RAVIJUHEND

HIV INFECTION PRE-EXPOSURE AND FOLLOW-UP PREVENTION AND HIV-POSITIVE TREATMENT OF PERSONS

Estonian treatment guide

RJ-A / 40.1-2019

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Pre-exposure to HIV infection

and post-treatment prophylaxis and

treatment of HIV-positive individuals

Estonian treatment guide

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RJ-A / 40.1-2019

TARTU ÜLIKOOL

Eesti Haigekassa

The treatment guide has been prepared in accordance with the Estonian Handbook for the Preparation of Treatment Instructions (www.ravijuhend.ee)

Quality of scientific evidence (Balshem 2011) [1]

High	It can be very certain that the actual impact of the intervention is very close to the estimates made in the studies.
Moderate	It can be reasonably certain that the actual impact of an intervention is close to the estimates made in the studies, but it can also vary significantly.
Low	It is not possible to be sure in the assessments of the impact of the intervention, the actual impact may differ significantly from the assessments.
Very low	It is not possible to be sure at all in the assessments of the impact of the intervention, the actual impact is likely to be significantly different from the assessments.

Strength and direction of the recommendation (Guyatt 2008) [2]

Make a strong recommendation 	The strength of the recommendation reflects how confident it can be that the benefits of intervention outweigh the potential harms. The strength of the recommendation is determined by the following factors: - the magnitude of the difference between the desired and undesirable effects; - the quality of the scientific evidence; - the degree of variability in patient preferences; - cost of resources. A strong recommendation will be made if it is certain that the majority of well-informed patients would opt for this intervention. In the case of a weak recommendation, it is expected that the patient's attitude to the choice of intervention will depend on personal values and preferences. The doctor must be sure that they have been taken into account. A strong recommendation is expressed in the words "do, use", a weak recommendation in the words "can do, consider action".
Recommend rather do 	
Recommendation not to do 	
Strong advice not to do 	

Good practice guidelines

	The guideline contains guidelines based on the clinical experience of the members of the guideline team and that may be helpful in practice to achieve the best treatment outcome.

1 Balshem, H., Helfand, M., Schünemann, HJ, Oxman, AD, Kunz, R., Brozek, J., et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. April 2011; 64 (4): 401–6. Guyatt, GH, Oxman, AD, Vist, GE, Kunz, R.,

2 Falck-Ytter, Y., Alonso-Coello, P., et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. April 26, 2008; 336 (7650): 924–6.

Contents

Abbreviations

3TC	lamivudine, *lamivudine*
ABC	abacavir, *abacavir*
ARV / ARV treatment	antiretroviral therapy, *antiretroviral treatment - ART*
AZT or ZDV	zidovudine, zidovudine
ATV	atazanavir, *atazanavir*
ATV / r	atazanavir / ritonavir *atazanavir / ritonavir*
BIC	biktegravir, *bictegravir*
c	kobicistat, *cobicistat*
CI	confidence interval, *confidence interval*
CrI	confidence interval, *credibility interval*
CTx	C-terminal telopeptides, *C-terminal telopeptides - CTx*
d4T	stavudine, *stavudine*
DRV	darunavir, *darunavir*
DRV / r	darunavir / ritonavir, *darunavir / ritonavir*
DRV / c	darunavir / cobicistat, *darunavir / cobicistat*
DTG	dolutegravir, *dolutegravir*
EFV	efavirenz, *efavirenz*
EVG	elvitegravir, *elvitegravir*
EVG / c	elvitegravir / cobicistat, *elvitegravir / cobicistat*
FTC	emtricitabine, *emtricitabine*
HIV	human immunodeficiency virus, *human immunodeficiency virus*
HIV RNA	plasma levels of human immunodeficiency virus ribonucleic acid, *human immunodeficiency virus ribonucleic acid levels in blood plasma*
HBV	viral hepatitis B, *hepatitis B*
HCV	viral hepatitis C, *hepatitis C*
IDV / r	indinavir / ritonavir, *indinavir / ritonavir*
INSTI	integrase inhibitors, *integrase strand transfer inhibitor*
LPV	lopinavir, *lopinavir*
LPV / r	lopinavir / ritonavir, *lopinavir / ritonavir*
MSM	men having sex with men, *men having sex with men*
NNRTI	non-nucleoside reverse transcriptase inhibitors, *non-nucleoside reverse-transcriptase inhibitor*

NRTI	nucleoside reverse transcriptase inhibitors, *nucleoside reverse transcriptase inhibitor*
NSI	people injecting drugs *people who inject drugs - PWID*
NVP	nevirapine, *nevirapine*
OKR	directly controlled treatment, *directly observed treatment - DOT*
OR	odds ratio, *odds ratio*
PEP	post-exposure prophylaxis, *post-exposure prophylaxis*
PI	protease inhibitors, *protease inhibitors*
PrEP	pre-exposure prophylaxis, *pre-exposure prophylaxis*
r	ritonavir, *ritonavir*
RAL	raltegravir, *raltegravir*
RCT	randomized controlled trial, *randomized controlled trial*
RJNK	treatment guidelines council, *guideline advisory board*
RPV	rilpivirine, *rilpivirine*
RR	relative risk, *relative risk*
STLI	sexually transmitted infections, *sexually transmitted infections - STI*
TAF	tenofoviral phenamide, *tenofovir alafenamide*
TDF	tenofovir disoproxil, *tenofovir disoproxil*
VF	virological failure of treatment, *virological failure*
VL	number of virus copies, *viral load*
VMA	network meta-analysis, *network meta-analysis*
WHO	World Health Organization, *World Health Organization*
XTC	lamivudine or emtricitabine, *lamivudine or emtricitabine*

Definitions

adolopment	A method based on the GRADE methodology, in which the method is recommended by some existing treatment guidelines unchanged transposition, adaptation of the recommendation itself context and the formulation of a completely new recommendation.
AIDS	Acquired immune deficiency syndrome (*acquired immunodeficiency syndrome).* HIV destroys the immune system's CD4 cells, making the body susceptible to life-threatening and / or opportunistic infections. AIDS is the last stage of HIV infection, an immunodeficiency where the number of CD4 cells is usually less than 200 cells / mm 3.
Antiretroviral therapy (ARV treatment)	Treatment of human immunodeficiency virus (HIV) with drugs that prevent the virus from multiplying in the human body. The treatment regimen consists of a main component (or components) and an additional component.
CD4 cells	T lymphocytes include T helper cells, or T4 lymphocytes, which activate acquired immunity and assist other cells involved in immune protection. CD4 cell counts provide information about the state and ability of the immune system. CD4 cell counts should increase or remain high after initiation of ARV therapy.
Integrase inhibitors (INSTIs)	called HIV integrase, which prevent HIV from multiplying. A class of drugs used in the treatment of ARV that blocks an enzyme
Exposure prophylaxis with nofovir *prophylaxis, PrEP)*	disoproxil) with a significant risk of infection (*pre-exposure* By HIV-negative people to reduce and / or prevent The risk of HIV transmission. Preparations used in the treatment of ARVs (emtricitabine and
Post-exposure prophylaxis (*post-exposure prophylaxis, PEP)*	A 28-day course of ARV treatment, starting up to 72 hours after high-risk exposure (see Table 2) to reduce and / or avoid the risk of HIV transmission.
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	A class of drugs used to treat ARV that blocks an enzyme called HIV reverse transcriptase, which prevents HIV from multiplying.

Nucleoside reverse transcriptase inhibitors (NRTIs)	A class of drugs used to treat ARV that blocks an enzyme called HIV reverse transcriptase, which prevents HIV from multiplying.
Protease inhibitors (PIs)	A class of drugs used in the treatment of ARV that blocks an enzyme called HIV protease, preventing a new and immature virus from becoming a mature virus ready to be released that can infect other CD4 cells.
Stay on treatment	The success of HIV treatment depends on the following stages: diagnosing HIV, getting to a doctor, starting and staying on ARV treatment (including continuous and correct taking of ARVs, regular doctor and nurse appointments, and taking care of one's own physical and mental health)).
Consent to treatment	Take your medicine as directed by your doctor. Good adherence to treatment helps to achieve sustained suppression of the virus, reduces the risk of drug resistance and the risk of infection, and improves health and quality of life.
Recommendation transposition (*adoption)*	Transpose the recommendation unchanged from the existing treatment guide.
recommendation adjustment (*adaptation)*	Adapting an existing treatment guideline recommendation to your own context.
The virus suppression	A situation where ARV treatment reduces the reproduction of HIV to a level where the number of viral copies is below the laboratory limit. Suppression of the virus does not mean that a person is healthy. When ARV treatment is stopped, the virus starts to multiply again and the VL increases.
Number of viral copies	Number of HIVRNA copies per milliliter of blood. Before ARV treatment (VL) the sign is to slow the reproduction of HIV to a level where the number of copies of the virus is below the limit of laboratory detection.

Introduction

The need for a treatment guide

HIV is a chronic viral infection that leads to damage to the immune system.

HIV can be transmitted through sexual contact or direct contact with the blood of an infected person (including sharing syringes). The virus can also be passed from mother to child during pregnancy, childbirth or breastfeeding (1).

The main risk groups for HIV infection are injecting drug users (NSIs), people involved in prostitution and men who have sex with men (MSM). Heterosexual transmission must also be taken into account, and many infected people do not belong to any of the usual risk groups (2).

Today, it is not possible to cure HIV, the infected person always remains a carrier of the virus, but drugs can slow down the reproduction of the virus in the body. Combination antiretroviral therapy (ARV) with different active substances is used. With good adherence to treatment, the number of copies of the virus in a person's blood cannot be determined and is not infectious to others (treatment = prevention). As it is not possible to get rid of the virus, it is important to avoid becoming infected with HIV. The pharmacological option for this is post-exposure prophylaxis (PEP). In recent years, pre-exposure prophylaxis (PrEP) programs have also been successful, with people at high risk of infection taking ARVs to prevent infection.

HIV in Estonia

The first HIV-infected person was registered in Estonia in 1988 (3). The number of those infected increased significantly in 2000 in Ida-Virumaa, mostly among people who inject drugs.

In 2019, a total of 178 new cases of HIV infection were diagnosed in Estonia (4). Almost 70% of new cases of HIV infection are detected in men (3). The primary incidence of HIV infection in Estonia has not decreased significantly in recent years (4), and Estonia continues to be one of the countries in Europe with the highest incidence of HIV infection (5). Data on the possible cause of infection were

In 2018, there were 58% of cases, with 13% of new cases of injecting drug use, 37% of heterosexual infections and 6% of homosexual infections.

According to HIV reports, since 2010, 91% of HIV-positive people have seen an infectious disease doctor. Of all HIV-positive individuals, 67% are alive and have received treatment and 10% are alive but have not received treatment. As of the end of 2017, 79% (n = 4090) of living HIV-positive persons have had at least one HIV treatment visit. Involvement in HIV treatment in Estonia is most likely underestimated, as some people still living in Estonia have left Estonia (36).

HIV patients are exposed to professionals in many disciplines. In Estonia, there are no uniform criteria for the treatment and monitoring of HIV-positive persons and for pre- and post-exposure pharmacological prophylaxis to prevent HIV infection in at-risk groups.

Scope and target group of the treatment guide

The purpose of this guideline is to provide guidance on the choice of antiretroviral agents when initiating and modifying treatment in the event of treatment failure, patient monitoring, and PrEP and PEP.

The treatment guide is intended for use by all healthcare professionals. The treatment guide covers HIV-positive adults and those at risk. People at risk of HIV (IDUs); persons involved in prostitution; MSM; sexual partners of the aforesaid persons; persons who have had sexual contact with an HIV-positive person; healthcare and other workers who have had occupational exposure to potentially infectious body fluids; persons who have been sexually abused; persons who have received repeated transfusions of blood or blood components.

The following topics are not covered in the treatment guide:

- HIV testing algorithm in laboratories;
- treatment of co-infections with HIV infection (tuberculosis, viral hepatitis);
- Perinatal prophylaxis of HIV infection;
- ARV treatment of children.

Vaccination of HIV-positive individuals is not covered separately in this guide. As vaccination is an important issue in the treatment of an HIV-positive patient, the working group recommends referring to the following Health Board document: “Target groups of persons to be vaccinated outside the immunization plan and vaccines indicated for them” (2017). Vaccination recommendations of the expert committee of immunoprophylaxis of the Ministry of Social Affairs.

The recommendations of the treatment guide are based on the results of evidence-based studies and clinical practice. The treatment guide does not replace the individual responsibility of the healthcare professional to make the right treatment decisions based on the individual patient. Not all recommendations may apply to all patients. The package leaflet does not provide detailed information on the medicinal product, in practice the summary of product characteristics (www.ravimiamet.ee).

