardless of the outcome of a screening test using HIV antibodies):

- Patients who describe symptoms or on examination detect symptoms suggestive of acute HIV infection within the previous four weeks. Patients with acute HIV infection may have viral syndrome (e.g. lymphadenopathy, fever, malaise and/or maculopapular eruption) and may initially have detectable HIV RNA in the absence of HIV antibody and antigen.
- Patients with an indeterminate antigen or antibody test.
- Patients reporting high-risk exposure (e.g., recent sexual exposure to a partner with documented and untreated HIV infection) within four weeks of starting PrEP therapy, regardless of symptoms (*Weight of Evidence Level, IB).*

Kidney function – serum creatinine should be determined before starting treatment with PrEP. This informs the suitability of drug selection for PrEP. Individuals with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 are not candidates for PrEP with either TDF – FTC or FTC TAF. Individuals with an eGFR of <60 mL/min/1.73 m2 are not candidates for PrEP using TDF – FTC. The use of TDF versus TAF is discussed in detail below in Mode Selection *(Weight of Evidence Level, IA).*

In patients with eGFR> 60 ml/min/1.73 m ^{2} but with risk factors for renal disease (e.g. diabetes, hypertension, age > 40 years, nephrotoxic medicinal products), baseline urine analysis should be performed to evaluate the presence of proteinuria and glycosuria. Although the guidance panels do not recommend basic urinalysis, we find this information helpful in monitoring these patients for PrEP (Table 4) (Weight *of Evidence Level, II).*

Several clinical studies with PrEP have evaluated the risk of kidney damage with TDF-FTC (Grant, 2010; Baeten, 2012; Van Damme, 2012;, Grohskopf, 2013, Mugwanya, 2015; Yacov, 2016). In general, the risk of kidney damage is low in HIV-free patients taking TDF – FTC (Mugwanya, 2015; Yacov, 2016; Pilkington, 2018).

Some risk factors have been associated with deterioration of renal function, such as eGFR <90 mL/min/1.73 m2, and age greater than 40 [(Gandhi, 2016). In addition, higher concentrations of tenofovir have been associated with impaired renal function – but there is insufficient evidence to incorporate therapeutic drug level monitoring into routine care.

Table 4*:* Monitoring of patients during administration of pre-exposure prophylaxis (PrEP) against HIV

Preventívne postupy	**Monitorovanie pacientov počas podávania preexpozičnej profylaxie (PrEP) proti HIV**
Jeden mesiac po začatí PrEP:	
☐	Vyhodnoťte a podporte dodržiavanie (adherenciu) k režimu PrEP. *
☐	Posúďte rizikové správanie a poskytnite poradenstvo zamerané na zníženie rizika.
☐	Vyhodnoťte vedľajšie účinky.
Tri mesiace po zavedení PrEP:	
☐	Vyhodnoťte a podporte dodržiavanie (adherenciu) k režimu PrEP. *
☐	Vykonajte test na HIV. ¶
☐	Posúďte rizikové správanie a poskytnite poradenstvo zamerané na zníženie rizika.
☐	Skontrolujte sérový kreatinín u všetkých pacientov. Δ
☐	Vyšetrite STI u osôb s vysoko rizikovým sexuálnym správaním, aj keď je osoba bez príznakov. ym
☐	Vylúčte tehotenstvo u pacientok, ktoré by mohli otehotnieť. §
Následne každé tri mesiace ¥ :	
☐	Vyhodnoťte a podporte dodržiavanie (adherenciu) k režimu PrEP. *
☐	Vykonajte test na HIV. ¶
☐	Posúďte rizikové správanie a poskytnite poradenstvo zamerané na zníženie rizika.
☐	Monitorovať kreatinínu u pacientov s rizikom ochorenia obličiek, Δ ǂ všetky ostatné by mali mať skontrolovať kreatinínu každých šesť mesiacov
☐	Vyšetrite STI u osôb s vysoko rizikovým sexuálnym správaním, aj keď je osoba bez príznakov. ym
☐	Vylúčte tehotenstvo u pacientok, ktoré by mohli otehotnieť. §
Po ukončení režimu PrEP†, ** (z bezpečnostných dôvodov na žiadosť osoby/ pacienta):	
☐	Vykonajte test na zistenie, či došlo k infekcii HIV. ¶¶
☐	Ak má pacient chronickú infekciu HBV, malo by sa rozhodnutie o prechode na iné liečivo alebo o sledovaní vzplanutia HBV prekonzultovať s poskytovateľom ZS, ktorý má skúsenosti s liečbou HBV.

FTC: emtricitabine; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human virus immunodeficiency; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection; TDF: tenofovir - disoproxil fumarate.

* Compliance should be evaluated at each follow-up visit and more frequently if inconsistent compliance is detected.

