# CLINICAL GUIDELINES FOR HIV AND AIDS TREATMENT

Partnerstvo za zdravlje
BOSNA I HERCEGOVINA

Ministarstvo zdravlja i socijalne zaštite Republike Srpske

Bosnia and Herzegovina

Federation of Bosnia and Herzegovina Federal Ministry of Health

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Sarajevo, 2021

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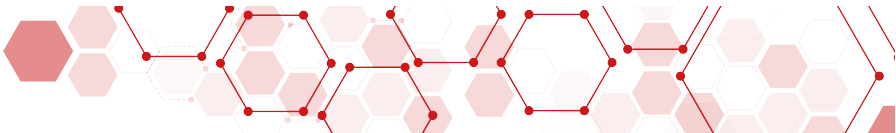


# Content

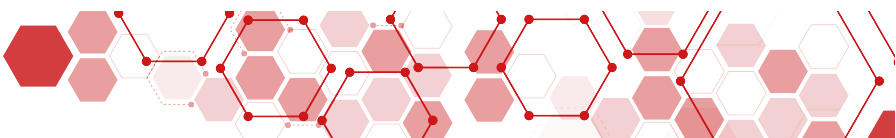
**Gender component**

These Clinical Guidelines imply an equal and equal relationship between both sexes, regardless of the grammatical gender in which these guidelines list persons who can be of both sexes. ITerms written only in the masculine gender refer equally to the masculine and feminine gender. In the designation of functions, titles and titles, gender-friendly language 1 will be used.

[1] Handbook for harmonization of laws with the Law on Gender Equality and with international standards in the field of

| Abbreviations and explanations | |
|---|---|
| **3TC** | Lamivudine |
| **ABC** | Abacavir |
| **ARV** | Antiretroviral |
| **ART** | Antiretroviral therapy |
| **ATV** | Atazanavir |
| **AZ** | Azidothymidine, Zidovudine |
| **BID** | Twice a day |
| **CCR5** | CCR5 is a protein found on cells of the immune system, a coreceptor for HIV when the virus enters the cell. |
| **CD4** | A test that counts how many CD4 lymphocytes are in a cubic millimeter of blood (mm3). CD4 cells are cells that are directly attacked by HIV. Their role is to send signals to other cells of the immune system, to know what and when to do. |
| **CD8** | Lymphocytes are cells whose role is to target and kill infected, i.e. altered cells. Cells of the immune system have the ability to distinguish foreign substances from those belonging to the body, with the aim of eliminating all foreign substances. |
| **CMV** | Cytomegalovirus |
| **Cobi** | Cobicistat |
| **CVD** | Cardiovascular disease |
| **d4T** | Stavudin |
| **ddI** | Didanosine |
| **DLV** | Delavirdin |
| **.DRV** | Darunavir |
| **DTG** | Dolutegravir |
| **EFV** | Efavirenc |
| **ETR** | Etravirine |
| **Evg** | Elvitegravir |
| **FPV** | Fosamprenavir |
| **FTC** | Emtricitabine |
| **HAART** | Highly active antiretroviral therapy (Eng. Highly Active Antiretroviral Therapy) |
| **HBV** | Hepatitis B virus |
| **HCV** | Hepatitis C virus |
| **HDL** | HDL cholesterol |
| **HLV** | Human immunodeficiency virus |
| **HLA-B*5701** | Human leukocyte antigen associated with hypersensitivity to Abacavir |
| **HSR** | Hypersensitive reaction |
| **IDV** | Indinavir |
| **GAME** | *Test interferon-γ release assay* |
| **THEM** | Myocardial infarction |
| **INSTI** | Class of antiretroviral drugs that block HIV enzyme integrase |
| **IRIS** | Immune reconstitution inflammatory syndrome |
| **LDL** | LDL cholesterol |
| **LPV/r** | Lopinavir/ritonavir |

| | |
|---|---|
| **MSM** | A man who has sex with men |
| **MVC** | Maraviroc |
| **NHL** | Non-Hodgkin's lymphoma |
| **NNRTI** | Non-nucleoside reverse transcriptase inhibitors |
| **NrTI** | Nucleotide reverse transcriptase inhibitor |
| **NVP** | Nevirapine |
| **OI** | Opportunistic infections |
| **PCR** | Laboratory test used to determine the number of copies of the virus in the blood (polymerase chain reaction) |
| **PEP** | Post-exposure prophylaxis |
| **PML** | Progressive multifocal leukoencephalopathy |
| **PMTCT** | Prevention of transmission of HIV from mother to child during pregnancy, childbirth or breastfeeding |
| **Prep** | Pre-exposure prophylaxis |
| **PWID** | People who inject drugs with a needle and a syringe directly into the blood (people who inject drugs) |
| **RAL** | Raltegravir |
| **RTV** | Ritonavir |
| **Spi** | Sexually transmitted infections |
| **SQV** | Saquinavir |
| **SW** | Sex workers |
| **T20** | Enfuvirtide |
| **TDF** | Tenofovir |
| **TPV** | Tipranavir |
| **UNAIDS** | United Nations Programme against HIV and AIDS Joint United Nations Programme on HIV/AIDS) |
| **VL** | Blood/viral load levels |
| **WHO** | World Health Organization |
| **ZDV** | Zidovudine |



## REVIEW

Standardized, high-quality and effective treatment of HIV and AIDS is a pillar of effective response to HIV. The World Health Organization wishes to commend Bosnia and Herzegovina for its efforts to continuously improve the availability and quality of HIV and AIDS treatment. We recognize the efforts of a team of experts, clinicians, civil society, ministries of health, who have worked tirelessly to develop updated Clinical Guidelines for hiv and AIDS treatment. The World Health Organization would like to thank the Federal Ministry of Health and the Ministry of Health and Social Welfare in the Government of the Republic of Srpska for their leadership and support in the development of clinical guidelines for the treatment of HIV and AIDS.

The revised clinical guides are a comprehensive document that will offer guidance to clinicians in the treatment of HIV and AIDS in different populations. This document will help health care providers at all stages of treatment and care, providing guidance for the treatment of children, adults and different population groups. Also, the revised clinical guidelines offer a solid basis for the introduction of PrEP throughout the country and improve its availability and availability to people at high risk of HIV infection. This approach is particularly relevant at a time when health systems and societies are facing the COVID-19 pandemic. The World Health Organization appreciates the opportunity to be part of the Working Group for the development of clinical guidelines for the treatment of HIV and AIDS in Bosnia and Herzegovina.

*Dr. Elena Vovc,*
*MPH World Health Organization*

# FOREWORD

The application of clinical guidelines in the approach and treatment of certain diseases is a generally accepted practice in
the modern medicine.

In order to ensure quality health services, as well as standardization of hiv and aids diagnosis and therapy, the Association "Partnership for Health" was among the first in Bosnia and Herzegovina to initiate the process of preparing clinical guidelines for the treatment of HIV and AIDS in cooperation with the Ministry of Health and Social Welfare in the Government of the Republic of Srpska and the Federal Ministry of Health, and with the support of the World Health Organization and the Global Fund for the Fight against AIDS, tuberculosis and malaria.

An expert group was formed whose members covered topics, each from their own field, i.e. procedures, procedures and guidelines that are adapted to the situation in Bosnia and Herzegovina, and which are comparable with modern procedures in the world.

Diagnostic and therapeutic attitudes are based on large multicenter studies and/or consensus of expert teams or working groups. Guidelines should be implemented so that doctors are assisted by their instructions based on scientific evidence.

The aim of clinical guides is:

- Application of modern doctrinal attitudes in diagnosis and therapy,
- Standardization of diagnostic and therapeutic procedures,
- Adoption of standards for medical supervision,
- Rationalization of health care costs,
- Developing and revising the list of essential drugs for the treatment of HIV and AIDS,
- Development of educational programs,
- Development and implementation of good medical practice and good clinical practice,
- Educating medical staff and patients..

The establishment of clinical guiding principles will give healthcare professionals a framework for the appropriate standard of health care they provide to their patients; it will give "standards" on the basis of which health professionals can follow their own clinical practice; and facilitate and streamline the work of physicians engaged in hiv and AIDS treatment.

Clinical guides will be revised, amended as necessary, preferably every other year in accordance with new knowledge about existing antiretroviral drugs, taking into account the availability of new medicines and the latest guidelines for antiretroviral treatment in Bosnia and Herzegovina.

# 1. INTRODUCTION TO CLINICAL GUIDELINES

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In the professional literature there is a large selection of terms for clinical guides. When translated from English, then the term "guidelines for clinical practice" becomes in our language clinical guidelines, guidelines for clinical practice, guide, etc.

In 2011, the American Institute of Medicine defined clinical guidelines as"statements containing recommendations intended to optimize care for patients, obtained from a systematic review of evidence and evaluation of the benefits and harms of alternative care options. Reliable clinical guidelines are based on a systematic review of the literature, conducted by a panel of multidisciplinary experts, provide a clear explanation of the logistical relationships between alternative care options and health outcomes, and show the level of quality of evidence and the strength of recommendations" (A. Novo: Klin-ičke vodilje, AKAZ, Sarajevo, 2017). Of course, all this requires adequate resources that Bosnia and Herzegovina does not have.

Also, Bosnia and Herzegovina, unlike others, has very few cases of HIV infections that do not allow serious and large-scale research, which also reduces the possibility of developing local guidelines. However, in order not to experience too much diversity, the Working Group on The Development of Clinical Guides agreed to make an examination and develop a clinical guide line for HIV infection based on existing guidelines (WHO); CDC; EACS).

Given that clinical guidelines should serve health professionals and patients, as well as purchases of services (Health Insurance Fund of the Republic of Srpska, Health Insurance And Reinsurance Institute of the Federation of Bosnia and Herzegovina), policy decision makers, etc., the Working Group agreed that the recommendations should serve and be used on the basis of available and registered medicines in Bosnia and Herzegovina.

We point this out for the reason that there is no confusion during the interpretation of the guidelines, because they also include drugs that are not available in Bosnia and Herzegovina. However, in case of urgent importation of such medicines, these guidelines can also serve service buyers to their bodies (commissions for medicines, etc.) assess the need for urgent procurement or take measures to add certain medicines to the list of medicines or delete them from it.

In the 1980s, the world was hit by the HIV pandemic. According to UNAIDS, in 2019, it was estimated that 77.5 million people have been infected with HIV worldwide (55.9 to 100 million). It is estimated that 32.7 million have died of AIDS (24.8–42.2 million). All countries reacted and after the Durban Declaration of Commitment to Aids in 2001, the Global Fund to Combat AIDS, Tuberculosis and Malaria (GFATM) was established and a systematic fight against the pandemic began. Along with pan-demia, the entire scientific community in the world has engaged in a better understanding of the nature of the HIV epidemic in order to prevent and treat it. By taking the above measures, exceptional results have been achieved in containment and control of the epidemic and treatment of patients. From the beginning of treatment with the first antiretroviral drug AZT (zidovudine), to the development of highly active antiretroviral therapy (sc. HAART) using different combinations of three or more active antiretroviral substances, to date, different classes of antiretroviral drugs have been developed. Thus, in recent years, in addition to nucleoside reverse transcriptase inhibitors (NrTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (INI) have been introduced into first-line treatment.

The goals proclaimed by the World Health Organization (WHO) and UNAIDS called "90-90-90" "To end the HIV epidemic by 2030" were well achieved, so HIV infection is now considered a chronic disease. However, despite the outstanding results achieved, the SARS-CoV-2 pandemic and the COVID-19 disease it provoked, have strongly slowed the achievement of the goals. Detailed analyses will show how much the COVID-19 pandemic has affected the achievement of the set goals. In addition to the above, since the beginning of the HIV pandemic, we have had several major epidemics caused by SARS, MERS, Ebola, bird and swine flu, but none of them caused as much panic, rapid spread of infection and death as the Covid-19 pandemic. However, the world reacted very quickly, as did the scientific community and pharmaceutical companies, and in about a year they developed the vaccines that started it.

The immunization process around the world to stop this pandemic that has shaken the world's health and economic system.

Bosnia and Herzegovina is no exception, and the fight against HIV infection – already weakened by the withdrawal of global fund support – has further slowed down the problems caused by the COVID-19 epidemic.

However, even in such difficult circumstances, work on the fight against HIV infection continues, and the best example is the recent work on updating the guidelines for HIV testing and the guide for the treatment of HIV infections.

# 2. ANTIRETROVIRAL TREATMENT

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In the treatment of HIV infection, potent high-activity antiretroviral therapy (ART) has been introduced into practice since 1996. This therapy enables a strong and long-lasting suppression of viral replication, with the possibility of reconstituting the immune system, even in cases of severe immunodeficiency. ART also has some limitations: it does not eradicate HIV, drugs are expensive, can cause many side effects, require a high degree of adherence to be effective and to prevent the occurrence of resistance . When deciding to start therapy, care must be taken of the expected benefits of ART in terms of morbidity and mortality, the possible risks of toxicity, drug interaction, drug resistance, as well as risks to comorbidities and adherence.

The latest guidelines recommend that ART be initiated as early as possible after hiv diagnosis, regardless of CD4 cell values, on the day of diagnosis or within a few days or weeks after diagnosis. In addition to the benefits of earlier initiation of therapy for an HIV-infected person, an additional reason is the decrease in sexual transmission to HIV-uninfected people.

Numerous new studies give hope that in the future it will be possible to find a functional cure, where the virus persists in the body in a permanent state of latency without the need to take ART.

## 2.1 Basic evaluation

**The basic evaluation includes an assessment of the condition of a patient with HIV** infection at the first and on the order examinations.

**First review**

C> Complete personal history, including family history (CVD, diabetes, hypertension), medications taken by the patient, lifestyle (alcohol consumption, cigarette, drug abuse), comborbidities, allergies;

C> History of Sexual and Reproductive Health;

C> Physical examination, including data on height, weight, BMI, blood pressure;

C> Laboratory analysis:

- Serological tests for HIV (screening and confirmation test);
- PCR HIV RNA;
- Genotyping and resistance test;
- Test R5 tropism (if available);
- Absolute and relative number of CD4 and CD8 lymphocytes;
- HLA-B*5701;
- CBC, hepatogram, proteinogram, glucose, creatinine, calculating creatinine clearance, amylase, eGFR, HbA1C;
- Lipid status (total cholesterol, LDL, HDL, triglycerides);
- Serology on toxoplasma, CMV;
- The amount of protein and glucose in the urine/*dipstick*;
- 25 OH vitamin D, DXA;
- PSA according to indications for HIV-negative population, alpha fetoprotein for people with cirrhosis (AFP).

C> Screening for sexually transmitted infections (STIs): serology for syphilis, NAAT on gonorrhea and chla- media;

C> Markers on hepatitis: A, B, C, D, E;

C> Pap smear, mammography;

C> pap test (MSM), anoscopy;

C> Tuberculin skin test (TST) if cd4 number is >400 cell./µL or interferon-γ *release assay* (IGRA) test);

C> X-ray of the lungs;

C> ECG, risk assessment (Framingham score);

C> Ultrasound and if necessary FibroScan;

C> Examination of the fundus;

C> Assessment of the patient's social and psychological condition: providing support and counseling if necessary;

C> Vaccination for hepatitis A and B (depending on serological findings), and vaccination against pneumococcus, annual vaccination against influenza.

**Next reviews:**

C> At least every 3-6 months:

- CBC, absolute and relative CD4 and CD8 lymphocyte counts, PCR HIV RNA

C> Every year:

- Physical examination;
- Assessment of social and psychological support, advocacy of smoking cessation;
- Serology for syphilis, hepatitis markers B and C (if previously negative or according to epidemiological indication), Pap smear;
- AST, ALT, LDH, lipid status.

If there are indications for this, counseling on possible abuse of psychoactive substances and health education in relation to mental health should be offered. Educating patients about the nature of their disease, methods of preventing transmission of HIV infection and availability of treatment should be integral parts of the initial management of treatment.

**CD4 values**

CD4 is the main indicator of immune function in patients with HIV infection and is the best predictor of disease progression. It is one of the key parameters in making the decision to in- and exclude prophylaxis for opportunistic infections (OI), as well as for assessing the urgency of initiating ART.

Today, ART is recommended for all HIV patients regardless of viral *load* or CD4 cell values, and the reasons for the frequency of monitoring CD4 cell values have become less important. However, the cd4 values are a factor in monitoring the therapeutic response. An adequate CD4 response to therapy is defined as an increase in CD4 values by 50-150 cells/µL per year. Patients who are initiating therapy with low CD4 values or who are elderly may experience a modest increase despite VL suppression.

CD4 monitoring: In patients who have not initiated ART, CD4 should be monitored every 3-6 months to assess the possible urgency of initiating ART and the need for OI prophylaxis. The cd4 value after initiating ART should be done every 3-6 months during the first two years or if the CD4 count is <300 cell./µL to assess immune reconstitution.

After two years on ART with sustainable HIV RNA suppression, and CD4 values between 300 and 500 cell./µL, monitoring should be done every 12 months, and at CD4 values >500 cell./µL for at least 2 years. In patients who fail to maintain viral suppression on ART, CD4 monitoring should be done every 3-6 months.

Cd4's response to ART varies. The modest response of CD4 to therapy in patients with virological co-pression in rare cases is an indication for modification of the ARV regimen. In the case of consistent viral suppression, CD4 values give limited information. The ARTEMIS study concluded that CD4 monitoring was not of clinical benefit in patients who had suppressed VL and values

CD4 >200 cell/µL after 48 weeks of therapy, and that the risk of *Pneumocystis jiroveci* pneumonia is extremely low in patients on suppressive ART who have CD4 values between 100 and 200 cel./µL. A decrease in CD4 values may occur in rare cases in virologically suppressed patients, which may be associated with unwanted clinical episodes, such as cardiovascular disease, malignancies, etc.

Factors that affect the absolute values of CD4 are: acute infections, smoking, stress, physical activity, contraceptives, menstrual cycle, time of day or season, and the use of drugs. The relative cd4 count (percentage) remains stable and may be a more appropriate parameter for the patient's immune function.

**HIV RNA testing**

Viremia is the most important indicator of the initial and sustainable response to ART and can be useful in pre-showing clinical progression. The goal of ARV treatment is to achieve and maintain permanent viral suppression within the detection limits, e.g. VL <20–75 copies/mL, depending on the type of test, and thus reduce the risk of disease progression to AIDS.

Viral load pretreatment values are an important factor for choosing an initial ARV regimen with the observation that some of the selected ARV drugs or regimens may be associated with poorer response in patients with high viral load basevalues.

Isolated "blips" or transientlow values of viremia, less than VL 200 copies/mL, are not uncommon in successfully treated patients who have a high degree of adherence and are not considered to pre-emit viral replication or to foreshadow virological failure. With modern ART regimens, about 10% of people per year can experience blips, although they have good adherence to ART.

Blips cause: the method of taking a blood sample and its processing, a laboratory error (contamination of testing equipment), intercurrent infections or vaccination. Blips must be differentiated from poor adherence and early virological failure.

Persistent viremia VL >200 copies/mL is associated with an increased risk of virological neu-success, which in the context of "Therapy as Prevention" (TasP), can lead to an increased risk of sexual transmission.

DHHS and AIDS Clinical Trials Group (ACTG) now define virological failure as confirmed values of VL >200 copies/ mL – a limit that eliminates the possibility of most cases of evident viral load caused by blips or differences in the detection limits of various types of test techniques and manufacturers.

In patients on an ARV regimen, viral suppression is achieved in 8-24 weeks, although in some patients this can last longer.

Recommendations for the frequency of RNA monitoring are:

C> After initiating ART or modifying therapy due to virological failure - Plasma *viral load* is measured within 2–4 weeks, and after that every 4–8 weeks until viremia is suppressed,

C> In virologically suppressed patients for whom ART has been modified for toxicity or regimen simplification – Viral *load* value measurement should be done within 4–8 weeks after the change of therapy to confirm the effectiveness of the new regimen.

C> In patients on a stable, suppressive ARV regimen - Measure the value of *viral load* should be repeated every 3-4 months with the aim of confirming continuous viral suppression. The possibility of monitoring every 6 months in patients with stable adherence and VL suppression for more than 2-3 years may also be considered.

C> If no viral suppression is achieved, a resistance test should be performed to include an alternative regimen.

**HLA-B*5701**

As part of the basic evaluation, it is necessary to conduct a screening test for HLA-B*5701 before initiating abacavir (ABC) to avoid the risk of hypersensitivity reaction (HSR). HSR is a multiorganic clinical syndrome seen within the first 6 weeks of treatment with ABC.

HLA-B*5701 positive patients should not be administered by ABC, and a positive result should be written into the history of the disease and educate the patient about the meaning of this test.

If the HLA-B*5701 test is not available, the ABC may be initiated with adequate clinical counseling and monitoring at any abs HSR mark.

## 2.2 Drug resistance testing

Resistance testing to ARV drugs is part of a routine hiv infection diagnostic algorithm. In routine diagnostics, **genotypic tests** are administered. They determine mutations in genes that encode reverse transcriptase and protease that cause the virus to resist drugs. The good side of genotype tests is their standardization. The finding of the genotypic test provides a list of ARV drugs, and the interpretation of the results of genetic analysis of the virus, i.e. information on whether the virus is resistant or susceptible to certain drugs. Genotypic tests provide information about resistance to NRTIs, NNRTI, INSTI and PI. Genotypic testing is preferred over phenotypic testing due to lower cost, shorter waiting times and greater sensitivity in the detection of wild types and resistant viruses.

**Phenotypic tests** measure the growth capacity of the virus in conditions of different concentrations of antiviral drugs. Phenotypic tests are very valuable in the analysis of resistance in patients treated with a large number of drugs, give us direct information about resistance regardless of multiple mutations and are the only possibility of determining resistance for new classes of drugs. Phenotypic tests are expensive and not widely available.

Resistance testing is indicated in the following situations:

- Newly discovered HIV-infected patients, regardless of whether their therapy will be initiated immediately or delayed. If delayed, testing should be repeated at the time when initiating ART is considered if we believe that there is a possibility of infection with a resistant virus or if the prevalence of resistance in the population exceeds 10%.
- The initiation of ART should not be postponed until the results of the resistance test come in. The mode can be modified after the test results are available.
- Patients with virological failure of treatment in whom the viremia exceeds 1,000 copies/mL. Drug resistance testing should be performed while the patient is on prescribed ARV drugs or within four weeks after the exclusion of therapy.

Patients with suboptimal suppression of viremia.

HIV-infected pregnant women, before initiating ART, as well as in those who became pregnant with detectable viremia while on therapy.

In patients with low viremia values, less than 500 copies/mL, drug resistance testing is not recommended.

After the appearance of resistance, it is necessary to change the combination of ARV drugs and choose a new one, to which the virus is sensitive. Resistance is most often the result of poor adherence to drugs, which leads to a reduced concentration of certain ARV drugs in the body that are no longer enough to stop the multiplication of the virus.

The results of determining resistance to certain ARV drugs enable targeted and more effective ART.

## 2.3 Testing of tropism coreceptors

The use of chemokine coreceptors CCR5 (a protein found on immune cells, corre- ceptor for HIV when the virus enters the cell) and/or CXCR4 to enter HIV into the cell is called corre-ceptor tropism. Hiv strains, given tropism, are divided into R5 strains, which use the CCR5 coreceptor; X4 strains, which use the CXCR4 coreceptor; strains of dual tropism that use both coreceptors, and in patients also appear heterogeneous populations of R5 and X4 strains (mixed tropism).

Testing of tropicism coreceptors should be done if the possibility of initiating CCR5 in-

A hybite (maravirox) that prevents HIV from entering target cells by binding to the CCR5 receptor. Genotypic and phenotypic tests are used.

The clinical indication for the determination of HIV tropicism is the virological failure of ARV treatment. It is pre-ordered simultaneously to determine resistance to reverse transcriptase inhibitors or protease or integrase, and to determine tropism to obtain complete information on all active ARV drugs, including maravirox (MVC). Tropism coreceptor testing is also recommended in patients who are planning to use CCR5 inhibitors due to side effects of treatment with other ARV drugs.

The determination of the tropism of the virus is necessary immediately before starting treatment with maravirox. Plasma viremia should be greater than 1,000 copies of HIV-1 RNA per mL of plasma. In people with viremia of less than 1,000 copies of HIV-1 RNA per mL of plasma or with immeasurable viremia, in whom the use of maraviroco is planned due to more severe side effects of ART, a genotypic tropism test is recommended in which proviral HIV-1 DNA is analyzed.

**HIV-2 infection**

HIV-2 infection is endemic in West Africa, but it is also possible in patients coming from countries that have social and economic ties to West Africa (France, Spain, Portugal, Brazil, Angola, etc.). There is a lack of accurate data on the prevalence of HIV-2 infection in the world, as there is no systematic monitoring of HIV-2 infection.

The possibility of possible HIV-2 infection should be considered in certain epidemiological conditions, when a person who has serologically confirmed HIV infection, but the values of HIV-1 RNA are low or undetectable, as well as in people who have CD4 cell values that decrease despite the virological suppression on ART. One-third of people who are not undergoing treatment and are infected with HIV-2 have VL below the detection limits.

In HIV-2 infection, the asymptomatic phase of the disease has a longer course, viral *load* values are lower compared to HIV-1 infection and lower mortality rates compared to HIV-1 infection.

The strategy for when people with HIV-2 infection include ART and which treatment regimen would be most effective has not been definitively defined because there have been no controlled, randomized studies.

It is believed that ART should be involved when diagnosing HIV-2 infection, as is the rule for HIV-1 infection, or immediately after diagnosis, with the aim of preventing disease progression and transmission of HIV-2 to other people.

HIV-2 is resistant to NNRTI, and NNRTI-based regimens are not recommended for HIV-2 treatment. The initial ART regimen for *ART-naïve* patients with HIV-2 monoinfection or HIV-1/HIV-2 co-infection should contain one INSTI and two NRTI, and the alternative regimen is bused PI (darunavir or lopinavir) with two NRTI.

Recovery of CD4 cell values in people with HIV-2 infection who are on ART is more modest than the recovery observed in people with HIV-1 infection. People with HIV-2 infection should be continuously checked for CD4 cell values, even when VL values are suprised, because the progression of the disease may occur despite undetectable viral *load* values.

**Goals of therapy**

The objectives of ART can be defined differently:

C> Maximum and sustained sustained plasma suppression of HIV RNA;

C> Reconstitution and preservation of immunological function;

C> Reducing HIV-related morbidity rates and prolonging survival, as well as improving quality of life;

C> Preventing HIV transmission.

Signs of virological success are: potent ARV regimen, excellent adherence, low basic vire-mia,

higher baseline CD4 values, rapid lowering of viremia in response to treatment.

## 2.4 When to include ARV treatment

Timely screening allows early diagnosis of HIV infection. In order for a person with HIV to take advantage of the benefits of early diagnosis, the guidelines recommend that ART be included immediately or as early as possible after diagnosis, with the aim of increasing the overall number of people who are on ART, including them in the care system, achieving virological suppression, and thus reducing the risk of HIV transmission to sexual partners and prevention of vertical transmission.

It starts from the assumption that the patient is ready and wants to start therapy, that he understands the benefits of it, but also the short-term and long-term side effects, as well as the necessity of regular medication for a longer period of time, and that he understands the necessity of safer behavior in order to prevent HIV transmission.

**Recommendations for inclusion of ART in patients without experience with ARV drugs, given by EACS, DHHS, IAS-USA, WHO and in BiH in 2020 are:**

- ART is recommended for all people living with HIV, regardless of CD4 cell values, with the aim of reducing morbidity and mortality, as well as to prevent hiv transmission to other people.
- It is recommended to include ART as early as possible after diagnosing HIV infection with the aim of earlier inclusion in the care system and achieving viral suppression.
- It is recommended to educate patients about the benefits that ART brings.

One should always take the time to prepare the patient to optimize adherence. Genotype resistance testing is recommended before initiating ART, in an ideal situation at the time of hiv diagnosis, and if this is not possible, then this testing should be done before initiating ART. If ART must be initiated before the results of genotype testing are known, it is recommended to include drugs with a high resistance barrier.

The primary goal of ART is to prevent HIV-related morbidity and mortality. Permanent viral suppression achieved by ART improves immune function, improves quality of life, reduces the risk of serious health complications, aids and *non-AIDS* defining complications, reduces the risk of HIV transmission to sexual partners, prevents perinatal transmission, and allows a person with HIV infection to reach a life expectancy that is no different from the lifespan of people who are not infected with HIV.

Two large, randomized, controlled studies START and TEMPRANO examined optimal time for initiating ART. Both studies have concluded that people living with HIV have a lower risk of developing AIDS or other more severe diseases if they were previously initiated with ART, when CD4 values are >500 cell./µL, than when the initiation of treatment is delayed, until cd4 values drop below 350 cel./µL. The benefits of incorporating ART in the earlier stages of HIV disease are a 72% reduction in the risk of developing severe INFECTIONS and AIDS-related cancers, reducing the risk of developing *non-AIDS* defining conditions by 39%.

Studies have proven that CD4 cell recovery is directly correlated with CD4 cell values at the time of initiating ART. Many people who are treated at CD4 values <350 cell/µL do not achieve CD4 values >500 cell/µL even after 10 years on ART, and have a shorter lifeexpectancy than people who have been treated at higher CD4 cell values.

The latest guidelines recommend that ART be initiated as early as possible after hiv diagnosis, regardless of CD4 cell values, on the day of diagnosis or within a few days or weeks after diagnosis, known as ***rapid ART***.

## 2.5 Treatment as prevention (eng. *Treatment as Prevention* – TasP)

Randomized clinical studies have proven that achieving viable viral suppression prevents sexual transmission of HIV. When ART is turned on to prevent HIV transmission, this strategy is called "Treatment as Prevention" - (*Treatment as Prevention* - TasP) or "*Undetectable* = *Untrans- mittable* or U=U, i.e. Undetectable = Non-transferable.

HIV-infected people receiving ART must also use other preventive measures with their sexual partner: condoms, pre-exposure prophylaxis (PrEP) for HIV-negative sex partners for at least the first 6 months after the introduction of the treatment and until the <200 copies/mL is achieved. HIV-infected people must maintain a high rate of adherence to ARV ter-apias since transmission is possible during periods of poor adherence or interruption of treatment. It is important to know that maintaining the value of viremia <200 copies/ml does not prevent infection or transmission of other sexually transmitted infections (STIs).

Earlier ART administration is a superior option that benefits both HIV-infected people and their uninfected partners. ART reduces viral load, i.e. infectivity of HIV-infected people, and reduces the risk of viral transmission. HPTN 052 is the first randomized multinational clinical study conducted by the HIV Prevention Trials Network (HPTN), which showed that the treatment of HIV-infected people with ART can reduce the risk of sexual transmission of HIV to uninfected partners. In the HPTN 052 study, involving 1,763 HIV discordant heterosexual couples from Africa, Asia and the Americas, ART initiated by patients with CD4 values between 350 and 550 cel./µL reduced the HIV incidence in their HIV-uninfected partners by 96%, compared to patients whose ART introduction was delayed until the moment when CD4 values were below 250 cel./µL. Among 877 couples, who were in the group with delayed initiation of ART, there were 27 hiv transmissions, unlike the second group, in which treatment was not necessary due to their own health, with the emergency introduction of ART there was only one hiv transmission. The HPTN 052 study provides compelling evidence for new approaches to HIV prevention and care and evidence that suppression of viremia in patients with good adherence to ART and without concomitant STIs drastically reduces the risk of HIV transmission.

Plasma *viral load* is the main determinant in HIV transmission. The risk of sexual transmission of HIV is directly correlated with plasma *viral load* values. Prospective cohort analysis among discordant heterosexual couples in Africa showed that HIV transmission was less common in those on ART. In this study, the majority of HIV transmissions (70%) occurred when viremia was more than 50,000 copies/mL.

Incorporating ART to HIV-infected patients can be an effective strategy in reducing HIV transmission. We have strong evidence that ARV drugs prevent HIV infection. Greater access to HIV testing and counseling, as well as ARV therapy, has led to new opportunities for the integration of prevention and care. The "test and treat" strategy, in which all people with a positive test are immediately involved with ART regardless of CD4 values, can lead to an essential advance in prevention.

It is also important to emphasize the necessity of good adherence to the ordered regimen with consistent use of condoms. Transmission is possible during periods of poorer administration or during temporary interruption of treatment. The European PARTNER study, which included only the MSM population and published its results in March 2014, stated that there was no case of HIV transmission after 44,500 sexual intercourse without a condom.

Rates of risky behavior can be increased in recipients of a powerful ART combination. One me-ta-analysis showed that the prevalence of unprotected sexual intercourse was increased in HIV-infected people who believed that if they received ART and had suppressed *viral load*, they therefore had protection against HIV transmission. A viable *viral load* below the detection limits can drastically reduce, but not guarantee, the absolute absence of HIV in genital secretions.

Consistent and effective use of ART results in a reduction in *viral load*, with consistent use of condoms, safer sexual intercourse, safer drug consumption, detection and treatment of STIs, all together are essential for the prevention of HIV transmission through blood or sexual intercourse.

## 2.6 Benefits of early introduction of ART

**Possible benefits of early introduction of therapy**: At CD4 >500 cell values/µL, the benefits are the pre-development of irreversible immune system damage, reducing the risk of HIV-related complications (TB, NHL, KS, peripheral neuropathy, HPV-related malignancies, cognitive connection disorders-

neither for HIV), reduced risk of neoportunisc complications and *non-AIDS* complications (CVD, kidney , liver disease, malignancies, infections), and lowering the risk for HIV transmission.

**HIV-related nephropathy (HIVAN)**: It can occur at any CD4 cell value. Viral replication is associated directly with renal damage. Therefore, ART should be initiated in patients with HIVAN already at the first signs of renal dysfunction, regardless of cd4 values.

**Co-infection with HBV and HCV**: In co-infected patients, ART can slow the progression of liver disease by preserving or recovering immune function and reducing HIV-related immune activation and inflammation. Some drugs that are active against HIV are also active against HBV (tenofovir – TDF, lamivudine – 3TC, emtricitabine – FTC) and can prevent the development of more severe liver disease by suppressing HBV replication. ARV drugs do not directly inhibit HCV replication. HCV treatment performs better when HIV replication is under control or when CD4 values are increased. Earlier initiation of treatment for HIV infection in co-infected with HBV and HCV may reduce the risk for the progression of liver disease.

**Cardiovascular disease**: Untreated HIV infection may be associated with an increased risk for CVD. Early control of HIV replication using ART can be used as a strategy to reduce the risk for CVD.

**Neurological diseases**: Earlier initiation of ART can prevent CNS dysfunction.

**Age**: Introducing therapy at a younger age can give a better immune and clinical outcome than introducing it in old age.

**T-cell inflammation**: ARV treatment lowers the level of Inflammation and Activation of T cells, which is associated with a reduced risk for AIDS-related morbidity and mortality.

**Prevention of perinatal transmission**: Combined ART during pregnancy reduces the rate of perinatal transmission of HIV to 0.5%.

**Prevention of sexual transmission**: Treatment of HIV-infected people can significantly reduce sexual transmission of HIV. A lower value of plasma viremia is associated with reduced concentrations of the virus in the genital secretions. Early ART is more effective in preventing HIV transmission than behavioral changes or biomedical interventions, such as condom use, circumcision, vaginal microbicides, and PEP. Viremia suppression in patients with good adherence reduces the risk of HIV transmission, although ART is not a substitute for condom use and behavioral change.

**Malignomies:** Initiating ART to suppress HIV replication and maintaining CD4 values >350-500 cell/µL can reduce the incidence of both AIDS-defining and *non-AIDS* defining malignancies.

**Poor adherence:** Adherence to therapy is crucial for achieving viral suppression and translating the occurrence of drug-resistant mutations.

**Costs:** One study concluded that the annual cost of care is 2.5 times higher for patients with CD4 <50 cell./µL than for patients with CD4 values >350 cell./µL. A large part of the cost of medical care in patients with advanced infection relates to hospitalization and ARV drugs.