Key recommendations

Pre-exposure prophylaxis (PrEP)		
1		For people who are at significant risk of contracting HIV [a], recommend PrEP in addition to the usual preventive measures (condom use) to prevent infection. Strong positive recommendation, high degree of evidence
2		Perform a 1.2 Ag + Ab HIV test and other necessary tests before starting PrEP.
3		Before starting PrEP, assess the risk of HIV infection. For example, the following questions about the behavior of the last six months can be used: • how many times have you had sexual intercourse with men, women, or both? • how many men / women have you had sex with? • how many times have you had vaginal or anal intercourse where neither you nor your partner used a condom? • how many of your sexual partners were or could be HIV-positive? • if any of them were HIV-positive, how many times did you have vaginal or anal sex without using a condom?
4		Prescribing PrEP and monitoring the patient should only be performed by an infectious disease physician.
Post-exposure prophylaxis (PEP)		
5		In case of exposure, assess the risk of HIV transmission, perform the necessary tests and start PEP if indicated. Emergency patients should be referred to an infectious disease physician.
6		For people at risk of HIV infection, use the combination TDF / FTC + RAL, TDF / FTC + DRV / r (c) or TDF / FTC + DTG for post-exposure prophylaxis. Start prophylaxis as soon as possible, preferably within 72 hours of exposure. Prevention lasts 28 days. Strong positive recommendation, low level of evidence
Antiretroviral therapy (ARV)		
7		Use the combination of 2 NRTIs + INSTIs when initiating ARV therapy in HIV-positive individuals for the first time. Strong positive recommendation, moderate degree of proof

8		When prescribing ARV therapy, give preference to once daily therapy over multiple daily therapy. Strong positive recommendation, low level of evidence
9		There are no specific criteria for defining virological treatment failure. If HIV RNA is above the laboratory limit of detection but less than 200 copies / ml, evaluate for compliance, side effects and drug-drug interactions, and psychosocial problems. Generally, no change of treatment is required. If HIV RNA is repeatedly equal to or greater than 200 copies / ml, there is an increased risk of developing drug resistance, so determine resistance in addition to the above and consider switching treatment. Strong positive recommendation, very low level of evidence
10		If treatment fails, evaluate compliance, drug interactions and side effects, test for resistance if necessary, and change treatment as soon as possible.
11		If NNRTI-based treatment fails, change the treatment regimen to at least two, preferably three, active substances according to the results of the resistance test. Strong positive recommendation, moderate degree of proof
12		For HIV-positive individuals on ARV treatment with a persistently suppressed viral load, recommend a physician visit every 6 to 12 months and the drug to be dispensed every 3 to 6 months. Weak positive recommendation, very low level of evidence
13		In HIV-positive individuals who have achieved viral suppression with ARV therapy, test for HIV every 6 to 12 months. Weak positive recommendation, very low level of evidence
14		Use the following measures to improve adherence and adherence to treatment: • psychosocial and behavioral interventions (incl. case management, support person service, motivational interviewing, experiential counseling); • directly controlled pharmacological treatment (ARV, Tbc and addiction treatment, treatment of viral hepatitis) combined with psychosocial interventions. Strong positive recommendation, low level of evidence

[a] Significant risk is more common in men who have sex with men and in transgender and heterosexual men and women whose sexual partners are undiagnosed or untreated people with HIV infection. Individual risk varies based on a particular person's risk behavior and sexual partners.

Recommendations of the treatment guide with a brief summary of the evidence

Pre-exposure prophylaxis (PrEP)

PrEP is the use of ARVs (emtricitabine and tenofovir disoproxil) in HIV-negative individuals at significant risk of infection to reduce and / or prevent the risk of HIV infection (6).

The risk of infection is considered significant if the primary incidence of HIV without PrEP is more than 3 cases per 100 human years. There is a significant risk of infection in MSM, transgender and heterosexual men and women whose sexual partners are undiagnosed or untreated people with HIV infection. Individual risk varies depending on a person's risk behavior and sexual partners (6).

Due to the high price of medicines, PrEP has been difficult to obtain in Estonia, but due to the launch of generic medicines in the near future, a significant increase in the use of PrEP can be expected.

PrEP is only effective if the treatment regimen is followed. PrEP does not protect against other sexually transmitted infections.

The prophylaxis scheme includes TDF / FTC 300mg / 200mg once daily. It must be started seven days before the first exposure, it can be stopped seven days after the last exposure.

1		For people who are at significant risk of contracting HIV [a], recommend PrEP in addition to the usual preventive measures (condom use) to prevent infection. Strong positive recommendation, high degree of evidence

This clinical issue was addressed by the WHO (2016) [1] in the guide. In order to find newer evidence, an additional search was performed (01.01.2015–12.07.2019), during which the WHO systematic search was repeated. A further search revealed a systematic review and meta-analysis (7) involving 11 randomized controlled trials (RCTs). Eight of these overlapped with WHO sources and three were not included in the WHO meta-analysis (8-10). Mutua *et al. (* 2012) and McCormacki *et al. (* 2016) studies did not address outcome measures and / or comparisons of interest to us and were discarded. Molina *et al. (* 2015) results are described below (9).

1 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

The cost-effectiveness of PrEP in Estonia was addressed in the 2018 Health Technology Assessment Report “Cost-effectiveness of the use of antiretroviral drugs in HIV-negative individuals”.

A WHO systematic review and meta-analysis of tenofovir disoproxil (TDF) -containing PrEP regimens (11) has shown that PrEP is effective in reducing the risk of HIV infection in at-risk groups. A meta-analysis of 10 RCT results (n = 17,423 subjects) found that the use of PrEP reduced the relative risk of HIV infection (RR) by 51% compared to placebo (RR 0.49 [95% CI 0.33; 0.73]) (11).

In separate analyzes of patients with different adherence levels, patients with good adherence (detectable in more than 70% of cases) had an RR of 0.30 (95% CI 0.2; 0.45) compared to placebo. RR 0.55 (95% CI 0.39; 0.76) in the group (blood detectable in 40-70% of cases) and RR 0.95 in the poor adherence group (less than 40% detectable in the blood) (95% CI 0.74; 1.23). There was therefore no protection in the latter group. Therefore, it was concluded that the effectiveness of protection depends significantly on treatment adherence (11).

However, the effectiveness of protection did not depend on age, gender, or the drug used for PrEP (TDF alone or TDF with emtricitabine (FTC)) (11).

Risk groups: The effectiveness of PrEP was similar in different risk groups. The efficacy of PrEP in rectal transmission was assessed by four RCTs (n = 3166). The HIV infection in the RR PrEP group compared to the placebo group was 0.34 (95% CI
0.15; 0.80). The efficacy of PrEP in vaginal transmission was assessed by six RCTs (n = 14,252). RR infection in the PrEP group was 0.54 (95% CI 0.32; 0.90) compared to the placebo group. Parenteral exposure was not analyzed separately because NSIs were included in only one study (11).

Adverse reactions: Adverse reactions were assessed by ten RCTs (PrEP n = 9922, control group n = 7308). Adverse reactions occurred in 77.3% of subjects in the PrEP group and in 78.2% of subjects in the control group (RR 1.01 [95% CI 0.99; 1.03]) (11). Grade III and IV adverse reactions occurred in 13.3% of subjects in the PrEP group and 11.9% of subjects in the control group (RR 1.02 [95% CI 0.92; 1.13]) (11).

Resistance: The development of resistance in HIV-infected individuals starting with PrEP was assessed by four RCTs. Resistance was found in 28% of the PrEP group and 5.9% of the control group (RR 3.34 [95% CI 1.11; 10.06]). The development of resistance in people who became infected while taking PrEP was assessed by three RCTs. Resistance was found in 3.2% of the PrEP group and 1.7% of the control group (RR 2.27 [95% CI 0.48; 10.6]). The risk of developing a resistant infection was assessed by three RCTs (PrEP group n = 3612, control group n = 2637). Resisted infection was obtained in the PrEP group

0.14% and 0.08% of subjects in the control group (RR 1.74 [95% CI 0.36; 8.38]) (11).

Molina *et al. (* 2015) study compared the need-based use of PrEP with MSM (n = 400) with placebo. The risk of HIV infection was found to be lower in the PrEP group compared to the placebo group (RR 0.14 [95% CI 0.02; 0.60]) (9).

2		Perform a 1.2 Ag + Ab HIV test and other necessary tests before starting PrEP.
3		Before starting PrEP, assess the risk of HIV infection. For example, the following questions about the behavior of the last six months can be used: • how many times have you had sexual intercourse with men, women, or both? • how many men / women have you had sex with? • how many times have you had vaginal or anal intercourse where neither you nor your partner used a condom? • how many of your sexual partners were or could be HIV-positive? • if any of them were HIV-positive, how many times did you have vaginal or anal sex without using a condom?

The working group considered it important to assess risk behavior before starting PrEP. As there is currently no questionnaire in Estonian for this, general questions can be used to assess risk behavior (12). In addition to risk assessment, HIV 1,2 Ag + Ab testing and appropriate tests (CBC-5Diff, renal function, viral hepatitis, STIs) should be performed prior to initiating PrEP (see Appendix 1).

4		Prescribing PrEP and monitoring the patient should only be performed by an infectious disease physician.

The team considered that it is not necessary for PrEP to be started by an infectious disease doctor alone, but that the doctor initiating treatment must have a thorough knowledge of PrEP, previous examinations, counseling and follow-up. There is drug-resistant HIV in Estonia. Because the main components of the medicine used to prevent and treat HIV are the same, there is a risk that untreated HIV infection may occur if there is no strict control. The working group found that in the beginning one must be conservative in the Estonian context. One year after the wider availability of PrEP, a review and, if necessary, a reassessment of the specialties that may prescribe PrEP (eg urology, gynecology, doctors working in sexual health clinics) should be carried out. Doctors in these specialties must be provided with the necessary training.

Post-exposure prophylaxis (PEP)

PEP is the use of ARVs by individuals at risk of HIV infection to reduce and / or prevent the risk of HIV infection (6).

There is currently no national PEP program in Estonia. In the event of an accident at work, prevention in Estonia is compensated by the employer; in the case of sexual abuse, it is possible to obtain PEP from state-purchased stocks.

5		In case of exposure, assess the risk of HIV transmission, perform the necessary tests and start PEP if indicated. Emergency patients should be referred to an infectious disease physician.

The practical recommendation of the working group is to assess the risk of HIV transmission individually for each exposure case. The types of exposure for which post-exposure prophylaxis may be required are listed in Table 1. For all types of exposure, a person's HIV status should be determined and a hepatitis B and hepatitis C test performed prior to initiating prophylaxis. Hepatic and renal function should be assessed in all individuals initiating PEP. Following sexual exposure, individuals should be tested for sexually transmitted infections (STIs) and have hCG in their blood (13). Detailed information on pre-prophylaxis, the tests to be performed and the frequency of measurements can be found in Appendix 2. If possible, the person potentially transmitting the infection should be tested (13). If it is found to be HIV-negative, PEP may be discontinued.

Table 1. Need for post-exposure prophylaxis (14)

Types of exposure for which post-exposure prophylaxis may be required
• Parenteral or mucosal exposure (sexual contact, splashes in the eye, nose or mouth)
• Exposure to the following body fluids: blood, bloody saliva, breast milk, genital secretions and cerebrospinal fluid, fetal fluid, rectal discharge, peritoneal fluid, synovial fluid, pericardial fluid, pleural fluid
Types of exposure for which post-exposure prophylaxis is not required
• A person who has been exposed to HIV is HIV-positive
• A person who has potentially transmitted the infection has been identified as being HIV-negative
• Exposure to body fluids that do not pose a significant risk: tears, bloodless saliva, urine, sweat.

6		For people at risk of HIV infection, use the combination TDF / FTC + RAL, TDF / FTC + DRV / r (c) or TDF / FTC + DTG for post-exposure prophylaxis. Start prophylaxis as soon as possible, preferably within 72 hours of exposure. Prevention lasts 28 days. Strong positive recommendation, low level of evidence

The types of exposure at risk of HIV infection are listed in the table

2. In order to reduce and / or prevent the risk of HIV transmission, PEP should be initiated and those who initiate it should be referred to an infectious disease physician.