¶ Patients should undergo HIV plasma tests, preferably a fourth-generation antigen/antibody test. If a patient has signs or symptoms suggestive of acute HIV infection, or has an indeterminate antigen/antibody test, further HIV RNA testing may be necessary. If HIV is positive, order and document the results of resistance testing and immediately contact HIV care. Dual treatment with TDF-FTC should not be continued. For more information on the clinical manifestations and diagnosis of acute HIV, see topics dealing with acute HIV infection.

Δ Interrupt Prep if glomerular filtration <60 ml/min/1.73 m2 or if there is evidence of moderate or severe proximal tubular dysfunction or Fanconi syndrome. For information on accessing patients who experience renal impairment with TDF - FTC treatment, see the topic that discusses PrEP administration.

◊ STI screening should include serum testing for syphilis and screening for gonorrhea and chlamydia on mucosal sites with potential risk (eg, throat, rectum, genitourinary). Read about STI screening under UpToDate.

§ PrEP can be used in pregnancy after an informed decision. For a more detailed discussion of PrEP during pregnancy, see the topic that discusses how to identify candidates for PrEP.

¥ In addition to routine monitoring, which is done at three-month intervals, HCV testing should be performed every 6 to 12 months for injectors and MSM who behave in high-risk ways.
‡ Risk factors for kidney disease include hypertension, diabetes, proteinuria and a history of renal insufficiency. In these patients, in addition to creatinine monitoring, we also receive urine analysis every six months. More frequent monitoring may be required in those who develop abnormal findings.
† We generally continue with PrEP for one month from the last high-risk exposure, unless PrEP is discontinued due to toxicity.
**Some patients may temporarily discontinue PrEP. It is important for clinicians to educate patients to restart PrEP before engaging in high-risk behavior. If a patient wishes to continue with PrEP, we repeat the same assessment as for those initiating PrEP for the first time. ¶¶ If HIV is negative, establish a connection with support services to reduce the risk as indicated.

Hepatitis B and C infection – individuals considering PrEP should undergo basic testing for hepatitis B virus (HBV) and hepatitis C virus (HCV).

- **Hepatitis B** infection – individuals should be screened for HBV infection before starting PrEP treatment. This includes testing for hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (anti-HBc) and hepatitis B surface antibodies (anti-HBs).
    - Persons with no signs of prior infection (i.e., Anti-HBs, anti-HBc, HBsAg-negative) should be vaccinated against HBV, as individuals who engage in high-risk sexual behavior and drug use are at increased risk of acquiring hepatitis B.
    - Individuals with a history of HBV (anti-HBs - and anti-HBc - positive) do not require vaccination, and no additional monitoring is required when starting PrEP therapy.
    - Patients with signs of chronic HBV infection (i.e., HBsAg positive) may still receive PrEP, but special consideration includes, however, the following areas:
        - in patients requiring antiviral therapy for HBV, TDF and TAF, they are considered first-line treatments. Thus, TDF or TAF can be used as part of a PrEP regimen and can also be used to treat chronic HBV.
        - For patients with chronic HBV who do not require treatment, the decision to use PrEP with TDF – FTC or TAF – FTC should be based primarily on an evaluation of patients' risks, benefits, and preferences of using PrEP as an HIV prevention strategy. If such patients choose to discontinue TDF - FTC or TAF - FTC
          (e.g., secondary to cost or side effects, or when PrEP is no longer needed), there is a theoretical risk that discontinuing treatment may lead to flare-ups of their HBV. Although data from the iPrEx study did not show flare-ups in six HBsAg-positive patients who discontinued TDF treatment, additional data will be useful in determining the relative risks and benefits of PrEP in this patient group (Solomon, 2016).
    - Some patients may only be positive for anti-HBc. This may mean that the patient has had or is recovering from an infection or has a low-level chronic

infection, which could also be a false positive test result. The approach to PrEP must be reviewed on a case-by-case basis.

- **Hepatitis C infection** – individuals who use injectable drugs and MSM who engage in high-risk sexual behaviors are at risk of transmitting HCV *infection (Weight of Evidence Level, IA).* Therefore, these patients should be tested for HCV as part of the initial laboratory test. Patients who test positive should be referred for treatment. It is important to note that certain drugs used to treat HCV (*ledipasvir – sofosbuvir*) may increase TDF levels, and patients taking these medications should be monitored for possible TDF toxicity (CDC, 2020).