## 2.7 Specific problems in patients with one of the opportunistic infections

In the advanced stages of HIV disease, OI or malignancies may require urgent management before engaging ART. The optimal time to initiate ART in people with some OI is not pre-planned, although data for most OI, including TB, speak in favor of initiating treatment immediately after the introduction of treatment for OI, as this improves survival rates, although the incidence of an inflammatory immune reconstitution reaction may be increased.

Today, the early introduction of treatment is considered useful except in the case of CNS-type OI-type cryptococcal meningitis and CNS tuberculosis. In cases of TB, PCP, cryptococcal meningitis, emergency therapy may increase the risk of IRIS (immune reconstitution inflammatory syndrome), and a shorter delay in initiating ART would be necessary. It is desirable to include ART within two sed-mics of the diagnosis of OI. In patients for whom there is no effective treatment except for op-

the development of immune function, as a result of ART (e.g. *Cryptosporidiosis, Mycrosporidiosis*, PML, HIV associated dementia), the benefits of powerful ART outweigh the increased risk, and therefore te-rapi a should be initiated as soon as possible.

For patients with malignancies, art initiation should not be delayed. Viral suppression achieved with ART is associated with prolonged survival of people who are involved treatments for AIDS-related lymphomas.

## 2.8 Components of ARV mode

For the treatment of HIV infection, the Food and Drug Administration (FDA) has approved more than 30 antiretroviral drugs, which are divided into several classes:

nucleoside/nucleotide reverse transcriptase inhibitor (NrTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (INSTI), fusion inhibitors, CCR5 antagonists. Two drugs, ritonavir (RTV) and cobicistat (Cobi), are used as boosters to improve the pharmacokinetic profile of PI and INSTI elvitegravir (EVG).

In order to achieve the goals of treatment through suppression of HIV replication to the lowest possible level, it is necessary to include multiple ARV drugs at the same time. The initial ARV regimens for *ART-naïve* patients are composed of two NRTIs, namely abacavir/lamivudine (ABC/3TC) or tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir dizoproxil fumarate/emtricitabine (TDF/FTC) plus some medicine from one of the following three classes: INSTI, NNRTI or busted PI. The latest guidelines support the use of a two-drug regimen for the initial treatment of people with HIV: dolutegravir (DTG) plus lamivudine (3TC). The efficacy of the two-drug regimen is similar to the efficacy of the three-drug regimen: DTG + TDF/FTC.

Successful management of HIV infection involves the inclusion of powerful ARV combinations. The ARV regimen must be taken as prescribed and continuously, i.e. lifelong, with the aim of suppressing chronic and incurable infection. The design of an ARV regimen is relatively simple in the initial therapy unless there is initial resistance, although it can become more complex if the treatment experiences neus-peel, that is, if drug resistance develops or if the patient experiences unexpected and severe side effects or drug interactions.

Choosing an ARV regimen is crucial, since a good choice, individualized for each patient and tailored to his needs, can result in recovery from the disease and give long-term benefits to the patient.

## 2.9 Choosing an initial ARV mode

Factors to consider before choosing an initial regimen are:

**Patient characteristics**: HIV RNA, CD4 cells, HIV resistance test results, HLA-B*5701 status, expected degree of adherence.

**Comorbidities:** cardiovascular disease, hyperlipidemia, renal disease, liver disease, osteo-porosis , psychiatric illness, pregnancy or possible conception, co-infections of HCV, HBV, TB.

**Characteristics of the regimen**: genetic barrier to resistance, possible side effects, interactions with other drugs, number of tablets, frequency of dosing, combinations in a fixed dose, necessity of taking with a meal of food, price and availability of the regimen.

**ARV medications to avoid in some clinical situations:**

C> **CD4 <200 cell/µL:** Do not include due to higher rates of viral failure RPV; DRV/r + RAL;

C> **HIV RNA >100 000 copies/mL:** Do not include due to higher rates of viral failure of RPV; ABC/3TC + EFV or ATV/r; DRV/r + RAL;

C> **HIV RNA >500 000 copies of mL:** Do not include due to higher rates of viral failure DT- G/3TC;

C> **HLA-B*5701 positive:** Do not include due to the risk of hypersensitivity of ABC.

## 2.10 Overview of the most commonly used components of ARV mode

Initial ARV regimens typically contain a dual NrTI "base" and a third, "supporting" drug.

**NRT-based modes**

The preferred combinations of Nrti are coformulations of two drugs in one tablet: ABC/3TC, TAF/FTC, TD- F/3TC, TDF/FTC. Coformulation improves the applicability and adherence of the patient. The drug 3TC can be included as an individual NrTI with DTG or with busted DRV. Dual Nrti are used in a van-nation with a single INSTI, NNRTI and PI busted with RTV and cobicistate; or with CCR5.

In clinical practice, older NRTI drugs (ZDV, ddI, d4T) are no longer recommended due to toxicity such as peripheral neuropathy, mitochondrial toxicity, hepatic steatosis, lactic acidosis, lipoatrophy, and bone marrow suppression.

**abacavir (ABC) + lamivudine (3TC)**

This co-formulation is dosed once a day. The drug ABC is a powerful NRTI, with no major interactions with other drugs. It is well tolerated in prolonged shelf life, although it can cause sometimes serious HSR. Hypersensitivity to ABC is closely related to HLA-B*5701, and ge- netic screening should be done before the introduction of ABC, with those who have a positive test result not including this drug. Patients with a negative HLA-B*5701 test result are much less likely to experience HSR and should be advised to monitor for possible symptoms of this reaction. ABC is associated with undesirable cardiovascular effects in some but not all studies; The use of ABC is associated with an increased risk for IM, especially in patients with pre-existing cardiac risk factors. In patients with high HIV VL prior to the inclusion of treatment (>100,000 copies/mL), per one study, regimens containing ABC/3TC were not as effective in suppressing HIV viremia compared to those containing TDF/FTC. Nevertheless, the ABC/3TC combination is still a good alternative option of dual NRTIs in some *ART-naïve* patients. ABC does not cause renal dysfunction and may be administered instead of TDF in patients who have active renal dysfunction or in those at risk of renal dysfunction.

Inclusion of ABC/3TC with EFV, ATV/r, ATV/c, DRV/c DRV/r or with RAL is recommended exclusively for patients with pre-treatment VALUES of HIV RNA <100 000 copies/mL. Resistance to ABC is similar to that of TDF, with the K65R mutation. TAM (thymidine analog mutation) can lower the strength of ABC.

DTG/ABC/3TC is available in fixed combination.

**tenofovir (TDF) + emtricitabine (FTC)**

It is a powerful coformulation that is taken once a day, and according to American and European guidelines is recommended as the preferred NRTTi combination in most patients. It is also available in co-formulation with EFV, EVG/c and RPV as a combination of three drugs in one tablet. In ARV-naïve patients, this coformulation showed powerful virological suppression. ABC/3TC has an inferior virological response in comparison with TDF/FTC in patients who had pretreatment values of HIV RNA >100,000 copies/mL.

TDF is usually well tolerated in short-term use, although it is associated with bone and renal toxicity, and renal function monitoring is required.

Risk factors include advanced HIV disease, a history of long-term treatment, low body weight, and previously existing renal disorders. There is a higher risk of renal dysfunction when TDF is included in PI-based regimens reinforced with PK boosters (RTV or Cobi), which increase the concentration of TDF. TDF has interactions, especially with ATV (lowers its levels). TDF in combination with either FTC or lamivudine is the preferred combination of NrTI, especially in patients with HIV/HBV co-infection, since these drugs are active against both viruses.

TDF-containing regimens are associated with a decrease in bone mineral density (BMD), especially if TDF/FTC is coadministered with RTV or Cobi boosters. A larger decline in BMD was reported in TDF/FTC recipients than in ABC/3TC recipients. Clinicians must monitor renal and bone parameters when they turn on TDF, especially with boosters for safety during therapy.

Hiv resistance of TDF involves the K65R mutation, which can lead to cross-resistance with some other drugs in this class.

**tenofovir alafenamide/emtricitabine (TAF/FTC)**

The combination of TAF/FTC is virologically non-inferior compared to TDF/FTC. TAF affects bone mineral density less than TDF and affects markers of renal tubular dysfunction less. Injecting TAF in *ART-naïve* patients is associated with weight gain compared to TDF and ABC. TAF/FTC is available in co-formulation with BIC, DRV/r, EVG/c and RPV.

TAF and FTC are recommended as nrti combination for initial ART for most people with HIV in combination with BIC, DTG or RAL. They are active against HBV. LDL and HDL and triglyceride values increased more in the TAF recipient group than in the TDF recipient group, with no changes in the ratio between total cholesterol and HDL.

**tenofovir (TDF) + lamivudine (3TC)**

There are no significant differences regarding treatment success between 3TC recipients and FTC recipients in combination with TDF. The virological efficacy of TDF/FTC was comparable to TDF/3TC when combined with some NNRTI or with some busted PI. TDF/3TC is available at a fixed dose with DOR 100 mg, EFV 600 mg and EFV 400 mg.

TDF/3TC and TDF/FTC are recommended NrTI combinations for most people with HIV if combined with DTG or with RAL.

**lamivudine (3TC) and emtricitabine (FTC)**

In the Nrti class, 3TC and FTC drugs are similar and can be used as alternatives. Either one or the other are included in the dual Nrti "baseline". Both drugs are very well tolerated, although ftc can cause hyperpigmentation, especially in people with darker skin color. The single mutation, M184V, refers to the high degree of HIV resistance at 3TC and FTC. Both of these drugs are also active against hepatitis B virus, although people with HBV co-infection with these drugs should necessarily include some HBV active drug.

**lamivudine (3TC) as a single drug of the NRTIs class**

The recommended regimen for initial therapy for most people with HIV infection in the latest directions is a fixed combination of DTG/3TC, which is not inferior compared to DTG + TDF/FTC in patients with HIV RNA values <500 000 copies/mL, who do not have HBV co-infection or have unknown HBV status. It is not recommended for people who initiate ART before the results of HIV resistance are known.

In cases where ABV, TDF or TAF cannot be included, 3TC/DTG or 3TC/ may be administered DRV/r.

**zidovudine (ZDV) + lamivudine (3TC) coformulation**

This combination appeared as the first coformulation and was widely used, with dosage twice a day. In the study on ABC/3TC and ZDV/3TC (both in combination with EFV), virological responses were approximately the same in both groups, and the increase in CD4 values was more pronounced in ABC/3TC recipients. ZDV can cause macrocytic anemia, sometimes very severe, a feeling of fatigue , mitochondrial toxicity, including lactic acidosis, hepatic steatosis and lipoatrophy. Given that ZDV/3TC has higher toxicity than TDF/FTC or ABC/3TC, and is dosed twice daily, ZDV/3TC is recommended as an acceptable option of dual NrTI. Since it has been the forefront of research into numerous studies on the prevention of perinatal transmission, zidovudine is still a precautionary NrTI for the treatment of pregnant women. This coformulation has minimal interactions with other ARV drugs. The zdv resistance barrier is quite wide.

**<u>INSTI-based modes</u>**

Integrase inhibitors in coadministration with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTI) are recommended as a first-line treatment for HIV infection, and fixed-dose combinations are preferred to achieve better regimen adherence. Drugs from the INSTI odo-breni class for use are: dolutegravir, biktegravir, raltegravir and elvitegravir.

These regimens have a high rate of viral suppression, minimal toxicity and a low risk of interaction with other drugs. BIC and DTG-based regimens have a higher barrier to resistance and can be administered in cases of rapid initiation of ART, immediately after hiv diagnosis, before the results of resistance testing are available. They have a lower number of tablets compared to regimens containing RAL. Nevertheless, RAL-based regimens may be preferred for fertile people who want to become pregnant.

INSTI regimens lead to weight gain. In eight randomised trials with *ART-naïve* patients, weight gain in week 96 was equally in the BIC-based group of recipients and dtg-based regimens, about 3.5 kg. More pronounced connection was observed after the initiation of TAF, as well as when switching from TDF to TAF, and especially with INSTI.

**biktegravir (BIC)**

Biktegravir is a drug from the INSTI class that has powerful antiretroviral activity, has shown high rates of virological suppression, is dosed once a day with emtricitabine and tenofovir alafenamide, has a high genetic barrier to resistance, low potential for possible interactions with other drugs, has fewer treatment-related side effects (incidence >5% were diarrhea, nausea and headache), and long-term tolerance.

An important advantage of a drug that is a fixed combination of biktegravir/emtricitabine/tenofovirafenamide (TAF) is that it contains tenofovir alafenamide (TAF) which has significantly fewer side effects than tenofovir disoproxil fumarate (TDF). TAF significantly lowers glomerular filtration compared to TDF. Also, proteinuria, albuminuria and lowering bone density are less common or absent in people receiving TAF.

The fixed bixtegravir / emtricitabine / tenofovir alafenamide combination has an advantage over the fixed dolutegravir/abacavir / lamivudine combination, as abacavir is associated with myocardial infarction, which is not the case with tenofovir. A fixed combination of biktegravir, emtricitabine and tenofovir alafenamide will find use in elderly patients in whom the use of abacavir is not desirable due to cardiovascular risk, and the use of TDF is not desirable due to impaired renal function.

BIC-based regimes were non-inferior compared to DTG-based regimes. In women of childbearing age who intend to become pregnant, DTG could be one of the alternatives due to the prevalence of NTD associated with exposure to DTG at the time of conception.

There is insufficient data to determine whether the use of BIC is safe at the time of conception and effort.

**dolutegravir (DTG)**

Dolutegravir is an integrase inhibitor that does not need busting and has shown efficacy even after the development of resistance to raltegravir, the first drug in the INSTI class. Although cross-re-zistention between dolutegravir, raltegravir and elvitegravir has been described, three drugs from the class, resistance to do-lutegravir is slow to develop. It has a higher generic barrier to resistance than other INSTI and a small number of interactions with other drugs. DTG has high efficiency in achieving HIV suppression. DTG-based regimens (with TAF/FTC or ABC/3TC) have shown the same virological efficacy as that of BIC/TAF/FTC. It is given once a day, with a meal or without food. It is well tolerated. In combination with ABC/3TC or TDF/FTC is the recommended regimen for ART-naïve patients. It has proven superior efficacy over efavirenc and darunavir/ritonavir and raltegravir in patients who have previously been on ART but have not received other integrase inhibitors. The most common adverse reactions are nausea (13%), diarrhea (18%) and headache (13%) which were rarely the reason for giving up further administration of the drug. Women of childbearing age should do a pregnancy test before initiating DTG. DTG performed well in patients who initiated treatment at VL >100,000 copies/mL values.

The latest guidelines recommend a two-drug regimen of DTG/3TC for initial therapy. DTG/3TC was non-inferior compared to the three-drug DTG+ TDF/FTC regimen in terms of virological efficacy. DTG/3TC is the recommended regimen for most people with HIV except for: people with pre-treatment

HIV RNA values >500,000 copies/mL; CD4 <200/cell/μL with confirmed hepatitis B virus co-infection or people who will initiate ART before hiv ge-notype testing results are available.

**raltegravir (RAL)**

Raltegravir is the first INSTI approved in *ART-naïve* patients and in patients with ARV experience. He has the longest experience in applying. It is dosed twice a day and is one of the preferred options for pregnant women. Its disadvantages are a larger number of tablets, it is dosed twice a day, it is not in STR, it has a lower barrier to resistance compared to BIC or DTG, and two mutations are enough to develop resistance to raltegravir. It showed similar efficacy compared to efavirenz, with the simultaneous use of tenofovir and emtricitabine. Raltegravir led to a faster decline in viremia than efavirenca. It is well tolerated and no significant lipid elevations have been observed. Of all the integrase inhibitors, it has the least interaction with other drugs. The most significant side effect is the elevation of creatine-kinase.

**elvitegravir (EVG)**

Elvitegravir is available as a fixed combination with cobicistat, tenofovir/emtricitabine. Cobicistat acts as a PK invigorating agent for the drug elvitegravir, and allows dosing once a day. It must be taken with food. It is only approved in patients with creatinine clearance >70 mL/min. It has a lower resistance barrier compared to regimens containing DTG or BIC and has a higher potency for interactions with other drugs due to the combination of EvG with cobicistat, which is a cytochrome P (CYP)3A4 inhibitor.

**Nnrti-based regimens**

Nnrtis-based regimens (DOR, EFV, RPV) may be one of the options for some patients, although these drugs, especially EFV and RPV, have a low barrier to resistance. Individual mutations can transmit cross-resistance within a class. They interact with many other drugs, including other ARV drugs. NNRTI-based regimens are used in patients who experience side effects with the use of INSTI or experience excessive weight gain with the use of INSTI. They showed virological strength and longevity.

Approved NNRTI medicinal products are: DLV, EFV, DOR, ETR, NVP and RPV. DOR, EFV, and RPV-based regimens fall into the Recommended *Initial Regimen category in some clinical situations for ART-naïve patients*.

**doravirin (DOR)**

Doravirin is the third generation nnrti that is available as a single tablet and as a fixed combination with 3TC/TDF, and is dosed once a day. It has a good resistance profile compared to nnrti, and it is not necessary to take it with a meal of food. It is non-inferior compared to EFV and DRV /r. It has a better CNS safety profile compared to EFV and a more favorable lipid profile compared to DRV/r and EFV. It has fewer interactions with other drugs than EFV or RPV, and unlike RPV, its virological efficacy is not compromised in patients with high viral and low CD4 cell values.

DOR-based regimens were not subject to direct comparison with INSTI-based regimens in clinical studies. There is currently no data on the safety of dor use in pregnancy.

**efavirence (EFV)**

Efavirenc has long been the preferred NNRTI because of its strength and tolerance, and was dosed once a day. Short-term toxicity is usually transistor and does not require interruption of treatment. The most common side effects that appear at the beginning of treatment are CNS symptoms, including non-restful, nightmarish dreams, dizziness, insomnia and memory loss. EFV is usually well tolerated over a longer period of time. It is virologically superior to some regimens that are new to PI. The virological advantage of EFV is most pronounced in patients whose VL values prior to the inclusion of ART >100 000 copies/mL. EFV may cause elevated ldl choleste-rol and triglyceride values.

Resistance to EFV is similar to that of other drugs in the class. Even with individual mutations, especially K103N and Y 181 C or I, there is usually high-grade resistance to NVP. On the other hand, the long serum half-life of EFV can allow for sustained activity and limited resistance, even with compromised adherence. The EFV is not inferior to RPV, and yet the EFV has caused more shutdowns due to side effects. In clinical studies, some regimens demonstrated superiority compared to EFVs based on fewer exclusions due to undesirable effects: DTG was superior compared to EFV; RAL was superior compared to EFV after 4-5 years due to frequent exclusions due to side effects in the EFV group than in the RAL group.

EFV has minimal interactions with rifamycins, making it an option for patients who are not treated with TB. As a single tablet regimen, EFV 600 mg is available with TDF/FTC or TD-F/3TC and as EFV 400 mg with TDF/3TC.

EFV at a reduced dose of 400 mg is non-inferior compared to EFV 600 mg (and with DTG) per hundred-pama viral suppression. Side effects and exclusion of treatment occurred less frequently in the EFV 400 mg recipient group, and a lower number of CNS adverse reactions were reported. A dose of 400 mg EFV is approved for initial treatment in HIV infection.

**Rilpivirine (RPV)**

Rilpivirine has significantly improved its safety profile compared to efavirenca, it has fewer side effects including restless, nightmarish dreams and dizziness. A regimen containing rilpivirine was the preferred option in the 2017 EACS guidelines. It is indicated in combination with other ARV drugs in the treatment of *ART-naïve* patients with VL <100 000 copies/mL and CD4 values >200 cell./µL. It is also available in coformulations with emtricitabine/tenofovir DF. It is administered once a day with a meal of food.

It should not be administered in conjunction with proton pump inhibitors, and must be dosed separately from H2 blockers and antacids. Rilpivirine has fewer side effects than EFV, a very good lipid profile and activity against hepatitis B infection. Among patients with virological failure, the development of resistance to both NNRTI and NRTI was more common in rilpivirine recipients than in efavirenc recipients.

**nevirapine (NVP)**

Nevirapine is administered twice a day and is available as a tablet taken once a day. Its short-term toxicity includes rashes, but not CNS side effects accompanying EFV. Nevertheless, NVP can cause sometimes severe or even fatal hepatic HSR in the first weeks of treatment. In some studies, this was more common in women with higher CD4 cell values when initiating NVP (women with CD4 values >250 cell/µL, men with values >400 cel./µL), and NVP should not be administered in such individuals. Patients who experience an increase in CD4 values above this threshold can safely continue treatment without the risk of side effects. Resistance to NVP is similar to that of efv. It is widely used during pregnancy, as it reduces the risk of HIV trans-mission to the fetus. For the first 14 days, NVP is administered 200 mg per day and then 400 mg per day as a maintenance therapy. It is recommended to monitor serum transaminases at the beginning, after two weeks after increasing the dose, and once a month during the first 18 weeks of treatment.

**PI-based modes**

PI-based regimens, especially when reinforced with PK, or with ritonavir (RTV) or with cobistat (Cobi), showed virological strength and a high barrier to resistance. PI-based regimens are recommended when early initiation of ART is required, before the results of resistance testing are available, and when it comes to patients whose adherence to therapy is questionable. Busting with RTV adds strength and convenience, allows for less frequent dosing and fewer tablets per dose, although this may have additional and side effects or drug interactions. Transient gastrointestinal disorders and metabolic disorders, such as hi-perlipidemia and insulin resistance, are associated with the use of PI. Their incidence varies from one PI to another. Newer PI differ in terms of propensity to cause metabolic complications, which depend on the dose of RTV. Two large observational *cohort* studies suggest that LPV/r, IDV, FPV or DRV/r may be associated with an increased rate of IM.

The criteria for classifying the preferred PI in *ART-naïve* patients are: demonstrated superiority in virological efficacy, dosage once a day, fewer tablets than older regimens based on PI and good tolerance. Based on these criteria, once daily dosed with DRV/r, DRV/c, ATV/c or ATV/r in combination with two NRTIs are recommended PI. DRV/c/TAF/FTC is now also available as a single-tablet mode.

Other PI, LPV/r, FPV/r unbuffered AtVs and SQV/r are no longer recommended therapeutic options for initial therapy as they have a higher number of tablets, lower efficacy and increased toxicity.

**atazanavir (ATV)**

The ATV is switched on once a day with a meal of food, and can be used with RTV or with cobicystate. Busting with ritonavir raises drug levels without additional toxicity and has improved virological activity compared to an unbusted ATV. In the guidelines, ATV/r or ATV/c is an alternative therapeutic option. It is usually well tolerated and has fewer GI and lipid effects than other PI; it often causes indirect hyperbilirubinemia. Untested ATV should not be included with TDF, since this NrTI lowers its concentration levels, and absorption may be reduced due to the simultaneous use of drugs that suppress gastric acid.

**darunavir (DRV)**

DRV must be included with busting with RTV or cobicistat. DRV/r is used both in initial therapy and in the "salvation regimen". The ARTEMIS study compared DRV/r to LPV/r, both in combination with TDF/FTC, and proved that DRV/r was not inferior to LPV/r. At week 96, the virological response to DRV/r was superior to LPV/r. Among participants whose initial viral values were greater than 100,000 copies/mL, the rates of virological response were lower with LPV/r than with DRV/r.

The FLAMINGO study compared DRV/r and DTG, both in combination with two NRTIs, and proved that rates of virological suppression at week 96 were higher in DTG recipients.

The DRIVE-FORWARD study compared DRV/r and DOR in combination with two NRTIs. DOR was uninferi-oriented compared to DRV/r.

DRV/r is the recommended PI for initial ART. It is relatively well tolerated, although it can cause GI disorders and hyperlipidemia. It has a high genetic barrier to resistance. It is administered once a day with a meal of food.

DRV/c/TAF/FTC is now also available as a single-tablet regimen, not recommended in patients with CrCl <30 mL/min, and drv/c + TDF/FTC is not recommended in crcl patients <70 mL/min.

**lopinavir (LPV)/ritonavir (RTV)**

This coformulated busted PI can be included once or twice a day. It is associated with more metabolic complications (hyperlipidemia, especially hypertriglyceridemia) and gastrointestinal side effects than AV or DRV that are enhanced with PK. It is also associated with an increased risk for cardio-vascular episodes, and is recommended in the Other *PI/r* category. The ACTG 5142 study showed that the regimen with LPV/r with two NRTIs had lowered virological efficacy when compared with EFV, but that cd4 response was better with LPV/r, and there was less resistance from virological failure. It is powerful and has a wide resistance barrier. PI is recommended for use in pregnant women; The dosage should not be used once a day in pregnant women, especially during the third trimester.

## 2.11 Choose between INSTI, NNRTI, or PI-based modes

The choice between an INSTI, NNRTI or PI as a third drug in the initial ARV regimen is based on the regimen's efficacy profile, genetic barrier for resistance, drug side effects, patient comorbidities and possible drug interactions. INSTI-based regimens are very effective, have few side effects, have no significant interactions associated with CYP3A4, and are better tolerated compared to DRV/r-based regimens as PI. Due to these reasons, all three available INSTI are included in the Recommended *Regimens* category.

Alternative modes are based on NNRTI or PI.

For some patients, NNRTI-based regimens are optimal, as they have low genetic barriers to resistance, especially in patients with suboptimal adherence. EFV-based regimens also have high viral efficacy in patients with high viremia (except when EFV is associated with ABC/3TC). Due to CNS side effects, EFV-based regimens are less tolerated. RPV has fewer side effects than EFV, has a desirable lipid profile and is available in a coformulated tablet. However, RPV has lower virological efficacy in patients with basic HIV RNA values >100,000 copies/mL and low CD4 values <200 cell./µL.

The advantage of busted PI regimens is that a very small number of patients who experience a virological failure develop mutations (requiring multiple mutations). Most PI-based regimens include RTV or cobicistat; they can be dosed once or twice a day and have a higher number of tablets than NNRTI regimens. Drug-to-drug interactions in PI regimens busted with RTV or cobicistat are more common than in NNRTI-based regimens. If a decision is made to start ART with a busted PI, a busted DRV would be the best option. In terms of side effects, a higher incidence of gastrointestinal side effects and an increase in triglycerides and total cholesterol were reported in patients receiving LPV/r than was the case with DRV/r.

ATV/r has shown excellent virological efficacy in clinical studies and has a small number of metabolic side effects compared to other PI regimens. The latest clinical studies have shown that ATV/r had higher rates of side effects associated with discontinuation of the drug than was the case with DRV/r and RAL/r. Due to these facts, efv, rpv and atv/r-based modes are not preferred modes, but are categorized as *alternative modes*. Nevertheless, some alternative regimens may be optimal for some patients.

**CCR5 antagonists**

**Maravirok (MVC)** is the only drug available in this class. It is only active against HIV, which exclusively uses the CCR5 coreceptor, and expensive testing for coreceptor tropism must be done to determine whether treatment with this drug is appropriate. It is dosed twice a day, and its doses must be adjusted in accordance with other coadministered drugs in therapy. Initially, it was primarily used as a single component in the "salvation regime". There are few known unintentional actions; there is no data on its long-term safety. Resistance to MVC is described. The virusologically weak response to MVC usually occurs due to the presence of viral tropism of CXCR4 cortex- ceptor.

**Fusion inhibitors**

**Enfuvirtide (ENF, T-20)** is given subcutaneously twice a day; it usually causes injection site reactions. It is active against HIV, which is resistant to other classes of ARV drugs, and has been used in "rescue regimens". Since newer classes for hiv resistance have become available , enfuvirtide use has decreased.

## 2.12 Available ARV drugs

ARV drugs are classified into six classes according to the mechanism of action:

1. NRTIs – Nucleoside/nucleotide reverse transcriptase inhibitors;
2. INSTI – Integrase strand transfer inhibitors;
3. NNRTI – Non-nucleoside reverse transcriptase inhibitors;
4. PI – Protease inhibitors;
5. Fusion inhibitors;
6. CCR5 antagonists.

| ARV DRUGS: DOSAGE AND SIDE EFFECTS | | | | |
|---|---|---|---|---|
| **INN ARV drug** | **Abbreviation** | **Factory name and shape** | **Dosage** | **Side effects** |
| **NRTIs and NtRTI - Nucleoside/nucleotide reverse transcriptase inhibitors** | | | | |
| abacavir | ABC | Ziagen tbl. | 2x300 mg or 1x600 Milligrams | Hypersensitive reaction, nausea, rash, headache |
| emtricitabine | FTC | Emtriva Capt. | 1x200 mg | Diarrhea, rash, headache, lactic acidosis |
| lamivudine | 3TC | Epivir tbl. | 2x150 mg or 1x300 Milligrams | Diarrhea, lactic acidosis, rash, headache |
| zidovudine | ZDV | Retrovir caps. | 3x200 mg or 2x300 Milligrams | Anemia, neutropenia, lactic acidosis, hepatitis, myositis, headache |
| ABC+3TC | KVX | Kivexa tbl. | 1x600/300 mg | |
| TDF+FTC | TVD | Truvada tbl. | 1x300/200 mg | |
| ZDV+3TC | CBV | Combivir tbl. | 2x300/150 mg | |
| tenofovir/ dizoproxil fumarate | TDF | Wiread tbl. | 1x300mg | Renal insufficiency |
| tenofovir-alafenamide | TAF | | Only as a fixed comb; TAF/FTC; TAF/FTC/RPV; TAF/FTC/BIC; TAF/FTC/ ELV/c | Exacerbation of hepatitis B after treatment |
| **NNRTI – Non-nucleoside reverse transcriptase inhibitors** | | | | |
| efavirence | EFV | Stocrin tbl. | 1x600 mg | Dizziness, headache, non-sledding, nightmares, loss of concentration, hepatitis |
| nevirapine | NVP | Viramune tbl. | 1x200 mg 14 days followed by 2x200 mg | Rash, hepatitis |
| | | Viramune XR tbl. | 1x200 mg 14 days followed by 1x400 mg | |
| etravirine | ETV | Intelence tbl. | 2 x 200 mg | Rash, nausea |
| rilpivirine | RPV | Edurant tbl. | 1x25mg | Depression, fewer side effects than EFV |
| doravirin | DOR | Pifeltro tbl. | 1x100mg | Insomnia, depression, headache |
| **PI - Protease inhibitors** | | | | |
| atazanavir | ATV | Reyataz Capt. | 1x400 mg 1x300 mg + 1x100 mg RTV | Hyperbilirubinemia, nausea, rash |
| lopinavir/ ritonavir | LPV/r | Kaletra tbl. | 2x400/100 mg or 1x800/200 mg | Diarrhea, meteorism, vomiting, dyslipidemia, hyperglycemia |
| ritonavir | RTV | Norvir tbl. | 2x300 mg for 10 days, then gradually increase to 2x600 mg | Dyslipidemia, hepatitis, diarrhea |

| | | | | |
|---|---|---|---|---|
| Darunavir | .DRV | Prezista tbl. | 2x600 mg + 100mg (DRV/RTV; or 1x800 mg/ + 1x150 mg DRV/Cobi | Rash, nausea, headache, hyperglycemia, hepatotoxicity, elevated creatinine (Cobi) |

| Integrase inhibitors | | | | |
|---|---|---|---|---|
| raltegravir | RAL | Isentress tbl. | 2x400mg | Nausea, headache, diarrhea, CPK elevation |
| dolutegravir | DTG | Tivicay tbl. | 1x50 mg; or 2x50 mg if take with EFV, NVP or TPV | Nausea, diarrhea, rash, insomnia, dizziness |
| elvitegravir | Evg | Vitekta tbl. | 1x85 mg with ATV/r or with LPV/r; 1x150 mg with DRV/r or with FPV/r | Stomach pain, vomiting, rash, depression, insomnia |
| biktegravir | BIC | Biktarvy tbl. | 1x50/200/25 mg (BIC/FTC/TAF) | Headache, diarrhea |
| **Fusion inhibitors** | | | | |
| enfuvirtide | ENF | Fuzeon inj. | 2x90 mg sc | Skin irritation |
| **CCR5 antagonists** | | | | |
| maravirok | MVC | Selzentry tbl. | 2x150; or 2x300; or 2x 600, depending on the combination | Abdominal pain, dizziness, rash, hepatotoxicity, orthostatic hypotension |

## 2.13 ARV regimens recommended for initiation of therapy in ART-naïve patients

A strong combination of drugs should be administered. Three main combinations apply:

- 1 INSTI + 2 NrTI
- 1 PK-busted PI + 2 NrTI
- 1 NNRTI + 2 NrTI

A fusion inhibitor, a CCR5 antagonist, is not recommended for initial ARV therapy.

**Regimens for ART-naïve patients**

INSTI-based regimens are preferred for *ART-naïve* patients due to their high virological effectiveness, excellent safety and tolerance profile, and because of the lower number of interactions with other drugs. For patients who have poor adherence, the preferred drugs of the INSTI class are BIC and DTG, as well as PI/r-based regimens given the high genetic barrier to resistance.