Table 2. HIV transmission risk assessments per exposure type (15)

Exposure type	Risk assessment of one per exposure (%)
blood transfusion	92.50 (95% CI 89.00; 96.10)
mother-to-child transmission	22.60 (95% CI 17.00; 29.00)
anal sex (host)	1.38 (95% CI 1.02; 1.86)
sharing a needle for injecting drugs with a needle	0.63 (95% CI 0.41; 0.92)
piercing the skin	0.23 (95% CI 0.00; 0.46)
anal sex (insertion)	0.11 (95% CI 0.04; 0.28)
vaginal intercourse (host)	0.08 (95% CI 0.06; 0.11)
vaginal intercourse (insertion)	0.04 (95% CI 0.01; 0.14)

The international guidelines on PEP do not address the need to start PEP, as this is standard practice. An additional search (01.01.2014–17.07.2019) was conducted to find studies on the effectiveness of PEP, which was limited to the last five years.

In strengthening the recommendation, the Working Party took into account that the use of PEP to reduce and / or prevent the risk of HIV transmission is common practice worldwide. The team found that because the duration of prophylaxis is less than one month and the risk of serious side effects was not significantly different from placebo, the benefits outweigh the potential benefits.

The first evidence of the efficacy of ARV drugs in humans as PEPs comes from a 1997 pilot study. The study showed that healthcare workers who had dermal exposure to HIV-positive human blood had a 81% (95% CI 48%; 94%) lower risk of developing HIV when they took zidovudine after exposure (16). Due to ethical considerations, it was not possible to perform RCTs to evaluate the efficacy of PEP. Subsequent evidence for the efficacy of PEP comes from animal or follow-up studies.

- Several descriptive follow-up studies with a very low level of evidence showed high efficacy of PEP. The studies evaluated the effectiveness of PEP in healthcare professionals after exposure to body fluids from HIV-positive or unknown individuals (17–21), after sexual contact (22–27), including MSM (25), and after sexual violence (28, 29).

- A systematic review and meta-analysis (n = 408) involving animal experiments demonstrated that primates receiving PEP had a significantly lower chance of seroconversion (OR 0.11 [95% CI 0.05; 0.23]). There was a significant association between time to PEP administration and HIV incidence (β coefficient <0.01 [95% CI <0.01; -0.01]; p = 0.03), a lower incidence of HIV was also observed among tenofovir users (β coefficient −0.23 [95% CI −0.42; –0.38]; p = 0.02) (30).

Evidence of the main component used in PEP comes from WHO (2016)[2] from the guide. The WHO decided not to update this clinical issue in the 2018 guideline because no significant new products had been added. Therefore, no further search was performed for the main components in this guide.

The WHO systematic review and meta-analysis included three RCTs. The results showed that HIV-positive subjects treated with TDF + lamivudine or emtricitabine (XTC) (n = 804) compared to subjects treated with zidovudine + lamivudine (AZT + 3TC) (n = 818), there was a significantly lower risk of discontinuation due to adverse reactions (RR 0.61 [95% CI 0.51; 0.72], I^2 0%) (31).

The WHO systematic review and meta-analysis that accompanied the four RCTs showed that TDF + FTC vs. placebo did not result in significantly more treatment discontinuation as pre-exposure prophylaxis (RR 1.30 [95% CI 0.97; 1.74], n = 9001). The proportion of serious adverse reactions or any adverse reactions was not significantly higher in the TDF + FTC group compared to placebo (serious adverse reactions: RR 0.99 [95% CI 0.84; 1.16], n = 8939, any adverse reactions: RR 1.01 [95% CI 1.00; 1.03], n = 9011). The TDF + FTC group had more nausea (RR 1.73 [95% CI 1.03; 2.89], n = 8939) and diarrhea (RR 1.13 [95% CI 0.97; 1.32], n = 8939). The proportion of creatinine elevations (level 1) was significantly higher in the TDF + FTC group compared to placebo (RR 1.39 [95% CI 1.05; 1.85], n = 8939) (32).

The WHO compiled a systematic review that included 15 follow-up studies of PEP (starting with a total of 1830 PEPs), of which 12 were AZT + 3TC and 3 were TDF + XTC. The study showed that the proportion of subjects who completed the full 28-day course was 56.6% (95% CI 50.9; 62.2%, τ^2

2 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

0.25). The rate of PEP discontinuation was 78.4% among subjects using the TDF-based regimen (95% CI 66.1; 90.7%) and 58.8% among those using the AZT-based regimen (95% CI 47.2; 70.4%). PEP discontinuation was addressed in 12 studies that showed a lower PEP discontinuation rate in the TDF + XTC group (0.3% [95% CI 0.0; 1.1%]) than in the AZT + 3TC group (3.2% [95% CI 1.5;
4.9%]). Discontinuation rates were highest for non-occupational exposure (65.6% [95% CI 55.6; 75.6%]) and lowest among victims of sexual violence (40.2% [95% CI 31.2; 49.2%]). The highest rate of treatment discontinuation was among MSM (67.2% [95% CI 59.5; 74.9%]) (33).

Evidence of preparations used in PEP comes from WHO (2018) [3] from the guide. The systematic search carried out by WHO (01.01.2018–31.05.2019) was additionally repeated, as a result of which the results of two more follow-up studies were included.

A systematic review by the WHO, including 11 follow-up studies and seven RCTs, showed that the rate of completion of the 28-day course of PEP varied by treatment regimen (AZT + XTC + efavirenz (EFV) 12.2%, ; 29.7%) to TDF
+ XTC + darunavir / ritonavir (DRV / r) 93.3% (95% CI 89.4; 97.2%). Schemes with a termination rate of more than 75% were TDF + XTC (71.6% [95% CI 53.6;

89.4%]), TDF + XTC + raltegravir (RAL) (75.1% [95% CI 55.4; 94.7%]), TDF
+ XTC + DRV / r (93.3% [95% CI 89.4; 97.2%]) and TDF + XTC + dolutegravir (DTG) (89.6% [95% CI 83.7; 95.5 %]). The proportion of subjects who discontinued PEP prematurely was lowest in TDF + XTC (0.7% [95% CI 0.0; 2.4%]), TDF + XTC + DRV / r (0.9% [95% CI 0, 0; 2.4%]) and TDF + XTC + DTG (1.4% [95% CI 0.9;

3.8%]) groups and the highest AZT + XTC + EFV (87.8% [95% CI 70.3; 100.0%]) group (34).

A multicenter follow-up study (n = 163) evaluated treatment discontinuation and adverse events in TDF + FTC + rilpivirine (RPV) subjects receiving PEP. 92% of the exposures were related to sexual intercourse and 8% were not. 56.7% of exposures related to sexual intercourse were among MSM, 61.5% of exposures related to asexual intercourse were related to work and 38.5% were not. 136 (86.1%) subjects completed a 28-day course of treatment. Of the 143 subjects who received PEP, 31 (21.7%) experienced nausea, 28 (19.6%) had diarrhea, 23 (16.1%) had abdominal pain, 9 (6.3%)) vomiting, 50 (35.0%) fatigue, 10 (7.0%) muscle and joint pain, 14 (9.8%) sleep disturbances, 13 (9.1%) dizziness, 16 (11.2%) had headaches (22).

3 World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO; 2018.

One follow-up study evaluated treatment compliance in individuals receiving PEP. It was found that 66.4% of the 1881 subjects receiving PEP completed a 28-day course of treatment. Higher compliance was higher in men (OR 2.28 [95% CI 1.83; 2.85], p <0.0001) and in MSM (OR 1.98 [95% CI 1.60; 2.44] , p <0.0001) and lower adherence to treatment in victims of sexual violence (OR 0.34 [95% CI 0.26; 0.45], p <0.0001). There was no difference in treatment between AZT + 3TC + indinavir / ritonavir (IDV / r) and stavudine (d4T) + 3TC + lopinavir / ritonavir (LPV / r) regimens (OR 0.89 [95% CI 0.68;

1.20) (35).

ARV treatment preparations

Initiation of ARV therapy is recommended for all HIV-positive individuals regardless of CD4 cell count. Treatment should be started as soon as possible after the diagnosis of HIV. The ARV drug classes available in Estonia are presented in Table 3 and the possible 2 NRTIs + INSTI treatment regimens in Table 4.

In Estonia, ARV treatment for all HIV-positive people is provided from the state budget and is offered in five hospitals (SATartu University Hospital, AS Lääne-Tallinn Central Hospital, Pärnu Hospital Foundation, Ida-Viru Central Hospital Foundation, Narva Hospital Foundation) and one private clinic (Linda HIV Foundation). . In Estonia, ARV treatment is prescribed and the health status of HIV-positive persons is monitored by infectious disease doctors.

Table 3. HIV drug classes available in Estonia and their representatives (37)

Drug class	Active substance (acronym)
nucleoside reverse transcriptase inhibitors (NRTIs)	abacavir (ABC), lamivudine (3TC), emtricitabine (FTC), zidovudine (AZT), tenofovir disoproxil (TDF)
non-nucleoside reverse transcriptase inhibitors (NNRTI)	rilpivirine (RPV), efavirenz (EFV)
integrase inhibitors (INSTI)	dolutegravir (DTG), raltegravir (RAL), elvitegravir (EVG)
protease inhibitors (PIs)	darunavir (DRV)

7		Use the combination of 2 NRTIs + INSTIs when initiating ARV therapy in HIV-positive individuals for the first time. Strong positive recommendation, moderate degree of proof

Table 4. 2 NRTIs + INSTI regimens

Treatment regimen and dosage	Notes
ABC / 3TC + DTG 600 mg / 300 mg + 50 mg once daily **ABC / 3TC / DTG** 600 mg / 300 mg / negative result only 50 mg once daily	• ABC: potential cardiovascular risk • use with caution in high cardiovascular risk (> 20%) • Need for HLA-B * 57: 01 testing, use • Exclude chronic before prescribing treatment Hepatitis B. • high resistance barrier
TAF / FTC 25 mg / 200 mg + DTG • TDF: Possible kidney and bone damage 50 mg once daily **or** **TDF / FTC** 300 mg / 200 mg + DTG 50 mg once daily **or** **TDF / 3TC** 300 mg / 300 mg + DTG 50 mg once daily	• Possible weight gain • high resistance barrier
TAF / FTC 25 mg / 200 mg once daily + RAL 1200 mg once daily or 400 mg twice daily **or** **TDF / FTC** 300 mg / 200 mg once daily + RAL 1200 mg one once daily or 400 mg twice • low resistance barrier per day **or** **TDF / 3TC** 300 mg / 300 mg once daily + RAL 1200 mg once daily or 400 mg twice daily	• TDF: possible kidney and bone damage • Dosage of RAL: possible 1200 mg one once daily or 400 mg twice daily (the latter for recommended for pregnant women, co-administration of antiepileptic and calcium, magnesium tuberculosis drugs, sium and iron
TAF / FTC / BIC 25 mg / 200 mg / 50 mg once daily	• high resistance barrier

Evidence for first-line ARVs was addressed by the WHO (2016)[4] in the guide. In order to find newer evidence, an additional search was performed (01.01.2014–21.10.2019), during which the WHO systematic search was repeated. An additional search revealed two RCTs, the results of which were included in the evidence review. The WHO updated the ARV first-line treatment certificate in 2019, adding only a comparison of DTG with EFV.

4 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

In formulating the recommendation, the working group took into account that in the Estonian context it is not reasonable to make a recommendation on the basis of one preparation. Therefore, comparisons between different products in the same class are not included in the review of evidence. In addition, in formulating the recommendation, the working group took into account the results of the University of Tartu Health Technology Assessment Report "Cost-effectiveness of the use of antiretroviral drugs in HIV-negative individuals".

The aim of the WHO Systematic Review and Network Meta-Analysis (VMA) (2015) was to compare 2 NRTIs + INSTI (DTG, RAL, EVG / c) and 2 NRTIs + EFV in first-line treatment in treatment-naïve patients. The study included 136 articles, which in turn described 76 RCTs (n = 35,270). Data from five studies that met the inclusion criteria were not included in any of the analyzes, so the data from this VMA are based on 71 studies. The WHO assessed the overall quality of the studies as good, with the most likely shift being due to the lack of blackout (38).

Virological suppression:

RAL had a higher odds ratio (OR) for virological suppression at week 48 (OR 1.40 [95% CrI 1.02; 1.96]) and week 96 (OR 1.44 [95% CrI 1.06; 1.95]).

Change in CD4 cell count:

The mean difference in CD4 cell count was greater for RAL compared to EFV at week 48 (20.1 [95% CrI 7.04; 33.11]) and week 96 (19.2 [95% CrI 3.30; 35.1]) and EVG / cl higher than EFV at week 48 (18.5 [95% CrI 1.27; 35.4]).

Mortality:

Mortality was not different for RAL compared to EFV (OR 1.75 [95% CrI 0.36; 7.00]) or for EVG / cl compared to EFV (1.40 [95% CrI 0.23; 8, 68]).