Osteoporosis – you need to get information about your history (or risk factors) for osteoporosis because TDF has been associated with decreased bone density. Bone loss appears to be greatest during the first 6 months and then stabilizes (Mulligan, 2015; Thigpen, 2012) *(Weight of Evidence level, IA).* The presence of osteopenia or osteoporosis speaks of choosing the appropriate regimen for PreP - if only TDF - FTC is available, the risk of further bone loss must be compared with the risk of HIV infection. The need for routine bone density screening before starting PrEP is unclear *(weight of evidence level, unevaluated evidence).* It is recommended that basic X-ray absorption (DXA) be performed in patients with a history of osteoporosis if recent results are not available (not older than a year) as well as in patients at high risk of osteoporosis (*Weight of Evidence level, IB).*

The bone loss seen with TDF may pose additional risks in adolescents MSM that are not detected in adults (Havens, 2017). Importantly, in adolescents, bone loss appears to occur before maximum bone mass is reached (Mulligan,
2015). *(Weight of Evidence level, IB).*

There are no proven strategies to mitigate bone loss in patients taking PrEP. Vitamin D3 and calcium supplementation have been found to alleviate bone loss in HIV patients taking a TDF-based antiretroviral treatment regimen (Overton, 2015). While there is no data on the use of vitamin D to alleviate bone loss associated with PrEP, measures to maintain adequate vitamin D levels could theoretically be helpful (Havens, 2013) (Weight of Evidence *Level, Unevaluated Evidence).*

Pregnancy – Women of childbearing age should be given a pregnancy test *(Weight of Evidence Level, II) before starting PrEP treatment*. For pregnant women, the risk of acquiring HIV needs to be weighed against the risk of taking antiviral drugs during pregnancy and limited data on the effectiveness of PrEP during pregnancy.
In general, TDF and emtricitabine (both category B drugs of pregnancy) are considered safe for use in pregnancy. However, there are concerns about fetal bone development associated with the use of TDF. TAF and its safety during pregnancy is uncertain.

Evaluating PrEP Adherence
Potential barriers to adherence (e.g., depression, substance use, stigma) need to be identified and addressed (Taylor, 2017). There is a clear association between the effect of pre-exposure prophylaxis (PrEP) in reducing HIV transmission and adherence (Andreson, 2012; Grant,

2010, Amico, 2014). A relationship between adherence and efficacy of PrEP was found in all populations (e.g., high correlation is in groups: men who have sex with men, transgender women, heterosexual men, and women).

Categories of recommendations for the prevention of infections related to the prevention of the spread of HIV in the community with increased risk in the Slovak Republic

We generally use tenofovir – disoproxil fumarate – emtricitabine (TDF – FTC) as pre-exposure prophylaxis (PrEP) to non-HIV patients who are at high risk for HIV, have normal kidney function, and want to adhere to daily medication use and close monitoring at regular intervals. We offer TAF – FTC as another PrEP option for select patients who don't have vaginal intercourse. PrEP is generally not necessary in patients who consistently behave in a low-risk manner (e.g., consistent condom use during or vaginal intercourse, no mucosal exposure to genital secretions).

Special precautions for patients who have hepatitis B virus infection, osteoporosis or are pregnant are given above.

Adults – We recommend PrEP for the following groups of adult patients who are at high risk of contracting HIV based on clinical trial data demonstrating the effectiveness of PrEP in reducing the risk of acquiring HIV and for low risk of serious adverse events associated with TDF use – FTC and TAF – FTC:

- Men and women without HIV who have a sexual partner with HIV with a detectable viral load (not detectable). While PrEP can be considered in all non-HIV individuals who have a serodiscordant partner, there is a very low likelihood of transmission if the partner with HIV adheres to their antiretroviral treatment (ART) regimen and has a confirmed stable controlled HIV RNA plasma concentration (note: usually within six months after starting ART therapy). If the partner of the person requesting PrEP has recently started taking ART, it is possible that PrEP treatment will not need to be continued long-term. The duration of PrEP in this case is discussed elsewhere (standard PrEP administration procedure).
- Men who have sex with men (MSM) and transgender women who have sex with men if they have engaged in high-risk sexual behavior or had a documented bacterial sexually transmitted infection (STI) in the past six months (CDC, 2020). High-risk behaviors include sex without a condom with multiple or anonymous sexual partners (or main/stable partners with HIV risk factors).
- Heterosexually active men who have sex with a condom but with female partners from regions with a high incidence and prevalence of HIV epidemics (no known status of female partners). According to the World Health Organization (WHO), this refers to geographical areas or populations where HIV prevalence is ≥ 2% (Saag, 2018; WHO, 2016) *(weight of evidence level, II).*

Based on the recommendations, we recommend considering PrEP for the following groups as well:

- Heterosexual cisgender women and transsexuals who have been diagnosed with a bacterial STI in the last six months or who have had sex with men who are at high

risk of HIV infection (e.g. drug injectors, bisexual partners, partners from areas with high HIV prevalence).
- Drug injectors reporting needle and/or equipment sharing in the last six months.