**EACS Guidelines 2020**
**Regimen for initial combination in *ART-naïve* HIV-positive adults**

| Mode | Special requirements | Additional instructions |
|---|---|---|
| **Recommended regimens** | | |
| **2 NrTI + INSTI** | | |
| ABC/3TC + DTG ABC/3TC/DTG | HLA-B*5701 negative HBsAg negative | ABC: HLA-B*5701, cardiovascular risk; Increased body weight (DTG) |
| TAF/FTC or TDF/FTC or TDF/3TC + DTG | | Increased body weight (DTG, TAF) TDF: Renal and bone toxicity. TAF dosing |
| TAF/FTC/BIC | | Increased body weight (BIC) |

| | | |
|---|---|---|
| TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid | | TDF: Renal and bone toxicity . TAF dosing RAL: Dosage |

| | | |
|---|---|---|
| **1 NRTI + INSTI** | | |
| 3TC+DTG or 3TC/DTG | HBsAg negative<br>HIV-VL <500 000 copies/ml | |
| **Alternative regimes** | | |
| **2 NrTI + NNRTI** | | |
| TAF/FTC or TDF/FTC or TDF/3TC+ DOR or TDF/3TC/DOR | | TDF: Renal and bone toxicity . TAF dosage DOR: HIV-2 |
| TAF/FTC or TDF/FTC or TDF/3TC+RPV or TAF/FTC/RPV or TDF/FTC/ RPV | CD4 count >200 cells/µL HIV-VL <100,000 copies/mL<br>It should not be on a proton pump inhibitor | TDF: Renal and bone toxicity. TAF dosage RPV: HIV-2 |
| **2 NrTI + PI/r or PI/c** | | |
| TAF/FTC or TDF/FTC or TDF/3TC + DRV/c or DRV/r or TAF/FTC/DRV/c | With a meal of food | TDF: Renal and bone toxicity. TAF dosing DRV/r: Cardiovascular risk |
| **Other combinations** | | |
| **2 NrTI + INSTI** | | |
| ABC/3TC + RAL qd or bid | HBsAg negative HLA-B*57:01 negative | ABC: HLA-B*5701, cardiovascular risk<br>RAL: Dosage |
| TDF/FTC/EVG/c or TAF/FTC/ EVG/c | With a meal of food | TDF: Renal and bone toxicity<br>EVG/c: Use for renal damage |
| **2 NrTI + NNRTI** | | |
| ABC/3TC + EFV | HLA-B*5701 negative HBsAg negative HIV-VL <100,000 copies/mL<br>Before bedtime or 2 hours before Dinner | ABC: HLA-B*5701, Cardiovascular risk EFV: Neuropsychiatric adverse episodes<br>HIV-2 or HIV-1 group 0 |
| TAF/FTC or TDF/FTC or TDF/3TC + EFV or TDF/FTC/EFV | Before bedtime or 2 hours before Dinner | TDF: Renal and bone toxicity. TAF dosage EFV: Neuropsychiatric adverse episodes<br>HIV-2 or HIV-1 group 0 |
| **2 NrTI + PI/b** | | |
| ABC/3TC + ATV/c or ATV/r | HLA-B*5701 negative HBsAg negative HIV-VL <100,000 copies/mL; not on a proton pump inhibitor;<br>With a meal of food | ABC: HLA-B*5701, cardiovascular risk ATV/b: Renal toxicity, hyperbilirubinemia |
| ABC/3TC + DRV/c or DRV/r | HLA-B*5701 negative HBsAg negative<br>With a meal of food | ABC: HLA-B*5701, Cardiovascular risk VIII<br>DRV/r: Cardiovascular risk |
| TAF/FTC or TDF/FTC or TDF/3TC+ ATV/c or ATV/r | It should not be on a proton pump inhibitor<br>With a meal of food | TDF: Renal and bone toxicity. TAF dosage ATV/b: Renal toxicity, hyperbilirubinemia |
| **1 INSTI + PI/b** | | |
| RAL 400 mg bid + DRV/c or DRV/r | HBsAg negative<br>HIV-VL <100,000 copies/mL<br>CD4 >200 cells/µL<br>With a meal of food | DRV/r: Cardiovascular risk |

## DHHS Guidelines 2020 Recommended and Alternative ARV Regimens

**Recommended initial regimens for most people with HIV**

**INSTI + 2 NRTI**

C> **BIC/FTC/TAF**

C> **DTG/ABC/3TC (if HLA-B*5701 is negative)**

C> **DTG +(TAF or TDF) + (FTC or 3TC)**

C> **RAL + (TAF or TDF) + (FTC or 3TC)**

**INSTI + 1 NRTI**

C> **DTG/3TC, except in people with HIV-1 RNA > 500,000 copies/mL, HBV co-infection or those who are not yet familiar with the results of HIV genotype testing**

**Recommended regimens in some clinical situations**

**INSTI + 2 NRTI**

C> **EVG/c/(TAF or TDF)/FTC**

**Busted PI + 2 NRTI**

**Busted DRV is preferred over busted ATV.**

C> **(DRV/c or DRV/r) + (TAF or TDF) + (FTC or 3TC)**

C> **(ATV/c or ATV/r) + (TAF or TDF) + (FTC or 3TC)**

C> **(DRV/c or DRV/r) + ABC/3TC (if HLA-B*5701 is negative)**

**NNRTI + 2 NRTI**

C> **DOR/TDF/3TC or DOR+TAF/FTC**

C> **EFV + (TAF or TDF) + (FTC or 3TC)**

- **EFV 600 mg + TDF + (FTC or 3TC)**
- **EFV 400 mg/TDF/3TC**
- **EFV 600 mg + TAF/FTC**

C> **RPV/(TAF or TDF)/FTC (if HIV-1 RNA is < 100,000 copies/mL and CD4 > 200 cells/µL)**

**When ABC, TAF and TDF cannot be included**

C> **DTG/3TC** except in people with HIV-1 RNA > 500,000 copies/mL, HBV co-infection or those who are not yet familiar with hiv genotype testing results

C> **DRV/r + RAL (if HIV-1 RNA is <100,000 copies/mL and CD4 >200 cells/µL)**

C> **DRV/r +3TC**

## IAS-USA Guidelines 2020

| Recommended regimens for most people with HIV |
|---|
| C> **BIC/FTC/TAF** |
| C> **DTG plus:**<br>▶ **FTC/TAF**<br>▶ **TDF/FTC**<br>▶ **TDF/3TC** |
| C> **DTG/3TC** |

## WHO: Preferred and alternative ART regimens from the second line

| Population | Unsuccessful mode from the front line | Preferred second-line modes | Alternate modes from the second line |
|---|---|---|---|
| **Adults and adolescents** | TDF+3TC (or FTC) + DTG | AZT + 3TC + ATV/r (or LPV/r) | AZT+3TC+DRV/r |
| | TDF+ 3TC (or FTC) + EFV (or NVP) | AZT+3TC+DTG | AZT + 3TC + ATV/r (or LPV/r or DRV/r) |
| | AZT+3TC+EFV (or NVP) | TDF+ 3TC (or FTC) + DTG | TDF+ 3TC (or FTC) + ATV/r (or LPV/r or DRV/r) |
| | ABC+3TC+DTG | AZT+ 3TC + LPV/r (or ATV/r) | AZT+3TC+DRV/r |

## Art from the first line: Comparison of international guidelines

| DHHS | IAS-USA | EACS | WHO |
|---|---|---|---|
| Recommended initial regimens for most PLWH | Generally recommended initial regimens | Recommended regimens (Preferred) | Preferred mode from the first line |
| C> BIC/FTC/TAF | C> BIC/FTC/TAF | C> BIC/FTC/TAF | C> DTG+XTC/TDF |
| C> DTG/ABC/3TC | C> DTG+FTC/TAF | C> DTG/ABC/3TC | |
| C> DTG+(FTC or 3TC)+(TAF or TDF) | C> DTG+TDF/FTC | C> DTG+FTC/TAF or FTC/ TDF | |
| C> RAL+(FTC or 3TC)+(TAF or TDF) | C> DTG+TDF/3TC | C> RAL+FTC/TAF or FTC/ TDF | |
| C> DTG/3TC | C> DTG/3TC | C> DTG/3TC | |

## Recommended and alternative ARV regimes in BiH in 2020

| Recommended initial regimens for most people with HIV |
|---|
| **INSTI + 2 NRTI** |
| C> **DTG+TDF/FTC** |
| C> **DTG+TDF+3TC** |
| C> **DTG/ABC/3TC (if HLA-B*5701 is negative)** |
| C> **RAL + TDF/FTC or TDF + 3TC** |
| C> **BIC/FTC/TAF** |
| **INSTI + 1 NRTI** |
| C> **DTG/3TC, except in people with HIV-1 RNA >500,000 copies/mL, HBV co-infection or those who are not yet familiar with the results of HIV genotype testing** |
| **Recommended alternative regimens** |
| **Busted PI + 2 NRTI** |
| C> **LPV/r + TDF/FTC** |
| C> **LPV/r + ABC/3TC (if HLA-B*5701 is negative)** |
| C> **LPV/r+3TC** |
| **NNRTI + 2 NRTI** |
| C> **RPV/TDF/FTC (if HIV-1 RNA is < 100,000 copies/mL and CD4 >200 cells/μL)** |
| C> **EFV a 600 mg + TDF/FTC** |
| C> **EFV a 600 mg + TDF+ 3TC** |
| **When ABC, TAF and TDF cannot be included** |
| C> **DTG/3TC** except in people with HIV-1 RNA >500,000 copies/mL, HBV co-infection or those who are not yet familiar with the results of HIV genotype testing |
| C> **LPV/r+3TC** |

## Recommended regimens for rapid ART

| IAS-USA Recommended Regimens for Rapid ART |
|---|
| **Recommended regimens** |
| C> **DTG+ (FTC or 3TC)/(TAF or TDF)** |
| C> **BIC/FTC/TAF** |
| C> **DRV/RTV + (FTC or 3TC)/(TAF or TDF)** |
| **Regimens that are not recommended** |
| C> Regimens based on NNRTI due to potential drug resistance transmission (K103N). |
| C> ABC-containing modes until the HLA-B*5701 test results are ready |

**Advantages and disadvantages of InSTI ARV components recommended for initial ARV therapy**

| INN ARV Cure | The year of the award. | Advantages | Disadvantages |
|---|---|---|---|
| **biktegravir** | 2018 | C> STR once a day with FTC/TAF<br>C> Non-inferior compared to dolutegravir in comparative studies<br>C> Dosage once a day<br>C> High resistance barrier<br>C> Relatively few drug interactions<br>C> Can be taken with or without meals of food<br>C> Can be turned on without testing HLA-B*5701 | C> Coformulation makes it impossible to combine with other ARV drugs<br>C> cannot be included with rifampin<br>C> Shorter experience in longer periods of use in practice than with other drugs in the InSTI class<br>C> Increases serum creatinine (≈0.1 mg/dL) by inhibition of tubular creatinine secretion<br>C> Insufficient data for use in pregnant women |
| **dolutegravir** | 2013 | C> Non-inferior compared to bixtegravir in 2 comparative studies and superior compared to darunavir and efavirencom in Comparative studies.<br>C> Dosage once a day<br>C> Available as a single drug, allowing it to be used in other combinations<br>C> High resistance barrier<br>C> Can be taken with or without meals of food<br>C> Superior compared to raltegravir in patients with ARV experience | C> Increaseserum creatinine (0.1-0.15 mg/dL) by inhibition of tubular creatinine secretion<br>C> Higher rates of insomnia and headache than in comparative drugs in some studies<br>C> Coformulated with abacavir/lamivudine, in the form of the largest tablet among the coformulated regimens in a single tablet; abacavir requires testing for HLA-B*5701<br>C> Open question regarding neural tube defects in children whose mothers became pregnant at the time they received dolutegravir |
| **elvitegravir** | 2012 | C> Dosage once a day<br>C> Coformulated with TDF/emtricitabine or TAF/emtricitabine in the form of a complete regimen | C> Necessary pharmacological busting for cobicistat for dosing once a day.<br>C> Lower resistance barrier than biktegravir and dolutegravir<br>C> Frequent drug interactions thanks to cobicistat busting<br>C> Cobicistat increases serum creatinine (0.1-0.15 mg/ dL) by inhibition of tubular creatinine secretion<br>C> It must be taken with a meal of food<br>C> Do not include pregnant women |

| ARV drug | The year of the award. | Advantages | Disadvantages |
|---|---|---|---|
| **raltegravir** | 2007 | C> Superior compared to ATV/r or DRV/r ritonavir busted darunavir in comparative clinical studies<br>C> Long Safety Data time period<br>C> Lowest number of interactions with other drugs<br>C> Can be taken with or without food | C> No coformulations Like part of the entire regime.<br>C> Lower resistance barrier than biktegravir or dolutegravir<br>C> More pills than others InSTI |

**Initial treatment with Non-InSTI-based ARV regimens**

| Mode | Advantages | Disadvantages |
|---|---|---|
| **darunavir (busted with cobicistat or ritonavir) plus TAF/emtricitabine or TDF/emtricitabine** | C> Low risk for resistance with virological failure, even with moderate adherence<br>C> Available in one tablet mode in Europe and soon in the U.S. (darunavir/cobicistat/TAF/emtricitabine)<br>C> Can be initiated and without test results HLA-B*5701, hepatitis B and resistance | C> Pharmacological busting necessary; many interactions with other drugs<br>C> Ritonavir busted darunavir was inferior to RAL and DTG in some comparative studies, mainly due to low tolerance<br>C> Cobicistat should not be included in pregnancy due to inadequate plasma values |
| **efaviren/TDF/emtricitabine** | C> High efficacy in patients with BASIC VALUES of HIV RNA >100,000 copies/mL<br>C> Extensive experience in practice in patients with TB co-infection<br>C> Available worldwide<br>C> Available as a generic coformulation with 600 or 400 mg with TDF/lamivudine | C> Relatively high rates of rashes<br>C> Not available in a single tablet with TAF<br>C> Efavirenc may cause neuropsychiatric side effects<br>C> Increased risk of suicide; avoid inclusion in patients with a history of depression |
| **rilpivirine/TAF (or TDF)/emtricitabine** | C> Lowest risk of rash compared to all NNRtI-based regimens<br>C> Low risk of metabolic side effects | C> Not recommended for patients with HIV RNA values >100,000 copies/mL or CD4 cell count <200/µL due to an increased risk of viral failure<br>C> It must be taken with a meal of food for optimum absorption<br>C> Should not be included in conjunction with proton pump inhibitors; lower dosage if included with one of the H2 blockers |

## 2.14 ART monitoring

There are no standards for laboratory monitoring of ART. Most doctors check vl within a few

weeks of initiating ART to assess initial virological response and adherence. At the same time, side effects can be discussed, since they affect adherence over a longer period of time and can be reduced by changes in treatment or symptomatic treatments. Laboratory testing soon after the initiation of ART is used-

but for the detection of drug toxicity. The early undesirable effects of ARV drugs are hepatotoxicity, dyslipidemia and anemia. The frequency of toxicity monitoring depends on the specifics of the drugs involved, and on the possible clinical signs or symptoms, as well as on the patient's specific problems.

The goal of the initial ART – to reduce plasma VL below the detection limits – is usually achieved within 12 weeks, but can take up to 24 weeks from the start of treatment, especially if the initial VL was extremely high. Today, there are sensitive tests, the lower limit of which is detectability of 20-50 copies of HIV RNA in mL. The development of virus resistance is considered to be disabled or very limited if the viremia is less than 50 copies/mL. Prolonged viremia in terms of exposure to ARV drugs will result in drug resistance, which will limit the possibility of ART success.

Before starting treatment, it is recommended to measure HIV RNA in plasma and CD4 cell values. After four weeks, viremia and CD4 cell values are re-determined, and in the case of us-pedestrian treatment, a pronounced decrease in viremia is registered by 1.5 to 2 log10. After that, the values of HIV RNA and CD4 cells are determined every 3-4 months. If after 6 months viremia persists more than 50 copies in mL plasma in patients in whom cooperation is not a problem, a change of treatment may be considered. In patients who initially had more than 100,000 copies/mL, maximum suppression of the virus usually occurs later.

The frequency of clinical and laboratory monitoring in patients with undetectable plasma HIV titers is variable. Many clinicians schedule appointments every 3-6 months. In very stable patients, this interval can be gradually extended to 6 months. Although it is more expensive, HIV *viral load* testing is crucial for registering virological failure, and the lack of possibility of this test increases the risk of treatment failure, which will not be detected until a high rate of ARV resistance occurs.

In patients who have not initiated ART, CD4 should be monitored every 3-6 months to assess the possible urgency of initiating ART and the need for OI prophylaxis. Testing of CD4 values after initiating ART should be done every 3-6 months during the first two years or if the CD4 count is <300 cell./μL to evaluate immune reconstitution.

After two years on ART with sustainable HIV RNA suppression, and CD4 values between 300 and 500 cell/μL monitoring work every 12 months, and at CD4 values >500 cell./μL for at least 2 years. In patients who fail to maintain viral suppression on ART, CD4 monitoring should be done every 3-6 months.

### 2.14.1. Viral failure

**Virological failure is considered to be persistent values of PLASMa HIV RNA >50 and <500–1,000 copies/mL of plasma.**

Viral failure is increasingly becoming a rare occurrence with the latest recommended ART regimens. For the selection of a new regimen, it is necessary to evaluate inadequate adherence, drug interaction, as well as a comparison of all resistant mutations identified by genotype, and ART history.

In patients who do not achieve a therapeutic goal, undetectable viremia, or who experience a viral jump, a resistant mutation may develop on one or more components of the ARV regimen.

Virological failure can be caused by factors associated with the patient, but also by factors that are associated with ARV treatment. Higher pretreatment values of viremia, lower CD4 nadir, pre-diagnosed AIDS, comorbidities (e.g. active consumption of narcotics, psychiatric illness, neurocognitive deficit), as well as the presence of a drug-resistant virus, whether resistance is transmitted or acquired, poor adherence, failure to attend regular check-ups are factors that can cause virological failure and are associated with **the patient factor.**

The causative agents of virological failure can also be associated with **an ARV regimen**: suboptimal virological power of the drug combination, low genetic barrier for resistance, poor absorption, unwanted interactions between ARV drugs and other drugs taken simultaneously, side effects of lijekov , a large number of tablets and the necessity of taking drugs with a meal of food, previous exposure to suboptimal regimens.

When evaluating a possible virological failure, it is necessary to thoroughly assess all the above factors – first the patient's adherence to the regimen: identify and try to eliminate the causes that affect incomplete adherence (drug intolerance, depression, active drug consumption) and, if possible, simplify the regimen. Assess the patient's tolerance to the regimen he is taking, the duration of side effects, keeping in mind even minor side effects that can affect adherence. If necessary, associate symptomatic treatment (antiemetics, intestinal eubiotes) or switch to a regimen from one class of medicines to another (e.g. from NNRTI to PI or TO INSTI) if necessary.

A resistance test should be performed in each case of unsatisfactory suppression, if it is possible, while the patient is still on a regimen experiencing failure or within 4 weeks after the treatment is excluded if the patient's HIV RNA >1,000 copies/mL or if it is between 500 and 1,000 copies/ml.

When a virological failure is confirmed, the ARV regimen should be changed as soon as possible to avoid pro-gresion accumulation of resistant mutations.

When changing an ARV regimen in patients with HVB/HIV co-infection, ARV drugs that are active against HVB should continue to remain included as an integral part of the new regimen.

The exclusion of these drugs can lead to reactivation of HVB, which can result in severe hepatocellular damage.

The new ARV regimen should contain two, and preferably three new active drugs from classes that have new mechanisms of action (fusion inhibitor, CCR5 antagonist or new drugs from existing classes).

- **INSTI**: DTG, BIC; **NNRTI**: DOR, ETR, RPV; PI: DRV, TPV) with a previously implemented resistance test. The inclusion of a drug that the patient has never received before does not guarantee that the drug will be fully active. There is a possibility of cross-resistance among drugs from the same class. New active drugs should be selected based on the patient's ART history and analysis of drug resistance results.

Factors associated with a better virological response to the new ARV regimen are lower VALUES of HIV RNA, higher CD4 values at the time of the introduction of the new therapy, and the inclusion of drugs with new mechanisms of action that will allow to suppress hiv RNA values below the detection limit.

**Management of viral failure with the first regimen**

First of all, the degree of drug resistance, the duration of viral failure, vi- sinu viremia, exposure to ART drugs, and the degree of adherence should be evaluated.

**HIV RNA above the detection limit and <200 copies/mL:**

C> Assess drug adherence and drug interactions

C> Patients with transient increases in HIV RNA (blips) do not need to change treatment

C> In persistent values of HIV RNA above the detection limit but <200 copies/mL, the risk of resistance is believed to be relatively low:

- Such patients should remain on the current regimen, and their values of viremia should be monitored every 3 months to assess whether it is necessary to change their ART in the future.

**HIV RNA > 200 but < 1,000 copies/mL**

C> Assess drug adherence and interaction

C> Patients with persistent >200 copies/ml often develop resistance, especially in those with HIV RNA >500 copies/mL

C> Persistent VALUES of HIV RNA in the range of between 200 and 1,000 copies/mL should be treated as a virological failure; resistance should be tested, especially if HIV RNA values are >500 copies/mL.

- The management should be the same as in patients with viremia values >1,000 copies/ML.

**HIV RNA > 1,000 copies/mL when resistance is not detected**

C> If **resistance is not detected,** such cases are associated with suboptimal ad-herence.

C> It is necessary to determine the degree of adherence, to identify and solve the cause of adherence, to simplify the regime.

C> If the current regimen is well tolerated and if there are no significant drug interactions, **apply** treatment with the same regimen.

C> If medicines are less tolerated or if there are significant drug interactions, consider the possibility of **regimen change.**

C> Two to four weeks after continuing the same therapy or after initiating a new ARV regimen, repeat HIV RNA testing.

- If HIV RNA is still >500 copies/mL, do genotypic testing.

**HIV RNA >1,000 copies/mL and resistance detected**

If hiv rna virus is detected again >1,000 copies/mL **with registered resistance**, include new ARV drugs with a new mechanism of action. The goal of the new regimen is HIV RNA <400 copies/mL after three months, HIV RNA <50 copies/mL after six months.

**Failure with the first regime**

**Unsuccessful regimen with NNRTI + NrTI**: Most often it is viral resistance to NNRTI, with or without resistance to 3TC and FTC. The options for such patients are busted PI with 2 NRTIs or with INSTI. Patients with NRTIs can often be treated with PI/r + NRTIs or RAL. The second generation NNRTI (ETR) or other INSTI (EVG or DTG) combined with PI/r may be some of the options in such cases. The lpv/r+ral mode was just as effective as lpv/r+2nrTI. Although data is limited, DTG combined with busted PI may be one of the options.

**Unsuccessful regimen with PI/r + NRTIs:** In this case, most patients either have no resistance or have resistance limited to 3TC and FTC. Failure in this situation is often caused by poor adherence or drug interactions. Staying on the same regimen, with efforts to improve adherence, is just as effective as switching to a new regimen with or without drugs from some other classes. In such cases, in addition to testing resistance, an assessment of the adherence and tolerance of the regime should be done. If the regimen is well tolerated and there is no interaction between the left , the regime n od diagnostic can be continued. If intolerance and interactions contribute to virological neus- humering, the regimen may be modified and include another PI/r + 2 NRTI or other PI/r + INSTI or INSTI + 2 NRTIs. DTG is the recommended INSTI. There are limited data on the effectiveness of BIC or EvG in such situations .

**Treatment failure with INSTI+NRTIs**: A virological treatment failure containing RAL+NRTIs or EVG/c+TDF/FTC may be associated with resistance to 3TC and FTC, and possibly to INSTI. Viruses that are resistant to INSTI are often susceptible to DTG. The options for unsuccessful treatment of INSTI + NRTIs are: PI/r + 2 NRTIs, PI/r + some of the INSTI (with resistance to RAL and EVG, DTG can be included).

**Resistance to multiple drugs without treatment options that allow complete virological suppression:** In this case, the goals of ART should be to preserve immune function and prevent clinical progression. Prolonging therapy, even if there is a presence of viremia and when there is no increase in CD4 cell value, reduces the risk of disease progression. Studies suggest that there are immunological and clinical benefits even from modest reductions in HIV RNA values. All these possible benefits should be balanced with the constant risk of accumulation of additional resistant mutations. Adding one active ARV drug to the regimen is not recommended because of the risk of rapid development of resistance.

Patients with detectable viremia who do not have enough remaining treatment options may be candidates for the use of **an inhibitor of ibalizumab (IBA).**

Ibalizumab, which is an anti-CD4 monoclonal antibody that inhibits HIV from entering and connecting to the host cell, is active against CCR5 and C-X-C *chemokine* receptor 4 (CXCR4)-tropical HIV isolate and may be as useful as some fully active drug in patients with a virus that is

resistant to multiple classes of drugs. Nearly 50% of adults with viral failure and HIV who are resistant to a large number of drugs achieved undetectable VALUES of HIV RNA after 24 weeks per administration every 15 days of intravenous ibalizumab (800 mg) with at least one other active drug.

### 2.14.2. Unsuccessful ARV treatment

| | |
|---|---|
| **Viral failure** | **Virological failure:** Failure to achieve or maintain HIV RNA < 200 copies/mL; |
| | **Incomplete virological response:** confirmed HIV RNA >200 copies/ mL after 24 weeks on ART; |
| | **Virological** *rebound*: confirmed HIV RNA > 200 copies/mL after virological suppression. |
| **Immune failure** | CD4 enlargement <25-50 cells/µL in the first year of therapy or decrease in CD4 values below baseline |
| | Remark: The average increase is about 150 cells/µL in the first year with therapy in ARV-naïve patients |
| **Clinical failure** | The occurrence of an event of HIV >3 months after the initiation of ART |
| | Remark: The possibility of immune reconstitution syndrome must be ruled out |

## 2.15 ARV medicines available in Bosnia and Herzegovina

Medicines for therapy from the following review are available in Bosnia and Herzegovina at the expense of funds
Health insurance:

| Br. | INTERNATIONAL NON-PROPRIETARY NAME | ACRONYM |
|---|---|---|
| 1. | zidovudin* | ZDV |
| 2. | lamivudine* | 3TC |
| 3. | abacavir | ABC |
| 4. | tenofovir* | TDF |
| 5. | tenofovir/emtricitabine* | TDF+FTC |
| 6. | zidovudine/lamivudine* | ZDV/3TC |
| 7. | abacavir/lamivudine* | ABC/3TC |
| 8. | nevirapine* | NVP |
| 9. | efavient* | EFV or EFZ |
| 10. | lopinavir/ritonavir* | LPV/r |
| 11. | ritonavir | RTV |
| 12. | raltegravir | RAL |
| 13. | dolutegravir | DTG |
| 14. | rilpivirine/tenofovir/emtricitabine | RPV/TDF/FTC |

*Medicines available in Republika Srpska

## 2.16 Inflammatory immune reconstitution syndrome (IRIS)

In most patients, the introduction of ART improves the immune response to a wide range of opportunist infections. A small percentage of patients develop an inflammatory response to specific OI (TB, MAC, CMV, PCP, toxoplasmosis, HBV, VZV, cryptococcus) a few weeks or months after the introduction of ART. The inflammatory response is called inflammatory immune reconstitution syndrome (IRIS), which can manifest itself as an exacerbation of partially or fully treated tunistic infection before the start of antiretroviral treatment, but after retroviral

treatment the disease worsens and new symptoms and signs of the disease appear. It is **a paradoxical form of IRIS**.

Another form of IRIS is **revealing** in which previously subclinically undiagnosed and untreated- an opportunistic disease becomes visible after initiating ARV treatment.

IRIS predominantly occurs within a few months after the introduction of ART, and is in the context of a rapid and significant increase in CD4 values, which were low before treatment (often <50-100 cell/mL).

IRIS is caused by an increased immune response to antigens that are specific to a disease, leading to the production of inflammatory mediators. Sometimes it is difficult to identify it in clinical practice, since its clinical presentation is not specific to it.

It must be differentiated from a new opportunistic infection, a failed treatment of previously identified OI, or from drug toxicity. Treatment of IRIS requires the continuation of the ART regimen if possible, the treatment of OI, and the inclusion of anti-inflammatory therapy, if necessary, to suppress the inflammatory process. The risk of IRIS is higher if ART is started shortly after oi treatment is initiated and if CD4 values rise sharply in the first weeks or months of ART. The optimal time to start ART in terms of OI treatment is after two weeks from the diagnosis of opportunistic infection.

## 2.17 Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis (PEP) is an emergency medical intervention to prevent HIV transmission after possible exposure. PEP includes: risk evaluation, HIV testing with informative consent and counseling, and depending on the outcome of the risk assessment, 28-day ARV treatment, prevention of sexually transmitted diseases (STIs) and prevention of unwanted labor are included.

Healthcare professionals are at risk of occupational exposure to HIV infection. The CDC has suggested that each person's blood is considered potentially infectious since it is not always possible to know who is infected with some of the blood-borne microorganisms. Therefore, in the workplace, health workers must use means of protection (gloves, masks, glasses, aprons, etc.), depending on the degree of expected exposure to patients' bodily fluids, in order to prevent professional exposure to HIV in health care institutions.

The criteria for the application of PEP are:

- the exposure occurred within the last 72 hours;
- the exposed person is not HIV-infected;
- the source of exposure is HIV-infected or of unknown HIV status.

PEP is recommended in the case of: occupational, non-professional (sexual) exposure to HIV and ex-composition in case of sexual violence, including rape.

C> Occupational EXPOSURE to HIV - contact with blood:

- Subcutaneous or intramuscular penetration with a needle or intravascular instrument is an original patient of HIV-positive or unknown serostatus with present risk factors;
- Percutaneous injury by a sharp instrument (lancet), intramuscular or subcutaneous ig- lom if the original patient is infected with HIV;
- Contact of mucous membranes or damaged skin for more than 15 minutes if the original patient is infected
  HIV.

C> Unprofessional (sexual) exposure to HIV, exposure in cases of sexual violence, including rape - contact with genital secretions:

- Receptive or vaginal intercourse if the source is an HIV-positive person with viremia or unknown serological status with risk factors;
- Receptive oral sex with ejaculation if the source is an HIV-positive person with vire- mia;
- Contact with the attacker's blood or ejaculation on the mucous membranes or on damaged skin during sexual violence;

- The victim of the attack was under the influence of narcotics or for other reasons was not conscious at the time of the attack, and she is not sure how the exposure could possibly have occurred.

C> The exposure occurred through the joint use of syringes, needles and narcotics injection kits with an HIV-positive person.

PEP is exclusively intended for HIV-negative people. PEP should be ruled out if the exposed person turns out to be HIV-positive.

When exposure occurs, it is first of all necessary to realize clinical and epidemiological **evaluation of the risk of the person who is the source of the incident** to HIV, HVB, HVC infection, with serological testing.

If the source is an HIV patient:

- collect data on the clinical stage of HIV infection, CD4 cell values, viremia (VL), and on current and previous ARV therapy;
- if VL is measurable, do an HIV resistance test;
- if VL is undetectable, HIV PEP is not recommended.

It is necessary to carry out a clinical and epidemiological **evaluation of the exposed person**, that is, to conduct testing for HIV, HVB and HVC infection, and in the case of a negative HIV test, repeat the testing after 4 weeks, 3 months and 6 months.

Consider the possibility of pregnancy at the time of exposure, be sure to offer a pregnancy test, and if the test is negative, emergency contraception should be offered.

Testing of both exposure sources and exposed persons must be voluntary, with prior informational consent.

After the incident, offer post-exposure prophylaxis. PEP is administered only if it is made a detailed evaluation of the nature and mode of exposure, i.e. the risk of transmission by a polished doctor, which will be administered by PEP if necessary. The exposed person with informational advice should sign the form "Information consent". It is necessary to fill out the exposure application form, regardless of whether PEP is coordinated or not.

PEP is defined as ARV therapy initiated immediately after exposure to HIV. PEP should be switched on within 2 to 72 hours.

PEP is carried out over 28 days and is made up of triple ARV therapy in the following combination:

- tenofovir/emtricitabine 1x1 tbl. + raltegravir 2x1 tbl. or dolutegravir 1x1 tbl. or lopinavir/ ritonavir 2x2 tbl.

After the involvement of PEP, clinical and serological monitoring of the exposed person is necessary. On the first, fifteenth and thirtieth day to perform laboratory tests: CCC, shuk, urea, creatinine, ASAT, ALAT. Regular medical examinations are necessary to monitor the side effects of therapy and whether therapy is taken regularly.

After exposure, the exposed person must have protected sexual wear for the next six months, must not be a blood and organ donor, and mothers must not breastfeed newborn babies for the next six months.

It is necessary to check the vaccination status of the exposed person for hepatitis B, hepatitis C and teta- nus. If the markers for hepatitis B are negative, prophylaxis for HVB infection with specific hepatitis B immunoglobulin (HBIG) and HVB vaccine should be carried out in the first 24 hours. There is no prophylaxis for HVC, serological monitoring is necessary. If the original person is HVC positive, realize HVC PCR RNA, HVC serology and transaminases after four weeks of exposure. The risk of HVC infection is higher after exposure to the blood of a person with HIV/HVC co-infection. In these cases, follow-up was pre-ordered for both viruses for up to 12 months, as cases of late seroconversion were described.

**After the accident, the following procedures at the site of exposure are recommended:**

C> Stab incident – necessary wound treatment :

- Let the wound bleed for a few seconds;
- Do not suck, do not squeeze blood from the puncture site, do not rub;
- Immediately rinse with running water, wash with soap and warm water.

C> Contact of unharmed skin with blood:

- Remove contaminated clothing;
- Rinse the skin with running water, then wash with soap and warm water;
- Do not rub the skin; rinse and dry.

C> Contact of the conjunctiva and mucous membranes with blood:

- Immediately rinse abundantly with clean water.

Exposure risk assessment and testing of an exposed person:

- Check the vaccination status of the exposed person (hepatitis B and tetanus);
- Evaluation and testing of sources/informed consent.

**Reporting and documenting accidents**

Reporting sexual violence, including rape, should not be a prerequisite for initiating PEP or other services after sexual assault.

The results of hiv blood tests, whether positive or negative, are always communicated in person, never over the phone, or by e-mail or by another person. If "rapid tests" are available, results can be obtained within an hour. If "rapid tests" for HIV are not available, the results are waited for a day.

Adherence to treatment and confidentiality of information are crucial. The client must be thoroughly informed that PEP does not give 100% protection. It is important to identify clinical facilities to provide in-person care and monitoring for survivors of sexual violence. It is necessary to perform se-rology on SPI a month from sexual exposure.

Risk of HIV infection: after one episode of a prescriptive voluntary vaginal sexual act, the risk is between 0.1% and 1%. After a receptive sexual act, the risk is between 1% and 5%. The risks may be elevated in a traumatic sexual act. The risks of transmission are also elevated if some STIs are present.

## 2.18 Pre-exposure prophylaxis (PrEP) in HIV prevention

There are numerous methods of HIV prevention available: condoms for men and for women, voluntary medical circumcision for men, prevention of mother-to-child HIV transmission (PMTCT), and strategies to reduce harm, such as the division of sterile injection kits and opiate substitute therapy for PWID. All of the above has contributed to mitigating the rise in rates of new infections in some countries.

Two European studies on pre-exposure prophylaxis (PrEP), titled PROUD and IPERGAY, which examined the efficacy of pre-exposure tenofovir/emtricitabine (TDF/FTC) pre-exposure therapy, explained the results in February 2015 and proved that PrEP was highly effective in HIV pre-efficacy, reducing new infections by 86%.

The effectiveness of PrEP in the PROUD study is 86%, which means that PrEP prevented more than 17 out of every 20 potential HIV infections that would have occurred if there were no protection with PrEP. There was also no increase in SPI in participants who took PrEP. The results of the PROUD study suggest that prep application must be part of all relevant primary HIV preventive strategies and must be part of the spectrum of services offered in all clinical programs that focus on sexual health. PrEP should be routinely offered to those who might benefit from it.

Cdc guidelines recommend that the inclusion of PrEP to all uninfected people at risk of contracting HIV should be considered. PrEP is a way in which people who are not infected with HIV, by taking one TDF/FTC tablet every day, can prevent HIV infection. It turned out that

It is a method that is very effective and inexpensive, and that the risk of hiv infection is even up to 92% lower if the drugs are taken consistently.

PrEP is one of the strategies of HIV prevention, aimed at ending the HIV epidemic. One of the future goals should be to increase the use of PrEP in populations at risk of HIV transmission. Sexual partners of HIV-infected people are not candidates for PrEP if their partner has undetectable viremia for more than 6 months.

### 2.18.1. Indications and recommendations for PrEP

**Men who have sex with men (MSM)**

C> without acute or active HIV infection;

C> any male sexual partner in the past 6 months;

C> were not in a monogamous relationship with a recently tested HIV-negative male;

C> unprotected sex (insertive or receptive) in the past 6 months;

C> had a sexually transmitted infection (syphilis, gonorrhea, chlamydia) diagnosed in the past 6 Months.

**Heterosexual men and women**

C> without acute or active HIV infection who have not been in a monogamous relationship with a recently tested HIV-negative partner and any type of sexual intercourse with a partner of the opposite sex in the last 6 months;

C> men who have bisexual behavior;

C> people who rarely use protection during sexual intercourse with one or more partners of unknown HIV status who are at risk (IDU, bisexual male partner);

C> partner who is in a sexual relationship with an HIV-positive partner who does not have achieved viral suppression;

C> had an infection (syphilis, gonorrhea, chlamydia) diagnosed in the past 6 months;

C> joint use of narcotics injection equipment in the past 6 months;

C> transgender people.

In July 2012, the FDA approved the use of tenofovir DF-emtricitabine as a therapeutic option for PrEP. Discover study data showed that tenofovir alafenamide-emtricitabine is non-inferi- oran compared to tenofovir DF-emtricitabine for PrEP in MSM and was approved by the FDA for use in October 2019. The FTC/TAF has an advantage over the FTC/TDF in achieving an effective concentration above 90% within 1-2 hours versus the 3-4 daily doserequired with the FTC/ TDF. THE FTC/TAF is an effective strategy in HIV prevention, especially in people who are at risk of renal dysfunction or from reduced bone mineral density.

Tenofovir alafenamide-emtricitabine is not indicated for receptive vaginal intercourse since its effectiveness in such cases has not yet been evaluated.

Daily oral consumption of PrEP is extremely effective if it is accompanied by good adherence with 4 tablets per week.

The innovative PrEP with *integrase* inhibitor cabotegravir (CAB) is in the development phase as a long-term effective injection therapy, and is also evaluated in the prevention of infection.