Presence of AIDS-defining disease:

The incidence of AIDS-defining disease did not differ in RAL compared to EFV (OR 0.93 [95% CrI 0.31; 3.02]), but had a significantly higher chance compared to EVG / cd EFV (OR 43.8 [95% CrI 1.55; 364.1]).

Discontinuation of treatment and discontinuation of treatment due to adverse reactions:

Discontinuation was lower for RAL compared to EFV (OR 0.68 [95% CrI 0.50; 0.92]), but did not differ between EVG / c EFV (OR 0.74 [95% CrI 0.50; 1.06]). Discontinuation due to adverse events was lower for RAL compared to EFV (OR 0.46 [95% CrI 0.25; 0.86), but did not differ between EVG / c and EFV (OR 0.69 [95% CrI 0.41; 1.17]).

Serious side effects during treatment:

The chance of serious adverse events during treatment did not differ between RAL and EFV (OR 0.98 [95% CrI 0.57; 1.74) or between EVG / c and EFV (OR 2.08 [95% CrI 0.28 ; 64.16]).

The aim of the WHO systematic review and the VMA (2019) was to compare the combinations of 2 NRTIs + DTG and 2 NRTIs + EFV in first-line treatment in treatment-naïve patients. It was accompanied by 151 articles, which in turn described 68 studies.

In general, the quality of the studies included in the WHO systematic review and the VMA (2019) was high and the risk of bias was low. The WHO pointed out that there were significant differences between the endpoints in the studies. For example, the gender structure of the studies included in the meta-analysis varied from women to men only. The mean CD4 cell count ranged from 102 cells / mm3 (PHIDISAII) to 576.5 cells / mm 3 (GSUS-236-0140). HIV RNA ranged from 4.28 log $_{10}$ (Epzicom-Truvada) to 5.48 log $_{10}$ (ADVANZ; new study). In addition, there were significant differences in risk groups and other indicators of disease severity.

The WHO highlighted the following shortcomings of the systematic review and the VMA: there is insufficient information to conclude on the effect of DTG on the occurrence of neural tube defects. As time goes on, the more likely it is that DTG will increase the risk of neural tube defects, but it is still possible that the risk will not occur. More information is needed on the effects of DTG on body weight, as the effects appear to be individual. There were few cases of some significant adverse outcomes (eg resistance, certain neuropsychiatric outcomes) that affect the accuracy of the assessment. Treatment-related adverse events were not reported consistently. There is no information on the safety of long-term use of DTG as the study follow-up is up to 144 weeks.

Virological suppression:

DTG was more effective than 600 mg EFV in achieving virological suppression at week 4 (OR 9.81 [95% CrI 7.83; 12.25]), week 12 (OR 4.14 [95% CrI 3, 36; 5.11]), week 24 (OR 1.83 [95% CrI 1.32; 2.56]), week 48 (OR 1.64 [95% CrI 1.35; 1.96]), Week 96 (OR 1.94 [95% CrI 1.48; 2.56]) and week 144 (OR 1.44 [95% CrI 1.08; 1.95]). DTG was more effective than 400 mg EFV in achieving virological suppression at week 4 (OR 11.93 [95% CrI 7.05; 20.55]), week 12 (OR 3.30 [95% CrI 2.40; 4.65]), week 48 (OR 1.36 [95% CrI 1.02; 1.80]) and At week 96, OR 2.03 (95% CrI 1.18; 3.45). There was no difference between EFV 400 mg and EFV 600 mg in achieving virological suppression Week 4 (OR 0.82 [95% CrI 0.45; 1.45]), Week 12 (OR 1.25 [95% CrI 0.85; 1.88]), week 24 (OR 1.49 [95% CrI 0.76; 2.91]), week 48 (OR 1.20 [95% CrI 0.90; 1.63]) and at week 96 (OR 0.95 [95% CrI 0.60; 1.54]). VMAOR is presented.

Change in CD4 cell count:

The mean difference in CD4 cell count was greater for DTG compared to 600 mg EFV at week 24 (28.30 [95% CrI 15.24; 41.00]), and at week 48 (32.95 [95% CrI 20.43; 45.94]) and week 96 (24.03 [95% CrI 4.45; 43.78]) and higher compared to DTG 400 mg EFV at week 24 (21.99 [95% CrI 7, 80; 35.51]) and at week 48 (17.27 [95% CI 2.05; 32.48]). Mean differences in CD4 cell counts are statistically significant but may not be clinically relevant. The mean difference in CD4 cell counts between 400 mg EFV and 600 mg EFV did not differ at week 24 (6.33 [95% CrI 6.43; 19.48]) and was greater in the EFV 400 mg group at week 48 (15.81 95% CrI 1.44; 30.26]) and at week 96 (26.73 [95% CrI 4.21; 49.58]). The average difference of the VMA is presented.

Discontinuation of treatment:

Compared to DTG 600 mg EFV, DTG had a lower chance of discontinuation (OR 0.58 [95% CrI 0.48; 0.70]), discontinuation due to adverse events (OR 0.30 [95 % CrI 0.19; 0.46]), treatment-related serious adverse reactions (OR 0.11 [95% CrI 0.02; 0.50]) and treatment-related adverse reactions (OR 0.51 [95% CrI 0.42 ; 0.61]). Compared to DTG 400 mg EFV, there was a lower chance of treatment-related adverse events (OR 0.69 [95% CI 0.53; 0.90]). Compared to 600 mg EFV compared to 600 mg EFV, there was a lower chance of discontinuation due to side effects (OR 0.42 [95% CrI 0.23; 0.42]) and treatment-related adverse reactions (OR 0.75 [95% CrI 0.59; 0.92]). The average difference of the VMA is presented.

Neuropsychiatric side effects:

Compared to DTG 600 mg EFV, there was a lower chance of dizziness (all grades) (OR 0.18 [95% CrI 0.10; 0.35]). The average difference of the VMA is presented.

Resistance developed during treatment:

Compared with DTG 600mg EFV, there was a lower chance of general resistance (OR 0.13 [95% CrI 0.03; 0.60]), resistance to the main component drug (OR 0.13 [95% CrI 0.04; 0.48]) and NRTI resistance (OR 0.14 [95% CrI 0.04; 0.59]). Compared to DTG with EFV 400 mg, there was a lower chance of general resistance (OR 0.00 [95% CrI 0.00; 0.16]), resistance to the main component drug (OR 0.10 [95% CrI 0.02; 0.42]) and NRTI resistance (OR 0.00 [95% CrI 0.00; 0.024]). The odds ratio compared to 400 mg EFV versus 600 mg EFV was higher for overall resistance (OR 46.30 [95% CrI 0.59; 931.74]) and NRTI resistance (OR 262.3 [95% CrI 4.14; 9471.99]).

Viral suppression during childbirth

Viral suppression during childbirth (*rate difference)* were better among DGT users compared to EFV, LPV / r, atazanavir / ritonavir (ATV / r) and nevirapine (NVP), regardless of whether women who were exposed after pregnancy were compared (DTG vs. EFV 210 1000 per [95% CrI 141; 274], DTG vs. LPV / r 381 per 1000 [95% CrI 240; 521], DTG vs. ATV / r 312 per 1000 [95% CrI 124; 517], DTG vs. NVP 446 per 1000 [95% CrI 287; 599]), or both before and after pregnancy (DTG vs. EFV 210 per 1000 [95% CrI 141; 274] DTG vs. LPV / r 381 per 1000 [95% CrI 246 ; 529]) DTG vs. ATV / r per 310,000 [95% CrI 126; 519], DTG vs. NVP 447 per 1000 [95% CrI 286; 601]).

Difference in the risk of neural tube defects

The risk of prevalence of neural tube defects differed in the DTG group compared to the EFV group (Tsepamo 01.05.2018 0.89% [95% CI 0.31; 2.34], Tsepamo 31.03.2019 0.26% [95% CI 0.05; 0.66], Tsepamo + Botswana MoH / CDC 0.29% [95% CI 0.1; 0.68]), with a group of other ARV drugs (Tsepamo 01.05.2018 0.82% [95% CI 0.24 ; 2.27], Tsepamo 31.03.2019 0.2% [95% CI 0.01; 0.59], Tsepamo + Botswana MoH / CDC 0.23% [95% CI 0.04; 0.61]) or children of HIV - negative women (Tsepamo 01.05.2018 0.85% [95% CI 0.27; 2.3], Tsepamo 31.03.2019 0.22% [95% CI 0.05; 0.62], Tsepamo + Botswana MoH / CDC 0.25% [95% CI 0.07; 0.63]).

The chances of other negative births, preterm birth, low birth weight gestational age, and neonatal mortality were not higher in the DTG group.

The WHO systematic review and the VMA (2016) analyzed ARV toxicity separately. The study included 71 studies (126 research articles), for a total of 34,032 patients. The study compared different regimens based on the main component of NRTIs (39).

DTG versus EFV (OR 0.26 [95% CrI 0.14; 0.47]) and RAL versus EFV (OR 0.46 [95% CrI 0.24; 0.86]) had a significantly lower chance of stopping treatment due to side effects.

RAL, DTG and EVG / c did not cause significantly more severe treatment-related adverse reactions than other drugs (EFV, LPV / r, ATV / r, DRV / r, NVP, EFV 400, RPV).

Mortality and serious adverse reactions: The use of INSTIs does not increase mortality and treatment does not result in more serious side effects than other drugs (EFV and protease inhibitors, PIs). The exception is DRV / r, which caused less severe adverse reactions compared to RAL (OR 0.67 [95% CrI 0.42; 0.96]).

Treatment-related side effects: RAL and EVG / c cause fewer adverse reactions compared to EFV (RALOR 0.39 [95% CrI 0.22; 0.72], EVG / c OR 0.50 [95% CrI 0.26; 0.72]) .

Discontinuations and interruptions associated with side effects: DTG (OR 0.47 [95% CI 0.28; 0.78]) and RAL (OR 0.70 [95% CI 0.48; 0.99]) were associated with fewer treatment interruptions than EFV. The number of PI / ri treatment interruptions was comparable to RAL.

Renal impairment: At week 48 of treatment, EVGF / c and RAL had lower eGFR than ATV / ri and EFV. Creatinine clearance was lower for DTG and RAL than for EFV and all PIs / rs. The use of INSTIs increased serum creatinine levels more than non-INSTI regimens.

Bone density: RAL decreased bone density less than EFV (MD 1.62% [95% CrI 0.33; 2.99]).

Hepatotoxicity: There were no statistically significant differences between INSTI-containing and INSTI-free regimens.

Dyslipidemia: INSTI did not cause more dyslipidaemia than other HIV medicines.

Hypersensitivity reactions, rash, depression: INSTIs did not have differences with other HIV medicines, but the quality and number of studies may be too low to draw conclusions.

Other side effects: There are insufficient data to draw conclusions between Steven-Johnson syndrome, rhabdomyolysis, hepategaly and steatosis, glucosuria, albuminuria, Fanconi syndrome and INSTIs. Isolated case reports of raltegravir and lactic acidosis have been published.

An additional search (01.01.2014–09.10.2019), which repeated the WHO systematic search, also found four RCTs and one systematic review and VMA, which reported adverse reactions to ARVs and related outcome measures. The results of the studies found are described below.

Discontinuations associated with adverse reactions: The VMA showed that those treated with DTG
There are significantly fewer treatment interruptions associated with adverse events in patients compared to ATV / r, LPV / r and EFV. DTG did not show a significant difference in treatment discontinuation associated with adverse events compared to other ARVs (DRV / r, RPV, RAL, EVG / c, biktegravir (BIC)) (40). In the WAVES study, women in the TDF / FTC / EVG / c group had significantly fewer treatment-related treatment interruptions than the TDF / FTC / ATV / r group (41). In the ADVANCE study, there were significantly fewer treatment-related discontinuations in the DTG group than in the EFV group (42).

Side effects (of any severity): The VMA found that DTG and other
there was no significant difference between the drugs in the incidence of any serious adverse events, except for DTG compared to LPV / r, where DTG had significantly fewer adverse events (OR 0.33 [95% CrI 0.14; 0.73]).

Changes in bone metabolism: Tebas *et al. (* 2015) showed that in the EFV / FTC / TDF group, serum concentrations of the bone metabolic marker C-terminal telopeptides (CTx) used to assess bone resorption intensity were significantly higher at week 144 than in the DTG / ABC / 3TC group (change from baseline). 39% vs. 25%, p <0.002) (43). In the WAVES cohort, women in the TDF + FTC + ATV / r group were found to have significantly higher CTx elevations at week 48 than in the TDF + FTC + EVG / c group (41).