Some individuals seeking PrEP may not always report high-risk behaviors, but they still crave PrEP. In these circumstances, doctors (and possibly psychologists or social workers) should try to better understand the patient's reasons for taking PrEP and mediate a consultation with him/her about the risks and benefits of taking PrEP. Patients who engage in high-risk behaviors may not be satisfied with the disclosure of this information. Thus, we usually provide PrEP in consultation (or a series of consultations with other professionals for example) if we have a medical belief that the potential risks and benefits of treatment are fully understood and there are no underlying health barriers or behavioral barriers that would influence the decision.

Patients transitioning from post-exposure prophylaxis – For non-HIV infected patients not taking PrEP, an antiretroviral regimen containing three drugs may be administered after potential exposure to HIV. This regimen is given for 28 days and is referred to as non-professional post-exposure prophylaxis (nPEP). Patients who repeatedly receive nPEP should be offered PrEP. For those who choose to switch from nPEP to PrEP, a repeat HIV test should be performed at the end of the 28-day course.

- The patient can switch from their nPEP regimen to TDF - FTC or TAF - FTC for PrEP, if HIV testing is negative, there is no concern for acute HIV, and there are no other contraindications for TDF-FTC or TAF-FTC.
- Conversely, nPEP should be continued until further evaluation if HIV infection is suspected (e.g. vague HIV test, signs of acute infection).

PrEP Administration

For individuals starting pre-exposure prophylaxis (PrEP), tenofovir - disoproxil fumarate - emtricitabine (TDF - FTC) or tenofovir - alafenamide - emtricitabine should be taken daily.

Alternative dosing schedules with TDF – The FTC may be an option for certain individuals who can reliably determine when they will have sex without a condom, even if the U.S. Food and Drug Administration has not approved PrEP dosages other than for daily use. This should be carefully considered and offered only to selected adherent patients.

Patients receiving PrEP should be informed of other risk reduction methods and should be monitored every three months (currently this is a condition for contributing PrEP in the UK) to ensure that there is no toxicity associated with PrEP use and that there is no evidence of developing HIV infection. Patients should continue with PrEP as long as the risk of infection persists. A detailed discussion of how to administer and monitor patients taking PrEP is outlined in a separate procedure for Taking PrEP against HIV infection.

Information for patients and those applying for PrEP

Each healthcare facility (outpatient clinic) consulting PrEP applicants along with the SOP will also develop an informed consent instruction.

Additional recommendations

The need to monitor indicators related to this procedure for the performance of prevention according to the subsequently developed common methodology for this procedure is necessary. It is necessary to carry out a regular biannual evaluation in cooperation with the National Health Insurance Agency and relevant actors for the control and prevention of sexually transmitted infections and blood stream obtained in cooperation with the PHA SR, relevant professional societies, the Department of ŠKP, Health Care, the Department of VZPaS and IZA MZSR. If it is necessary to adapt the methodology for this procedure, such a change shall be made immediately after the half-yearly inventory analysis has been completed.

Additional questions from patient management and stakeholders

Local procedures at the level of infectological workplace (outpatient clinic) providing consultations and care for persons at risk for acquiring HIV and persons using PreP in the form of standard operating processes (SOP) should be developed and regularly reviewed by the management of the health facility in cooperation with the Slovak Infectological Society and the Public Health Authority, or other relevant actors and, if necessary, other specialists and interdisciplinary staff involved in the management of persons on PreP and, where applicable, their partners with or without HIV. These elaborated or revised SOPs are sent centrally by the healthcare provider with a list of actors involved in the elaboration or revision of the SOP at least once a year to the Department of the Ministry of Health of the Slovak Republic. Subsequently, in cooperation with the National Commission responsible for the NPKIO, these local procedures are reviewed and either approved or recommended for revision by clinical audit and only subsequently registered.

Recommendations for further audit and revision of the standard

The first audit and revision of this standard procedure is planned after the 1st year and every 3 years thereafter, respectively in case of known new scientific evidence of more effective management or new knowledge, in the current unclear procedures, a revision is necessary as soon as there is a possibility of introducing this procedure into the public-health, preventive and health care system in the Slovak Republic. Clinical audit, patient safety tools (including detailed informed consent) will be added in Review 1.

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Note:

Where the clinical condition and the special circumstances require a different approach to prevention, diagnosis or treatment than that provided for in this standard procedure, an alternative procedure is also possible if further investigations, comorbidities or treatments are considered, that is to say an evidence-based approach or on the basis of clinical consultation or clinical panelling.

Such clinical practice shall be clearly recorded in the patient's medical file.

Efficiency

This standard procedure shall enter into force from 1 December 2020.

Marek Krajčí
Minister of Health SR