**Basic laboratory testing**

In order for PrEP to be administered, clients must be at risk of contracting HIV and must be given a basic laboratory evaluation that includes:

- **HIV testing** for HIV-1/2 antigen/antibodies. Rapid tests are not recommended due to the low sensitivity of this type of testto diagnose a recent infection;
- **Renal function**: creatinine, creatinine clearance. People with creatinine clearance values

lower than 60 mL/min must not receive tenofovir DF-emtricitabine as a PrEP treatment, and clients with creatinine clearance values below 30 mL/min must not receive tenofovir alafenamide – emtricitabine;

- **Serological testing for sexually transmitted diseases**: syphilis, gonorrhea, chlamydia;
- **Pregnancy** testing for women of childbearing age;
- **Testing for hepatitis B** because HIV PrEP drugs serve both to treat HBV, and people with active hepatitis B infection could experience a flare-up of hepatitis after the exclusion of prEP medications. People with active hepatitis B may receive PrEP, but after the exclusion of PrEP they must be on continuous monitoring and evaluation for further management for hepatitis B infection;
- **Counseling** on adherence.

**Turn off PrEP**

The reasons for turning off PrEP are:

- decreased HIV riskbehavior of the client;
- side effects associated with drugs;
- fatigue by consuming tablets;
- positive test for HIV or pregnancy.

When turning off PrEP, it is recommended to always repeat HIV testing.

**Indications for the transition from non-occupation PEP to PrEP**

C> After exposure to HIV, a PEP regimen is started, and during the evaluation it becomes evident that the client is likely to have a significant risk of HIV infection after completing PEP therapy for 28 days.

C> The problem with switching from PEP to PrEP is that the client could have been infected with HIV after exposure that required the inclusion of non-occupational PEP (a three-drug regimen) and the resulting transition to PrEP (two-drug regimen), which means that they will only have partial treatment for HIV, with the possible development of HIV drug resistance. Therefore, it is suggested that the client, after treatment of 28 days for PEP, perform a rapid HIV test using the HIV1/2 antigen/antibody test. If the result of HIV testing is positive or suspected acute HIV infection, conduct confirmatory testing and prolong the non-occupational PEP with three drugs after 28 days, until the test results are known . If HIV infection is confirmed, a basic evaluation is required, which is provided for newly diagnosed people with HIV infection. If the HIV test results are negative, exclude the third drug from the non-occupational PEP regimen and continue with the PrEP regimen.

C> The client has again received PEP, and it is concluded that the inclusion of PrEP would be a more effective strategy
for HIV prevention.

**PrEP Mode**

PrEP is administered for a period of three months to ensure appropriate monitoring.

PrEP can be taken in two ways:

C> Continuous intake of TDF/FTC, one tablet per day. It is considered that it is necessary to take the drug seven days before the first exposure (due to the achievement of adequate concentration), and it is excluded seven days after the last exposure.

C> Another way to take PrEP is on demand, when two TDF/FTC tablets are taken 2-24 hours before sexual intercourse, then one tablet after 24 and 48 hours after the first dose of the drug. It is important to always finish taking the drug 48 hours after the last risk.

After the prescribed PrEP, client monitoring and rounds are carried out every three months to do: FOURTH GENERATION HIV testing, counseling on adherence to treatment, support in reducing

the risk in sexual behavior, evaluation of drug side effects, assessment of symptoms of STIs.

In the third month, renal function is evaluated (after that every 6 months). Every three months, conduct an oral and rectal test for STIs; an assessment of a possible pregnancy, a pregnancy test every 3 months; an assessment of the use of sterile needles and accessories.

Treatment is essential. In various studies, the level of protection varied depending on how good the adherence was. Taking treatment for 90% of the day or more of this treatment reduces the risk of HIV infection by 73%, and if the adherence is less than 90% of the scheduled days of treatment, the risk of HIV infection is reduced by only 21%.

People receiving PrEP should also use other preventive strategies to minimize the risk, namely constant, proper use of condoms, joint HIV testing with partners, the choice of less risky sexual behavior; for the PWID population and entry into addiction weaning programs and the use of sterile injection kits.

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# 3. HIV INFECTION IN CHILDREN

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According to the World Health Organization (WHO), 1.7 million children aged 0–14 lived with HIV at the end of 2018, and 160,000 children were newly infected. An estimated 100,000 children have died from AIDS-related diseases. To reduce HIV-related mortality and morbidity among this highly vulnerable population, early testing and treatment are essential . Without access to testing and treatment, 50% of children with HIV will die by age 2 and 80% will not live to be five.

The general natural course and pathophysiology of pediatric HIV infection are similar to those of adults; however, the method of infection, clinical picture and treatment often differ. Children infected with HIV have unique difficulties of engaging in society.

## 3.1 Epidemiology

In the U.S., HIV appeared in children almost simultaneously as it did in adults, but it was not clinically recognized for several years.

More than 90% of children in the U.S. have contracted the infection from their mother, either before or at the time of childbirth (vertical transmission). Most of the remaining (including patients with hemophilia or other coagulation disorders) were given infected blood or blood derivatives. Several cases have arisen due to sexual misconduct. In less than 5% the source of infection is not clear. Today, vertical transmission is responsible for almost all newcases in preadolescents.

Worldwide, there are about 2.5 million children infected with HIV (8% of the total number of cases in the world), and about 700,000 children are infected each year (16% of all newcases). In sub-Saharan Africa, where the epidemic lasts the longest, some prenatal protection clinics report that 25–40% of women of reproductive age are seropositive to HIV. HIV infection is spreading rapidly in India, the People's Republic of China, Northeast Asia and some areas of Eastern Europe and the Russian Federation. Worldwide , about 500,000 children die from HIV infection every year.

More than 1,500 children are infected with HIV every day. The vast majority of these children (more than 90%) get the infection from the mother. Since the beginning of the pandemic, over 5 million newborns have been infected with HIV, 90% of whom are in Africa. However, the number of cases in Central Asia, Eastern Europe, India and Southeast Asia is rising.

Transmission of HIV to a child is most common through:

- Infected mothers before birth or during birth
- after birth, through breastmilk, breastfeeding

In young children, HIV infection is almost always acquired from the mother. More than 95% of children infected with HIV in the U.S. have contracted the disease from their mother, either before or around the moment of birth (called mother-to-child transmission or Mother-to-child transmission ( MTCT). Children who are not infected in this way, and who are now living with AIDS, have acquired the infection through sexual activities, including rare sexual abuse. Due to improved safety measures in terms of blood and blood products, in recent years almost no infection has been due to the use of blood and blood products in the US, Canada or Western Europe. Experts aren't sure how many HIV-infected women give birth each year in the U.S., but the Centers for Disease Control and Prevention (CDC) estimates about 5,000.

However, transmission shrank significantly in the U.S. from about 25% in 1991 to less than 1% in 2018. Mother-to-child transmission has been reduced due to intense efforts to test and treat infected pregnant women during pregnancy and childbirth.

It is estimated that the risk of infection for the child of an HIV-positive mother who did not receive antiretroviral (ARV) therapy during pregnancy is 13–39%. The danger is greatest for the children of mothers who experience seroconversion during pregnancy and those with advanced disease, low peripheral CD4+ T-lymphocytecounts, prolonged rupture of the fruit membranes and high concentrations of the virus, eye HIV p24 antigenemia, quantitative virus cultures or RNA concentration. In vaginal births, the first twin is at greater risk than the second,

although this may not be true in developing countries .

Caesarean section can reduce the risk of MTCT. However, it is clear that MTCT can be significantly reduced by administering ARV drugs (including zidovudine [ZDV, AZT]) to the mother and newborn. ZDV reduces MTCT to about 8%; with the current highly active antiretroviral therapy ( HAART), in the U.S. the MTCT rate is <2%.

ARV drugs dolutegravir and emtricitabine/tenofovir alafenamide fumarate (DTG+FTC/TAF) may contain the safest and most effective HIV treatment regimen currently available during labor-night, researchers announced today. Their findings come from a multinational study of more than 640 pregnant women with HIV on four continents. The results of the research confirm the updated recommendations set by the WHO for HIV treatment of pregnant women. Previous research has shown that ARV therapy prevents perinatal TRANSMISSION of HIV. The current study compared three ARV regimens of the drug and found that dolutegravir -containing regimens (DTGs) were more effective at combating HIV than the usual efavirenne regimen (EFV).

HIV is detected both in the cells and in the acellular components of breast milk. The incidence of breastfeeding transmission is about 6/100 of breastfed children/year. Estimates of the overall risk of breastfeeding transmission range from 12 to 14%, which is due to the different duration of breastfeeding. Breastfeeding appears to be highest in mothers with high plasma concentrations of the virus.

Among infected infants who are not breastfeeding, about two-thirds of MTCT cases occur at the time of delivery and the remainder during pregnancy (mostly during the last two months). In societies where breastfeeding is the norm, MTCT accounts for approximately one-third of all transmissions. As a result, the proportion of newborns infected through MTCT in these societies is higher than in those where mothers with HIV infection can safely avoid breastfeeding.

The latest recommendations from the U.S. Department of Health and Human Services for preventing MTCT in the United States can be found at:
http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines

### 3.2 Other routes of transmission

HIV infection can also be transmitted through blood transfusion and the use of contaminated needles and syringes. In Europe, more than half of children with AIDS live in Romania, where they were infected in the late 1980s through contaminated blood products (used during transfusions) and syringes. Strategies such as reviewing all donated blood and avoiding inappropriate use of blood and/or its products have been put in place and manage to reduce transmission in this way. WHO guidelines for the prevention of HIV transmission by blood transfusion in emergency situations must be implemented in all areas. Child sexual abuse is another significant cause of HIV infections in childhood. Discussing child sexual abuse is taboo in many developing countries. Nevertheless, data from several studies suggest that sexual abuse may be a problem similar in size to that described in industrialized countries.

**Classification:** HIV infection provokes a number of diseases, the most severe of which is AIDS. The CDC's epidemiological classification defines the progression of clinical and immunological decline. In children <13 years, clinical group N indicates asymptomatic, A mild, B moderate, and C severe symptomatic HIV infection (division rests on the existence or absence of some common opportunistic infections or malignant tumors; see Table 1). In a similar way, mild immunocompromise is labeled category 1, moderate as 2, and severe as 3. The division rests on the number of CD4+ T-lymphocytes, which of course depends on the age of the child (see Table 2). Therefore, the child classified in stage B3 according to the classification will have moderately advanced clinical symptoms and severe immunocompromised.

### 3.3 Symptoms and signs

Perinatally infected children in the first few months of life usually have no symptoms. Although the median age of children in which symptoms appear is about 3 years, some children remain symptom-free
>5 years, and with proper ARV treatment they can be expected to live to a ripe old age. Before the introduction of ARV, in about 10–15% of children, the symptoms of the disease progressed rapidly, appearing in
1. Death occurred at 18 to 36 months. These children were thought to be infected with HIV earlier *in utero*. However, most children are probably infected at the time of delivery, so in them the

disease progresses more slowly (survival >5 years even before the routine introduction of ARV therapy).

The most common signs of HIV infection in children are generalized lymphadenopathy, hepatomegaly, splenomegaly, non-progression, oral candidiasis, CNS disease (including delay in development, which can be progressive), lymphatic interstitial pneumonitis, recurrent bacteremia, opportunistic infections, recurrent diarrhea, parotitis, cardiomyopathy, hepatitis, nephropathy and malignant diseases.

**Common symptoms of** HIV infection in untreated children include:

- Slow growth and maturation delay
- Enlargement of lymph nodes in several areas of the body
- Recurrent diarrhea
- Lung infections
- Enlargement of the spleen or liver
- Fungal infection of the mouth (thrush)

Sometimes children have repeated episodes of bacterial infections, such as a middle ear infection (oti-tis media), sinusitis, blood bacteria (bacteremia) or pneumonia.

As the child's immune system deteriorates, various symptoms and complications may occur. About a third of children infected with HIV develop pneumonia (lymphoid interstitial pneumonitis), accompanied by coughand breathing.

Children born with HIV infection usually have at least one episode of *Pneumocystis ji- rovecii*. This serious opportunistic infection can occur as early as 4 to 6 weeks of age, but it mainly occurs in newborns between the ages of 3 and 6 months who contracted HIV before or at birth. More than half of untreated children infected with HIV soon develop pneumonia. *Pneu-mocystic* pneumonia is the main cause of death for children and adults with AIDS.

In a significant number of HIV-infected children, progressive brain damage prevents or delays developmental milestones, such as walking and speaking. These children may also have psychomotor re-tardation and microcephaly. Up to 20% of untreated infected children gradually lose social and language skills and muscle control, and may become partially paralyzed.

Anemia is common among children infected with HIV. About 20% of untreated children develop heart problems, such as rapid or irregular heartbeat or heart failure.

**Complications:** *Pneumocystis jiroveci* (before *P. carinii*) pneumonia is the most common, severe opportunistic infection in children infected with HIV and has high mortality. Infants and children with *Pneumocystis* pneumonia characteristically develop subacute diffuse pneumonitis with resting dyspnea, tachypnea, O2 desaturation, unproductive cough and fever (unlike immunocompromised children and adults who are not infected with HIV, in whom the disease often begins abruptly and more tumultuously).

*Table 1: Clinical groups for children <13 years infected with HIV**

| **Group N: No symptoms** |
| --- |
| Children who have no signs or symptoms considered to be the result of HIV infection or have only one of the criteria listed for Group A |
| **Group A: Mild symptoms** |

Children with ≥2 following states, but no criteria specified for Group B or C

- Dermatitis
- Hepatomegaly
- Lymphadenopathy (≥0.5 cm in >2 places; bilateral = 1 place)
- Parotitis
- Recurrent or permanent upper respiratory infection, sinusitis or otitis media
- Splenomegaly

| Group B: Moderate symptoms |
| --- |
| Children with symptoms attributed to HIV infection, other than those listed for Group A, but not those It's for Group C.<br><br>Examples of conditions in Clinical Group B include, but are not limited to, the following:<br><br>• Anemia (<8 g/dl), neutropenia (<1000/µl) or thrombocytopenia (<100,000/µl) lasting ≥30 days<br>• Bacterial meningitis, pneumonia or sepsis (once)<br>• Candidiasis, oropharyngeal (soor), permanent (>2 months) in children with >6 months. Life<br>• Cardiomyopathy<br>• Cytomegalovirus infection that begins before 1 May. Life<br>• Diarrhea, recurrent or chronic<br>• Hepatitis<br>• HSV stomatitis, repeated (>2 times in 1 year)<br>• HSV bronchitis, pneumonitis or esophagitis that begins before 1 May. Life<br>• Herpes zoster, at least 2 times or that affects >1 dermatomas<br>• Leiomyosarcoma<br>• Lymphatic interstitial pneumonitis or lymphatic pulmonary hyperplasia complex<br>• Nephropathy<br>• Nocardiasis<br>• Permanent fever (>1 month)<br>• Toxoplasmosis, commencing before The 1st month. Life<br>• Varicella, disseminated (complicated chickenpox) |
| **Group C: Severe symptoms** |
| Severe symptoms include:<br><br>• Severe bacterial infections, multiple or recurrent (i.e., any combination confirmed with at least 2 cultures over a period of 2 years) of the following types: septicemia, pneumonia, meningitis, bone or joint infectious or abscess of an internal organ or body cavity (except otitis media, skin and mucosal abscesses and infection caused by a permanent catheter)<br>• Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)<br>• Coccidioidomycosis, disseminated (in places other than, or along the lungs or neck or hilar lymph nodes)<br>• Cryptococcosis, extrapulmonary<br>• Cryptosporidiosis or isosporiasis with diarrhea lasting >1 month<br>• Cytomegalovirus disease that causes symptoms at the age of >1 month (in places other than the liver, spleen or lymph nodes)<br>• Encephalopathy – at least one of the progressive findings that has existed for at least 2 months, and at the same time has no other diseases other than HIV infection, which could explain:<br><br>(1) failure to reach or lose basic developmental points, or loss of intellectual abilities driven according to the standard child development curve or based on the results of neuropsychological tests;<br><br>(2) impaired brain growth or acquired microcephaly demonstrated by measuring head circumference or brain atrophy proven with CT or MRI (in children <2 years of age, a series of imaging tests should be performed);<br><br>(3) acquired symmetrical motor deficit with ≥2 findings: paresis, pathological reflexes, ataxia, posture disorder<br>• HSV infection causes mucocutaneous ulcers that last >1 month; or bronchitis, pneumonitis or |

esophagitis regardless of duration in a child with >1 month of age

- Histoplasmosis, disseminated (in other places, or along the lungs or neck or hilar lymph nodes)

| Group C: Severe symptoms |
|---|
| • Kaposi's sarcoma<br>• Lymphoma, primarily in the brain<br>• Lymphoma (Burkittov) or immunoblastic or large B cell lymphoma<br>• Mycobacterium tuberculosis, disseminated or extrapulmonary<br>• Mycobacterium, other species or unidentified species, disseminated (to other places, or adjacent to the lungs, skin or neck or hilar lymph nodes)<br>• Pneumocystis jiroveci (formerly P. carinii) pneumonia<br>• Progressive multifocal leukoencephalopathy<br>• Salmonella (nontyphoid) septicemia, repeated<br>• Brain toxoplasmosis that begins at >1 month of life<br>• Body decay syndrome without a disease other than HIV infection that could explain:<br>(1) permanent weight loss of >10% of the initial weight *or*<br>(2) a decrease with crossing at least two of the following percentiles on the weight table with respect to age (e.g. 95, 75, 50, 25, 5) in a child with ≥1 years of age *or*<br>(3) <5. percentile on the age-related weight table 2 consecutive measurements with an interval of ≥30 days *plus* (1) chronic diarrhoea (i.e., at least two diarrhoeal stools per day ≥30 days) *or* (2) doxa- zana temperature (≥30 days, intermittent or permanent) |

*Groups are arranged by one-way hierarchy.

Modified by *Centers for Disease Control and Prevention. 1994 Revised classification system for HIV infection in children less than 13 years of age; official authorized addenda: HIV infection codes and official guidelines for coding and reporting ICD-9-CM. MMWR 1994: 43 12.*

Other common opportunistic infections are *Candida* esophagitis, disseminated cytomegalo-virus infection and chronic or disseminated herpes simplex and varicella-zoster infections, and less commonly, *Mycobacterium tuberculosis* and *Mycobacterium avium* complex infections, chronic enteritis along-term *with Cryptosporidium* or other pathogens, and disseminated CNS infection or infection caused by cryptococcus or *Toxoplasmom gondii*.

Malignancies in immunocompromised children with HIV infection are relatively rare, but leio-myosarcomas and some lymphomas, including CNS lymphomas and non-Hodgkin B cell lymphomas (Burkitt type) appear much more frequently than in immunocompetent children. Kaposhi's sarcoma is very rare in children infected with HIV.

*Table 2: Immunological groups for children <13 years old infected with HIV*

| | AGE-SPECIFIC CD4+ T-LYMPHOCYTE COUNT AND THEIR PERCENTAGE IN NOSE TO TOTAL LYMPHOCYTE COUNT | | | | | |
|---|---|---|---|---|---|---|
| **IMMUNOLOGICAL GRU- PA** | **<12 months** | | **1–5 yrs.** | | **6-12 yrs.** | |
| 1: No signs suppression | **CELL/ L** | **%** | **CELL/ L** | **%** | **CELL/ L** | **%** |
| | ≥1500 | ≥25 | ≥1000 | ≥25 | ≥500 | ≥25 |
| 2: Signs of moderate suppression | 750-1499 | 15-24 | 500-999 | 15-24 | 200-499 | 15-24 |
| 3: Severe suppression | <750 | <15 | <500 | <15 | <200 | <15 |

**Diagnosis**

**HIV tests:** In children >18 months of age, the diagnosis is made by serum testing for antibodies (enzyme immune essay [EIA] and confirmatory Western blot) as well as in adults. Very rarely will an older child infected with HIV lack antibodies to HIV due to considerable hypogammaglobulinemia.

Children <18 months retain maternal antibodies, which gives false positive EIA results, so that the diagnosis is made using PCR on HIV DNA, which can diagnose about 30% of cases at the time of delivery, and at the age of 4 to 6 months almost everyone. Growing HIV in culture has acceptable specificity and sensitivity but is technically more demanding and dangerous, and in most laboratories has been replaced by PCR on DNA. PCR on HIV RNA (test for "viral load" to monitor the effectiveness of treatment) in children who did not receive ARV treatment is probably as sensitive as PCR to DNA. However, due to possible insensitivity with ARV treatment and possible nonspecificity with lower RNA concentrations, PCR on HIV RNA is not recommended for diagnosis in infants . Adapted test for p24 antigen is less sensitive than PCR to HIV DNA and culture.

The initial PCR on DNA should be done within the first 2 weeks of life, with about a month of life and between 4 and 6 months. The positive outcome of the search should be confirmed immediately by means of the same or other search (e.g. cultivation in culture). If serial PCR tests on DNA are all negative, the child should be considered uninfected, with an accuracy of >95% (without any disease that defines AIDS). To exclude HIV infection and confirm seroconversion (loss of passively acquired HIV antibodies) monitoring is carried out by antibody tests (one EIA with >18 months, or 2 EIA between 6 and 18 months). HIV infection is diagnosed if a child <18 months with a positive antibody finding but negative virological tests develops an AIDS-defining disease (category C – see Table 1). Newly developed rapid HIV antibody tests that provide results in minutes or hours come from EIA tests. They can be carried out at the site of events on mouth secretions, full blood or serum. In the U.S., these tests are perhaps most useful in delivery rooms, for testing women of unknown HIV serostatus, thus allowing counseling, initiating ARV treatment to prevent MTCT and testing the child. Quick searches should be confirmed by other searches, e.g. Western blot test. If the expected prevalence of HIV is low, even a specific rapid test will give a mostly false positive result (low positive predictive value). However, if the expected likelihood- night of HIV (or seroprevalence) is high, the positive predictive value increases.

Before testing a child for HIV, the mother or caregiver (and the child, if he or she is old enough, i.e. at the age of 16) is advised about the possible psychosocial dangers and benefits of testing. Oral or written consent should be obtained, which is recorded in the history of the disease in accordance with state and/or local laws or hospital regulations. Counselling and obtaining consent shall not delay the examination if it is medically indicated; The refusal of a parent or guardian to grant consent does not relieve doctors of their professional and legal responsibility, and sometimes the approval for the search must be obtained by another means (e.g. by court order). Search results should be discussed personally with the family, caregiver and, if old enough, with the child; if the child is HIV-positive, appropriate counselling and subsequent monitoring must be provided. In all cases, maintaining confidentiality is essential.

**Other tests:** In order to determine the severity of the disease and prognosis, infected children should be determined the number of T-assistCD4+ and T-suppressor CD8+ lymphocytes, and the concentration of viral RNA in plasma (virus load) should be measured. Initially, the CD4+ number may be normal (e.g. above for age-specific category 1 limits in Table 2), but eventually falls. The CD8+ count usually rises at first and does not fall until late during infection. These changes in cell populations lead to an increase in the ratio of CD4+ to CD8+ cells, characteristic of HIV infection (although it sometimes occurs in other infections). Plasma viral RNA concentrations are in untreated children <12 months typically very high (mean about 200,000 RNA copies/ml). At 24 months, the congestion of the virus in untreated children falls (to an average of 40,000 copies/ml). Although in children the wide range of HIV RNA concentrations makes the data less predictive in terms of morbidity and mortality than in adults, the determination of plasma virus concentrations together with the number of CD4+ lymphocytes still provides more accurate prognostic data than the determination of only one of these indicators. Other, cheaper replacement indicators such as total lymphocyte counts and serum albumin levels can also predict AIDS mortality in children, which can be beneficial in developing countries.

Although not routinely measured, serum immunoglobulin concentrations, especially IgG and IgA, are frequently emphatically increased; sometimes children develop panhypogamaglobulinemia.

Patients may be allergic to skin antigen tests.

### 3.4 Prognosis

With proper ARV regimens, most perinatally infected children survive over 5 years of age. About 10–15% of untreated children from industrialized countries die before the age of 4, and most of them before 18 months of age. In developing countries, pediatric AIDS mortality during the first few years of life is much higher.

Opportunistic infections, especially *Pneumocystis* pneumonia, progressive neurological disease and severe physical deterioration are associated with poor prognosis; in *Pneumocystis* pneumonia, mortality with treatment is 5–40%, and without treatment almost 100%. The prognosis is also poor in patients in whom the virus was detected early (that is, by the 7th day of life) or the symptoms developed in the 1st year of life. However, since the introduction of antiretroviral therapy (ART) and antibiotic prophylaxis *P. jirovecis,* in children with good cooperativeness, the incidence of opportunistic infections and malignant diseases has drastically decreased. In adolescents who get HIV infection, the progression of the disease is slow, similar to that of adults.

### 3.5 Treatment

Along with ART, children with HIV infection do not necessarily develop symptoms of HIV infection. ART has significantly changed the way HIV infection manifests itself in children. Although children infected with HIV have bacterial pneumonia and other bacterial infections (such as bacteremia and recurrent middle ear inflammations) somewhat more frequently, opportunistic infections and growth failure are much less common than in the pre-ART era.

All children with HIV infection should get ART as soon as possible, ideally within 1 to 2 weeks of diagnosis. Children are treated mostly with the same ARV drugs as adults, typically art combination consisting of the following:

- Two nucleoside reverse transcriptase inhibitors (NRTIs) *plus*
- Protease inhibitor *or* integrase inhibitor

Rarely, a non-nucleoside reverse transcriptase inhibitor is given with two NRTIs.

However, not all drugs used for older children, adolescents and adults are available to young children, in part because some are not available in liquid form.

In general, children develop the same types of side effects as adults, but usually at a much lower rate. Among these, side effects of drugs can also limit treatment.

There are nearly two dozen ARV drugs in the U.S. (see Table 3), including preparations with a combination of several of them, each of which has side effects and interactions with other ARV drugs or commonly used antibiotics, anticonvulsants, and sedatives. New ARV drugs, immunomodulators and vaccines are being tested.

ART is a standard therapy that relies on a combination of drugs to achieve maximum viral co-oppression, while minimizing the occurrence of resistant strains. Most commonly, ART consists of a "base" consisting of 2 nucleotide analogues of reverse transcriptase inhibitors (ZDV plus lamivudine or abacavir plus lamivudine or tenofovir plus emtricitabine) in combination with either a protease inhibitor (lopinavir/ritonavir, darunavir, atazanavir) or a non-nucleotide reverse transcriptase inhibitor (nevirapine or efavirenen or rilpivirine) or with INSTI. There are other combinations (e.g., ZDV, lamivudine and abacavir; dual protease inhibitor regimens; teno-fovir-containing regimens), but there is less data to support their application as a 1st line of defense regimen. Monotherapy or only treatment with two reverse transcriptase inhibitors (other than zdv chemoprophylaxis in children exposed to HIV) is not recommended. Since the opinions of experts on treatment strategies are rapidly changing, constantly updated clinical practice instructions are recommended, which are available on several websites, the most useful of which are www.aidsinfo.nih.gov, www. hivguidelines.org and www.unaids.org.

*Table 3: Dosage and administration of antiretroviral drugs in children**

| MEDICINE | RECOMMENDED DOSAGE (ORALLY) | UNWANTED EFFECTS |
|---|---|---|
| **Nucleotide reverse transcriptase inhibitors (NRTIs)** | | |
| Abacavir (ABC) | <13 years: 8 mg/kg every 12 hours<br>≥13 years: 300 mg every 12 hours or 600 mg every 24 hours | More common: Nausea, vomiting, fever, rash, anorexia<br>Less common:~5% hypersensitivity syndrome, fever, fatigue, malaise, nausea, vomiting, abdominal pain, lymphadenopathy, rash - most often in the first 6 weeks. Do not repeat - the danger of hypotension, death.<br>Rare: Pancreatitis, lacticacidosis, hepatomegalia with steatosis |
| emtricitabine (FTC) | 0-3 month: 50 mg/m2 every 12 h<br>≥18 years: 200 mg every 24 hours or 300 mg every 24 hours | More common: Headache, nausea, diarrhea, rash, hyperpigmentation<br>Less common: Lactacidosis, hepatomegaly with steatosis |
| lamivudine (3TC) | 0-3 months: 2 mg/kg every 12 hours<br><13 years: 4 mg/kg every 12 hours<br>≥ 13 years: 150 mg every 12 hours or 300 mg every 24 hours | More common: Headache, fatigue, nausea, diarrhea, rash<br>Less common: Pancreatitis, neutropenia, peripheral neuropathy, lacticacidosis, hepatomegaly with steatosis |
| tenofovir† (TDF) | <18: Unknown<br>> 2 yrs. up to <12 yrs. 8 mg/kg 1x per day<br>≥18 years: 300 mg every 24 hours | More common: Nausea, vomiting, diarrhea<br>Less common: Lactacidosis, hepatomegaly with steatosis |
| zidovudine (ZDV, AZT) | 0-3 months: 2 mg/kg every 6 h<br>3 months-13 years: 160 mg/m2 every 8 h<br>≥13 years: 300 mg every 12 hours or 200 mg every 8 hours | More common: Anemia, granulocytopenia, macrocytosis, headache<br>Less common: Hepatotoxicity, myositis,<br>myopathy Rare: Lacticacidosis, hepatomegaly<br>with steatosis |
| **Combined preparations nrti** | | |
| ZDV/3TC | 300/150 mg every 12 hours | See individual remedies |
| ZDV/3TC/ABC | 300/150/300 mg every 12 h | See individual remedies |
| 3TC/ABC | 300/600 mg every 24 hours | See individual remedies |
| FTC/TDF | 200/300 mg every 24 hours | See individual remedies |
| **Non-nucleotide reverse transcriptase inhibitors (NNRTI)** | | |
| Efavient (EFV) | >3 years according to TT 1x per day<br><13 years: 200-400 mg every 24 hours<br>≥ 13 years: 600 mg every 24 hours | More common: Rash, cns side disturbances (predominantly in adults – drowsiness, insomnia, abnormal dreams, confusion); teratogen in primates; interactions with other drugs |

| | | |
|---|---|---|
| nevirapine (NVP) | <13 years: 120-200 mg/m2 every 12 h<br><br>≥13 years: 200 mg every 12 hours (introductory period with dose increase reduces complications at any age) | More common: Rashes (including Stevens-Johnson syndrome), fever, nausea, headache, interactions with other medications<br><br>Less common: Inflammation of the liver (rarely life-threatening), especially with active hepatitis B, hepatitis C, pregnancy, hypersensitivity reactions |

| Protease inhibitors (PI) | | |
|---|---|---|
| atazanavir (ATV) | <13: Unknown<br>≥13 years: 400 mg every 24 hours or 300 mg every 24 hours with ritonavir (RTV) 100 mg every 24 hours to enhance pharmacokinetics | More common: Asymptomatic indirect hyperbilirubinemia (30%), jaundice (10%), headache, arthralgia, nausea, vomiting, diarrhea, insomnia<br>Rarer: Pr interval prolongation in ECG Rare:<br>Hepatitis, hyperglycemia, diabetes |
| lopinavir/ ritonavir (LPV/r) | <13 years: 10-12 mg/kg lopinavir every 12 hours<br>≥13 yrs.: 400 mg lopinavir every 12 h<br>(LPV is combined with a small amount of RTV that enhances pharmacokinetics) | More common: Nausea, vomiting, headache, rash<br>Less common: Redistribution of adipose tissue, disorders lipids<br>Rare: Pancreatitis, hepatitis, hyperglycemia, ketoacidosis, diabetes |
| ritonavir (RTV) | <13 years: 400 mg/m2 every 12 hours<br>≥13 years: 600 mg every 12 h (introductory period with Increasing the dose reduces complications at any age) | More common: Nausea, vomiting, diarrhea, anorexia, headache, multiple interactions with other drugs<br>Less common: Paresthesia around the mouth, redistribution of adipose tissue, lipid disorders<br>Rare: Pancreatitis, hepatitis, ketoacidosis, diabetes |
| **Merger inhibitors** | | |
| enfuvirtide (T20) | <13 yrs.: 2 mg/kg SC every 12 h<br>≥13 years: 90 mg SC every 12 h<br>(NOTE: Oral preparation does not exist.) | More common: ~98% reactions at the injection site (pain, discomfort, induration, redness, nodules, ecchimosis)<br>Rare: Hypersensitivity reaction |

The most commonly recommended doses (including infant doses when known) and known side effects are listed; other doses, drug interactions, and side effects are possible. Working Group on Antiretroviral Therapy and Medical Management of the HIV-Infected Child convened by the National Pediatric and Family HIV Resource Center, Health Resources and Ser-vices Administration (HRSA), and the National Institutes of Health (NIH). Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available on http://www.aidsinfo.nih.gov.

†TDF is functionally classified with NrTI, and is actually a nucleotide reverse transcriptase inhibitor (NtRTI) by chemical composition.

The U.S . Food and Drug Administration has approved the first generic formulation of dolutegravir (DTG) 10 mg dispersible tablets. This approval is the result of an innovative partnership between Unitaid, CHAI and ViiV Healthcare, together with generic suppliers, which accelerated the development timeline by several years. This now means that the preferred first-line ARV treatment based on DTG, recommended by the WHO, is now available in more affordable and child-friendly ge- neric formulations for young children and newborns up to 4 weeks of age and weighing more than 3 kg. The rapid transition to this treatment, combined with improved diagnosis of HIV for children and other support measures, will help to urgently reduce the rate of 95,000 deaths of children associated with AIDS.

DTG-based HIV treatment leads to better outcomes for children. DTG is less likely to affect drug resistance and suppression of viremia is achieved before; Child-friendly dispersible tablets improve adherence due to lower tablet load and easier administration. These factors help children achieve and maintain the suppression of viremia, which is a golden stan-dard for measuring the effectiveness of HIV treatment. Treatment based on DTG is a standard of care for adults. Starting with this regimen from childhood, the need for changes in treatment is reduced as they mature through childhood, adolescence and adulthood. Fewer regimes and regime change

simplifies healthcare management, improves inventory management and reduces waste.

Since 2018, the WHO has recommended DTG-based HIV treatment to infants and children and provided recommendations for dosing infants and children over 4 weeks and over 3 kg in July 2020.

Treatment will be successful only if the family and child adhere to a complex therapeutic regimen. Non-cooperation leads not only to failure in HIV surveillance, but also to the development of drug-resistant strains of HIV, which limit future treatment. Restrictions on cooperation should be discussed before starting treatment. They include the availability and taste of pills or suspensions; The interaction of drugs with current therapy, pharmacokinetic factors such as the need to use some drugs with food or on an empty stomach; the fact that children to take drugs depend on others (and parents infected with HIV may themselves have difficulty in conducting their own therapy); and in adolescents denial or fear of their own infection, distrust of the health system and lack of maternal support.

## 3.6 Dosage recommendations for ARV drugs for newborns

**Newborns at low risk of perinatal HIV transmission**

| Recommended regimen | Recommended duration |
|---|---|
| ZDV | ZDV is given for 4 weeks in the doses listed below. |

**Newborns at high risk of perinatal HIV transmission**

| Recommended regimen | Recommended duration |
|---|---|
| HIV therapy with three drugs:<br>ZDV plus 3TC plus (NVP or RAL) | ZDV is administered for 6 weeks, without increasing the dose to 12 mg/kg, unless the infant has confirmed HIV infection. The dosage for 3TC, NVP and RAL is described below . The duration of these three drugs may vary. |

**Newborns with HIV infection**

| Recommended regimen | Recommended duration |
|---|---|
| HIV therapy with three drugs: ZDV plus 3TC plus (NVP<br>or RAL) | Lifelong therapy in accordance with current treatment according to guidelines. An ARV regimen should be in- dividualized based on infant age and clinical determinants. RAL can be used in infants who are born after postmenstruation ≥37 weeks (defined as the time from the first day of the mother's last menstruation to birth plus the time elapsed after birth) and who have a weight ≥2 kg. LPV/r can be used when an infant reaches postmenstrual age ≥42 weeks and postnatal age ≥14 days. DTG tablets for oral suspense (dispersible tablets) may replace LPV/r, NVP or RAL in infants aged at least 4 weeks and weighing at least 3 kg. |

**Doses of drugs according to gestational age at birth**

ZDV

Note: For newborns who do not tolerate oral medication, the IV dose is 75% of the oral dose while maintaining the same dosing interval.

**≥35 weeks pregnant at birth**

Birth to 4 weeks:

- ZDV 4 mg/kg orally, twice a day

Age >4 weeks:

- ZDV 12 mg/kg per dose orally, twice a day; increase this dose only for infants with confirmed HIV infection.