Weight gain: DTG had higher weight gain than EFV (42, 44).

Bone density of the spine: No differences were found in the change in vertebral bone density between the INSTI- and PI-containing groups (41). There was a difference between groups compared to EFV with DTG, but it was rather associated with a difference in the main component of NRTIs (42).

One-tablet-per-day regimen

The effectiveness of ARV treatment is highly dependent on adherence (45). Several solutions have been proposed to improve adherence, such as a once-a-day regimen or a fixed-dose once-a-day regimen. A fixed-dose one-tablet-daily regimen helps to reduce the risk of error and to avoid a situation where only one ARV treatment is taken. On the other hand, a fixed-dose one-tablet-daily regimen limits the ability to change only one drug in the regimen or to change the dose of only one drug (46).

8		When prescribing ARV therapy, give preference to once daily therapy over multiple daily therapy. Strong positive recommendation, low level of evidence

This clinical issue was addressed by the WHO (2016)[5] two systematic reviews and a meta-analysis in the guide (47,48). During the additional search (01.01.2013–26.05.2019), the WHO systematic search was repeated. One systematic review and meta-analysis was found, the results of which are described below.

5 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

In formulating the recommendation, the Working Party considered that the evidence for the efficacy of a fixed-dose single-tablet-daily regimen is unclear. Taking medicines once a day is better than taking medicines twice a day in terms of compliance. It is possible that adherence to treatment does not differ between a once-tablet-daily and a once-a-day-multiple-tablet regimen. In increasing the strength of the recommendation, it was considered that the effectiveness of ARV treatment is significantly related to treatment adherence. Poor adherence to treatment can lead to treatment failure and the development of resistance, and therefore the benefits of a once-a-day regimen outweigh the potential harms.

A systematic review and meta-analysis involving four RCTs (n = 806 subjects) evaluated the effect of a fixed dose (one tablet per day or combination of at least two agents) on achieving virological suppression compared to regimens involving multiple tablets, regardless of dosing frequency. Patients receiving a fixed dose tended to achieve virological suppression (RR 1.04 [95% CI 0.98; 1.10]) (48).

A systematic review and meta-analysis involving five RCTs (n = 873 subjects) evaluated the effect of a fixed dose on adherence compared to regimens that included more tablets. Patients receiving a fixed dose showed a trend towards better adherence (RR 1.10 [95% CI 0.98; 1.22]) (48).

A systematic review and meta-analysis based on six RCTs involving 2,582 patients evaluated the effect of a one-tablet-daily regimen on the achievement of virological suppression in treatment-naïve patients. There was no statistically significant difference between patients on the one-tablet-per-day and two-tablet-per-day regimens (RR
1.01 [95% CI 0.94; 1.09]) (47).

A systematic review and meta-analysis based on seven RCTs included 3,069 patients and evaluated the effect of a one-tablet-daily regimen on treatment compliance in naïve patients. Patients on the one-tablet-per-day regimen were found to have better compliance than patients on the two-tablet-per-day regimen (weighted mean difference 3.94% [95% CI 1.42; 6.47]) (47).

The systematic review and meta-analysis found as a result of the additional search included six RCTs (n = 2997 people). Patients on a one-tablet-per-day regimen were found to be more likely to achieve virological suppression (viral load <50 copies / ml at week 48) than patients on a more tablet-per-day regimen (RR
1.053 [95% CI 1.019; 1,087]).

ARV treatment failure

There are no uniform international criteria for defining virological treatment failure (VF) (49). In clinical trials, a viral load (VL) of 40 to 50 copies / ml, 200 copies / ml

ml, 400 copies / ml and 500 copies / ml (49).

9		There are no specific criteria for defining virological treatment failure. If HIV RNA is above the laboratory limit of detection but less than 200 copies / ml, evaluate for compliance, side effects and drug-drug interactions, and psychosocial problems. Generally, no change of treatment is required. If HIV RNA is repeatedly equal to or greater than 200 copies / ml, there is an increased risk of developing drug resistance, so determine resistance in addition to the above and consider switching treatment. Strong positive recommendation, very low level of evidence

WHO (2013) [1] The guideline recommended the use of VL> 1000 copies / ml to define VF, based on statistical modeling. WHO (2016) [2] The recommendation was not updated in the guide, as most of the techniques for determining VL have good accuracy at the above level. To support a systematic literature search, treatment guidelines for HIV treatment were mapped. In addition to WHO (2013) [6] and WHO (2016) [7] guidelines covered the VF EACS (2018) [8], DHHS (2018) [9] and BHIVA (2019) [10] instructions. In order to find evidence of VF, the secretariat of this treatment guide performed a systematic literature search (01.01.2014–15.08.2019).

The very low level of evidence is due to the type of studies (follow-up studies). The Working Party considered it important to point out that in case of suspicion of treatment failure, compliance with treatment should be assessed first and, if necessary, interventions to improve compliance should be implemented. When increasing the strength of the recommendation, it was considered that repeatedly measured HIVRNA ≥ 200 copies / ml significantly increases the risk of drug resistance and the risk of infection. Therefore, the expected results of the recommended interventions (determination of resistance and change of treatment if necessary) outweigh the adverse effects.

6 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for the treatment and prevention of HIV infection. WHO; 2013.

7 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for the treatment and prevention of HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

8 European AIDS Clinical Society. European Guidelines for the Treatment of HIV-Positive Adults in Europe 2018. EACS; 2018.

9 Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. DHHS; 2018.

10 British HIV Association. BHIVA guidelines on the routine investigation and monitoring of HIV-1-positive adults (2019 interim update). BHIVA; 2019.

A follow-up follow-up study in a Spanish tertiary hospital analyzed the effect of low viremia (LLV) on VF in HIV-positive adults receiving ARV therapy who had been on ARV therapy for at least six months and had a VL <25 copies / ml in the past. now LLV (VL 25-1000 copies / ml) was present. The risk of VF compared to controls was 25-50 copies / ml in the RR group 2.68 (95% CI 0.64; 11.2, p> 0.05), 51-200 copies / ml in the RR group 2.51 (95% CI % CI 0.51, 12.4, p

> 0.05) and> 200 copies / ml in the RR group 73.9 (95% CI 21.4; 255.3, p <0.001) (50).

Another longitudinal cohort study evaluated the effect of persistent HIV viremia on VF (n = 1860). The adjusted hazard ratio (HR) to VF for six months of LLV compared to the indeterminate VL group was 50–199 copies / ml in the HR group 2.22 (95% CI 1.60; 3.09, p <0.001), 200– 499 copies / ml in the HR 2.15 group (95% CI 1.46; 3.17, p <0.001), 500-999 copies / ml in the HR group 4.85 (95% CI 3.16;
7.45, p <0.001). The adjusted HR for VF for nine-month LLV was HR 2.32 (95% CI) in the 50-199 copies / ml group compared to the indeterminate VL group.
1.57; 3.42, p <0.001), 200-499 copies / ml in the HR 2.18 group (95% CI 1.37; 3.47, p = 0.001), 500-999 copies / ml in the HR 4.70 group (95 % CI 2.54; 8.71, p <0.001). The adjusted HRVF for 12-month LLV compared to the indeterminate VL group was 50 to 199 copies / ml in the HR group 1.90 (95% CI 1.16; 3.11, p = 0.011), 200 to 499 copies / ml in the group HR 1.60 (95% CI 0.81; 3.14, p = 0.174), 500-999 copies / ml in the HR 4.16 group (95% CI 1.68; 10.29, p = 0.002) (51).

A retrospective (2000–2011) pilot study analyzed the persistent LLV effects of subjects in the Swiss HIV cohort study. In the permanent LLV group, 107 (60%) of the 179 subjects had follow-up data for up to 24 weeks and 179 subjects had 155 (87%) follow-up data for up to 48 weeks. At study week 48, 102 of the 155 subjects (66%) continued to have persistent LLV. 19 of 155 subjects (12%) had developed VF and 34 (22%) had VL below the detection limit. None of the subjects with persistent very low viremia (VLLV; defined as VL 21-49 copies / ml) (n = 26) failed within 48 weeks. In subjects with VL between 50 and 200 copies / ml (n = 93) and with VL between 201 and 400 copies / ml (n = 36), 12% and 22% failed treatment up to 48 weeks after the last VL, respectively. setting.

Week 24 follow-up information was available for 42 (82%) of the 51 subjects and 48-week information was available for 39 (76%) of the 51 subjects. By week 24, 30 of 42 subjects (71%) had VL <20 copies / ml, compared with 28 of 86 subjects (33%) with no change in ARV treatment (p <0.001). VF occurred in two of 42 subjects (5%) after switching from ARV treatment and in 10 of 86 subjects (12%) who remained on the same ARV treatment (p =
0.3). By week 48, 29 of 39 subjects (74%) on ARV treatment had VL <20 copies / ml. However, in 19 of the 74 subjects (26%), ARV treatment remained the same (p <0.001). VF was not present in any of the 39 subjects treated with the modified treatment (0%). VF occurred in 7 of 9 subjects (9%) whose treatment was unchanged (p = 0.09) (52).

A follow-up cohort study that included data from 18 cohorts from Europe and North America analyzed the effect of LLV on treatment failure. Of the 17,902 subjects included in the analysis, 624 (3.5%) had LLV 50–199 and 482 (2.7%) had LLV 200–499. LLV 200–499 increased the risk for VF (HR 3.97 [95% CI 3.05; 5.17]) (53).

ARV treatment preparations in case of treatment failure

Repeated exposure to HIV RNA of ≥ 200 copies / ml increases the risk of developing drug resistance. In case of treatment failure, adherence to treatment and drug interactions and side effects should be assessed. If necessary, resistance tests should be performed which are more likely to succeed at higher viral loads.

10		If treatment fails, evaluate compliance, drug interactions and side effects, test for resistance if necessary, and change treatment as soon as possible.
11		If NNRTI-based treatment fails, change the treatment regimen to at least two, preferably three, active substances according to the results of the resistance test. Strong positive recommendation, moderate degree of proof

The WHO's aim has been to harmonize the use of first-, second- and third-line medicines in all sections of the population by recommending treatment regimens that are suitable for adults, children, pregnant women and people with co-infections.

The team found that one of the main causes of treatment failure is poor adherence, so it is very important to assess adherence and interventions to improve it. The WHO does not recommend a resistance test because it is expensive and not available in most countries. This is not important in the Estonian context. If a regimen needs to be changed, this should be done as soon as possible. The team found that in the event of failure of previous treatment, any drug may be included in the regimen when prescribing a new ARV. Therefore, it is not possible to formulate an active substance-based recommendation.

A systematic review and meta-analysis by WHO (2019) included 20 articles that in turn described six RCTs (2 LADY / ANRS / EDCTP, NCT00928187; DAWNING, NCT02227238; EARNEST, NCT00988039; HIVSTAR, NCT00627055; SEL00-LINE, NCT0000) and one cohort study (Laker *et al.* 2014), involving 3877 patients. Compared to the previous systematic review, two studies were excluded because they used drugs that are no longer considered acceptable (mainly saquinavir and indinavir). Taking into account the research question, complete publications and articles of DAWNING (NCT02227238) evaluating body weight results were added (54, 55).

Virus suppression:

The combination of DTG + 2 NRTIs was more effective at achieving virological suppression at week 4 (OR 6.36 [95% CrI 4.50; 9.13]) compared to the combination of LPV / r + 2 NRTIs, and at week 12 OR (4 , 30 [95% CrI 3.06; 6.09]), week 24 (OR 2.12 [95% CrI 1.46; 3.10]) and week 48 (OR 2.18 [95% CrI 1; 49; 3.22]). The combination of DTG + 2 NRTIs was more effective in achieving virologic suppression at week 12 (OR 1.96 [95% CrI 1.27; 2.94]) and week 48 (OR 2.00 [] compared to LPV / r + RAL [95% CrI 1.30; 3.12]). The combination of DTG + 2 NRTIs compared to the combination of DRV / r + 2 NRTIs was more effective in achieving virological suppression at week 4 (OR 1.5 [95% CrI 3.45; 50]),

At week 12 (OR 3.23 [95% CrI 1.89; 5.56]) and at week 48 (OR 2.56 [95% CrI 1.45; 4.35]).

Discontinuation of treatment:

The DTG + 2 combination of NRTIs had an LPV / r compared to the combination + 2 NRTIs less chance of discontinuation (OR 0.61 [95% CrI 0.38; 0.96]), discontinuation due to adverse events (OR 0.39 [95% CrI 0.14; 0.91]) , treatment-emergent adverse reactions (OR 0.30 [95% CrI 0.21; 0.45]) and treatment-related adverse reactions (OR 0.63 [95% CrI 0.45; 0.89]).

Frequency of doctor visits and dispensing of ARVs

HIV is a chronic disease that requires continuous ARV treatment and regular monitoring of disease progression and adherence by an infectious disease physician, even when the virus is suppressed. However, it has been found that younger HIV-positive people may prefer less frequent visits to a health care provider to reduce absenteeism (56). A systematic review published in 2017 also concluded that less frequent visits to a healthcare provider and a longer period for dispensing medicines can lead to better treatment (57) without compromising treatment effectiveness.

By decision of the Estonian Society of Infectious Diseases, an Estonian database of HIV-positive patients (E-HIV) was established on 8 April 2009. The aim of e-HIV is to collect and analyze clinical and demographic data of HIV-positive people living in Estonia in order to get an overview of HIV-positive clients, disease stage, co-morbidities, potential drug use and treatment regimen, and to monitor the course of the disease, analyze drug resistance predict HIV prevention measures and the need for real specific treatment and health care (58). E-HIV also makes it possible to monitor doctor's visits and the delivery of medicines to people on ARV treatment.

12	✔	For HIV-positive individuals on ARV treatment with a persistently suppressed viral load, recommend a physician visit every 6 to 12 months and the drug to be dispensed every 3 to 6 months. Weak positive recommendation, very low level of evidence

The clinical issue of the frequency of doctor visits and medication dispensations in HIV-positive ARVs was addressed by the WHO (2016)[11] in the guide. In order to find newer evidence, an additional search was performed (01.04.2016–17.08.2019), as a result of which no suitable new study was identified.

Among the potential harms, the WHO pointed out in its guidelines that less frequent visits to a doctor can have greater consequences for treatment and medication errors and delay their detection. In addition, with less frequent dispensing, patients may have difficulty storing large quantities of medication. However, the WHO believes that less frequent doctor visits reduce social, economic and geographical inequalities. Frequent medical visits put people living outside the cities in an unequal position (time and money spent on transport) and people on low incomes (frequent medical visits require absenteeism). The WHO also recommended that medical visits be combined with access to medicines in order to reduce the total number of visits to the healthcare provider.

In formulating this guideline, the Working Party took into account that much of the research in the systematic review and meta-analysis has been conducted in Africa and is circumstantial evidence for us. There is no long queue for access to an infectious disease doctor in Estonia and there is no significant waiting list for an appointment. Medicines are dispensed by a nurse and should be more frequent than a doctor's appointment. If a nurse's reception reveals problems with medication or adherence to treatment, the problem is identified more quickly, and timely intervention can improve treatment outcomes and reduce the risk of developing resistance. In case of complaints or problems, patients have the opportunity to contact a doctor themselves, which is already a common practice. If a patient does not go to the hospital in time to receive medication, nurses and / or experienced counselors will try to contact them and arrange for a visit to ensure consistent treatment. Pregnant women, nursing mothers, children and adolescents may need more frequent visits and this need to be assessed on an individual basis.

11 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

Evidence from the WHO Code of Practice is based on a systematic review and meta-analysis (57) published in 2015 (in part) and 2017 (in full) analyzing 11 studies from six different countries (USA, Uganda, South Africa, Malawi, Spain, Kenya). .

The meta-analysis compared the effects of different frequencies of doctor visits on the following endpoints, involving eight studies involving 11,804 patients.

Mortality: The frequency of physician visits did not affect patient mortality (OR 1.12 [95% CI 0.60; 2.10]).

Morbidity: Morbidity was defined as HIV stage III-IV (WHO classification) or increase in opportunistic infection. The frequency of doctor visits had no effect on morbidity (OR 0.61 [95% CI 0.35; 1.05]).

Adherence to treatment: Less frequent doctor visits improved treatment adherence (OR 1.90 [95% CI 1.21; 2.99]).

Consent to treatment: Less frequent doctor visits did not improve adherence (OR 2.00 [95% CI 0.53; 7.60]).

Treatment failure: The frequency of doctor visits had no effect on treatment failure (OR 0.83 [95% CI 0.51; 1.36]).

Frequency of dispensing: No significant difference was found between the frequency of drug delivery and adherence to treatment (OR 1.93 [95% CI 0.62; 6.04]). There were few studies included in the analysis and high heterogeneity (2 studies, 13,194 patients, I^2 = 95.4%).

Monitoring of ARV treatment

HIV RNA is detectable in plasma as early as 10 to 12 days after infection. HIV RNA analysis shows the number of copies of the virus in one milliliter of blood. In people receiving ARV, HIV RNA testing is used to monitor the course of the disease and the effectiveness of the treatment. In the case of viral suppression, the amount of virus in the sample is below the detection limit of the method (59).

13	✔	In HIV-positive individuals who have achieved viral suppression with ARV therapy, test for HIV every 6 to 12 months. Weak positive recommendation, very low level of evidence

The frequency of HIV virus copy number comparisons at 6 months and 12 months was discussed in WHO (2016) [12] in the guide. The WHO conducted a systematic search which did not result in any studies matching the research question. Within the framework of this guideline, the WHO systematic search was repeated to find relevant evidence (01.01.2015–29.05.2019), which also did not identify scientific articles on the research question.

In formulating the recommendation, the WHO took into account the results of a working group survey. It was considered important to provide clear and consistent guidance on the frequency of VL determination.

The team considered that HIV VL testing, along with other tests, should be done every six months to reduce the risk of developing resistance, identify potential side effects (including severe side effects), prevent interactions with other medicines (especially if the GP is not HIV-positive). aware of the diagnosis and add medication to the regimen), monitor renal and hepatic function and cholesterol levels, improve adherence and understanding of the disease. In HIV-positive individuals with persistently suppressed viral load, on ARV therapy, in highly motivated, and well-adhered patients, HIV VL may be detected less frequently (every 12 months).

Treatment consent and adherence to treatment

Lemsalu *et al. (* According to the 2018) report, in the last four years, 78% of all those who were alive and had ever received HIV treatment had turned to HIV treatment in a calendar year (36). The analysis of the impact of counseling supporting treatment adherence in Estonia within the research project HIV-BRIDGE of the University of Tartu and the Institute for Health Development (n = 230) showed that the factors supporting drug adherence (67%), support of close people (36%) and health or health awareness factors (31%). Those who had not injected drugs during their lifetime (OR 3.64 [95% CI 1.09; 12.21]) and who had no adverse drug reactions (OR 2.33 [95% CI 1.20;

4.54]). The odds of lower adherence were among those injected with the infection (OR 0.41 [95% CI 0.20; 0.84]) (60).

12 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

14		Use the following measures to improve adherence and adherence to treatment: • psychosocial and behavioral interventions (incl. case management, support person service, motivational interviewing, experiential counseling); • directly controlled pharmacological treatment (ARV, Tbc and addiction treatment, treatment of viral hepatitis) combined with psychosocial interventions. Strong positive recommendation, low level of evidence

Treatment adherence and adherence to treatment were addressed by the WHO (2016) [13] in the treatment guide under two different clinical questions. In order to find newer evidence, additional searches were performed (01.01.2014–02.10.2019 and 01.01.2014–03.10.2019), where systematic searches performed by the WHO were repeated.

In formulating the recommendation, the Working Party took into account that the positive effects of both psychosocial and behavioral interventions, including text-based interventions (text messages, reminders), on treatment adherence and retention are modest. In general, the treatment adherence of HIV-positive persons in Estonia is good and problems occur in certain population groups. The working group decided to increase the strength of the recommendation, as psychosocial and behavioral interventions do not directly harm people, the potential benefits are much greater. The working group found that directly controlled treatment (OKR) can be beneficial in Estonia. The clinical experience with OKR at Lääne-Tallinn Central Hospital is good. The working group considered that additional research is needed in Estonia to specify which interventions are effective in the NSI subpopulation. At present, services that improve treatment adherence are available in Harju County, Tartu County and Ida-Viru County, OKR only in Harju County. The working group pointed out that the problem of consent to treatment also exists among prisoners. There is currently no system for making contact between a person released from prison and an infectious disease doctor outside prison, and this needs to be addressed in the future.

Consent to treatment

The WHO systematic review of drug adherence and meta-analysis included 87 articles describing a total of 85 RCTs (16,271 subjects were randomized to 185 intervention groups). Sending SMS at different frequencies had a higher chance of compliance (OR 1.70 [95% CrI 1.16; 2.49]) compared to standard therapy.

13 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Recommendations for a public health approach - second edition. WHO; 2016.

The chances of better treatment compliance were also a support person for the combination [14] + telephone intervention compared to both standard care and advanced standard care [15]

(OR 4.91 [95% CrI 2.05; 12.52]; OR 4.63 [95% CrI 1.78; 12.65], respectively) (61).

Involvement of a support person increased the chance of achieving viral suppression (OR 1.28 [95% CrI 1.01; 1.71]). Behavioral skills training and stimuli or medication training to improve adherence and stimulation had a better chance of achieving viral suppression compared to advanced standard therapy (OR
3.25 [95% CrI 1.13; 9.88]) (61).

An additional search included 14 more RCT results (62–75).

Research involving counseling

The usual instructive n õ in the group (n = 150) *compared to* motivational interview (n = 147) group at six months, a similar number of subjects were> 95% compliant (82.9% *vs.* 79.5%, RR 0.96 [95% CI 0.85; 1.09], p = 0.51) (75).

There was no difference between cognitive behavioral therapy (CBT) (n = 22) and advanced standard care (n = 22). *from each other* in terms of total drug use during the active treatment period (b = 1.8 [95% CI −2.8; 6.3], p = 0.35). Three months after the intervention, there were significant changes in cognitive impairment (b = –13.6 [95% CI [–19.0, –8.3], p <0.001) in the COC group compared to the advanced standard care group; = 8.8 [95% CI 2.0; 15.6], p = 0.01) and cognitive ability (b = 12.3 [95% CI 6.1; 18.6], p <0.001) (63).

RCT among Estonian HIV-positive persons (n = 519) showed that in the intensive counseling group, where three counseling sessions on HIV, ARV treatment and problem-based skills in improving adherence to treatment were performed during a routine medical visit, there was no difference in treatment adherence. compared to controls 12 months after intervention (76.7% vs. 67.5%, RR 1.14 [95% CI 1.00; 1.28]). However, a higher need for ARV treatment was perceived in the intervention group after the intervention (1.32 [SD 1.22] vs. 1.08 [SD 1.12], p = 0.048) (74).

Research involving text messaging

Orrell *et al. (* 2015) found that notification messages with a 30-minute delay in taking the drug did not improve adherence. The median compliance was 82.1% (IQR 56.6%; 94.6%) in the intervention group (n = 130) and 80.4% (IQR 52.8%; 93.8%) in the control group (n = 130). (OR 1.08 [95% CI 0.77; 1.52]) (71).

14 Support person - an intervention that involved the involvement of a healthcare professional or a support person of the patient's choice (including peer support, home visits, treatment assistant, medication administrator, OKR or modified OKR)

15 Advanced standard care - standard care + intensive counseling to increase adherence to treatment

Ingersoll *et al. (* 2015) found that after 12 weeks of intervention, adherence improved significantly more in the group of patients receiving text messages (n = 33) (66% at baseline, 85% after intervention) than in the standard treatment group (n = 30) (62% at baseline, 71% after intervention). %) (p = 0.04). Three months after the intervention, treatment adherence no longer differed significantly between groups (67).

Sabin *et al. (* 2015) performed RCT (n = 120), consisting of a pre-intervention period (3 months) and an intervention period (6 months), to investigate the efficacy of a device that sends treatment-enhancing messages. Optimal adherence was defined as a situation in which the subject took ≥ 95% of ARVs on time. Six months after the start of the intervention, the intervention group had a higher rate of optimal adherence compared to controls (87.3% *vs.* 51.8%, RR 1.69 [95% CI 1.29; 2.21], p <0.001) and treatment adherence over a period of 4 to 6 months was also higher (82.5% *vs.* 51.8%, RR 1.59 [95% CI 1.21; 2.10], p <0.001) (72).

Haberer *et al. (* 2016) examined the effect of scheduled SMS, regular SMS notifications and standard SMS notifications in case of delayed medication on treatment compliance compared to the control group. Compliance was found to be 11.1% higher (p = 0.02) and there were fewer breaks of more than 48 hours and more than 96 hours (IRR 0.6; p = 0.02; IRR 0.3; p <0.001) only in the graphical intervention group compared to the control group (66).

Studies that include an audio message

One RCT studied the effect of individualized, automated interactive telephone reminders and picture messages on different ARV treatment outcomes (n = 631) over a 96-week period. There was no significant difference in treatment failure (HR 0.98 [95% CI 0.67; 1.47], p = 0.95) and suboptimal treatment compliance (IRR 1.24 [95% CI 0.93; 1.65], p = 0.14) (68).