**Simplified dosage in the weight range for newborns aged ≥35 weeks gestation from birth to 4 weeks**

| Weight | ZDV volume 10 mg/ml orally Syrup twice a day |
|---|---|
| 2 to <3 kg | 1 ml |
| 3 to <4 kg | 1.5 ml |
| 4 to <5 kg | 2 ml |

**≥30 to <35 weeks pregnant at birth**

From birth at 2 weeks old:

- ZDV 2 mg/kg orally, twice a day

From 2 weeks to 6 to 8 weeks:

- ZDV 3 mg/kg orally, twice a day Age >6 to 8

weeks:

- ZDV 12 mg/kg per dose orally, twice a day; increase this dose only for infants with confirmed HIV infection.

**<30 weeks pregnant at birth**

Birth to 4 weeks:

- ZDV 2 mg/kg per dose orally, twice a day

From 4 to 8–10 weeks:

- ZDV 3 mg/kg per dose orally, twice a day Age

>8 to 10 weeks:

- ZDV 12 mg/kg per dose orally, twice a day; increase this dose only for infants with confirmed HIV infection

**3TC ≥32 weeks pregnant at birth**

Birth to 4 weeks:

- 3TC 2 mg/kg per dose orally, twice a day Age

>4 weeks:

- 3TC 4 mg/kg orally, twice a day

**NVP ≥37 weeks pregnant at birth**

Birth to 4 weeks:

- NVP 6 mg/kg per dose orally, twice a day Age

>4 weeks:

- NVP 200 mg/m2 BSA orally, twice a day; increase this dose only for infants with confirmed HIV infection.

**≥34 to <37 weeks pregnant at birth**

From birth at the age of 1 week:

- NVP 4 mg/kg orally, twice a day

From 1 to 4 weeks:

- NVP 6 mg/kg per dose orally, twice a day Age

>4 weeks:

- NVP 200 mg/m2 BSA orally, twice a day; increase this dose only for infants with confirmed HIV infection.

**≥37 weeks of pregnancy at birth and weighing ≥2 kg**
**Birth up to 6 weeks:**

| RAL<br>Note: If the mother took RAL 2-24 hours before giving birth, the first dose of RAL of the newborn should be postponed until 24-48 hours after that | **Body weight** | **Body weight volume (dose) of RAL 10 mg/mL Suspension** |
|---|---|---|
| | Birth up to 1 week: Dosage once a day | Approximately 1.5 mg/kg per dose |
| | 2 to <3 kg | 0.4 ml (4 mg) once a day |
| | 3 to <4 kg | 0.5 ml (5 mg) once a day |
| | 4 to <5 kg | 0.7 ml (7 mg) once a day |
| | 1 to 4 weeks: Dosage twice a day | Approximately 3 mg/kg per dose |
| | 2 to <3 kg | 0.8 ml (8 mg) twice a day |
| | 3 to <4 kg | 1 ml (10 mg) twice a day |
| | 4 to <5 kg | 1.5 ml (15 mg) twice a day |
| | 4 to 6 weeks: Dosage twice a day | Approximately 6 mg/kg per dose |
| | 3 to <4 kg | 2.5 ml (25 mg) twice a day |
| | 4 to <6 kg | 3 ml (30 mg) twice a day |
| | 6 to <8 kg | 4 ml (40 mg) twice a day |

**Age >4 weeks and >3 kg:**

| DTG<br>Note: Only oral suspension tablets (dispersible tablets) are approved for use in infants older than 4 weeks and >3 kg | **Pediatric Body Weight** | **Recommended dose of dolutegravir dispersible tablets** | **Number of tablets** |
|---|---|---|---|
| | 3 to <6 kg | 5 mg once a day | 1 |
| | 6 to <10 kg | 5 mg once a day | 3 |
| | 10 to <14 kg | 20 mg once a day | 4 |
| | 14 to <20 kg | 25 mg once a day | 5 |
| | ≥20 kg | 30 mg once a day | 6 |

*Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (Updated Dec. 29, 2020; Reviewed Dec. 29, 2020)*

**Indications:** ARV is recommended for all HIV-infected children regardless of CD4 values. Experts differ in recommendations for ARV. The aim is to suppress (reduce) HIV replication, and to preserve the normal number and percentage of CD4+ T-lymphocytes for the age in question.

ARV therapy is recommended for all children older than 12 months with severe clinical or immune disease (clinical group C or immune group 3 – see Tables 1 and 2), regardless of the amount

of HIV RNA in plasma. Children with mild to moderate symptoms older than 12 months should also be treated.

(clinical group A or B or immune group 2) and children with plasma >100,000 copies/ml of HIV RNA. Some experts use lower limit values (e.g. >50,000 copies/ml of HIV RNA or 15-20% CD4+ T-lymphocytes). Children without clinical signs of disease or immunosuppression (group N1) should be carefully monitored without ARV therapy if the amount of HIV RNA in plasma <50,000 to 100,000 copies/ml.

All children under 12 months of age with clinical symptoms or immunosuppression (clinical group A, B, C or immune group 2 or 3) should be treated regardless of the viral load in the plasma. Many experts treat children under 12 months of age without symptoms (group N1) because HIV infection can progress rapidly in the first year of life.

**Supervision:** Clinical and laboratory surveillance is important for detecting drug toxicity and therapeutic failure. Physical examination and control of the CCC, the amount of HIV RNA and a subgroup of lymphocytes should be determined every 3 to 4 months; biochemical serum tests, including liver enzymes, lipidogram and amylase and lipase levels, should be repeated at least once or twice a year.

Almost all children infected with HIV should receive routine childhood vaccines, including the following:

- Diphtheria, tetanus and pertussis (DTaP)
- Inactivated vaccine against polio
- Influenza (inactivated, not live vaccine)
- *Haemophilus influenzae*
- *Streptococcus pneumoniae*
- Hepatitis A and hepatitis B

Recently, a conjugated meningococcal vaccine has been recommended for routine and recoverable use in children, adolescents and adults infected with HIV.
Some vaccines containing live bacteria, such as the Calmette-Guérin bacillus (used to prevent tuberculosis in some countries) or live viruses, such as oral polio virus, var- icele and measles-mumps-rubella, can cause severe or fatal illness in children with HIV whose immune systems are severely weakened. However, a live measles, mumps and rubella vaccine and a live vaccine against varicella are recommended for children with HIV infection whose immune system *is not* seriously damaged.
Annual inactivated (not live) influenza immunization is also recommended for all HIV-infected children older than 6 months, and inactivated or live immunization is recommended for host members.
However, the effectiveness of any vaccination is lower in children with HIV infection. Children infected with HIV with very low CD4+ cell counts are considered susceptible to preventable diseases with vaccines.
**Vaccination in case of symptomatic HIV infection:** Generally, live viral vaccines (e.g. oral polio vaccine, varicella vaccine) and live bacterial vaccines (eg BCG) should not be administered in children with AIDS or other signs of advanced HIV infection that indicate immunosuppression. The exception is the measles-parotitis-rubella vaccine in patients who are not strongly immunocompromised; This vaccine should be administered at the age of 12 months to increase the likelihood of an immune response, preferably before the immune system deteriorates. The second dose can be administered as early as 4 weeks later in an attempt to induce as early seroconversion as possible. If the risk of measles exposure is increased, as during an epidemic, the vaccine should be administered at a younger age, e.g. between the ages of 6 and 9 months of age.
Other vaccines administered in childhood, e.g. against diphtheria and tetanus in combination with acellular vaccine against pertussis (DTaP), hepatitis B, *Haemophilus influenzae* type b and conjugated vaccine against *Streptococcus pneumoniae* and inactivated poliovirus (IPV), are administered according to the usual vaccination schedule. Also, pneumococcal poly-saccharide vaccine at the age of 2 years and annual vaccination against influenza starting

from the 6th month of life are recommended.

Since children with symptomatic HIV infection generally react poorly to vaccines , when exposed to diseases against which they have been vaccinated, such as measles or tetanus, they should be considered susceptible, regardless of being vaccinated. Therefore, if there is an indication, passive immunoglobulin immunoglobulin immunization should be carried out. Immunoglobulin should also be given to all non-immunized household members who are exposed to measles.

**Vaccination in case of asymptomatic HIV infection:** Such children should receive a vaccine against DTaP, IPV, *H. influenzae* type b and a conjugate vaccine against *S. pneumoniae,* a hepatitis B vaccine and a vaccine against measles-parotitis-rubella, according to the usual vaccination calendar. Although the oral polio vaccine (OPV) in such patients was administered without side effects, live viruses from OPV can be excreted and transmitted to immunosuppressed individuals, creating an increased risk of paralytic poliomyelitis (which is no longer a problem in parts of the world such as the US, where only IPV is administered).

The varicella vaccine is harmless and recommended for patients with early stage HIV infection. Because HIV-infected children aged ≥2 years. in an increased risk of invasive pneumococcal infection, she should be given a pneumococcal polysaccharide vaccine at the age of 2 years (with a series of conjugated pneumococcal vaccines in infancy). It is recommended to get vaccinated once every 3 to 5 years. The inactivated flu vaccine should be administered to HIV-infected children aged ≥6 months of age every year. In the U.S. and areas with low TB prevalence, it is not recommended to administer the BCG vaccine. However, in developing countries, where the prevalence of TB is high, WHO recommends that BCG be administered to all children without symptoms at the time of birth, regardless of the mother's HIV infection. Several cases of disseminated BCG infection have been described in severely immunocompromised AIDS patients.

Passive immunization after exposure to measles, tetanus and varicella is advised.

### 3.7 Prevention

**Prevention of perinatal transmission:** Appropriate prenatal ARV therapy attempts to improve maternal health, discontinue MTCT and minimize *in utero* toxicity of drugs. In the U.S. and countries where ARV drugs are available and there is infrastructure for HIV diagnosis, ART is standard for all PREGNANT WOMEN INFECTED with HIV.

All pregnant women with HIV should take ART during pregnancy for their own health and to prevent MTCT. Most ARV therapy is safe to use during pregnancy. In general, HIV drugs do not increase the risk of birth defects. In general, pregnant women with HIV can use the same ART regimens recommended for adults unless the risk of any known side effects on a pregnant woman or her child outweighs the well-being of the regimen. All pregnant women with HIV should start taking ART as soon as possible during pregnancy. In most cases, women who are already on an effective ART regimen, when they become pregnant, should continue to use the same regimen throughout the night . Pregnant women with a high or unknown viral load are recommended a planned caesarean section, to prevent transmission of HIV from mother to child. Caesarean section is recommended for the 38th week of pregnancy (2 weeks before the expected due date).

HIV-infected women who have not previously received ARV drugs, and who do not meet the criteria for ART, ZDV is administered orally at a dose of 300 mg 2×/day, starting at 14 to 34 weeks of gestation and continues in pregnancy, and during childbirth IV is administered at a dose of 2 mg/kg for 1 hour, and then at a dose of 1 mg/kg/h until delivery.

Babies born to HIV-infected women receive ART as soon as possible after birth, by possibility within 6 to 12 hours after delivery. HIV testing is recommended for all babies born to women with HIV at 14 to 21 days of age, at 1 to 2 months and again at 4 to 6 months.

The ART that the child receives depends on the mother's viral load and other factors. Babies at higher risk of MTCT receive three ARV drugs up to 6 weeks after birth.

An ARV regimen for newborns administered in doses appropriate to the gestational age of the

infant should be started as close as possible to the time of birth, preferably within 6 hours of delivery. The arv regimen of the newborn should be determined based on the factors of the mother and infants that affect the risk

from perinatal transmission of HIV. Administration of ARV regimen in newborns includes: (1) ARV pro-phylaxis: Administration of one or more ARV drugs to a newborn without documented HIV infection to reduce the risk of perinatal HIV acquisition. (2) Presumed HIV therapy: Administration of a three-drug ARV regimen to newborns at highest risk of perinatal HIV acquisition. Presumed HIV therapy is intended for the previous treatment of a newborn who is later documented to have HIV, but also serves as a prophylaxis against the acquisition of HIV for those newborns who are exposed to HIV in the womb, during the birth process or during breastfeeding and who do not acquire HIV. (3) HIV therapy: Administration of a three-drug ARV regimen in doses of treatment of newborns with documented HIV infection. The prevention regimen for the use of zidovudine for 4 weeks can be used in newborns whose mothers received ART during pregnancy and had a suppression of the virus near childbirth (defined as confirmed levels of HIV RNA <50 copies/ml). For newborns with HIV infection, ART should be started. The use of ARV drugs other than ZDV, lamivudine and nevirapine may not be recommended for any indications in premature babies (<37 weeks gestational age) due to lack of dosage and safety data.

The optimal duration of presumed ART in newborns at high risk of perinatal HIV transmission is unknown. If possible, newborns who are at high risk of contracting HIV should receive ZDV for 6 weeks. Additional medicines, such as 3TC, RAL or NVP, may need to be administered for 2 to 6 weeks. A newborn is given ZDV at a dose of 2 mg/kg PER 4×/day for the first 6 weeks of life. Women whose clinical or immune condition does not meet the criteria for ART are recommended to start ART regardless if the plasma virus is >1000 copies/ml. Immediately after delivery, it can be decided whether the treatment of the mother will continue or not. Women whose clinical or immunological condition meets the therapeutic criteria are given a regimen of multiple drugs, which preferably includes ZDV.

Pregnancy is not a contraindication to the ART regimen, although the expectant mother and her doctor should discuss the possible dangers and benefits of such treatment because there are no data on harmlessness. Many ARV combinations reduce MTCT from 25% to 8%. In addition to existing ART regimes, the MTCT rate in the U.S. is
<2%. Therefore, although the final decision to accept ARV therapy depends on the pregnant woman, it should be emphasized that the proven benefit of therapy outweighs the theoretical danger of toxicity to the fetus.

Most experts believe that an HIV-infected woman receiving combined ART, when she becomes pregnant, should continue treatment, even in the 1st trimester; another option is to abolish all drugs until the beginning of the 2nd trimester when treatment should be continued.

To reduce MTCT in pregnant women in childbirth, without prior treatment (or even for newborns of untreated, HIV-infected women), clinicians also applied combinations of ARV drugs and caesarean section. Rapid testing of pregnant women whose childbirth has begun, and who do not have documentation of their se-rolological status can enable the urgent implementation of these measures. In such circumstances, a pediatric or maternal hiv infection specialist should be consulted immediately.

Breastfeeding (or donating to milk banks) in HIV-infected women should be decisively discouraged in countries where safe and accessible feeding methods exist. However, in countries where infectious diseases and malnutrition are important causes of early childhood mortality and dairy preparations are not available, the benefit that breastfeeding provides in protecting against mortality caused by respiratory and digestive infections outweighs the danger of HIV transmission. For these developing countries, the WHO recommends that mothers continue breastfeeding.

Prevention of transmission in adolescence: Since adolescents are at particular risk of HIV infection , they should be taught, have HIV testing available, and know their serological status. Teaching should include data on transmission, the meaning of infection and prevention methods, including giving up high-risk behavior and conducting safe sex (single use of condoms) for those who are sexually active.

Prevention of opportunistic infections: Prophylaxis *of Pneumocystis* pneumonia is indicated in HIV-infected children with significantly damaged immune systems (i.e., in immune group 3), although older adolescents and children on ART with immune system recovery (intercourse, immune group 1 or 2 over several months) may stop prophylaxis for so long

Stay in group 1 or 2. *Pneumocystis* prophylaxis is also recommended in all children exposed to HIV who are born to HIV-infected mothers, starting at 4 to 6 weeks of age. Prophylaxis can be interrupted when HIV is ruled out by repeatedly repeating tests – PCR for HIV or cultures. The drug of choice is trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 75 mg TMP/375 mg SMX/m2 PO 2×/day for 3 days in a row (e.g. Monday-Tuesday-Wednesday); other options include an equal total dose once/day for 3 days/week or twice a day every day of the week or every other day. Patients aged ≥5. those who do not tolerate TMP-SMX can be given pentamidine once a month in the form of an aerosol (300 mg with a special inhaler). Pentamidine is also administered iv, but it appears to be less effective and potentially more toxic. Another option, especially for children <5 years. is oral administration of dapsone daily (2 mg/kg, no more than 100 mg). Other useful drugs are pyrimethamine with dapsone, pyrimethamine-sulfadoxine and atovakon orally. However, experiences with these drugs are very limited, so they should be taken into account only when pre-ordered regimens are not tolerated or cannot be administered.

Prophylaxis of infection with *Mycobacterium avium* complex in children ≥6 years with CD4 +<50/µl (or children aged 2 to 6 years with CD4+ number <75/µl, aged 1 to 2 years with <500/µl, or <1 years and <750/µl) is carried out with azithromycin 1×/week or clarithromycin daily, and another possibility is the daily use of rifabutin. Data on the prophylaxis of other opportunistic infections, e.g. cytomegalovirus, fungal infections and toxoplasmosis encephalitis, are limited.

### 3.8 Socialization of HIV-infected children

Children living with HIV continue to be left neglected by the global AIDS response.

In 2019, only 53% (950,000) of the 1.8 million children living with HIV (aged 0-14) were diagnosed and treated globally, compared to 68% of adults. The remaining
850.00 children living with HIV have not been diagnosed and do not receive life-saving HIV treatment. Two-thirds of missing children are 5-14 years old and do not routinely visit traditional health facilities . Engaging communities and families of people living with HIV, tuberculosis and other related diseases and providing family services are needed to find and start therapy for missing children. An estimated 95,000 children died from AIDS-related diseases in 2019. In part, due to the lack of early HIV diagnosis in newborns and children and the immediate association with optimal HIV treatment regimens. Untreated, 50% of newborns infected with HIV during or around the moment of birth will die before the age of two.

The infection of the child affects the whole family. Serological examination of siblings and parents is recommended. The doctor's task is to teach and permanent counseling.

An infected child should be taught hygiene and behavior to reduce the danger to others. How much he is told about his illness depends on age and maturity. Older children and adolescents should be aware of their diagnosis and the possibility of sexual transmission, and accordingly they should be consulted. The family does not have to inform people outside the narrow family circle about the disease, as this can lead to social isolation. Guilt is common. Family members, including children, can be depressed, and need counseling.

Since HIV infection is not acquired through the usual touch that occurs among children, i.e. through saliva or tears, most children infected with HIV should be allowed to attend school without restrictions. Likewise, there is no reason to limit custody, adoption and nursing of HIV-infected children. Some conditions can pose a danger to others (e.g. aggression with a bite or changes in the skin that moisturize and cannot be covered), so special measures should be taken.

The number of school employees who are aware of the child's illness should be minimized to ensure proper care. The family has the right to inform the school, but those involved in the care and education of an infected child must respect his or her right to privacy. Data can only be disclosed with the informed consent of parents or legal guardians or with the consent of a child who is then at the appropriate age.

*Multidisciplinary approach*

Children living in FAMILIES affected by HIV also suffer from socioeconomic and psychological problems in addition to the medical problems they face. Many will become orphans. A medical approach alone is not enough to guarantee effective support to these children and their families. Flexible multidisciplinary care models involving the community, social workers, counselors, nurses, doctors and teachers are needed to respond to the diversity of needs of children living with HIV/AIDS and their families.

*Children's rights*

Under the UN Convention on the Rights of the Child, all children living with HIV must have access to treatment, counselling, education, recreation and social support, and be protected from any form of discrimination. Children should not only be passive objects of clinical and social intervention.

As they grow older, they should gradually be given the opportunity to play an active role in their own care. A special effort is needed to make it easier for children to participate in all issues affecting them, including HIV, and to put their human rights into practice.

*Integration of pediatric issues on the HIV agenda*

The needs and problems of infected and affected children should be integrated into HIV-related activities in all sectors – in particular health, education, agriculture, social services and finance.

UNAIDS - Joint statement calling for an immediate extension of the approach to optimal HIV treatment for infants and children living with HIV in the country (UNAIDS. Joint statement calling for urgent coun- try scale-up of access to optimal HIV treatment for infants and children living with HIV, 22 De- cember 2020, https://w ww.unaids.org/en/keywords/children)

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# 4. HIV/AIDS TREATMENT AND CARE OF DRUG INJECTORS (PWID)

# 4. HIV/AIDS TREATMENT AND CARE OF DRUG INJECTORS (PWID)

It is estimated that there are about 15.9 million PWID people in the world; 47% of this population is from only five countries: the People's Republic of China, the Socialist Republic of Vietnam, Malaysia, the Russian Federation and Ukraine. Globally, about 3 million, or 13.1% of PWID, are living with HIV. But only 4% of them receive antiretroviral therapy (ART). Among the regions where the prevalence of HIV is high among people who use drugs are Eastern Europe, Central Asia and East and Southeast Asia.

Therefore, the World Health Organization (WHO) strongly supports evidence-based harm reduction programs as an approach to HIV prevention, treatment and care PWID, which includes the following nine interventions:

1. Syringe and needle exchange programs
2. Opiate substitution therapy and other ways to treat addiction diseases
3. HIV testing and counseling
4. ART
5. Prevention and treatment of sexually transmitted diseases (STIs)
6. Condom sharing PWID and their sexual partners
7. Education and information of addicts and their sexual partners
8. Vaccination, early diagnosis and treatment of viral hepatitis
9. Prevention, diagnosis and treatment of tuberculosis

Studies constantly confirm that syringe and needle exchange programs result in a reduction in HIV transmission by up to 33-42% in some cases, while opiate replacement therapy (with methadone and buprenorphine) is highly effective in reducing injection, which puts addicts at risk of acquiring HIV infection, while improving access and adherence to ART treatment, and reducing mortality. HIV testing and counseling is a particularly important path to HIV treatment and care of patients, which includes the use of ART. In general, PWIDs have poorer accessibility to ART compared to others, despite the fact that the application of ART with PWID brings benefits to the wider community, as well as evidence that PWID can successfully undergo this treatment and benefit from it.

Explosive growth is one of the characteristics of the HIV epidemic based on drug injection. HIV prevalence within this population has risen from 12% to 60-70% in just a few years.

PWIDs usually acquire HIV infection while still young, more often men, are sexually active, who then transmit the infection to their sexual partners, men or women, who transmit the infection to their children (mother-child transmission). SW, which offers sexual services for drugs or to support drug use, can present themselves as a transmissive bridge between drug users and the population that does not use them!

**The explosion of the HIV epidemic** among PWID may be due to a lack of prevention and treatment in combination with blood transmission of the virus during the sharing of used syringes and needles, and other drug injection kits. High viremia characteristic of the first weeks and months after seroconversion is also important.

Pre-exposure prophylaxis (PrEP) is the prophylaxis of antiretroviral (ARV) drugs that are taken before possible exposure to HIV. Studies have been conducted on the potential use of PrEP for PWID in Bangkok, and the use of tenofovir reduced HIV transmission by 49%. However, studies like this are rare, and the WHO does not yet recommend PrEP for PWID.

## 4.1 Health and social consequences of injecting drugs

C> Health problems PWID:

- Infections with blood-borne viruses - hepatitis B, C and D viruses, with consequent liver disease

- Bacterial infections: tuberculosis, bacterial pneumonia, endocarditis and sepsis
- Overdose (eng. overdose)
- Alcoholism and alcoholic liver disease
- Psychiatric problems, including depression
- Other common health problems PWID: deep vein thrombosis and pulmonary embolism, soft tissue and blood vessel infections (skin abscesses, thrombophlebitis), and an increased risk of chronic diseases associated with tobacco smoking!

C> Social problems:

- Stigmatization, discrimination and social marginalization
- Poverty
- Homelessness
- Unemployment
- Family and social dysfunction
- Criminal behavior and prison stays

### 4.2 Substitution therapy of opiates

The total number of opioid addicts receiving prescribed methadone is more than half a million and is increasing in virtually all regions. In Europe, 76% of pwid replacement treatment programs use methadone, but the number of those taking buprenorphine is increasing.

### 4.3 Organization and management of HIV treatment in PWID

In the treatment of addicts living with HIV/AIDS, four services are essential, interconnected and closely related:

1. General medical care and/or infectious diseases department
2. Harm Reduction Program
3. Drug addiction treatment
4. Psychosocial support

**1. General medical care includes:**

C> availability

C> gratuity

C> friendly approach to the patient

C> adaptation to the needs of the individual

C> continuous care of the patient through health care, community, family...

In order to ensure this, a multidisciplinary approach is necessary, which is favored by the WHO, which means that the team that cares for these patients must consist of:

C> clinician, infectologist or other specialist

C> nurse

C> social worker

C> advisor

C> psychiatrist or psychologist

**Medical care must be comprehensive and provide:**

C> HIV/AIDS treatment

C> addiction treatment, including opiate substitution therapy

C> the diagnosis and treatment of other concomitant and injectable drug-related diseases

C> HIV-specific prophylaxis/suppression of OI

C> vaccination against hepatitis B

C> care and treatment of patients with advanced disease

**However, it is extremely important to ensure that:**

C> patient's cooperation

C> reducing drug use and sexually risky behavior

C> education on techniques for the use of injections to reduce the number of infections

C> support for sexual partners

C> social support

C> reduction of stigmatization and discrimination with guaranteed confidentiality of data

**2. Harm Reduction Program**

"Harm Reduction" refers to policies, programs and practices whose primary goal is to reduce the harmful social and economic consequences of using legal and illegal psychoactive drugs, which does not necessarily include reducing drug use. Implementing a harm reduction program is beneficial for addicts, their families and the community.

The key components of this part are:

C> community fieldwork, with an emphasis on peer support groups

C> the process of behavioral change by different means of

communication C> exchange of syringes and needles

C> treatment of addiction, especially with the use of opiate substitution therapy

C> HIV testing and counseling

C> distribution of condoms, prevention of sexually transmitted diseases and their treatment

C> primary care, including hepatitis B vaccination, drug injection-related infections, overdose treatment

C> support in legal regulations

C> ensured the sustainability of *drop-in* centers

C> programs of psychosocial support, rehabilitation, resocialization and social integration

**3. Addiction treatment**

There is no single, elaborate effective method of treating addiction to psychoactive agents. Since addiction to psychoactive agents is a complex medical and social problem, accordingly there are diverse treatment programs with associated different techniques used in the treatment. Treatment begins with drug therapy to establish detoxification and initial abstinence in order to implement further techniques at all, and these include individual and group psychotherapy, sociotherapy with occupational therapy, family therapy, support groups and psychosocial interventions, and the rapecommunity as a method of long-term rehabilitation and resocialization.

The main route of infection with the hepatitis C virus (HCV) in Europe is the injection of drugs. According to estimates, there are about one million current or former intravenous drug users in Europe who may have chronic HCV infection. HCV infection rates are often very high among intravenous drug users, ranging from 12% to 85%.

It is possible to become infected with hepatitis C even with only one drug injectable with non-sterile utensils; the risk of infection certainly increases with the length of service of injection of the drug. It is often recorded- on and co-infection (simultaneous infection) by different types of hepatitis and HIV viruses, which leads to

rapid deterioration of the liver, the development of cirrhosis, liver failure and death. The fact that most people infected with HCV do not have clear symptoms of the disease and are not aware of their infection, opens the way for the spread of the infection to other populations of drug users and sexual partners.

Hepatitis B infection in drug users is one of the first infections caused by the use of other people's injection kits, recorded as early as the 70s and 80s of the last century. Given the existence of an effective vaccine that prevents hepatitis B virus infection, and thus the development of chronic complications (liver cirrhosis and liver cancer), hepatitis B vaccine is part of all vaccination programs (in European Union countries) of people at increased risk of contracting hepatitis B as well as intravenous drug users.

Despite the increased disease among drug users in relation to the general population, the introduction of preventive programs and the involvement of civil society organizations have led to a decrease in the number of new infections in the PWID population. Preventive programs include a multicomponent approach through harm reduction programs, counseling, and treatment programs.

Preventive programs affect the behavior of the user population through:

C> adoption of safer drug use: ensure legal access to clean drug injection kits, including sufficient free availability of sterile needles and syringes

C> vaccination: vaccine against hepatitis B, tetanus, influenza, and especially for HIV-infected people

C> drug addiction treatment: provide substitution therapy with opiate agonistand other effective treatments for drug addiction

C> testing: voluntary and confidential testing with informed consent for HIV, hepatitis B and C

C> treatment of infectious diseases: antiviral treatment of hepatitis C and HIV infection

C> treatment of other infectious diseases

C> adopting safer sexual habits (protected sexual relations)

In order to further reduce the number of patients with infectious diseases in the PWID population, it is necessary to continue the implementation of preventive programs through the partnership approach of all participants involved in the issue of addiction (health, social, public, judicial, civil society organizations and others).

It also involves a multidisciplinary approach. The team consists of doctors, nurses, counselors, social workers and pharmacists. Authorities, citizens' associations and communities should be involved in the activities of these teams.

Addiction treatment, including opiate replacement therapy, is particularly useful in the prevention and treatment of HIV/AIDS:

C> improving access to HIV treatment and general health care

C> by maintaining active PWID in treatment

C> by reducing HIV transmission, viral hepatitis and bacterial infections

C> reducing the need for hospitalization

C> by improving and encouraging consent to HAART treatment It also

affects:

C> reducing illicit drug use

C> reduction of criminal activity

C> reduced overdose mortality

C> reduction of high-risk behavior for HIV transmission

C> improved social integration

The benefits of substitution therapy can be maximized if:

C> prescribed higher doses of methadone or buprenorphine

C> program directs maintenance, not abstinence

C> offer assessment and treatment of accompanying psychiatric and social problems

C> ensure easy access to the service by properly selecting its location, working hours and arriving at a reasonable price

C> provide a friendly environment and atmosphere

When replacement therapy is available, HIV/AIDS medical care should be offered and HAART provided at the same place where replacement therapy is provided. Such an approach can:

C> achieve the maximum level of supervision treatment

C> improve efficiency

C> reduce the risk of developing ARV resistance

C> improve surveillance of interactions between methadone and HIV/AIDS drugs

**4. Psychosocial support**

Psychosocial treatment includes counseling work, various educational and preventive activities. Services provided include social and counselling services, psychosocial assistance and support, occupational therapy and occupational activities, health care and psychological support.

Implies the existence of:

C> support service for proper use of prescribed ARV therapy

C> psychological support, such as group therapy for PWID and their family members

C> peer support group

C> education program

C> psychiatric/psychological services for the diagnosis and treatment of impaired mental health

C> social services that will solve problems related to employment, finances, legislation, discrimination...

C> psychotherapeutic and sociotherapeutic support models

C> psychosocial support services through the work of counseling centers for the prevention and treatment of addiction diseases

**5. Models of comprehensive HIV/AIDS care PWID:**

C> IN ONE PLACE HIV/AIDS medical care and addiction treatment

C> Separatehiv/AIDS medical care and addiction treatment, with good coordination and awareness

C> Primary care for addiction and HIV/AIDS through a family medicine specialist

**6. Close**

Prison facilities must provide adequate treatment to all addicts who are serving their sentences, as well as those who have been given a court measure of compulsory treatment. Continuity of protection and power for addicts must be ensured between all stages, from arrest, detention, serving of sentences and after dismissal.

It is necessary to ensure adequate conditions for the treatment of female addicts in prison.

Psychosocial treatment includes counseling work, various educational and preventive activities and more. Services provided include social and counseling services, psychosocial assistance and support, occupational therapy and occupational activities, health care and psychological support.

Comprehensive inmate medical care programs include:

C> information, education and conversations about HIV/AIDS

C> voluntary, advised testing

C> condom distribution

C> syringe and needle exchange program

C> availability of disinfectants

C> substitution therapy

## 4.4 Clinical management of HIV-infected PWID

Taking care of HIV-positive PWID must be directed towards:

- a substance on which a person is dependent
- psychological and social consequences of addiction
- medical complications associated with drug injection and HIV/AIDS

### 4.4.1. Determining dependency

The patient addict must be examined first. A physical examination may indicate dependence on a particular substance or complications related to drug use. It is necessary to define dependence, i.e. the following must be known:

- what substances are used, including alcohol and drug combinations
- The age at which the drug was taken for the first time
- ways of introducing drugs
- How long do drugs take?
- changes in the effects of drugs over time
- history of tolerance, overdose and withdrawal syndrome
- periods of abstinence and attempts to stop
- complications of drug use (hepatitis, abscesses...)
- ongoing problems, including the severity of addiction
- Types and outcomes of previous addiction treatments

### 4.4.2. Determination of HIV/AIDS status

In health care, PWID must be offered voluntary, advised and informed HIV testing . The patient has the right to refuse the test. If he agrees to it, it is mandatory:

- pre-test counselling and information about HIV infection
- do a serological HIV test (commonly ELISA and/or rapid test), with the following Western blot
  Confirmatory test.
- post-test counselling, including information on risk reduction, regardless of whether the test result is positive or negative

### 4.4.3. Further clinical evaluation

The aim is to formulate a clinical management strategy of PWID living with HIV, which includes:

- History
- physical examination
- Assessment of mental health and social status

- assessment of readiness for treatment

- routine laboratory tests.
- determination of CD4 lymphocytes and assessment of the severity of immunodeficiency
- Determination of PCR HIV RNA quantitatively
- A history of contraception and a pregnancy test if indicated
- hepatitis B and C tests
- review on TB
- Testing for a sleep.
- assessment of psychiatric disorder
- body weight
- other tests that determine the patient's current state of health

Most PWID comes to treatment in the advanced stages of HIV infection, and it is necessary to evaluate and active OI. Anamnesis and physical examination normally determine:

- oral candidiasis and difficulty swallowing, suggesting esophageal candidiasis
- non-healing of genital or ulceration, suggesting herpes *simplex*
- elevated body temperature with cough and shortness of breath, suggesting bacterial pneumonia, LUNG TB or PCP

### 4.4.4. Psychosocial assessment

Research suggests that 25-50% of PWID has impaired mental health! Therefore, the initial evaluation should be focused on:

- any source of instability that may adversely affect susceptibility to treatment
- Depression
- Other psychiatric problems Social

factors important for assessment include:

- social stability, support of family and community
- homelessness
- financial security
- nutrition

### 4.4.5. Opiate addiction management

Addiction management is essential in the care of PWID living with HIV; HIV infection and addiction of the same person are not isolated problems; each of them affects the progression of the other.

Addiction treatment ranges from complete abstinence to providing safe injectable heroin.

#### *4.4.5.1. Substitution therapy of opiates*

There are two main modalities in the treatment of opiate addiction: pharmacotherapeutic and psychological. Farm- co-therapy includes:

- maintenance therapy with agonists, with methadone or levo-alpha-acetyl-methadone (LAAM)
- maintenance therapy with a partial agonist, with sublingual buprenorphine or combination of buprenorphine and naloxone
- maintenance therapy with an antagonist, oral naltrexone
- Detoxification programs

IN EUROPE, TWO OPIATE REPLACEMENT THERAPIES ARE MOST COMMONLY AVAILABLE: META-
Don and buprenorphine. High doses of methadone (>60 mg) and buprenorphine better reduce the level of illicit opiate uptake compared to a low dose of methadone (<60 mg).

**It is important to keep in mind that:**

- Stabilization of opiate addiction through opiate substitution therapy is a key composite of successful HIV/AIDS treatment, including HAART.
- Opiate replacement therapy is not available to everyone, and most HIV-positive PWIDs that occur for TREATMENT with ART still take heroin or other drugs.
- The unavailability of opiate replacement therapy should not prevent PWID from treating ART-
  om.
- Active injection of drugs should not exclude HAART.

# 5. ANTIRETROVIRAL DRUG INTERACTIONS

# 5. ANTIRETROVIRAL DRUG INTERACTIONS

Treatment of HIV infection is a demanding process that, in addition to all aspects of human-related treatment , requires a thorough knowledge of the interaction between drugs and other preparations (food or alternative medical preparations). People living with HIV very often take medications to treat other health conditions or dietary supplements aimed at boosting immunity. Taking two or more different preparations together can result in a change in efficacy or side effects of one or more antiretroviral drugs (AVs), and some preparations should not be taken in combination with certain ARV.