Other studies

Linnemayr *et al. (* 2017) examined the effect of a low-value stimulus (US $ 1.50) on treatment adherence in Kampala, Uganda (n = 155). There was a significant difference in 90% compliance between the intervention group and the control group (23.7% [95% CI 6.7; 40.7%]). During the first nine months of the study, 63.3% (95% CI 52.9; 72.8%) of subjects in the intervention group were able to maintain at least 90% compliance compared to 39.6% in the control group (95% CI 25.8; 54.7%). (70).

Bogart *et al. (* 2017) analyzed the impact of problem-based intervention on treatment adherence. A total of 215 study intervention groups were randomized (n =
107) and the standard treatment group (n = 108). One month of intensive intervention (3 times 60 minutes of counseling in weeks 1, 2 and 4 and one group counseling in the first month) and two additional sessions at weeks 12 and 20 were used. Adherence was better in the intervention group than in the standard treatment group (one-month OR = 1.30 [95% CI 1.12; 1.51] p <0.001), showing a large cumulative effect at six months (OR = 4.76, Cohen's d = 0, 86) (64).

The RCT (n = 494) of Latin American subjects in the United States assessed the effect of Spanish-language computer-based intervention on treatment adherence. Treatment compliance and viral load did not differ significantly between the intervention and control groups (69).

Gross *et al. (* 2015) examined a modified partner-based OKR *impact* treatment failure (HIV RNA> 400 copies / ml) and compliance in patients with prior ARV treatment failure (HIV RNA> 1000 copies / ml). At week 48, 26% (34/129) in the mOKR group and 18% (23/128) in the standard treatment group failed new treatment (p = 0.13). Median compliance was similar in the groups Q1: 95% *vs.* 96% p = 0.38; Q2: 91% *vs.* 94% p = 0.40; Q3: 90% *vs.* 93% p = 0.17; Q4: 90% *vs.* 93% p = 0.36 (65).

Abdulrahman *et al. (* 2017) examined the impact of combined intervention (SMS notifications and calls and group counseling) on treatment adherence. At six months, treatment compliance was higher in the intervention group (95.7% [95% CI 94.39; 96.97]) compared to the control group (87.5% [95% CI 86.14; 88.81]). The intervention group had a higher (> 95%) proportion of subjects with good adherence compared to the control group (92.2%). *vs.* 54.5%), less non-attendance at a doctor's appointment (14.0% *vs.* 35.5%) (p =

0.001), lower viral load (p = 0.001) and higher increase in CD4 cell count (p = 0.017) (62)

Stay on treatment

A systematic review by the WHO was accompanied by six articles describing five studies (76). One cohort study sample consisted of children under 16 years of age and another sample of adults from 16 years of age (inclusive). The other three studies included adults only.

One RCT (n = 350) examined the effect of peer intervention (mOC and psychosocial support, peer care and adherence training) and standard care on adherence to treatment for six weeks. At 12 months, the intervention group was more likely to remain on treatment (RR 1.14 [95% CI 1.02; 1.27]) (77).

A large-scale prospective cohort study in South Africa examined the impact of community-based interventions (regional health professionals who provide psychosocial counseling, home visits, and household risk assessments) on treatment survival in children (<16 years, n = 3563) (78) and adults. among (≥ 16 years of age, n = 66,953) (79). The intervention group was more likely to maintain treatment at 36 months in children (RR 1.07 [95% CI 1.03; 1.11]) and at 60 months in adults (RR 1.07 [95% CI 1.07; 1, 08]). The risk of not following follow-up did not differ between the pediatric groups at 36 months (RR 0.82 [95% CI 0.5; 1.35]), but was lower in the intervention group at 60 months (RR 0.75; [95% CI 0; 72;

0.78]). The risk of dying was significantly reduced in both children at 36 months (RR 0.46 [95% CI 0.26;
0.82]) as well as in adults at 60 months (RR 0.85 [95% CI 0.81; 0.89]).

In Peru, a prospective cohort study (n = 120) was conducted using a multi-component (health-monitored OKR with emotional and other support) community-based intervention. It was found that both at month 12 (RR 1.38 [95% CI 1.13; 1.70]) (80) and at month 24 (RR 1.68 [95% CI 1.29; 2.18]) (81), treatment adherence was significantly better in the intervention group. In addition, both decreased at month 12 (RR 0.4 [95% CI
0.17; 0.98]) (80) as well as at month 24 (RR 0.35 [95% CI 0.15; 0.83]) (81) in the intervention group.

A prospective cohort study in Rwanda (n = 610) examined the impact of OKR and social and nutritional support, financial support for transportation, and, where appropriate, socio-economic counseling on health care survival and mortality. The intervention improved the combined outcome of treatment adherence (RR 1.06 [95% CI 1.0; 1.11]) and the risk of no mortality or follow-up (RR 0.50 [95% CI 0.28; 0.90]) 12. bullet (82).

As a result of the additional search, five more RCTs were included (83-87).

Joseph Davey *et al. (* 2016) found that sending SMS improved treatment adherence only among urban residents (RR 0.54 [95% CI 0.31; 0.95]), especially among those who had just started ARV treatment (HR 0 , 20 [95% CI 0.06; 0.64]) (87).

In RCT in Peru (n = 356), no significant difference was found between OKR and control group at month 12 (0.81 vs. 0.73) and at month 24 (0.76 vs. 0.68) using the intent-to-treat analysis.). A statistically significant difference was found at month 12 when using a protocol-based analysis or a treatment-based analysis (0.83 vs. 0.73, p = 0.02 protocol-based, p = 0.01 treatment-based) (86).

McNairy *et al. (* 2017) found that in the combined intervention group (initiation of accelerated ARV treatment, mobile-based appointment reminders, health education packages and non-monetary incentive), the proportion of those remaining in treatment was
At month 12, significantly higher than the control group (RR 1.48 [95% CI 1.18; 1.86], p = 0.002) (83).

RCT in South Africa (n = 377) compared rapid initiation of ARV treatment (at the first visit) with initiation of ARV treatment within the standard time frame (3–5 health care visits, 2–4 weeks). In the rapid-onset group, a higher proportion of subjects started treatment and had achieved virological suppression by 10 months (64% *vs.* 51%, RR 1.26 [95% CI 1.05; 1.50]). In the rapid start-up group, a higher proportion of patients had started treatment by day 90 at the latest compared to the control group (97% *vs.* 72%, RR

1.36 [95% CI 1.24; 1.49]). Among subjects who had started treatment by day 90 at the latest (n = 318), treatment adherence did not differ between the intervention and control groups (84).

In the RCT of drug-using subjects (n = 120), the distribution of low-value gift cards found an increase in the number of visits to the ARV treatment center (49 vs. 33, p = 0.002) and the initiation of ARV treatment (HR 2.33 [95 % CI 1.15; 4.73]). There was no difference between groups in viral suppression (85).

Preparation of treatment instructions

In 2016, the Ministry of Social Affairs initiated the preparation of a treatment guide on the topic “Early detection, treatment and further treatment of HIV-positive persons”. The corresponding topic was included in the work plan for 2017 and a working group on treatment guidelines and a secretariat were formed. The working group held two meetings on 23 March and 24 May 2017. As a result of the meetings, the scope of the treatment guideline was completed and approved at the meeting of the Treatment Guidelines Council on 30 May 2017. The preparation of the treatment guideline slowed down due to various factors. In connection with the establishment of a permanent secretariat for treatment guidelines at the University of Tartu

In 2018, the EHIF also handed over the organization of the preparation of ongoing treatment guidelines. As a result of interviews with persons involved in the development of the HIV treatment guideline and various stakeholders, it was realized that in order to successfully complete the treatment guideline, the scope needs to be narrowed and the treatment of HIV infection divided between several treatment guides. This guideline addresses the prevention of PrEP and PEP and the treatment of HIV-positive individuals and is the first to be developed.

Once again, a working group and secretariat for the treatment guide were formed, which included representatives of various relevant professions, a representative of the Estonian Health Insurance Fund and a representative of patients. The scope of the treatment guide consists of 10 clinical questions in PICO format. The scope was approved in April 2019 by the Treatment Guidelines Council. The treatment guidelines were compiled on the basis of the principles of the Estonian Handbook for the Preparation of Treatment Guidelines (2017). The guideline's thematic initiative, scope, full version, summaries of evidence, guideline implementation plan, minutes of meetings and summary of declarations of interest of the guideline authors are available at

www.ravijuhend.ee .

The team held six meetings and one Skype meeting to discuss clinical issues and formulate recommendations. At the beginning of each meeting, the declarations of potential conflicts of interest of the members of the Working Group and the Secretariat were examined and the bias of decision-makers was verified. The meeting had a quorum if at least 3/4 of the members of the working group were present. The decisions of the meetings were unanimous.

In addition to the strength of the scientific evidence, the recommendations also took into account the health benefits of the intervention (including the potential benefits and harms), patients' preferences and values. Account was also taken of the recommendation to leave patients in an unequal position and the opportunities and resources for implementing the recommended activities in the Estonian context.

Once approved, the guide will be updated as new relevant information is added or after five years.

Finding and evaluating evidence

It is effective and practical to use evidence and recommendations based on existing treatment guidelines when developing national treatment guidelines. It should be borne in mind that, although the clinical evidence is always international, the values and preferences of the target group, the costs and the implementation of the recommendations are always country-specific (88). The drafters of the guideline usually have three options: 1) transposing existing recommendations (*adoption)* unchanged 2) adaptation of existing recommendations (*adaptation)* or 3) formulate a new recommendation on the basis of the available evidence (*de novo) (* 89). Increasingly, the combination of the above three with a single method based on the GRADE methodology, called *adolopment (* 89).

Predominantly used in this treatment guide *adolopment* method. This was based on evidence from two WHO treatment guidelines "Consolidated guidelines for the use of antiretroviral drugs for the treatment and prevention of HIV infection" (2016) and "Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV "(2018) and two WHO systematic reviews and the VMA for updating recommendations (2019) (Table 5). The WHO HIV Treatment Guidelines team made the full texts of the WHO Treatment Guidelines, search protocols for systematic reviews and meta-analyzes and full texts with GRADE tables, as well as in EtD format available to the drafters of the Estonian HIV Treatment Guidelines. *Evidence toDecision)*

the arguments for drawing up the recommendation and the reasons for the decisions taken.

The quality of WHO treatment guidelines was assessed with the AGREE II tool. Both guidelines were evaluated independently by two members of the secretariat. There were no significant differences in the quality assessments of the treatment guidelines when taking into account the access to relevant documents provided by WHO. The team considered it necessary to include both treatment guidelines in the work. As the EACS (European AIDS Clinical Society) treatment guidelines "European Guidelines for the treatment of HIV-positive adults in Europe" (2018) are also used in clinical practice, it was also evaluated with the AGREE II tool. The EACS treatment guide could not be included because there is no clear reference in the guide to the evidence used and the authors of the guide do not agree to share the evidence behind the decisions with third parties.

Table 5. Treatment guidelines and systematic reviews included in the work of the Estonian HIV treatment guide together with a meta-analysis of the network

Publisher of the Year		Title
2016	WHO	Consolidated guidelines on the use of antiretroviral drugs for the treatment and prevention of HIV infection
2018	WHO	Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV Systematic literature review and network
2019	WHO	meta-analysis to assess first-line ART treatments to inform the WHO consolidated ARV guidelines
2019	WHO	Systematic Review to inform the World Health Organization Consolidated Antiretroviral Therapy Guidelines: Which ART regimen to switch to when failing first-line treatment

When the WHO Code of Practice recommendation was based on evidence that had been systematically searched for more than a year ago, the WHO search in the Pubmed database was repeated. Systematic reviews, meta-analyzes, and individual studies were preferred to summarize additional evidence, with a preference for randomized controlled trials. Scientific articles found with additional searches and used in compiling the treatment guide are referenced in the text of the guide. For additional searches on each clinical issue, the Secretariat compiled a summary of the evidence using the GRADE web-based tool. The working group drafted and endorsed the final recommendations with direction and strength. Summaries of the evidence on which treatment guidelines are based, together with search strategies, are available at www.ravijuhend.ee .