Pharmacokinetic interactions between ARV with each other as well as other drugs are common and can lead to an increased or decreased effect of ARV. Not infrequently, there may be an increase in toxicity or an impact on the therapeutic response of a particular drug. When prescribing or changing one or more ARV, clinicians must take into account the potential of drug interactions – both those that affect ARV and drugs for other health conditions. A thorough insight into the overall therapy in consultation with the ARV-prescribing clinician and the clinical pharmacologist will help design an ARV treatment regimen that minimizes unwanted interactions. The management of interactions includes reasonable, medically justified and for the patient favorable use of drugs and other preparations with the least level of inconvenience and harm to the patient's health. Recommendations for managing a particular drug interaction may vary depending on whether a new ARV is started in a patient with a stable treatment of an accompanying health condition or a new drug for concomitant disease is just being introduced with an existing stable ARV regimen. The size and significance of interactions is difficult to predict when several drugs with competitive metabolic pathways are prescribed at the same time. Therefore, it is necessary to introduce treatment, individually or in groups for which we have reliable evidence or knowledge of tolerability. When prescribing drugs that interact with each other, clinicians should exercise caution in monitoring the therapeutic efficacy and/or toxicity associated with concentration.

Pharmacokinetic interactions may occur during the absorption, metabolism, or elimination of ARV and/or other drugs. The most common examples of interactions of selected ARV available in Bosnia and Herzegovina are lowering the concentration of biktegravir, dolutegravir and raltegravir by concomitant use with polyvalent cations such as Ca, Mg, Al, Fe and Zn, and elevated gastric acidity reduces rilpivirine absorption.

## 5.1 Pharmacokinetic interactions that affect the absorption of the drug

The extent of oral absorption of drugs can be affected by the following mechanisms:

- Acidity-reducing agents, such as proton pump inhibitors, H2 antagonist or antacids, can reduce the absorption of ARV that require acidity in the stomach (e.g. rilpivirine) for optimal absorption.
- Products containing polyvalent cations, such as dietary supplements, iron preparations or antacids containing aluminum, calcium or magnesium, can bind to integrase inhibitors (INSTI) and reduce the absorption of these ARV.
- Drugs that induce or inhibit the enzyme cytochrome P450 (CYP) most commonly 3A4 or p-glycoprotein outflow transporter in the gut may reduce or enhance the absorption of other drugs.

## 5.2 Pharmacokinetic interactions that affect liver metabolism

The two main enzyme systems are most often responsible for clinically significant drug interactions:

1. The CYP450 enzyme system is responsible for the metabolism of many drugs, including non-nu-cleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), CCR5 antagonist (maravirox), and some INSTI. CYP3A4 is the most common enzyme responsible for the metabolism of the drug, although multiple enzymes may be involved in the metabolism of the drug. ARV and concomitant medicines may be inducers, inhibitors and/or substrates of these enzymes.

2. The enzyme uridine diphosphate glucuronosyltransferase (UGT) 1A1 is the primary enzyme responsible for the metabolism of INSTI raltegravir. Drugs that induce or inhibit the enzyme UGT can affect the pharmacokinetics of this INSTI.

INSTI biktegravir and dolutegravir have mixed metabolic pathways, including CYP3A4 and UG-T1A1. Drugs that induce or inhibit these enzymes can have a different effect on the pharmacokinetics of both of these INStIs.

## 5.3 Pharmacokinetic boosters (boosters)

Pharmacokineticenhancement is a therapeutic strategy used to increase exposure to desired ARV by concomitantly administering a drug that inhibits enzymes that metabolize desired ARV. Currently, two drugs are used as pharmacokinetic enhancers: ritonavir (RTV or /r) and cobicistat (Cobi). Both drugs are potent inhibitors of CYP3A4 enzymes, so concomitant administration with AVs metabolized by CYP3A4 results in a greater effect of primary ARV. It is important that RTV and Cobi have different effects on other enzymes and metabolism of CYP- or UGT-metabolism. Complex or unknown pharmacokinetic mechanisms of interactions make it impossible to extrapolate rtv drug interactions with certain Cobi interactions, such as interactions with warfarin, phenytoin, voriconazo-lom , oral contraceptives and some HMG-CoA reductase inhibitors.

## 5.4 Other mechanisms of pharmacokinetic interactions

Knowledge about the carriers of active drug molecules is in constant development, which further clarifies the mechanisms of interaction societies of ARV with other drugs and preparations. For example, DTG reduces the renal clearance of metformin by inhibiting the carriers of the organic cation in renal tu- bular cells. Similar carriers help clearance of the liver, kidneys and bile, and may be sensitive to drug interactions. ARV and concomitant medicines may be inducers, inhibitors and/or substrates of these carriers of active drug molecules. The impact of drug carriers on drug interactions is complex, and the clinical significance of these interactions is not fully understood and is therefore constantly being investigated. Therefore, continuous research and understanding of the pathways of transfer of the active molecule and the clinical significance of these mechanisms of interaction are needed.

## 5.5 The role of therapeutic monitoring of medicinal products in the management of drug interactions

Therapeutic monitoring of medicinal products (TDM) may be carried out by dosing certain drugs using measured concentrations of ARV or other drugs to increase the likelihood of desired therapeutic and safety results. Drugs suitable for TDM are characterized by a known relationship of exposure, response, and therapeutic extent of drug concentrations. Therapeutic volume is the range of concentrations established by clinical trials that are associated with a higher likelihood of achieving the desired therapeutic response and/or reducing the frequency of adverse reactions associated with the medicinal product. Determining the concentration of an individual ARV requires a quality laboratory that can provide reliable data.

When simultaneous use of ARV and another drug is required, which is likely to result in a clinically important interaction, the first step is to assess whether other, equally effective treatment options can be used to avoid interaction. If this is not possible, TDM may be useful in assessing whether dose adjustment is required.

Drug concentration analyses for some ARV are commercially available. However, reporting results may take time. When interpreting the test results, clinicians should take into account compliance with existing patient therapy, the time of the last dose of ARV and blood draw, and the time that has elapsed since the joint administration of the drug combination interaction. If necessary, when interpreting the results and deciding what actions to take, you should contact a clinical pharmacy collologist who knows the ARV. If dose adjustment is required, TDM must be repeated after the dose-adjusted drug reaches a stable state to ensure therapeutic concentration through the appropriate dosage.

TDM data should not be interpreted and used separately, but must be taken into account in conjunction with clinical information, including virological response, signs and symptoms of drug toxicity, to ensure safe and effective therapy.

## 5.6 Interactions between food and antiretroviral drugs

People living with HIV in recent years have been paying more and more attention to proper and varied nutrition, thereby wanting to maintain a healthy body mass and quality absorption of ARV and thus to non-farm-

kological way to improve your health. Modern food products are often rich in certain nutrients and have enhancers of taste and smell, which can realize adverse reactions with ARV. Although newer active molecules have a good pharmacological profile and do not have a lot of in-activity with food ingredients, it may be necessary to consult a dietitian about proper nutrition during ARV treatment. Table 1 shows the dietary methods with ARV regimens available in Bosnia and Herzegovina

*Table 1. ARV and diet*

| Ordinal number | Generic name | Acronym | Factory name | Eating habits |
|---|---|---|---|---|
| 1. | abacavir | ABC | Ziagen | Common |
| 2. | abacavir + lamivudine | ABC/3TC | Kivexa | Common |
| 3. | bixtegravir + tenofovir alafenamide + emtricitabine | BIC/TAF/ FTC | Biktarvy | Common |
| 4. | dolutegravir | DTG | Tivicay | better taken with a meal |
| 5. | efavirence | EFV | Stocrin | Don't take it with a fatty meal or 2 hours before meals |
| 6. | lamivudine | 3TC | Zeffix | Common |
| 7. | lopinavir + ritonavir | LPV/r | Aluvia, Kale-tra | taken with a meal |
| 8. | nevirapine | NVP | Viramune | Common |
| 9. | raltegravir | RAL | Isentress | Common |
| 10. | rilpivirine + tenofovir dizoproxil fumarate + emtricitabine | RPV/TDF/ FTC | Eviplera | taken with a meal |
| 11. | tenofovir dizoproxil fumarate + emtricitabine | TDF/FTC | Truvada | take with meals or later |
| 12. | zidovudine | ZDV | Retrovir | none, taking it with a meal reduces nausea |
| 13. | zidovudine + lamivudine | ZDV/3TC | Combivir | none, taking it with a meal reduces nausea |

**U ovom pregledu su data uputstva samo za one ARV koji su odobreni i koji se koriste u Bosni i Hercegovini. S obzirom na stalnu dinamiku u istraživanju interakcija u lijekovima i stalno obogaćivanje tržišta brojnim ljekovitim preparatima, uputno je da kliničar kod svakog novog lijeka ili preparata provjeri moguće interakcije. Besplatni mrežni alat visokog kvaliteta Univerziteta u Liverpulu iz Ujedinjenog Kraljevstva je dostupan na adresi https://www.hiv-druginteractions.org/checker.**

Also, the Working Group in the development of clinical guidelines did not give preference to any group of drugs, considering generic and originator drugs equally valuable.

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# 6. TREATMENT OF PATIENTS WITH CO-INFECTIONS

# 6. TREATMENT OF PATIENTS WITH CO-INFECTIONS

Viral hepatitis is an inflammation of the liver caused by a virus. In Bosnia and Herzegovina, the most common causes of viral hepatitis are hepatitis A virus, hepatitis B virus and hepatitis C virus. Some forms of vi-runny nose hepatitis can be obtained in the same way that HIV can be obtained through sexual contact and sharing syringes, needles or other equipment for injecting drugs.

Hepatitis B virus (HBV), hepatitis D virus (HDV), hepatitis C virus (HCV) and HIV have very similar routes of transmission, but hepatitis B virus is thought to be about 100 times more infectious than HIV. Si- multane infections with these viruses usually lead to more pronounced and progressive liver disease, higher incidence of cirrhosis, hepatocellular carcinoma (HCC) and mortality of the co-infected person. Therefore, it is more likely that early treatment of co-infected people is more likely. In general, the dominant virus is responsible for liver disease and should be identified initial treatment targeted according to that virus. For these reasons, according to the World Health Organization (WHO), almost 70% of people living with HIV will show that they have positive markers of hepatitis that indicate past or present contact with HBV. The lucky circumstance is that HBV nevertheless shows a lower incidence in the development of liver cirrhosis than hepatitis C. Namely, it is believed that 5-10% will develop chronic hepatitis, and 30% of chronic active hepatitis B in the next 30 years will pass into cirrhosis of the liver. Approximately one quarter of cirrhosis patients will experience decompensation over the next five years, and cancer will occur in about 5-10% of patients.

People with HIV have an increased risk of developing chronic viral hepatitis and liver disease. This means that they could have a co-infection or two or more infections at the same time. Because people can get HIV and hepatitis B in the same way, a large number of adults at risk of CONTRACTING HIV are also at risk of hepatitis B.

As hepatitis C is a virus transmitted through direct contact with the blood of an infected person, HIV and hepatitis C co-infection is common (62-80%) among PWID (people injecting drugs) with HIV. Although transmission via injectable drugs is still the most common way for people to contract hepatitis- with C, sexual transmission is an important way of getting sick in homosexual and bisexual men. Hepatitis C is one of the primary causes of chronic liver disease in the world, and liver damage associated with hepatitis C progresses faster among people infected with HIV. Hepatitis C infection can also affect the management of HIV infection. The guidelines recommend that all people with HIV be screened for hepatitis C and that people at increased risk undergo annual testing.

**People with HIV and hepatitis A**

People with HIV are at risk of severe illness caused by hepatitis A infection. Therefore, the CDC and ACIP recommend vaccination against hepatitis A for this population.

Since the response to the vaccine could be reduced in people with HIV infection who are immune-pressive, it is necessary to conduct serological post-vaccination testing for all people with HIV infection
≥1 month after the end of vaccination against hepatitis A. All people with HIV infection who receive a hepatitis A vaccine, regardless of the results of serological testing after vaccination, should be explained that the vaccine may not provide long-term protection against hepatitis A. Therefore, it may be necessary to receive immunological globulin (IG) after high-risk contact (e.g. sexual contact).

In immunocompromised individuals, the serological response to HAV vaccination may be reduced. In people infected with HIV, seroconversion rates range from 52% to 94%.

**People with HIV and hepatitis E**

The clinical presentation of chronic hepatitis E viral (HEV) infection is mainly described in the conditions of organ transplantation, but is similar in other immunosuppressed groups, including patients with hematological disorders, people living with HIV, and patients with rheumatic disorders receiving strong immunosuppression.

Among patients with HIV infection, chronic HEV infection is mainly described in those with CD4+

T-cell broth <200/mm. In other immunosuppressed groups, predictive factors for the development of chronic HEV infection have not been established.

Sexual transmission of HEV was reported in men who have sexual intercourse with men (MSM), but in another study of a cohort of HIV patients found no evidence of sexual transmission.

Treatment of chronic HEV infection in untransplanted immunosuppressive patients, i.e. patients with hematological disorders or HIV, has been documented in several cases and in small batches. Pegylated interferon-α, ribavirin or a combination thereof have been effective in treating HEV infection in patients with hematological disorders and those with HIV. Kamar and colleagues report on the pegylated interferon-α-2a effect in three liver transplant patients who have had chronic, active HEV infection. Three patients received a three-month regimen pegylated interferon 135 μg/week after giving informed consent.

**People with HIV and hepatitis B**

Hepatitis B virus and HIV are viruses that are transmitted primarily through sexual contact and the use of injections. Hepatitis B spreads when the blood, semen or other bodily fluids of a person infected with the virus enter the body of a person who is not infected. This can happen through sexual contact; by distributing needles, syringes or other equipment for injecting medication; or from mother to baby at birth. Not all people who are newly infected with HBV have symptoms that can include fatigue, poor appetite, abdominal pain, nausea and jaundice. For many people, hepatitis B is a short-term disease. For others, it can become a long-term, chronic infection that can lead to serious, even life-threatening health problems such as cirrhosis or liver cancer. The risk of chronic infection is associated with the age of acquiring infection: about 90% of newborns with hepatitis B further develop a chronic infection, while only 2-6% of people who become infected with hepatitis B in adulthood become chronically infected. Due to these common modes of transmission, a high proportion of adults at risk of CONTRACTING HIV are also at risk of HBV infection. People with HIV who contract HBV are at increased risk of late complications in terms of liver cirrhosis and liver cancer. The best way to prevent hepatitis B is to get vaccinated. It is estimated that 5-15% of the 34 million HIV-infected people worldwide have chronic hepatitis B co-infection, especially in Southeast Asia and sub-Saharan Africa.

There is, of course, the question of the mutual influence of these two viruses, i.e. whether and in what way they lead to an exacerbation of another disease, that is, infection. A faster progression of chronic HBV towards cirrhosis and/or hepatocellular carcinoma has been demonstrated if it is HBV/HIV-co-infected patients than if it is only HBV infection. In some cohort studies, it was found that mortality due to liver damage is 2-3 times higher in HIV/HBV co-infection than in those with hiv monoinfection. Also, HIV can alter the acute course of HBV infection, with less icteric syndrome and a lower percentage of spontaneous removal of HBV from the body. People with co-infection have higher levels of HBV DNA, lower release rates than HBeAg, and lower serum transaminase levels.

To prevent HBV infection in people with HIV, ACIP recommends a universal hepatitis B vaccine for all vulnerable people infected with HIV. The first dose of the vaccine can be administered immediately after taking blood for pre-vaccination serological examination, regardless of the CD4+ lymphocyte count. In order to confirm an adequate immune response, it is necessary to carry out serological protrusions of protective antibody titers on the hepatitis B surface antigen after vaccination, 1-2 months after the end of vaccination against hepatitis B. People with HIV who have a positive Test for HBV should receive HIV antiviral drugs with anti-HBV activity (e.g. tenofovir and entekavir).

## 6.1 Diagnosis of HBV/HIV co-infection

The rule is that all HIV-positive people are tested for the presence of HbsAg. If HbsAg is negative, it should be tested for the presence of HbcAb and HbsAb in the next step so that we can evaluate earlier infection control or vaccination. Since HBV DNA can remain indefinitely in the body, if there is a presence of HbcAb, reactivation of the virus can occur even if the presence of HbsAb develops more severe immunosuppression due to the presence of HIV. What can cause isolated HBcAb, even in the absence of HBsAg or HbsAb:

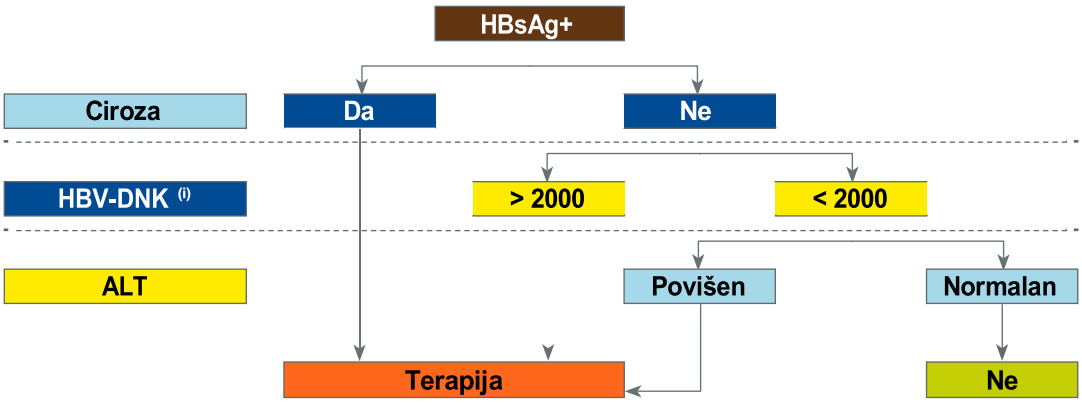
1. Occult viremia: HBV viremia can be proven in 4-88% of people who are HbcAb poses-

tivne. The clinical significance of this occult viremia is unknown, but we must still take into account that even low viremia can lead to liver damage and the onset of liver disease. For this reason , some experts believe that these patients should also be treated as patients with chronic HBV infection.

2. Weak HbsAb response: Antibody loss can occur over time, especially if the patient has a weakened immune system. However, these patients can respond positively to the booster vaccine. Complete vaccination should be completed with three doses.
3. The presence of an isolated anti-HBc test result usually means HBV infection in the past with subsequent loss of anti-HBs and occurs in 7-19% of HIV patients. The clinical significance of isolated anti-HBc is unknown, but in people with HIV infection it may indicate chronic or, more likely, recovered HBV infection. In a country with a low prevalence, such as the United States, isolated anti-HBc can also represent a false positive result.

*Note*: Image Algorithm 1 is taken from "EACS Guidelines", version 6.1, November 2012

***Algorithm 1. Assessment of therapeutic indications for HBV infection in HIV-positive people***




[i] = IJ/mL

*Note*: In patients with significant chronic liver fibrosis (F2-F3), HBV treatment may be considered even when serum HBV/DNA is below 2000 IJ/mL and liver enzymes are not elevated.

## 6.2 Treatment of HBV/HIV co-infection

It is necessary to advise each patient a hygienic-dietary regimen (non-use of alcohol, diet, bed rest, sparing from heavy physical exertion), and carefully examine the condition of both infections (an- amnesis, clinical examination, CD4 cell count and *viral load*, hepatitis markers, transient elastographi- I-FibroScan, and if indicated liver biopsy). If the doctor decides that it is necessary to treat the disease, there may be different options.

Full antiretroviral therapy (ART) should be used in people with HIV/HBV co-infection, but at least two drugs must be used to treat HBV. Drugs that have potential to act on both viruses are FTC, 3TC and TDF.

*Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; In 2013,* updated in 2015, HBV/HIV co-infected individuals should start ART in all those with evidence of severe chronic liver disease regardless of CD4 cell count and all those with CD4 count ≤500 cell count/mm3 regardless of stage of liver disease.

The latest European and US guidelines from 2017/18 on the treatment of HIV-infected patients recommend starting ART in patients who are infected with HIV/HBV, regardless of CD4 cell count, due to an increased risk of fibrosis, cirrhosis and HCC. All people with HIV/HBV co-infection should receive ART, including tenofovir disoproxil fumarate (TDF) or tenofo-vir alafenamide (TAF), which have antiviral action against HIV and HBV. Stopping Art containing TDF or TAF in people with HIV/HBV co-infection should be avoided due to the high risk of severe complications of liver decompensation, after reactive hepatitis HBV. The toxicity of the li-

the chest (kidney, bone density, liver) should be carefully monitored during ART. ETV represents an alternative to the treatment of HBV without significant effect on the HIV virus. There are limited data on the use of TAF in patients with HIV/HBV. People with cirrhosis of the liver and low CD4 lymphocytes require careful supervision in the first months after the onset of ART in order not to overlook the syndrome of immune reconstitution and subsequent decompensation of the liver due to the activation of the disease, which is accompanied by elevated activity of aminotransferases.

Since TDF, TAF and ETV monotherapy can cause MUTATIONS in HIV resistance, all HbsAg positive patients should be tested for HIV before these drugs are used in the treatment of HBV infection.

All HIV-positive patients with HBV infection should start ART independently of cd4 cell levels. Patients infected with HIV/HBV should be treated with a TDF-based ART regimen or TAF (EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection Euro-pean Association for the study of the Liver).

In contrast, the presence of HBV does not seem to affect the progression of hiv infection. However, some liver complications are also described that can lead to a resurgence of HBV infection. Discontinuation of double active ART therapy or toxicity of ART medications may affect the treatment of HIV infection if there is co-infection with HBV. This can cause the following consequences:

1. FTC, 3TC and TDF are drugs that have double activity towards both HIV and HBV. Discontinuation of treatment with these drugs can lead to serious hepatocellular damage, which in turn leads to reactivation of HBV.
2. Entekavir also has an effect on HIV (although significantly less than TDF), but its use to treat HBV without ART in people with HIV co-infection may lead to mutation selection M184V, shared with FTC and 3TC. Therefore, entekavir should only be used with a full ARV treatment regimen for HIV/HBV co-infection.
3. 3TC resistance develops after four years in 90% of people receiving 3TC as the only cure for HBV infection.

Tenofovir is the basis of recommended treatment. Treatment should include tenofovir/lamivudine, emtricitabine/tenofovir or (provided that there are no contraindications to tenofovir), together with a third drug, efavirence, to prevent the choice of HIV-resistant mutants. Tenofovir is available together with lamivudine or emtricitabine and efavirence. This treatment strategy achieved high rates of HBV DNA suppression (90%), HBeAg loss (46%) and HBsAg loss (12%) in HbeAg positive patients after five years of treatment, with no evidence of resistance. Progression in cirrhosis is reduced, with no significant difference in response to those with or without HIV co-infection. To date, no case of viral resistance to tenofovir *in vivo* has been described. Although the risk of developing cirrhosis is negligible in HBV/HIV co-infected individuals on long-term treatment of tenofovir with emtricitabine or lamivudine, the risk of HCC persists, but is low.

In people who cannot be given tenofovir due to renal insufficiency or other intolerance, entecavir (as a second-line regimen) may be administered with a dose adjustment to reproductive function, although its effect on HIV is weaker.

*Table 1: Recommendations for the first line of ART regimens for adults, adolescents, pregnant and lactating women and children, including people with HBV/HIV co-infection*

| The first line of ART | Preferred first-line modes | Alternate first-line modes, [b] |
|---|---|---|
| **Adults and adolescents (including pregnant and lactating women, and adults with TB co-infection and HBV co-infection)** | TDF+ 3TC (or FTC) + EFV as fixed combination<br>*(Firm recommendation, moderate quality evidence)* | AZT+3TC+EFV<br>AZT+3TC+NVP<br>TDF+ 3TC (or FTC) + NVP<br>*(Firm recommendation, moderate quality evidence)* |

| The first line of ART | Preferred first-line modes | Alternate first-line modes, [b] |
|---|---|---|
| **Children ≥ 3 years old.** | ABC+3TC+EFV | ABC+3TC+NVP<br>AZT+3TC+EFV<br>AZT+3TC+NVP<br>TDF+3TC (or FTC) +EFV<br>TDF+ 3TC (or FTC) + NVP |
| **Children <3 years old** | ABC (or AZT) + 3TC + LPV/r | ABC+3TC+NVP AZT+3TC+NVP |

*3TC – lamivudine; ABC – abacavir; ATV – atazanavir; AZT – zidovudine; d4T – stavudine; DRV – darunavir; EFV – efavirenc; FTC – emtricitabine; LPV – lopinavir; NVP – nevirapine; r – ritonavir; TDF – tenofovir*

[a] ABC or enhanced PI (ATV/r, DRV/r, LPV/r) may be used in special circumstances.

[b] States should suspend the use of d4T in first-line regimens due to its well-known metabolic toxicities *(solid recommendation, moderate quality evidence)*. In adults, the use of d4T as an option in the first-line regimen should be suspended and limited to special cases in which other ARV drugs cannot be used, and limited to the shortest possible period with immediate monitoring. In children, the use of d4T should be limited to situations where AZT toxicity is suspected or confirmed and unavailability of ABC or TDF. The duration of therapy with this drug should be limited to the shortest possible period.

When using ART, an increase in serum transaminases is often observed, which can be a result of the hepatotoxic action of drugs, the natural course of hepatitis, but also the immune reconstituted inflammatory response (IRUO). IRIS). What is the practical significance of this increase is not known with certainty because even with the continuation of therapy can lead to an improvement in the course of the disease and a decrease in transaminases.

Nevertheless, some authors recommend discontinuing treatment with these ART drugs if transaminases (ALT) are raised by 5-10 times above the highest normal values.

In addition to all of the above, an increase in the value of transaminases can also be a sign of Seroconversion HbeAg, and before discontinuing these drugs, the condition of HbeAg should necessarily be evaluated.

All HIV-positive people who are HbsAg or HbsAb negative or do not have occult viremia should be compulsory vaccinated.

**Monitoring the patient**

HBV/HIV co-infections require frequent controls. For patients who are on an ART regimen with PI, or NNRTI, and these are practically all, it is necessary to monitor serum aminotransferase levels every month for the first three months of therapy, and then every three months to detect drug-related hepatotoxicity . The number of CD4 cells should be monitored every 3-6 months, and the level of HIV DNA in plasma every 6-12 months.

**In conclusion**

C> Before starting ART, all patients who have a positive test for hepatitis B surface antigen (HBsAg) should be tested for Hepatitis B Virus DNA (HBV) using a quantitative examination to determine the level of HBV replication.

C> Since emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF) and tenofo-vir alafenamide (TAF) act against both HIV and HBV, the ART regimen for HIV and HBV patients should include TAF or TDF plus 3TC or FTC as a nucleoside reverse transcriptase inhibitor (NRTI).

C> If TDF or TAF cannot be used safely, the alternative recommended Treatment of HBV is en-tekavir with a fully suppressive ARV regimen.

C> Entekavir acts against HIV; its use for the treatment of ART-free HBV in patients with double infection may result in the selection of the M184V mutation that at 3TC and FTC gives HIV resistance. Therefore, entekavir must be used with a fully suppressive ARV regimen when given to patients with HBV/HIV co-infection.

C> Peginterferon alpha monotherapy may also be considered in certain patients.

C> Other HBV treatment regimens, including adefovir alone or in combination with 3TC or FTC and telbivudi- nom, are not recommended for patients with HBV/HIV co-infection.

C> Discontinuation of anti-HBV agents may cause serious hepatoce-lullary damage resulting from HBV reactivation; patients should be advised not to stop taking these medicines and monitor them closely during discontinuation of HBV treatment.

C> If ART needs to be modified due to HIV virological failure, and the patient has adequate HBV co-pression, ARV drugs active against HBV should continue to be administered for the treatment of HBV in combination with other suitable ARV agents to achieve HIV suppression.

C> Reactivation of HBV has been observed in people with HBV infection during treatment of HCV without interferon. For this reason, all patients who start HCV therapy should be tested for HBV. People with HCV/HIV co-infection and active HBV infection (established by a positive HBsAg test) should receive ART involving two agents with anti-HBV activity before initiating HCV therapy.

### 6.3 People with HIV and hepatitis C

Most people who develop hepatitis C develop a long-term (chronic) infection. Hepatitis C is one of the primary causes of chronic liver disease worldwide, and hepatitis C-related liver damage progresses faster in people who have HIV at the same time. Many people who have hepatitis C do not know that they are infected and have no symptoms nor do they feel sick. If left untreated, chronic hep-atitis C can cause serious health problems, including liver damage, cirrhosis, liver cancer, and even death. The most common way of transmission of HCV infection is the joint use of syringes, needles or other injection equipment. Many PWIDs who have HIV also have hepatitis C. It is less commonly spread through sexual contact. Sexual transmission of hepatitis B occurs more often than such transmission of hepatitis C.

The prevalence of HCV/HIV co-infection varies considerably depending on the risk group - e.g. MSM, high-risk heterosexuals and PWID. Co-infection with HIV and HCV is common (62-80%) among injectable drug users who have HIV. Although drug injection transmission is still the most common way of getting HCV in the United States, sexual transmission is an important mode among MSM, including those who have unprotected intercourse or use sex toys. HCV infection can also affect the management of HIV infection. The American Liver Disease Study Association (AASLD) and the American Society for Infectious Diseases (IDSA) also recommend that people who are infected with HIV and HCV be given antiviral drug therapy with direct-acting antiviral drugs to treat their HCV infection.

According to the WHO, there are about 71 million people in the world today who are chronic carriers of HCV. If we look at the European region, the prevalence of HCV infection among people living with HIV is on average 40%, but in urban areas it reaches 50-90%. In BiH, the PWID population unfortunately still has a high percentage of the practice of distributing injection kits. The number of people identified with HIV transmission this time shows a tendency to decline from 14% to 8% in BiH, but there is still a high prevalence of HCV. The latest research into risk behaviors among PWID, conducted by UNICEF, shows the prevalence of HCV infection within this population in residential environments ranging from 19% to 46%. This is a worrying fact if we take into account the fact that studies of long-term follow-up of people with chronic hepatitis C have shown that 2-20% develop cirrhosis of the liver within 20 years. This percentage increases even more if it is associated with other risk factors such as alcoholism or HIV infection or injecting drugs, and increases with a person's age. In meta-analyses, it has been shown that in the case of co-infection with HIV, the risk of developing cirrhosis triples, and further increases inversely proportional to the number of CD4 cells. Taking into account the aforementioned fact that most ART also has a hepatotoxic effect, this complicates the treatment of HIV infection and contributes to the weaker effects of these drugs. The prognosis for this co-infection is significantly worse than all others and is associated with higher mortality and the risk of developing HCV liver damage in people who are HIV-positive. One large observational cohort study on the toxicity of specific ART regimens showed no significant differences, although interactions must always be taken into account. For example, ribavirin has important pharmacological interactions with ABC, AZT, ATV, d4t and ddI that increase toxicity if used simultaneously. New studies have shown that a viable virological response to HCV therapy is identical in people co-infected

HIV virus as well as when it comes to monoinfection with HCV.

**Assessment of the situation**

All people living with HIV should be tested for the presence of HCV. If the test is negative, it should be repeated at least once a year. People who are seropositive for HCV should be prescribed HCV RNA qualitatively and quantitatively to determine the existence of an acute infection.

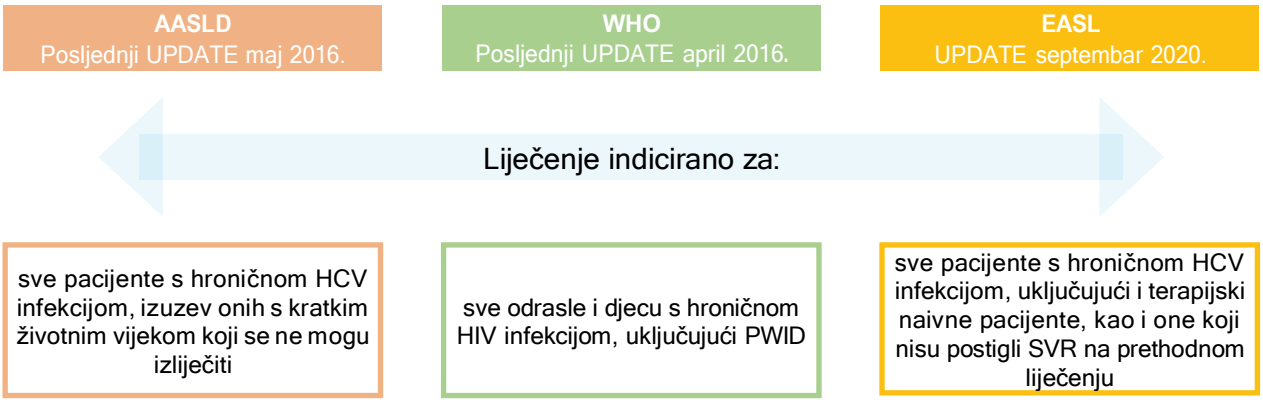
Every patient with HCV/HIV co-infection should, similar to HBV/HIV co-infection, be advised a hygienic and dietary regimen (non-use of alcohol, diet, bed rest, evaluation of HBV markers), and, if necessary, advise and carry out immunization for hepatitis A and B. Treatment of HCV infection according to strictly defined criteria is available in BiH, regardless of whether it is an independent disease or co-infection with HIV. Of course, a complete assessment of the state of HCV in-fection must be carried out . In addition to the complete examination and evaluation of all laboratory parameters, especially the estimated PCR method of HCV RNA, genotyping should also be done. This is important especially if therapy is carried out with antiviral drugs that are not pangenotypic. Transient elastography is required, and sometimes a liver biopsy is necessary to determine the existence of *bridgeging* necrosis or portal fibrosis.

## 6.4 Treatment of HCV/HIV co-infection

In the guidelines for the treatment of HCV infection, since 2018, who has recommended for people over the age of 12 to be treated with direct-acting antiviral drugs (CDC). Direct-Acting Antiviral Med-ications – DAA) for all genotypes, which have proven to be more effective (can cure most people
– 95% – with HCV infection). The duration of treatment with their use is shortened (usually 8-16 weeks, depending on liver damage or cirrhosis findings) and they have fewer side effects, but their price is high, and they are not available to everyone.

While treatment availability has improved, there is still room for improvement. It is estimated that in 2017, out of 71 million people living with hepatitis C, 19% (13.1 million) knew about the diagnosis, and of those diagnosed with chronic hepatitis C, about 5 million were covered by DAA drug treatment.

**International guides - treatment for all**




In recent years, there have been major changes in the field of hepatitis C treatment, and with it hcv/HIV co-infection. Namely, there has been the introduction of new drugs – directly acting anti-tivirus drugs. The duration of treatment has significantly decreased, clinical treatment before the introduction of antiviral therapy is simpler, there are fewer excluding factors for the introduction of antiviral therapy, monitoring therapy is not only shorter but also simpler, and the treatment is more comfortable, efficient and safe for the patient, with very rare adverse events.

These are the reasons why THE DAA almost completely suppressed the earlier therapeutic option that pre-orders treatment with hepatitis C peginterferon (pegylated interferon alpha 2a or alpha 2b) and fish-virin. Some of the earlier therapeutic modalities such as HCV NS3/4A bottle protease inhibitor-previr or telaprevir are a thing of the past today.

According to the latest treatment guidelines for most countries in Europe (Table 2), chronically infected people are treated with direct-acting antiviral drugs (DAA). However, in some cases, treatment is carried out with a combination of pegylated interferon and ribavirin.

*Table 2: Indications for the treatment of chronic hepatitis C in 2019: who and when to treat?*

| **Treatment is indicated in:** |
|---|
| • all untreated and treated patients with compensated or decompensated disease Liver |
| **Preference in treatment is given to:** |
| • patients with significant fibrosis (F3 by Metavir) or cirrhosis (F4), including decomposed cirrhosis<br>• patients with HBV or HIV co-infection<br>• patients with indication for liver transplantation<br>• patients with recurrent HCV infection after liver transplantation<br>• Patients with HCV infection before and after solid organ transplantation<br>• patients with clinically significant extrahepatic manifestations of infection |
| **Treatment can be delayed:** |
| • in patients without or with mild liver fibrosis (F0-F1 according to Metavir) and without extrahepatal manifestations |
| **Treatment is not recommended:** |
| • patients with limited life expectancy due to second comorbidity |

*Table 3: Approved medicines for the treatment of HCV in the European Union in 2019*

| Medicine | Shape | Dosage per day |
|---|---|---|
| ribavirin* | 200 mg capsules | 2, 0, 3 capsules (body weight <75 kg)<br>3, 0, 3 capsules (body weight >75 kg) |
| sofosbuvir | 400 mg tablets | 1 tablet |
| voksilaprevir | 100 mg in combination with 400 mg of sofosbuvir + 100 mg velpatasvira | 1 tablet |
| daklatasvir | 30 or 60 mg tablets | 1 tablet |
| sofosbuvir / ledipasvir | 400 mg sofosbuvir + 90 mg ledipasvir tablets | 1 tablet |
| paritaprevir / ombitasvir / ritonavir | 75 mg paritaprevir + 12.5 mg ombitasvir + 50 mg ritonavir tablets | 2 tablets |
| **Medicine** | **Shape** | **Dosage per day** |
| dasabuvir | 250 mg tablets | 1, 0, 1 tablet |
| grazoprevir / elbasvir | 100 mg gazoprevir + 50 mg elbasvir tablets | 1 tablet |
| sofosbuvir / velpatasvir | 400 mg sofosbuvir + 100 mg velpatasvir tablets | 1 tablet |
| glekaprevir / pibrentasvir | 100 mg glekaprevir + 40 mg pibrentasvir | 3 tablets |

* In addition to combinations of direct-acting antiviral drugs in decompensated cirrhosis

The same treatment regimens without IFN, without ribavirin, should be used in HIV-infected patients as in patients without HIV infection, because the virological results of therapy are identical. In HIV-infected patients, treatment changes or dose adjustments should be made in case of interactions with ARV drugs.

**Protocols for the use of certain combinations of drugs**

***sofosbuvir and ledipasvir***

A combination of sofosbuvir (400 mg) and ledipaspipe (90 mg) in one tablet administered once a day for 12 weeks. Therapy is not recommended for previously treated patients with genoti- pm 1a.

***grazoprevir in elbasvir***

A combination of grazoprevir (100 mg per day) and elbasvir (50 mg per day) in one tablet of the remark once a day for 12 weeks. Therapy is not recommended for patients with genotypes 1a and 4 if they have hcv RNA >800 000 IU/ml.

***sofosbuvir and velpatasvir***

A combination of sofosbuvir (400 mg per day) and velpatasvira (100 mg per day) in one tablet administered once a day for 12 weeks. Patients with compensated cirrhosis are treated with a combination of sofosbuvir and velpatasvira with the addition of ribavirin for 12 weeks (1000 or 1200 mg depending on body weight, in divided doses). Treatment without ribavirin is considered if the paci- jent does not have a Y93H mutation. If the patient cannot take ribavirin, and the presence of Y93H has been proven, treatment lasts 24 weeks. Patients with decompensated cirrhosis are treated with a combination of sofosbuvir and velpatavir with the addition of ribavirin for 12 weeks (1000 or 1200 mg depending on body weight, in divided doses), or 24 weeks if they cannot take ribavirin.

***glekaprevir and pibrentasvir***

A combination of glekaprevir (100 mg per day) and pibrentasvira (40 mg per day) in one tablet. It is administered at a dose of 3 tablets (300 mg / 120 mg) once a day for 8 weeks for patients without cirrhosis or 12 weeks for patients with compensated cirrhosis. In patients with genotype 3 and compensated cirrhosis who have previously been unsuccessfully treated with peginterferon + ribavirin/±sofosbuvir or sofosbuvir + ribavirin, treatment lasts 16 weeks.

***sofosbuvir, velpatasvir and voksilaprevir***

A combination of sofosbuvir (400 mg per day), velpatavir (100 mg per day) and voksilaprevir (100 mg per day) in one tablet administered once daily for 12 weeks for patients without cirrhosis or with compensated cirrhosis, including all genotypes of HCV.

Therapy is not recommended for patients with decompensated cirrhosis.

**Assessment of therapeutic efficacy**

The SVR (HCV RNA) is determined 12 weeks after the end of treatment.

**Monitoring of viremia (HCV RNA) during the use of drug combinations without interferon**

It is recommended to determine HCV RNA at the end-of-treatment response (ETR), and 12 weeks after the end of treatment (sustained virologic response - SVR 12).

It is recommended to use a "real-time" PCR test that has a lower detection limit ≤15 IU/ml seru.

**Assessment of the stage of fibrosis according to the finding of fibroelastography**

F1 <7.0

F2 ≥7.0<9.5

F3 ≥9.5

F4 ≥12.5

**Cirrhosis indicators (one of the indicators is enough)**

1. Biopsy: F4 (Metavir) or F5/6 (Ishak)
2. Fibroleastography ≥12.5 kPa on 2 occasions
3. APRI ≥2 on at least 2 occasions
4. Presence of portal hypertension (varices or ascites)

In patients infected with HIV and HCV, sofosbuvir/velpatasvir may be administered with most ARV drugs. Exceptions are inducing drugs efavirenc, etravirin and nevirapine. Efavirenc causes a 50% reduction in velpatasvir exposure. Sofosbuvir/velpatasvir also increases exposure to tenofovir by P-gp inhibition. This means that patients on a TDF-containing regimen will need monitoring of adverse renal events.

In hiv/hcv infected patients, sofosbuvir/velpatasvir/voksilaprevir is not pre-ordered with inducing drugs efavirence, etravirin and nevirapine and pro-tease inhibitors atazanavir/ritonavir and lopinavir/ritonavir. Caution should be exercised for darunavir/ritonavir, darun- avir/cobicistat and atazanavir/cobicistat twice a day as there are no data. Efavirenen causes a 50% reduction in velpatasvir exposure and atazanavir causes a fourfold increase in exposure to voxilaprevir. Sofosbuvir/velpatasvir/voksilaprevir also increases tenofovir exposure by P-gp inhibition. This means that patients on a TDF-containing regimen should be monitored for adverse renal events.

In HIV/HCV, glekaprevir/pibrentasvir is contraindicated with regimens containing atazanavir and is not recommended with other HIV protease inhibitors. Similarly, inducing non-nucleoside reverse transcriptase inhibitors of efavirenca, etravirin and nevirapine is not recommended due to the expected decrease in plasma exposure to glekaprevir/pibrentasvir. All other ARV drugs can be administered simultaneously, including cobicistat, when used with an integrase inhibitor elvite-gravir.

Drug interactions are key factors in the treatment of HIV/HCV-infected patients. In the treatment of HIV/HCV, special attention should be paid to the interaction of these drugs with each other and to the interaction of antiviral drugs with the drugs taken by the patient in connection with other acute or chronic diseases.

It is also important to know the interaction with drugs from other groups of drugs. Significant data can be obtained in the Liverpool HIV Interactions database, https://w ww.hiv-druginteractionslite.org.

*Table 4: Drug interactions between HCV DAA and ARV drugs*

| | | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|---|
| NrTI | Abacavir | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Emtricitabine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Lamivudine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Tenofovir dizoproxil fumarate | ♦ | ■* | ■* | ♦ | ♦ |
| | Tenofovir alafenamide | ♦ | ♦ | ♦ | ♦ | ♦ |
| NNRTI | Doravirin | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Efavirenc | ♦ | ● | ● | ● | ● |
| | Etravirine | ♦ | ● | ● | ● | ● |
| | Nevirapine | ♦ | ● | ● | ● | ● |
| | Rilpivirine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Protease inhibitors | Atanazavir/ritonavir | ♦ | ♦* | ● | ● | ● |
| | Atanazavir/cobicistat | ♦ | ♦* | ● | ● | ● |
| | Darunavir/ritonavir | ♦ | ♦* | ■* | ● | ● |
| | Darunavir/cobicistat | ♦ | ♦* | ♦* | ● | ● |
| | Lopinavir/ritonavir | ♦ | ♦* | ● | ● | ● |

| | | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|---|
| Integrase inhibitors | Biktegravir/emtricitabine/tenofovir alafenamide (TAF) | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Kabotegravir | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Dolutegravir | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Elvitegravir/cobicistat/emtricitabine/tenofovir dizoproxil fumarate (TDF) | ♦ | ■* | ■* | ♦ | ● |
| | Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF) | ♦ | ♦ | ♦ | ♦ | ● |
| | Maravirok | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Raltegravir | ♦ | ♦ | ♦ | ♦ | ♦ |

*DAAs – direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; NNRTI – non-nucleoside reverse transcriptase inhibitor; NRTIs – nucleoside reverse transcriptase inhibitor; PIB – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ Potential interaction that may require dose adjustment, change in administration time, or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

* Known or expected increase in the concentration of tenofovir in regimens containing tenofovir disoproxil fumarate. Caution and frequent monitoring of the kidneys.

No drug-to-drug interactions have been reported between sofosbuvir and ARV drugs.

A fixed combination of sofosbuvir and ledipasvira can be used with all antiretrovirals. However, this regimen should not be used with a combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/cobicistate whenever possible, or should be used with caution and with frequent renal supervision.

*Table 5: Drug interactions between HCV DAA and illegal/recreational drugs*

| | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|
| Amphetamine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Cannabis | ♦ | ♦ | ♦ | ♦ | ♦ |
| Cocaine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Diamorphine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Diazepam | ♦ | ♦ | ♦ | ♦ | ♦ |
| Fentanyl | ♦ | ♦ | ♦ | ■ | ■ |
| Gamma-hydroxybarbiturate | ♦ | ♦ | ♦ | ■ | ■ |
| Ketamine | ♦ | ♦ | ♦ | ♦ | ♦ |
| MDMA (ecstasy) | ♦ | ♦ | ♦ | ♦ | ♦ |
| Mephedrone | ♦ | ♦ | ♦ | ♦ | ♦ |
| Methadone | ♦ | ♦ | ♦ | ♦ | ♦ |
| Methamphetamine | ♦ | ♦ | ♦ | ♦ | ♦ |

| | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|
| Oxycodone | ♦ | ♦ | ♦ | ■ | ■ |
| Phencyclidine (PCP) | ♦ | ♦ | ♦ | ♦ | ♦ |
| Temazepam | ♦ | ♦ | ♦ | ♦ | ♦ |

*DAAs – direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; P&B – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ A potential interaction that may require dose adjustment, change in administration time , or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

*Table 6: Drug interactions between HCV DAA and lipid-lowering drugs*

| | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|
| Atrovastatin | ♦ | ■ | ● | ● | ■ |
| Bezafibrate | ♦ | ♦ | ♦ | ♦ | ♦ |
| Ezetimib | ♦ | ♦ | ■ | ■ | ♦ |
| Fenofibrate | ♦ | ♦ | ♦ | ♦ | ♦ |
| Fluvastatin | ♦ | ■ | ● | ■ | ■ |
| Gemfibrozil | ♦ | ♦ | ♦ | ■ | ■ |
| Lovastatin | ♦ | ■ | ● | ● | ■ |
| Pitavastatin | ♦ | ■ | ● | ■ | ♦ |
| Pravastatin | ♦ | ♦ | ■ | ■ | ♦ |
| Rosuvastatin | ♦ | ■ | ● | ■ | ■ |
| Simvastatin | ♦ | ■ | ● | ● | ■ |

*DAAs – direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; P&B – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ A potential interaction that may require dose adjustment, change in administration time , or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

*Table 7: Drug interactions between HCV DAA and central nervous system drugs*

| | | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|---|
| Antidepressants | Amitriptyline | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Citalopram | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Duloxetine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Escitalopram | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Fluoxetine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Paroxetine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Sertraline | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Trazodon | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Venlafaxine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Antipsychotics | Amisulpride | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Aripiprazole | ♦ | ♦ | ♦ | ■ | ■ |
| | Chlorpromazine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Clozapine | ♦ | ♦ | ♦ | ■ | ♦ |
| | Flupenthixol | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Haloperidol | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Olanzapine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Paliperidone | ♦ | ♦ | ■ | ■ | ♦ |
| | Quetiapine | ♦ | ♦ | ♦ | ■ | ■ |
| | Risperidone | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Zuclopenentthixol | ♦ | ♦ | ♦ | ♦ | ♦ |

*DAAs – direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; P&B – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ Potential interaction that may require dose adjustment, change in administration time, or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

*Table 8: Drug interactions between HCV DAA and cardiovascular drugs*

| | | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|---|
| Antiarrhythmics | Amiodarone | ● | ● | ● | ■ | ■ |
| | Digoxin | ♦ | ■ | ■ | ■ | ♦ |
| | Vernakalant | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Flecainid | ♦ | ♦ | ♦ | ♦ | ♦ |
| Beta-blockers | Atenolol | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Bisoprolol | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Carvedilol | ♦ | ■ | ■ | ■ | ♦ |
| | Propanolol | ♦ | ♦ | ♦ | ♦ | ♦ |
| Calcium channel blockers | Amlodipine | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Diltiazem | ♦ | ■ | ■ | ■ | ♦ |
| | Nifedipine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Means for hypertension and heart | Losartan | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Doxazosin | ♦ | ♦ | ♦ | ♦ | ♦ |
| | Enalapril | ♦ | ♦ | ■ | ■ | ♦ |

*DAAs – direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; P&B – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ Potential interaction that may require dose adjustment, change in administration time, or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

*Table 9: Drug interactions between HCV DAA and immunosuppressants*

| | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|
| Azathioprine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Cyclosporine | ♦ | ♦ | ● | ■ | ● |
| Etanercept | ♦ | ♦ | ♦ | ♦ | ♦ |
| Mycophenolate | ♦ | ♦ | ♦ | ♦ | ♦ |
| Sirolimus | ♦ | ♦ | ■ | ■ | ■ |
| Tacrolimus | ♦ | ♦ | ■ | ■ | ■ |

*DAAs – direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; P&B – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ A potential interaction that may require dose adjustment, change in administration time , or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

*Table 10: Drug interactions between HCV DAA and antiplatelets and anticoagulants*

| | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|
| Clopidogrel | ♦ | ♦ | ♦ | ♦ | ♦ |
| Dabigartan | ♦ | ■ | ● | ● | ■ |
| Tikagrelor | ♦ | ■ | ■ | ■ | ■ |
| Rivaroxaban | ♦ | ■ | ■ | ■ | ■ |
| Apixaban | ♦ | ■ | ■ | ■ | ■ |
| Edoxaban | ♦ | ■ | ● | ■ | ■ |
| Warfarin | ■ | ■ | ■ | ■ | ■ |

DAAs – *direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; PIB – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ A potential interaction that may require dose adjustment, change in administration time , or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

*Table 11: Drug interactions between HCV DAA and anticonvulsants*

| | SOF | SOF/VEL | SOF/VEL/VOX | GLE/TIN | GZR/EBR |
|---|---|---|---|---|---|
| Carbamazepine | ● | ● | ● | ● | ● |
| Clonazepam | ♦ | ♦ | ♦ | ♦ | ♦ |
| Eslikarbazepine | ♦ | ● | ● | ● | ● |
| Ethosuximide | ♦ | ♦ | ♦ | ♦ | ♦ |
| Gabapentin | ♦ | ♦ | ♦ | ♦ | ♦ |
| Lakosamide | ♦ | ♦ | ♦ | ♦ | ♦ |
| Lamotrigine | ♦ | ♦ | ♦ | ♦ | ♦ |
| Levetiracetam | ♦ | ♦ | ♦ | ♦ | ♦ |
| Oxcarbazepine | ● | ● | ● | ● | ● |
| Phenobarbital | ● | ● | ● | ● | ● |
| Phenytoin | ● | ● | ● | ● | ● |
| Primidon | ● | ● | ● | ● | ● |
| Topiramate | ♦ | ♦ | ♦ | ♦ | ♦ |
| Valproat | ♦ | ♦ | ♦ | ♦ | ♦ |
| Zonisamide | ♦ | ♦ | ♦ | ♦ | ♦ |

*DAAs – direct-acting antiviral drugs; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; P&B – pibrentasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

**Legend in color**

♦ No clinically significant interaction is expected.

■ Potential interaction that may require dose adjustment, change in administration time, or additional monitoring.

These medicines should not be taken at the same time.

Note:

Some medications may require dose adjustmentdepending on liver function. For dosing instructions, see the product label for individual medicines.

The symbol (green, amber, red) used to rank the clinical significance of drug interaction is based on the www.hep-druginteractions.org (University of Liverpool). For additional inter-drug actions and a more extensive range of drugs, detailed data on pharmacokinetic interactions and dosage adjustment, see the above-mentioned *website* .

*Table 12: Recommendations for simplified treatment of adults (≥18 years) and adolescents (12–17 years) patients with chronic hepatitis C without cirrhosis or with compensated (Child-Pugh A) cirrhosis, monoinfected with HCV or HCV/HIV, including patients who have not been treated (defined as patients who have never been treated for HCV infection) and patients who have been previously treated (defin- isan as patients who have been previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin)*

<table>
<tr><th>Type of treatment</th><th>Genotype</th><th>Cirrhosis status</th><th>Previous treatment experience</th><th>Sofosbuvir/ velpatsavir</th><th>Glekaprevir/ pibrentasvir</th><th>Sofosubvir/ velpatasvir/ voksilaprevir</th><th>Grazoprevir/ elbasvir</th></tr>
<tr><td rowspan="4">Simplified treatment, without determining genotype/ subtype</td><td rowspan="4">All genotypes</td><td rowspan="2">No cirrhosis</td><td>Treatment-naïve</td><td rowspan="3">12 weeks</td><td rowspan="2">8 weeks</td><td rowspan="3">No</td><td rowspan="3">No</td></tr>
<tr><td>Treatment-experienced</td></tr>
<tr><td rowspan="2">Compensated cirrhosis (Child- Pugh A)</td><td>Treatment-naïve</td></tr>
<tr><td>Treatment-experienced</td><td>12 weeks</td></tr>
</table>

*IFN – interferon*

*Table 13: Recommendations for the treatment of adults (≥18 years) and adolescents (12–17 years) - monoinfected with HCV or HCV/HIV-infected patients with chronic hepatitis C without cirrhosis or with com- reimbursed (Child-Pugh A) cirrhosis, including patients who have not been treated (defined as patients who have never been treated for HCV infection) and patients who have been previously treated (defined as patients who have been previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, fish-virin and sofosbuvir; or sofosbuvir and ribavirin).*

| Vrsta tretmana | Genotip | Status ciroze | Prethodno iskustvo tretmana | Sofosbuvir/ velpatsavir | Glekaprevir/ pibrentasvir | Sofosbuvir/ velpatasvir/ voksilaprevir | Grazoprevir/ elbasvir |
|---|---|---|---|---|---|---|---|
| Pojednostavljeni tretman, bez utvrđivanja geno-tipa/ podtipa | Genotip 1a, 1b, 2, 4, 5, i 6 | Bez ciroze | Tretman-naivan | 12 sedmica | 8 sedmica | Ne | 12 sedmica (samo genotip 1b) |
| | | | Tretman-iskusan | | | | |
| | | Kompenzirana ciroza (Child-Pugh A) | Tretman-naivan | | | | |
| | | | Tretman-iskusan | | 12 sedmica | | |
| | Genotip 3 | Bez ciroze | Tretman-naivan | 12 sedmica | 8 sedmica | Ne | Ne |
| | | | Tretman-iskusan | | 12 sedmica | | Ne |
| | | Kompenzirana ciroza (Child-Pugh A) | Tretman-naivan | 12 sedmica s ribavirinom na bazi težine[a] | 8-12 sedmi-ca[b] | 12 sedmica[a] | Ne |
| | | | Tretman-iskusan | | 16 sedmica | | Ne |
| | Podtip 1l, 4r, 3b, 3g, 6u, 6v ili bilo koji drugi podtip koji prirodno sadržava ne-koliko NS5A RAS | Bez ciroze | Tretman-naivan | Nepoznato | Nepoznato | 12 sedmica | Ne |
| | | | Tretman-iskusan | | | | |
| | | Kompenzirana ciroza (Child-Pugh A) | Tretman-naivan | | | | |
| | | | Tretman-iskusan | | | | |

*IFN – interferon; RASs – resistance-associated substitutions*

[a] If a resistance test is conducted, only ns5A Y93H RAS patients should be treated with sofosbuvir/velpatasvir and ribavirin or sofosbuvir/velpatasvir/ voksilaprevir, while patients without Y93H RAS should only be treated with sofosbuvir/velpatasvir.

[b] In untreated patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glekaprevir/pibrentasvir may be shortened to 8 weeks, but more data are needed to consolidate this recommendation.

| IFN-free, RBV-free, regimens recommended according to genotype | | | | | | |
|---|---|---|---|---|---|---|
| **Genotype** | **PANGENOTYPIC REGIMEN** | | | **GENOTYPE SPECIFIC REGIMEN** | | |
| | **SOF/VEL** | **GLE/TIN** | **SOF/VEL/VOX** | **SOF/LDV** | **GZR/EBR** | **OBV/PTV/r+DSV** |
| 1a | Yes | Yes | No* | Yes†‡ | Yes‡ | No |
| 1b | Yes | Yes | No* | Yes | Yes | Yes |
| 2 | Yes | Yes | No* | No | No | No |
| 3 | Yes§ | Yes | Yes | No | No | No |
| 4 | Yes | Yes | No* | Yes†‡ | Yes¶ | No |
| 5 | Yes | Yes | No* | Yes†‡ | No | No |
| 6 | Yes | Yes | No* | Yes†‡ | No | No |

* *Triple combination therapy is effective, but not useful due to the effectiveness of the dual-combination regimen;*

† *TN patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis;*

‡ *TN and TE patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with HCV RNA <800,000 IU/ml (5.9 Log10 IU/mL);*

¶ *TN and TE patients without cirrhosis;*

§ *TN and TE patients with compensated (Child-Pugh A) cirrhosis;*

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*Table 14: Recommendations for the treatment of patients who are monoinfected with HCV or HCV/HIV co-infected, with chronic hepatitis C without cirrhosis, including patients who have not been treated (defined as patients who have never been treated for HCV infection) and patients who have been previously treated (defined as patients who have been previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, fish- virin and sofosbuvir; or sofosbuvir and ribavirinoma)*

| Patients | Previous experience in treatment | SOF/VEL | GLE/TIN | SOF/VEL/ VOX | SOF/LDV | GZR/EBR | OBV/PTV/ r+DSV |
|---|---|---|---|---|---|---|---|
| Genotype 1a | Treatment-naïve | 12 seventh. | Eight seven. | No | 8-12 seven. | 12 seventh. (HCV RNA ≤800,000 IU/mL) | No |
| | Treatment-experienced | 12 seventh. | Eight seven. | No | No | 12 seventh. (HCV RNA ≤800,000 IU/mL) | No |
| Genotype 1b | Treatment-naïve | 12 seventh. | Eight seven. | No | 8-12 seven. | Eight seven. (F0-F2)<br>12 seventh. (F3) | Eight seven. (F0-F2)<br>12 seventh. (F3) |
| | Treatment-experienced | 12 seventh. | Eight seven. | No | 12 seventh. | 12 seventh. | 12 seventh. |
| Genotype 2 | Treatment-naïve | 12 seventh. | Eight seven. | No | No | No | No |
| | Treatment-experienced | 12 seventh. | Eight seven. | No | No | No | No |
| Genotype 3 | Treatment-naïve | 12 seventh. | Eight seven. | No | No | No | No |
| | Treatment-experienced | 12 seventh. | Eight seven. | No | No | No | No |
| Genotype 4 | Treatment-naïve | 12 seventh. | Eight seven. | No | 12 seventh. | 12 seventh. (HCV RNA ≤800,000 IU/mL) | No |
| | Treatment-experienced | 12 seventh. | Eight seven. | No | No | No | No |
| Genotype 5 | Treatment-naïve | 12 seventh. | Eight seven. | No | 12 seventh. | No | No |
| | Treatment-experienced | 12 seventh. | Eight seven. | No | No | No | No |
| Genotype 6 | Treatment-naïve | 12 seventh. | Eight seven. | No | 12 seventh. | No | No |
| | Treatment-experienced | 12 seventh. | Eight seven. | No | No | No | No |

*DAA – direct-acting antiviral drugs; DSV – dasabuvir; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; HCV – hepatitis C virus; HIV – human immunodeficiency virus; LDV – ledipasvir; OBV – ombitasvir; PIB – pibrentasvir; PTV – paritaprevir; r – ritonavir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

*Table 15: Recommendations for the treatment of patients who are monoinfected with HCV or HCV/HIV-co-infected, with chronic hepatitis C, with compensated (Child-Pugh A) cirrhosis, including patients who have not yet been treated (defined as patients who have never been treated for HCV infection) and patients who have previously been treated (defined as patients who have previously been treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirinoma)*

| Patients | Previous experience in treatment | SOF/VEL | GLE/TIN | SOF/VEL/ VOX | SOF/LDV | GZR/EBR | OBV/PTV/ r+DSV |
|---|---|---|---|---|---|---|---|
| Genotype | Treatment-naïve | 12 seventh. | 12 seventh. | No | 12 seventh. | 12 seventh. (HCV RNA ≤800,000 IU/mL) | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1a | Treatment-experienced | 12 seventh. | 12 seventh. | No | No | 12 seventh. (HCV RNA ≤800,000 IU/mL) | No |
| Genotype 1b | Treatment-naïve | 12 seventh. | 12 seventh. | No | 12 seventh. | 12 seventh. | 12 seventh. |
| | Treatment-experienced | 12 seventh. | 12 seventh. | No | 12 seventh. | 12 seventh. | 12 seventh. |
| Genotype 2 | Treatment-naïve | 12 seventh. | 12 seventh. | No | No | No | No |
| | Treatment-experienced | 12 seventh. | 12 seventh. | No | No | No | No |
| Genotype 3 | Treatment-naïve | No | 12 seventh. | 12 seventh. | No | No | No |
| | Treatment-experienced | No | 16 seven. | 12 seventh. | No | No | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Genotype 4 | Treatment-naïve | 12 seventh. | 12 seventh. | No | 12 seventh. | 12 seventh. (HCV RNA ≤800,000 IU/mL) | No |
| | Treatment-experienced | 12 seventh. | 12 seventh. | No | No | No | No |
| Genotype 5 | Treatment-naïve | 12 seventh. | 12 seventh. | No | 12 seventh. | No | No |
| | Treatment-experienced | 12 seventh. | 12 seventh. | No | No | No | No |
| Genotype 6 | Treatment-naïve | 12 seventh. | 12 seventh. | No | 12 seventh. | No | No |
| | Treatment-experienced | 12 seventh. | 12 seventh. | No | No | No | No |

*DAA – direct-acting antiviral; DSV – dasabuvir; EBR - elbasvir; GLE – glekaprevir; GZR – grazoprevir; HCV – hepatitis C virus – HIV, – human immunodeficiency virus; LDV – ledipasvir; OBV – ombitasvir; PIB – pibrentasvir; PTV – paritaprevir; r – ritonavir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voksilaprevir*

For most HIV/HCV co-infected patients, including those with cirrhosis, the benefits of ART outweigh concerns about drug-induced liver damage, and the introduction of ART should be considered in all HIV/HCV co-infected regardless of CD4 count. It is true that both diseases can be treated simultaneously , but this is not recommended because of the larger amount of drugs and thus poorer adherence, increased hepatotoxicity and stronger drug interaction.

The initial combination of ART is the same as in people living with HIV without co-infection, but drug interactions and toxicity overlap must be taken into account, which should guide the doctor in stabbing or modification of treatment. Although treatment should be taken in most HCV/HIV co-infected regardless of CD4 cell count, in ART-naïve patients with CD4 counts greater than 500/mm3, the doctor may consider delaying ART until hcv treatment is completed (according to the 2012 DHHS Guide guidelines).

In patients with lower CD4 counts (e.g. below 200/mm3) it may be preferable to start ART and delay treatment with HCV until the cd4 count is increased during ART.

## 6.5 Currently approved drugs for the treatment of chronic HCV infection in BiH

Fixed combination (100 mg glekaprevir and 40 mg pibrentasvir): Adults and adolescents aged 12 to 18 years. The recommended dose of this drug is 300 mg / 120 mg (three tablets of 100 mg / 40 mg at once), administered orally once a day, with food.

*Table 16: Recommended duration of treatment with a fixed combination drug 100 mg glekaprevir/40 mg pibrentasvir, in patients who have not previously received treatment for HCV*

| Genotype | Recommended duration of treatment | |
|---|---|---|
| | No cirrhosis | With cirrhosis |
| GT 1, 2, 3, 4, 5, 6 | 8 weeks | 8 weeks |

*Table 17: Recommended duration of treatment with a fixed-combination drug 100 mg glekaprevir/40 mg pibrentasvir, in patients who have not successfully responded to prior treatment with peginterferon + ribavirin +/- sofosbuvir or sofosbuvir + ribavirin*

| Genotype | Recommended duration of treatment | |
|---|---|---|
| | No cirrhosis | With cirrhosis |
| GT 1, 2, 4, 5, 6 | 8 weeks | 12 weeks |
| GT 3 | 16 weeks | 16 weeks |

*Table 18: Drug interactions with a fixed combination of 100 mg glekaprevir/40 mg pibrentasvir and hiv antivirotics*

| | |
|---|---|
| atazanavir + ritonavir 300/100 mg once daily | Concomitant use with atazanavir is contraindicated due to the risk of elevation of ALT values. |
| darunavir + ritonavir 800/100 mg once daily | Simultaneous use with darunavir is not Recommended. |
| efavirence / emtricitabine / tenofovir disoproxil fumarate 600/200/300 mg once a day | Concomitant use with efavirenca may lead to a reduced therapeutic effect of the drug with a fixed combination of 100 mg glekaprevir/40 mg pibrentasviri is therefore not recommended. No clinically significant interactions with tenofovir disoproxil fumarate are expected. |
| elvitegravir / cobicistat / emtricitabine/ tenofovir alafenamide | It is not necessary to adjust the dose. |
| lopinavir/ritonavir 400/100 mg twice daily | Simultaneous application is not recommended. |
| raltegravir 400 mg twice a day | It is not necessary to adjust the dose. |

Fixed combination, 400 mg / 100 mg film-coated tablets – Each film-coated tablet contains 400 mg sofosbuvir and 100 mg velpatasvira.

Fixed combination, 200 mg / 50 mg film-coated tablets – Each film-coated tablet contains 200 mg sofosbuvir and 50 mg velpatasvira.

Dosage: In adults, the recommended dose of a fixed-combination drug (sofosbuvir/velpatasvir) is one tablet of 400 mg / 100 mg, orally, once daily with or without food. 3 In pain killers aged 6 to 18 years and weighing at least 17 kg, the recommended dose of the fixed-combination drug (sofosbuvir/velpatasvir) is based on body weight as indicated.

*Table 19: Recommended treatment and duration of treatment in adults regardless of hcv genotype*

| Population of adult patients | Treatment and duration |
|---|---|
| Patients without cirrhosis and patients with compensated cirrhosis | Fixed combination (sofosbuvir/velpatasvir) for 12 weeks<br>For patients infected with genotype 3 with compensated cirrhosis, ribavirin may be considered |
| Patients with decompensated cirrhosis | Fixed combination (sofosbuvir/velpatasvir) + ribavirin for 12 weeks |
| ribavirin | Two capsules in the morning and three capsules in the evening if the body weight <75 kg or three capsules in the morning and three capsules in the evening |

*Table 20: Drug interactions with a fixed combination of glekaprevir/pibrentasvir and hiv antivirotics*

| | |
|---|---|
| tenofovir disoproxil fumarate | Patients receiving tenofovir disoproxil fumarate and fixed-combination medicine (sofosbuvir/velpatasvir) simultaneously should be monitored for adverse reactions associated with tenofovir disoproxil fumarate. |
| efaviren / emtricitabine / tenofovir disoproxil fumarate (600/200/300 mg once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | The concomitant use of a fixed-combination drug (sofosbuvir/velpatasvir) with efavirenc/emtricitabine is expected to take / tenofovir disoproxil fumarate reduce the concentration of velpatasvira. Concomitant use of the fixed-combination drug (sofosbuvir/ velpatasvir) with regimens containing efavirence is<br>not recommended. |
| emtricitabine / rilpivirine / tenofovirdisoproxil fumarate (200/25/300 mg once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | No dose adjustment of the fixed-combination drug (sofosbuvir/velpatasvir) or emtricitabine/rilpivirine/tenofovirdisoproxil fumarate is not required. |
| atazanavir enhanced with ritonavir (300/100 mg once a day) + emtricitabine / tenofovir disoproxil fumarate (200/300 mg once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | No dose adjustment of the fixed combination drug (sofosbuvir/velpatasvir) is required. |
| ritonavir enhanced darunavir (800/100 mg once a day) + emtricitabine/ tenofovir disoproxil fumarate (200/300 mg once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | No dose adjustment is required. |
| raltegravir (400 mg twice daily) + emtricitabine / tenofovir disoproxil fumarate (200/300 mg once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | No dose adjustment is required. |
| elvitegravir / cobicistat / emtricitabine / tenofoviralafenamide fumarate (150/150/200/10 mg once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | No dose adjustment is required. |

| | |
|---|---|
| elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate (150/150/200/300 mg once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | No dose adjustment is required. |
| dolutegravir (50 mg/once a day) / sofosbuvir / velpatasvir (400/100 mg once a day) | No dose adjustment is required. |

### 6.6 Acute viral hepatitis C and reinfection

The diagnosis of acute hepatitis C can only be reliably made if the recent seroconversion into anti-HCV antibodies can be documented, given that there is no serological marker that establishes acute HCV infection. Not all patients with acute hepatitis C will test positive for antibodies during diagnosis. In such cases, acute hepatitis C may be suspected if clinical signs and symptoms are compatible with acute hepatitis (alanine aminotransferase (ALT) level >10 times the upper limit of normal and/or jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a probable recent source of transmission of infection can be identified. In all cases, HCV RNA (or HCV nucleus antigen) can be detected during the acute phase, although their levels can vary considerably, and breaks (up to several weeks) are possible during which HCV RNA (or HCV nucleus antigen) is undetectable. Therefore, individuals negative for HCV RNA (or HCV antigen) should be tested again for HCV RNA (or HCV nucleus antigen) 12 weeks and 24 weeks after a negative result to confirm a definitive clearance.

Hepatitis C virus reinfection can occur after spontaneous or HCV-induced cliché-induced therapy, essentially – if patients at high risk of infection are exposed again. Re-infection is defined as the recurrence of HCV RNA (or HCV nucleus antigen) after reaching the SVR and showing that the infection is caused by a different strain of HCV (a different genotype or strain that is further related, which is determined by phylogenetic analysis if the genotype is the same). Reinfection should be suspected in cases of recurrence of HCV infection after SVR12 or SVR24 if risky behavior has continued.

**In conclusion:**

C> Patients at high risk of HCV infection should be screened annually and whenever an incidental HCV infection is suspected.

C> Antiretroviral therapy (ART) can slow the progression of liver disease by preserving or enhancing immune function and reducing IMMUNE ACTIVATION and INFLAMMATION associated with HIV. For most people with HCV/HIV co-infection, including those with cirrhosis, the benefits of ART outweigh concerns about drug-induced liver damage. Therefore, ART should be started in all patients with HCV/HIV co-infection regardless of cd4 T lymphocyte count.

C> Initial ART regimens recommended for most patients with HCV/HIV co-infection are the same as those recommended for people without HCV infection. However, when treatment for both HIV and HCV is indicated, ART and DAA treatment regimens should be selected with special reference to potent drug interactions and overlapping toxicity.

C> In all patients with HCV/HIV co-infection, the stage of their liver fibrosis should be assessed to determine the duration of therapy and predict the subsequent risk of hepatocellular carcinoma and complications of liver disease.

C> People with chronic HCV/HIV co-infection should be screened for active and previous hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies on the surface and nucleus of hepatitis B (HBsAb, total or immunoglobulin G). People who are not immune to HBV infection (HBsAb negative) should be vaccinated against HBV.