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ADD 1

Table 6. Initiation of PrEP and monitoring of treatment [16]

	Heterosexuals have sex with men	men and women	Drugs people injecting
Important for HIV infection risk	• HIV positive sexual partner • Recent bacterial STIs • Large sexual partners number • Inconsistent or missing condoms use • Prostitution	• HIV positive sexual partner • Recent bacterial STIs • Injectables • Large sexual partners number • Inconsistent or missing condoms use • Prostitution • As the place of in the social circle is high in HIV prevalence	• Drugs "Injection buddy" is HIV positive sharing
Clinically suitable	• The HIV 1.2 Ag + Ab test before prophylaxis is negative • There are no symptoms of acute HIV infection • Normal renal function (Crea, eGFR) • Do not take other medicines that are contraindicated or have interactions • Documented hepatitis B virus infection status (HBsAg, HBsAb, HBcAb) and vaccination status		
Medicines and issuance	• The prophylaxis regimen includes TDF / FTC 300 mg / 200 mg once daily. It should be started seven days before the first exposure and may be stopped seven days after the last exposure. • Dispense medicines for up to 90 days at a time		

<table>
<tr><td rowspan="2">Others services</td><td colspan="3">Regular follow-up visits at least every 3 months:
• Perform an HIV 1.2 Ag + Ab test
• assess the symptoms of STIs, test for bacterial STIs every 3 to 6 months
• provide counseling to improve adherence to treatment
• Assess the occurrence of side effects
• support the reduction of behavioral risk
Three months after starting treatment and every six months thereafter, renal function (Crea, eGFR) should be assessed. Renal function (Crea, eGFR) should be assessed.</td></tr>
<tr><td>• Test for STIs • Evaluate the request</td><td>get pregnant
• Perform every three monthly blood hCG</td><td>• Access to the syringe / needle exchange program and drugs waiver support services</td></tr>
</table>

STIs - a sexually transmitted infection

16 Table adapted: Centers for Disease Control and Prevention & US Department of Health and Human Services. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2017 Update: a clinical practice guideline. CDC & DHHS; 2018.

ANNEX 2

Table 7. Initiation of PEP and monitoring of treatment [17]

Test	Potent socially infection on carried person	A person who is at risk of becoming infected with HIV			
	Together-touch after	Together-touch after	4-6 weeks after together-disability	3 months after together-disability	6 months after together-disability
For all exposure types					
S-HIV1,2 Ag + Ab [a]	•	•	•	•	• [b]
Hepatitis B virus surface antigen (HBsAg); Hepatitis B virus surface antigen amount of antibodies (HBsAb); Hepatitis B virus nucleus antibodies to the antigen (HBcAb)	•	•	-	-	• [c]
Anti-hepatitis C virus antibodies (HCVAb)	•	•	-	-	• [d]
After sexual contact					
Treponema pallidium antibodies (*T. pallidum* Ab) [e]	•	•	•	-	•
N. gonorrhoeae DNA [f]	•	•	• [g]	-	-
C. trachomatis DNA [f]	•	•	• [g]	-	-
hCG blood	-	• [h]	• [h]	-	-

17 Table adapted: Centers for Disease Control and Prevention & US Department of Health and Human Services. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV - United States, 2016. CDC & DHHS; 2016.

In individuals who started with PEP					
Serum / plasma creatinine, estimated glomerular filtration rate (eGFR)		•	•	-	-
Alanine aminotransferase (ALAT), Aspartate amino-transferase (ASAT)		•	•	-	-
All persons diagnosed with HIV at any reception					
Number of copies of the HIV virus (HIV RNA)	•	•			
HIV resistance determination	•	• [i]			

[a] a positive result always requires a confirmatory test

[b] only if hepatitis C infection occurred during the initial exposure

[c] if the exposed person was susceptible to hepatitis B after exposure if the exposed person was

[d] susceptible to hepatitis C after exposure if syphilis was diagnosed and treatment was started,

[e] should be retested six months after treatment

[f] if gonorrhea or chlamydia was diagnosed, it should be retested three months after treatment

[g] if no preventive treatment or follow-up complaints have been initiated after exposure

[h] woman of childbearing potential, did not use effective contraception and had vaginal exposure

[i] in case of treatment failure

ANNEX 3

Table 8. Preparations for the treatment of ARV by class of medicinal product and their dosage [18]

Active substance	Dose
Nucleoside reverse transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250-300 mg twice daily
Nucleotide reverse transcriptase inhibitors (NtRTIs)	
Tenofovir disoproxil (TDF) 300 mg	once daily
Tenofovir alafenamide (TAF) 10 mg	or 25 mg once daily depending on drug combination
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400-600 mg once daily
Rilpivirine (RPV)	25 mg once daily
Doravirin (DOR)	100 mg once daily
Integrase Inhibitors (INSTI)	
Dolutegravir (DTG)	50 mg once daily
Raltegravir (RAL)	400 mg twice daily or 1200 mg once daily
	Considerations for individuals receiving concomitant tuberculosis treatment: • DTG 50 mg twice daily and RAL 800 mg twice daily should be used during treatment with rifampicin and treatment should be closely monitored. • No dose adjustment is required during treatment with rifabutin
Biktegravir (BIC)	50 mg once daily
Protease inhibitors (PIs)	
Darunavir + ritonavir (DRV / r)	800 mg + 100 mg once daily or 600 mg + 100 mg twice a day
Darunavir + cobicistat (DRV / c)	800 mg + 150 mg once daily

18 World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO; 2018.

ANNEX 4

Table 9. Possible side effects of drugs used in the treatment of ARV and their treatment [19]

ARV drug	The main possible side effects	Risk factors	Recommended treatment
Abacavir (ABC)	Hypersensitivity reaction	Presence of the HLA-B * 5701 gene in the presence of the gene	• Do not use ABC HLA-B * 5701 • Replace with AZT or TDF
Zidovudine (AZT)	Anemia, neutropenia	• When starting treatment for anemia or neutropenia • CD4 cell count ≤ 200 cells / mm^3	• Replace with TDF or ABC • Consider a low dose use of sivovudine
	• Lactic acidosis or severe hepatomegaly with steatosis • Lipoatrophy, lipodystrophy, myopathy	• BMI> 25 kg / m^2 or body weight> 75kg • Long-term exposure NRTIs	Replace with TDF or ABC
Biktegravir (BIC)	Serum bilirubin and creatinine increase in value (actual eGFR not affected)	Occur very rarely	
Dolutegravir (DTG) *	• Hepatotoxicity • Hypersensitivity reaction	• Concomitant hepatitis B or Hepatitis C. • Concomitant liver disease	Replace with another class of medicinal product (EFV or boosted PI)
	Insomnia	• Age more than 60 years • ~~Female~~	Consider morning dosing or replace with EFV, boosted PI or RAL
Doravirin (DOR)	Hepatotoxicity	• Concomitant hepatitis B or Hepatitis C. • Concomitant liver disease	Not clinically relevant
	Skin hypersensitivity reaction		Reversible upon discontinuation of treatment

19 World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO; 2018.

Darunavir + ritonavir (DRV / r)	Hepatotoxicity	• Concomitant liver disease • Concomitant hepatitis B or Hepatitis C. • Concomitant hepatotoxic use of medicines	• When used as a third line option, the options are limited • In case of hypersensitivity reactions replaced with another class of medicine
	Severe skin or sensitivity reactions	Sensitivity to sulphonamides	
Efavirenz (EFV)	Persistent central nervous system toxicity (dizziness, insomnia, disturbed dreams) or symptoms of a mental disorder (anxiety, depression, confusion)	• Previous or accompanying depression or other mental disorder • Medication daily dosing	• Central nervous system symptoms try evening dosing. Weight reduction of the EFV dose to 400 mg • If EFV dose reduction does not reduce symptoms, a switch to DTG should be considered
	Seizures	Previously occurred seizure	
	Hepatotoxicity	• Concomitant liver disease • Concomitant hepatitis B or Hepatitis C. • Concomitant hepatotoxic use of medicines	Severe hepatotoxicity or in case of hypersensitivity reaction replace boosted PIs in another class of medicinal product (INSTI or treatment)
	Severe skin or hypersensitivity reactions	Risk factors unknown	
	Gynecomastia	Risk factors unknown	Replace with another class of medicine (INSTI or boosted PI)
Raltegravir (RAL)	Rhabdomyolysis, myopathy and myalgia	Concomitant with other myopathy and risk of rhabdomyolysis use of medicines (incl statins)	• Discontinue ARV therapy Replace after symptoms another class of medicine (etravirine, boosted PIs)
	• Hepatitis and liver failure • Severe skin and sensitivity reactions	Risk factors unknown	

Rilpivirine (RPV)	Hepatotoxicity	Concomitant liver disease	Replace with another class of medication
	Mild symptoms of depression In phase III studies		Assess the presence and worsening of depression, replace if necessary with other preparations
	Cardiotoxicity, QT prolongation	Concomitant heart disease or drugs that prolong QT interval	Avoid drug interactions, replace if necessary preparations
Tenofovir, alafenamide (TAF)	Renal impairment	Concomitant kidney disease	The clinical significance is unknown
Tenofovir isoproxil (TDF)	Chronic kidney disease	• Concomitant kidney disease • Age more than 50 years • BMI <18.5 kg / m^2 or body weight <50 kg, especially in women • Untreated diabetes or hypertension • Concomitant nephrotoxic drugs or boosted Use of PIs	Do not initiate treatment with TDF if the eGFR is <50 ml / min in patients with diabetes, untreated hypertension or • History of osteomalacia with renal insufficiency or pathological fracture
	Bone density decrease	• Risk factors for osteoporosis • Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	• Long-term exposure nucleoside analogues • Obesity • Liver disease	

* DTG - suspected higher risk of neural tube defects in children exposed in the first trimester of pregnancy.

ANNEX 5

Table 10. Monitoring of an HIV-positive patient receiving ARV therapy [20]

	Execution frequency		
	Infection - 4-8 weeks after starting ARV treatment diseases to the doctor for reverse or modification refusal [a]		**Further monitoring**
CD4 cells number	•		**Every 3-6 months:** For the first two years after starting ARV treatment. If viremia develops during ARV therapy or if the CD4 cell count is <300 cells / mm^3 After two years of ARV treatment and continuous viral suppression **Every 12 months:** CD4 cell count 300-500 cells / mm^3 **Optional:** CD4 cell count> 500 cells / mm^3 **Other situations:** If treatment fails In clinical indication
HIV viral load	•	•	**Every 6 to 12 months:** If viral suppression is achieved **Other situations:** In clinical indication
Resistance testing			**Other situations:** If treatment fails
HLA-B * 5701 determination	• If are considered treatment with ABC		
Hepatitis B. serology (HBsAg, HBsAb, HBcAb serum)	•		**Every 12 months:** It can be repeated if the patient is immune and does not have chronic HBV. If HBsAg, HBsAb and HBcA are negative, it is recommended that hepatitis B vaccination be discussed with the patient. **Other situations:** Before starting treatment for hepatitis C with antiviral medicines

Hepatitis C. screening (HCV antibodies or if necessary HCV RNA)	•		**Every 12 months:** Repeat HCV screening in patients at risk (people who inject drugs, people who have been in prison, HIV-positive men who have sex with men, people who have had skin or parenteral contact with blood). **Other situations:** In clinical indication
Main clinical chemistry **analyzes**	•	•	**Every 3-6 months:** Na, K, HCO3, Urea, Crea and eGFR Phosphorus assessment in patients with chronic kidney disease treated with tenofovir alafenamide (TAF) or tenofovir disoproxil (TDF) **Other situations:** Patients with chronic kidney disease may need more frequent evaluation (see treatment guide "Prevention and treatment of chronic kidney disease") in a clinical indication.
Pay- indicators	•	•	**Every 3-6 months:** ALT, AST, bilirubin **Other situations:** In clinical indication
Hemato-logical analyzes	•		**Every 6 months:** Hemogram with five - part leukogram
Lipid profile	•		**Every 6 months:** If the previous measurement did not remain within the normal range **Every 12 months:** If the previous measurement was within normal limits **Other situations:** In clinical indication
Fasting glucose or HbA1c	•		**Every 3-6 months:** If the previous measurement did not remain within the normal range **Every 12 months:** If the previous measurement was within normal limits **Other situations:** In clinical indication
Urine analysis	•		**Every 6 months:** If the treatment regimen includes tenofovir alafenamide (TAF) or tenofovir disoproxil (TDF) **Every 12 months:** For other treatment regimens **Other situations:** In clinical indication
hCG blood fertile age in women (recommended)	•		In clinical indication

[a] if the start of ARV treatment is delayed, it may be necessary to repeat the start of treatment

20 Table adapted: Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. DHHS; 2019.

Notes

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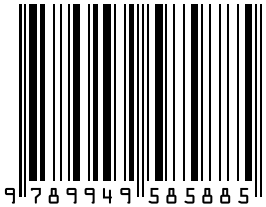
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