C> HBV reactivation has been observed in people with HBV infection during treatment of HCV anti-

direct-acting viral drugs (DAA). Accordingly, before initiating HCV therapy, people with HCV/HIV co-infection and active HBV infection (HBsAg positive) should receive ART that includes two agents with anti-HBV therapy activity, people with HCV/HIV co-infection and active HBV infection (HBsAg positive) should receive ART that includes- is two agents with anti-HBV activity.

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## 6.7 Opportunistic infections

Opportunistic infection (fr. – opportunité, i.e. lat. – opportunitas) is an infection caused by pathogens that usually do not cause disease if the immune system is healthy. The compromised immune system, therefore, presents a suitable opportunity for infection with a given pathogen. Any opportunistic infection or cancer associated with acquired immunodeficiency syndrome (AIDS) can also occur in the absence of HIV infection, although they usually develop in patients with some other form of immunosuppression or defect. The possibility of contracting HIV must be considered on a case-by-case basis. Other causes of immune suppression (e.g. chemotherapy, immune disorders, severe combined immune deficiency, severe malnutrition) should be considered. For example, an adult with leukemia who has undergone chemotherapy is at high risk for many opportunistic infections.

Opportunistic infections (OI) are infections that occur more frequently and are more severe in people with weakened immune systems, including people with HIV. Many of them are considered conditions that define AIDS. This means that if a person with HIV has one of these conditions, they are diagnosed with AIDS. Imu-nosuppression is damage to the immune system that increases the risk of infection. Immunosuppression can also weaken the inflammatory response. Because of all this, infection:

- It's easier to develop,
- is more often caused by otherwise harmless microorganisms (OI),
- is more often caused by rare pathogens,
- it is more difficult to recognize (that is, the symptoms and signs are minimal or atypical),
- it is more difficult to eradicate or monitor.

**Who's at risk?**

People living with HIV (PLHIV) are at highest risk of OI when their CD4 cell count drops below 200. However, some OI may occur when the CD4 cell count is below 500. This is because a weakened immune system makes it difficult for the body to fight HIV-related OI. OI is now less common than in the first days of HIV and AIDS when there was no treatment. Today's HIV drugs (antiret-rovirus therapy or ART) reduce the amount of HIV in the human body and keep the immune system stronger and more capable of fighting infections.

**Are OI common in people with HIV?**

OI is less common among people with HIV in the U.S. now than in the past. As HIV drugs are widely used, fewer and fewer people with HIV are getting OI. However, OI continues to pose a problem for many people with HIV. Some people with HIV get OI for the following reasons:

- Maybe they don't know they have HIV, so they're not being treated for it. OI may be the first sign that they have HIV.
- They may know they have HIV, but they are not being treated for HIV.
- They may be being treated, but HIV drugs don't control their HIV.

Acquired immunodeficiency syndrome (AIDS) is defined in terms of either the number of CD4+ T cells below 200 cells per µL or the occurrence of specific diseases associated with HIV infection. In the absence of a specific treatment , about half of people infected with HIV develop AIDS within a decade. The most common initial conditions that warn of the presence of AIDS are *Pneumocystis pneumonia* (40%), cachexia and can-didiasis of the esophagus. Other common signs include recurrent respiratory tract infections.

OI can be caused by bacteria, viruses, fungi and parasites that are normally controlled by the immune system. Which infections occur depends in part on which organisms are common in the environment of the person. These infections can affect almost any organ system.

People with AIDS have an increased risk of developing various types of cancer caused by viruses, including Kaposhi sarcoma, Burkitt lymphoma, primary central nervous system lymphoma (CNS), and cervical cancer. Kaposhi's sarcoma is the most common cancer that occurs in 10-20%

of people with HIV. The second most common cancer is lymphoma, which is the cause of death of almost 16% of people with AIDS and represents the initial sign of AIDS in 3-4%. Both of these cancers are associated with human virus 8 (HHV-8). Cervical cancer

uterus is more common in people with AIDS due to association with human papillomavirus (HPV). Conjunctival cancer is also more common in people with HIV.

In addition, people with AIDS often have systemic symptoms such as prolonged fever, sweating (especially at night), swollen lymph nodes, chills, weakness and unwanted weight loss. Proliv is another common symptom, present in about 90% of people with AIDS. They can also be affected by various psychiatric and neurological symptoms that are independent of OI and cancer.

HIV has become responsible for considerable morbidity and mortality due to basic immune suppression that leads to life-threatening OI natural course. The scientific articles state that about 90% of THE morbidity and mortality associated with HIV are caused by OI compared to 7% due to opportunistic cancers and 3% due to other cases.

Since the onset of highly active antiretroviral treatment (HAART), the incidence of OI in PLHIV has decreased. However, OI continues to cause morbidity and mortality in HIV/AIDS patients even after HAART. Opportunistic diseases such as *Candida* esophagitis, pneumonia *Pneumocystis carinii* (PCP), active pulmonary tuberculosis, infection with the *Mycobacterium avium* complex (MAC), cytomeg- allovirus (CMV), cryptococcal meningitis (CRM), Kaposi's sarcoma (KS) and herpes zoster were prevalent.

Human immunodeficiency virus infection is often associated with anemia where patients with advanced HIV or lower CD4 cell counts had a higher rate of anemia. Severe anemia is associated with a much faster rate of progression of HIV disease and has confirmed that anemia is a powerful non-vis-vis predictor of death. In different study settings, the prevalence of anemia is estimated to be 30% in patients with asymptomatic HIV infection and 63-95% in people with AIDS.

The CD4 number <200/mm3 has been found to be an independent predictor for the development of OI, as CD4 cells play a central role in activating humoral and cellular immunity in the fight against infection.

Opportunistic infections and conditions include the following (* - added in the AIDS surveillance case definition
from 1993):

- Candidiasis of the bronchi, trachea or lungs;
- Candidiasis, esophagus;
- Cervical cancer, invasive*;
- Coccidioidomycosis, disseminated or extrapulmonary;
- Cryptococcosis, extrapulmonary;
- Cryptosporidiosis, chronic intestinal (duration >1 month);
- Cytomegalovirus disease (except liver, spleen or nodes);
- Cytomegalovirus retinitis (with vision loss);
- Encephalopathy, associated with HIV;
- *Herpes simplex*: chronic ulcer or ulcer (duration >1 month) or bronchitis, pneumonitis or esophagus- tis;
- Histoplasmosis, disseminated or extrapulmonary;
- Isosporiasis, chronic intestinal (duration >1 month);
- Kaposi's sarcoma;
- Lymphoma, Burkitt (or equivalent term);
- Lymphoma, immunoblastic (or equivalent term);
- Primary brain lymphoma;

- Complex *Mycobacterium avium* or infection *Mycobacterium kansasii*, disseminated or extrapulmonary;
- Tuberculosis infection, any place (pulmonary* or outside the lungs);

- Infection with mycobacteria of other species or unidentified species, disseminated or extrapulmonary;
- Pneumonia *pneumocystis*;
- Pneumonia, recurrent*;
- Progressive multifocal leukoencephalopathy;
- Salmonella septicemia, repeated;
- Toxoplasmosis of the brain;
- Decay syndrome due to HIV infection.

Although malaria is not usually considered an opportunistic infection, its incidence has been found to be significantly higher among children in Tanzania who are perinatally infected with HIV than those who do not have HIV infection. This was true of clinical malaria diagnosed by a doctor, a probable malaria that includes laboratory testing of parasitemia, as well as malaria that was confirmed by a blood smear .

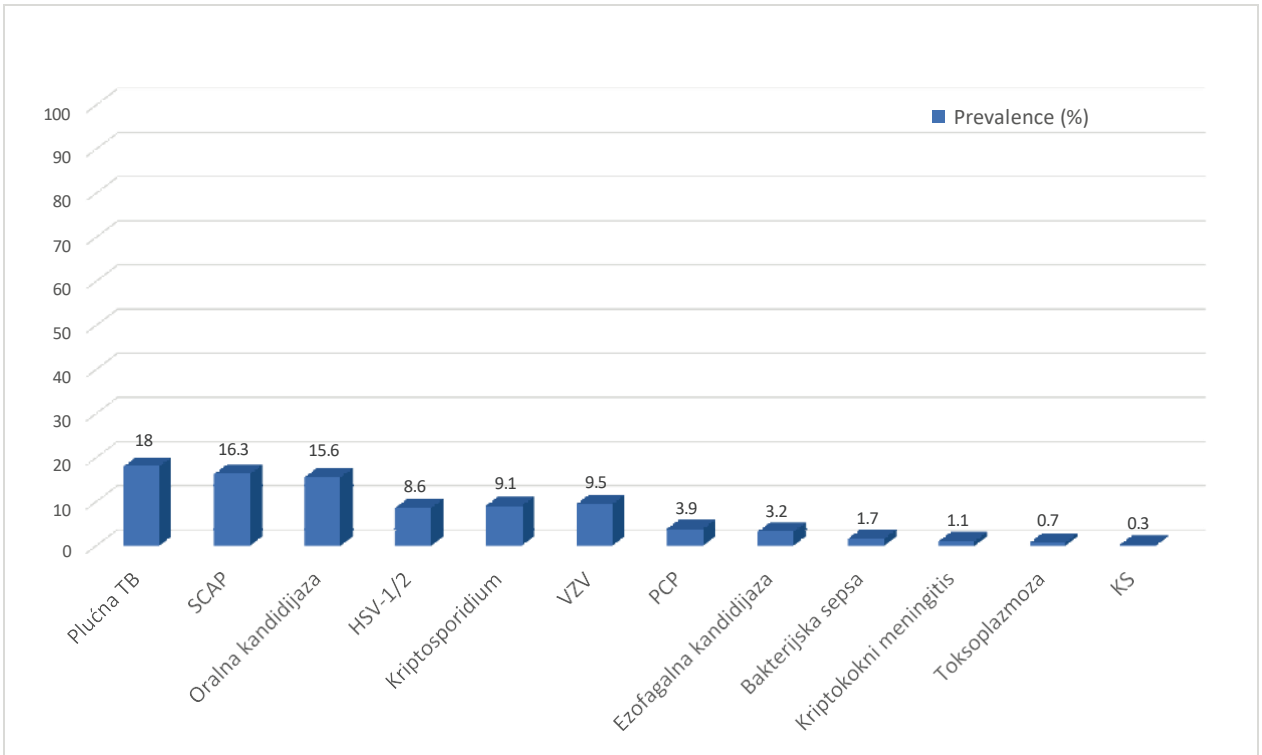
People with AIDS have an increased risk of developing various types of cancer caused by viruses, including Kaposhi's sarcoma, Burkitt lymphoma, primary CNS lymphoma and cervical cancer.

**Kaposhi's sarcoma** (KS) is the most common cancer that occurs in 10-20% of people with HIV. KS is caused by a virus called Kaposhi herpesvirus sarcoma (KSHV) or human herpesvirus 8 (HHV-8). KS causes abnormal growth of small blood vessels and can occur anywhere in the body. KS appears as solid pink or purple spots on the skin that can be raised or flat. KS can be life-threatening when it affects organs in the body, such as the lungs, lymph nodes or intestines.

The second most common cancer is **lymphoma**, which is the cause of death of almost 16% of people with AIDS and is a common sign of AIDS in 3-4%. This carcinoma is also associated with human virus 8 (HHV-8). Lymphoma refers to cancer of the lymph nodes and other lymphoid tissues in the body. There are many types of lymphoma. Some species, such as non-Hodgkin's lymphoma and Hodgkin's lymphoma, are associated with HIV. Cervical cancer is more common in people with AIDS due to its association with human papillomavirus (HPV). Conjunctival cancer is also more common in people with HIV.

In a study of 6,036 HIV-infected patients who achieved HIV suppression with ART, the researchers found that the incidence of non-Hodgkin lymphoma (NHL) remained high (171 per 100,000 people, far exceeding the rate of10 to 20 per 100,000 people recorded in HIV-uninfected popu-lacia. A high incidence of NHL was observed even in patients with the lowest CD4 >200 cells/µl (140 per 100,000). Taking into account older age, white race, male sex, HCV co-infection and time-varying CD4 cell count, the risk of NHL was higher when HIV viremia was above the detection limit (50 copies/ml).

| HIV-related infections and diseases | | | | |
|---|---|---|---|---|
| **Bacterial infections** | **Fungal infections** | **Viral infections** | **Parasitic infections** | **Other diseases** |
| Tuberculosis<br>Bacterial respiratory infections<br>Bacterial enteric infections<br>Atypical mycobacteriosis<br>Bartonellosis | *Candida* esophagitis<br>Cryptocosis<br>Histoplasmosis<br>*Pneumocystis jirovecii* Pneumonia (PCP)<br>Coccidioidomycosis | Herpes simplex virus (HSV)<br>Varicella-zoster virus (VZV)<br>Cytomegalovirus (CMV)<br>Human herpes virus 8 (HHV8), also known as Kaposi sarcoma herpes virus (KSHV)<br>Human papillomavirus (HPV)<br>Progressive multifocal leu-conencephalopathy<br>Hepatitis B and C (the natural course of in-fecation exacerbated by HIV co-infection) | Toxoplasmosis<br>Cryptosporoidosis<br>Microsporoidosis<br>Isosporiasis<br>Lishmaniasis | Kaposi's sarcoma (KS)<br>Non-Hodgkin lymphoma (NHL)<br>Cervical cancer uterus<br>Vacuolar myelopathy |




*Legend: TB – tuberculosis; KS – Kaposi's sarcoma; PCP – Pneumocystis carinii pneumonia; SCAP – severe outpatient pneumonia; VZV – varicella zoster virus; HSV – herpes simplex virus.*

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Permanent suppression of the virus eliminates most, but not all, of the OI. Tuberculosis, pneumococcal disease and der-matomal zoster are examples of infectious diseases that occur in a higher incidence in people with HIV, regardless of cd4 count. However, the probability of each of these OI occurring is different from the CD4 number. When certain OIs occur – primarily tuberculosis and syphilis – they can increase plasma viral load, which accelerates the progression of HIV and increases the risk of hiv transmission. Therefore, clinicians still need to be instructed in the prevention and treatment of HIV-related OI.

Since most AIDS-indicator infections are due to endogenous reactivation of previously acquired pathogens, the frequency of reported OI partially reflects the geographical specificity of en-dem infections. For example, toxoplasmosis and cryptococcosis are more common in Africa and Haiti. Similarly, the risk of extrapulmonary tuberculosis in the U.S. is among foreign-born people, most notably in Haiti, the Philippines, Central America and Africa. Among U.S.-born people, those at increased risk for extrapulmonary tuberculosis include southern and Northeastern residents, blacks and Hispanics, and intravenous drug users.

| Number OF CD4 | Organisms to consider | Clinical traces |
|---|---|---|
| >500 | Organisms acquired in the community | More likely to get bacterial pneumonia, more likely to reactivation of HSV and zoster |
| 200-500 | Tuberculosis | Hemoptysis, night sweats, weight loss |
| <200 | *Pneumocystis jiroveci* | Activity-induced hypoxia, interstitial infiltrates, ↑ LDH |
| | Cryptosporidia | Abundant watery diarrhea |
| | Candida | Oral candidiasis, oral lesions |
| | Fungal pneumonia | Cavitational lesions or diffuse infiltrates on x-ray |
| <100 | Toxoplasmosis | Lesions that enlarge the ring on a CT scan of the brain |
| | Candidase, HSV or CMV esophagitis | Odinophagia, dysphagia |
| <50 | Cytomegalovirus | Visual changes, esophagitis, enteritis, encephalitis |
| | Cryptococcosis | Headache, altered mental status |
| | *Mycobacterium avium* complex | Night sweats, weight loss, diarrhea, malaise |
| | Primary CNS lymphoma (associated with EBV) | Focal neurodeficits, seizures, weight loss, confusion |

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**Bacterial pneumonia and PCP** are the most common causes of HIV-related illness, and recurrent pneumonia (two or more episodes over a period of one year) are conditions that define AIDS. Bacterial pneumonia can be the first manifestation of HIV infection and can occur at any stage of HIV disease and at any level of CD4 count. High rates of bacterial pneumonia in HIV-infected people are likely the result of multiple factors, including qualitative defecation and B-cells that impair the ability to produce pathogen-specific antibodies; impaired function or numbers of neutrophils or both. Risk factors associated with an increased risk of bacterial pneumonia include low CD4 count (<200 cells/mm3), occasional discontinuation of ART, cigarette smoking, injectable drug use and chronic viral hepatitis.

Other specific pathogens occur relatively rarely and include cytomegalovirus infections (CMV), *Aspergillus*, *cryptococcus* and *herpes simplex* virus.

The use of combined ART reduced the incidence of all these complications, with evidence of a greater decline in PCP than in bacterial pneumonia. Long-term use of prophylaxis against *Pneumocys-tis* (especially trimethoprim-sulfamethoxazole-TMP/SMX) and *Mycobacteriumavium* complex (mac- rolide antibiotics) reduces the incidence of bacterial pneumonia. In people infected

with HIV, as well as in people who are not infected with HIV, *Streptococcus pneumoniae* and *Haemophilus* are the most commonly identified causes of bacterial pneumonia acquired in the community. Atypical bacterial

Pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydophila species* they have been recorded as rare causes of community-acquired pneumonia.

Given the increased incidence of tuberculosis, in hiv-infected people, the diagnosis of tuber- vines should always be considered in patients who have pneumonia. Vaccination against *S. pneumoniae* and influenza and the use of a combination of ART are important measures in the prevention of bacterial pneumonia. People infected with HIV who have never received the pneumococcal vaccine should receive a single dose regardless of their CD4 count. Patients with cd4 count ≥200 cells/mm3 should then receive a dose of 23-valence PPV (PPV23) at least 8 weeks later.

The duration of the protective effect of PPV23 is unknown; A one-time revaccination with PPV is recommended if it has been 5 years since the first dose has passed. The inactivated flu vaccine should be administered annually during the flu season to all HIV-infected people.

***Pneumocystis pneumonia*** (PCP) is caused by the fungus *Pneumocystis jirovecii* (formerly *Pneumo- cystis carinii*). Initial infection with *P. jirovecii* usually occurs in early childhood; two-thirds of healthy children have antibodies to *P. jirovecii* between the ages of 2 and 4. The disease occurs due to the formation of a new infection and the reactivation of a latent infection. PCP is associated with 20–40% mortality in people with deep immunosuppression. Approximately 90% of PCP cases occurred in patients with CD4 T-lymphocytes <200 cells/mm3. The frequency of PCP has decreased significantly with the widespread use of PCP prophylaxis and ART. Most cases now occur in patients who are unaware of their HIV infection and in people with advanced immunosuppression (CD4 number <100 cells/mm3). Patients with PCP often have respiratory failure characteristics such as shortness of breath and cyanosis. The symptoms can be very serious; A PCP attack can lead to death if left untreated early and effectively . Hypoxemia, the most characteristic laboratory abnormality, can range from mild to severe. Chest radiography usually shows diffuse, bilateral, symmetrical interstitial infiltration originating from a butterfly-shaped hillus. Atypical radiographic presentations also occur, such as nodules, cysts, asymmetric localization of the upper lobe, intrathoracic adenopathy and pneumothorax. Spontaneous pneumothorax in patients with HIV infection should raise suspicion of PCP. Cavitation and pleural effusion are rare in the absence of other pulmonary pathogens or malignancy. Computed tomography (CT) is a useful additional method, since even in patients with moderate symptoms and a normal Chest X-ray CT will be abnormal, showing changes in the form of "milk glass" that may be uneven, while a normal CT scan has a high negative predictive value. Since the clinical picture, blood tests and chest X-rays are not pathognomonic to PCP, and because the organism cannot routinely cultivate, histopathological or cytopathological diagnostics of tissue organisms, bronchoalveolar lavat (BAL) or induced sputum samples are required for the final diagnosis. Polyme- raze chain reaction (PCR) is an alternative method for diagnosing PCP. PCR is highly sensitive and specific to detecting *Pneumocystis;* However, PCR cannot reliably distinguish colonization from disease. TMP-SMX is the treatment of choice for PCP. TMP-SMX is just as effective as parenteral pentamidine. Patients with documented or suspected PCP and moderate to severe disease, defined by pO2 <70 mm Hg should receive adjunctive corticosteroids as soon as possible and certainly within 72 hours after starting PCP therapy. So far, there is no evidence of the optimal dose or duration of corticosteroid therapy. The following 21-day oral regimen with prednisone is recommended: 40 mg orally twice a day for 1-5 days, 40 mg once a day for 1-6 days, and 10 and 20 mg once a day for days 11 to 21. If parenteral administration is required, it is recommended to use methyl-prednisolone in 75% of the appropriate dose of prednisone. The recommended dose of prednisone for children is 1 mg/kg body weight twice a day for 1-5 days, 0.5 mg/kg once a day for 6-10 days and 0.5 mg/kg once a day for days 11 to 21. Alternative therapeutic regimens include dapson and TMP, which may have an efficacy similar to TMP-SMX and fewer side effects. Adults and adolescents infected with HIV, including pregnant women, should receive hemoprophylaxis against PCP if they have a CD4 count <200 cells/mm3, and people who have a percentage of CD4 cells <14%. Art should be started in patients who are not already on it, within two weeks of being diagnosed with PCP. Paradoxical immune reconstructive syndrome (IRIS) is rare after PCP.

Many HIV-related gastrointestinal disorders such as *Candida esophagitis*, biliary cryptosporidiosis, and cytomegalovirus (CMV) colitis, represent OI resulting from advanced

immunosuppression, while other gastrointestinal processes, such as chronic viral hepatitis B or C

Infections can occur at any stage of HIV disease.

Changes in the mouth include soor (caused by the fungus *Candida*), oral hairy leukoplakia (a consequence of EBV infection) and aphthous ulceration. **Oral haired leukoplakia** occurs in the form of white lesions along the lateral sides of the tongue.

Esophageal diseases often occur among people with HIV and usually cause symptoms of dysphagia, odinophagia, nausea, anorexia and weight loss. The most common is **infectious esophagitis**, which is a resu-ltat infection with *Candida albicans*, but it can also be caused by viruses, such as herpes *simplex* virus (HSV), CMV and *varicellazoster* (VZV), and less often by other infectious agents.

Common esophageal ulcerations are caused by CMV and herpes *simplex* virus.

Patients with advanced HIV disease with or without the presence of oral candidiasis should be empirically treated for esophageal candidiasis with antifungal therapy (e.g. fluconazole 100 mg/day). Most patients with advanced HIV disease (up to 77%) who do not respond to antifungal therapy have esophageal ulcerations.

The risk of **bacterial diarrhea** varies according to CD4 T-lymphocyte count and is highest in people with <200 CD4 cells/mm3. The bacteria most often isolated from culture in HIV-infected people are *Sal- monella* (especially *Salmonella enterica* and *Enteritidis*), *Shigella* and *Campylobacter. Clostridium difficile* (CDI) infection is common in HIV-infected patients; low CD4 count (<50 cells/ mm3) is an independent risk factor for diseases alongwith traditional risk factors such as exposure to a health care facility or antibiotics.

Some sexually transmitted **rectal infections** (e.g. proctitis due to *lymphogranuloma venereum* or *Neisseria gonorrhoeae)* can produce symptoms similar to those of colitis due to *Salmonella*, *Shigelle* and *Campylobacter spp*. If stool culture fails to give enteric bacterial pathogens in patients with symptoms of proctitis or colitis, a diagnostic assessment of sexually transmitted diseases with anoscopy and biopsy should be considered.

Diseases of the gallbladder and gallbladder that affect people with HIV include common flats that are not associated with AIDS, such as cholelithiasis, and AIDS-related conditions, such as acalculous cholecystitis and cholangiopathy. CMV, *Cryptosporidium* and *microsporidia* are pathogens that are most often associated with acalculosis cholecystitis. The use of atazanavir protease inhibitors can lead to the development of gallstones containing significant concentrations of the drug.

Liver disease can be the result of acute or chronic viral hepatitis (considered in the head about viral hepatitis).

**Toxoplasmic encephalitis** (TE) is caused by protozoa *Toxoplasma gondii*. The disease seems to occur almost exclusively due to the reactivation of latent cysts in the tissue. Primary infection is occasionally associated with acute cerebral or disseminated disease. The clinical disease is rare among patients with CD4 T-lymphocyte counts >200 cells/µL. Patients with CD4 <50 cells/µL are at greatest risk. Primary infection occurs after eating undercooked meat that keeps tissue cysts or ingestions of oocysts that are expelled in cat feces. In the U.S., an important risk factor is the consumption of raw shellfish and oysters. Up to 50% of people with documented primary infection do not have an identifiable risk factor. Infection can occur in the lungs, retina of the eye, heart, pancreas, liver, colon, testicles and brain.

Among AIDS patients, the most common clinical display of T . *gondii* infection is focal encephalitis with gla- headache, confusion or motor weakness and fever. Focal neurological abnormalities may be present at physical examination, and in the absence of treatment, advanced- the disease results in seizures, drowsiness, coma and death.

Ct or magnetic resonance imaging (MRI) of the brain will usually show multiple lesions that enhance conrast in the gray matter of the cortex or basal ganglia, often with associated edema. HIV-infected patients with TE are seropositive for antibodies against toxoplasma immunoglobulin G (IgG). Antibodies against toxoplasma immunoglobulin M (IgM) are usually absent. Detection by *T. gondii* PCR in cerebrospinal fluid has high specificity (96–100%), but low sensitivity (50%), especially after specific antitoxoplasmic therapy has been initiated. The differential diagnosis of focal neurological disease in AIDS patients most commonly includes

primary CNS lymphoma and progressive multi-focal leukoencephalopathy (PML). In the absence of inflammatory immune reconstitution syndrome (IRIS), PML (but not lymphoma) can be distinguished based on imaging diagnostics. In patients

with *mass* lesions, the detection of EBV and JCV PCR in cerebrospinal fluid suggests CNS lymphoma, i.e. PML.

HIV-infected people should be tested for IgG antibodies to toxoplasma shortly after being diagnosed with HIV to detect a latent T. *gondii* infection. They should also be advised regarding the sources of toxoplasma infection, especially if they lack IgG antibodies to toxoplasma. Tocosoplasma-seropositive patients with CD4 <100 cells/µL should receive prophylaxis against Te. All patients at risk of toxoplasmosis are also at risk of developing pneumonia *Pneumocystis jirovecii* (PCP) and should receive PCP prophylaxis. They should be administered as follows: patients receiving trimethoprim-sulfamethoxazole (TMP-SMX) or atovakon for PCP prophylaxis do not require additional medications; patients receiving dapsone should be added a pyrimethamine and leukovorin regimen or switched to TMP-SMX or atovakon. The daily dose of TMP-SMX tablet, which is the preferred regimen for PCP prophylaxis, is also effective against TPP and is recommended. The alternative is TMP-SMX, one double-strength tablet three times a week. If patients cannot tolerate TMP-SMX, the recommended alternative is dapson-pyrimethamine plus leukovorin, which is also effective against PCP.

Prophylaxis against TPP should be discontinued in adult and adolescent patients receiving ART and whose CD4 count increases to >200 cells/µL for more than 3 months.

The initial therapy of choice for TPP consists of a combination of pyrimethamine plus sulfadiazine and leukovo- rin. Pyrimethamine effectively penetrates the parenchyma of the brain, even in the absence of inflammation. Pyrimethamine plus clindamycin plus leukovorin is the preferred alternative regimen for patients with TPP who cannot tolerate sulfadiazine hours or do not respond to first-line therapy. This combination, however, does not prevent PCP, and therefore additional PCP prophylaxis must be applied. However, if pyrimethamine is not available, TMP-SMX should be used instead of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin. There is no parenteral formulation of pyrimethamine, and the only widely available parenteral sulfonamide is sulfamethoxazole, TMP-SMX.

Although tuberculosis can be prevented and cured, it is the global leading cause of death from infectious disease. Tuberculosis is the leading cause of morbidity and mortality among people living with HIV worldwide (see chapter on tuberculosis). Organisms of the ***Mycobacterium avium*** (MAC) complex are everywhere in the environment. In the pre-availability of effective ART, *M. avium* was an etiological agent in >95% PLHIV with advanced immunosuppression in which disseminated MAC disease was formed. MAC disease usually occurs in PLHIV people with CD4 T-lymphocyte count (CD4) <50 cells/mm3. The incidence of disseminated MAC disease is 20-40% in PLHIV with advanced immunosuppression in the absence of effective ART or chemoprophylaxis. The overall incidence of MAC disease among PLHIV has continued to decline in the modern ART era to the current level of <2 cases of MAC as the first OI. In addition to the CD4 count <50 cells/mm3, factors associated with an increased risk of MAC disease are plasma levels of HIV RNA >1,000 copies/ml and continuous replication of the virus despite ART. Symptoms may include fever, night sweats, weight loss, fatigue, diarrhea, and stomach pain. Laboratory abnormalities specifically associated with disseminated MAC disease include anemia (often disproportionate to that expected in the HIV phase) and elevated levels of alkaline phosphatase in the liver. Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, paraaortic or less often peripheral) can be identified by physical examination or CT or MRI examination. Localized syndromes include cervical, intra-abdominal or mediastinal lymphadenitis, pneumonia, pericarditis, osteomyelitis, skin or soft tissue abscesses, bursitis, genital ulcers or CNS infection. The diagnosis of disseminated MAC disease is based on compatible clinical knowledge and symptoms associated with the isolation of MAC from cultures of blood, lymph nodes, bone marrow or other normally sterile tissues or body fluids.

Primary prophylaxis against disseminated MAC disease is not recommended for adults and adolescents with HIV who immediately start ART. People with HIV who do not receive ART or who still remain viremic on ART but do not have instant apossibility for a fully suppressive art regimen should receive chemoprophylaxis against MAC disease if they have a CD4 count <50 cells/mm3. Primary MAC prophylaxis, if previously initiated, should be discontinued in adults and adolescents who continue with a completely suppressive ART regimen. Initial treatment

of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the occurrence of resistance. Clarithromycin is the preferred first agent; azithromycin may replace clarithromycin

when drug interactions or intolerance exclude the use of clarithromycin. Testing MAC isolates for sensitivity to clarithromycin or azithromycin is recommended for all people with HIV. Etam- butol is the recommended second drug for the initial treatment of MAC disease. Some clinicians would add rifabutin as a third drug. One randomized clinical trial showed that the addition of rifabutin to the combination of clarithromycin and etambutol improved survival, and in two randomised clinical trials, this approach reduced the occurrence of drug resistance in people with AIDS and disseminated MAC disease.

People with HIV will need continuous antimycobacterial treatment unless ART results in immune reconstitution. Given the complex drug interactions, if rifabu-tin is used, dose adjustment is required for people with HIV receiving protease inhibitors (PI), efaviren, rilpivirine or doravirin; rifabutin should not be used with elvitegravir/kobicistate or biktegravir.

**Oropharyngeal and esophageal candidiasis** is common in HIV-infected patients. The vast majority of such infections are caused by *Candida albicans*, although in recent years infections have also been reported- is caused by other types *of Candida*. The occurrence of candidiasis oropharyngeal or esophagus is recognized as an indicator of immune suppression and is most commonly observed in patients with CD4 T-lymphocyte counts
<200 cells/mm3. The emergence of ART has led to a drastic decline in the prevalence of oropharyngeal and esophageal candidiasis.

Oropharyngeal candidiasis is characterized by painless, white plaque-like lesions that may occur on the oral surface, hard or soft palate, mucous membrane of oropharyngs or the surface of the tongue. Lesions can easily be scraped off using a tongue depressor or other instrument. Since some HIV-infected patients with oropharyngeal candidiasis also exhibit esophageal involvement, clinicians should determine if there are symptoms that indicate esophageal disease in patients with oropharyngeal candidiasis. Candidiasis of the esophagus usually occurs with retrosternal burning pain or discomfort along with odinophage. Endoscopic examination reveals whitish plaques similar to those observed in oropharyngeal disease. Occasionally plaques can progress to superficial ulcerations of the esophageal mucosa with central or peripheral whitish exudates.

**Cytomegalovirus (CMV)** is a double-stranded DNA virus in the herpes virus family that can cause disseminated or localized disease in HIV-infected patients with advanced immunosuppression. Most clinical diseases occur in people who have previously been infected with CMV (seropositive) and therefore represent either a reactivation of a latent infection or a re-infection with a new strain. CMV-induced organ disease occurs in patients with advanced immunosuppression, usually with CD4 T-lymphocytes <50 cells/mm3, who either do not receive or have not responded to ART. Other risk factors include previous OI, high levels of CMV viremia (most often measured by polym-eraze chain reaction [PCR]) and high levels of HIV RNA in plasma (> 100,000 copies/ml). Prior to strong ART, approximately 30% of AIDS patients had CMV retinitis. The incidence of new cases of CMV's disease decreased by ≥95% with the onset of ART.

**Progressive multifocal leukoencephalopathy (PML)** is an opportunistic infection of the CNS, caused by the JC (JCV) virus and characterized by focal demyelination. The virus has a global distribution, with seroprevalence 39-69% among adults. Primary JCV infection usually occurs asymptomatically in childhood. Prior to the advent of combined ART, PML developed in 3-7% of aids patients and was almost always deadly; Spontaneous remissions were rare. With the widespread use of ART in the developed world, the incidence of PML is significantly reduced la. Although most CNS OI is almost completely prevented when CD4 T-lymphocyte counts are maintained above 100-200 cells/mm3, PML can still sometimes occur in patients who are effectively treated with ART. PML manifests itself as a focal neurological deficit, usually with insidious onset and steady progression. Because demyelinating lesions can involve different areas of the brain, specific deficits vary from patient to patient. Any region of the CNS can be affected, although some areas appear to be preferred, including occipital lobes (with hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits). Initial recognition of PML relies on a combination of clinical and neuroradiological imaging: persistent progression of focal neurological deficits with MRI almost always shows pronounced white matter lesions in areas of the brain corresponding to clinical deficits. The usual first step in confirming a diagnosis is

examined-

is a cerebrospinal fluid by polymerase chain reaction (PCR) to the presence of JCV DNA. The test is positive in approximately 70-90% of patients who do not take ART, for whom a positive result can be considered diagnostic in an appropriate clinical context, JCV can be detected in cerebrospinal fluid in only 60% of patients treated with ART. Since the viral load of JCV DNA in csf can be very small even with active PML, highly sensitive PCR performance is preferred. Sensitive tests are now available that reveal only 50 copies/ml. The detection of JCV virus in cerebrospinal fluid in any quantity with appropriate clinical findings strongly supports the diagnosis of PML.

**Cryptococcosis** is caused by infection with the fungus *Cryptococcus neoformans*. Cryptococcosis usually affects the lungs or CNS (brain and spinal cord), but can also affect other parts of the body. It is formed by the inhalation of soil contaminated with encapsulated yeasts *Cryptococcus neoformans*. Inflammation of the cerebral ovaries is usually manifested by microscopic multifocal intracerebral lesions. Meningeal granulomas and larger focal lesions of the brain may be present. Inflammation is not extensive; The patient is usually subfebrile, but can be afebrile. Cryptococcal meningitis in AIDS patients can cause minimal or no symptoms, and cerebrospinal fluid parameters can be normal except for positive findings on many yeasts. Most of the symptoms of cryptococcal meningitis are attributed to brain edema, and are usually nonspecific, including headache, vague vision, confusion, depression, agitation, or other behavioral changes. Except for the clenched eyes or face (muscle weakness, difficulty or impossible to perform movements, paralysis), focal signs are rare until the relatively late stage of the disease. Blindness can develop due to brain edema or direct involvement of the optic tract.

Pulmonary cryptococcosis is usually expressed by asymptomatic and primary lesions of the lungs that pass spontaneously. In immunocompetent people, these isolated lung lesions sometimes heal spontaneously, without dissemination, even without antimycotic therapy. Pneumonia usually causes cough and other non-specific respiratory symptoms. However, cryptococcal lung infection within AIDS can manifest itself with severe, progressive pneumonia with acute dyspnea and radiological nalase that indicates *pneumocystis infection.* Dissemination can occur in any infected person. Dermatological spread is the most common, and is manifested by pustular, papular, nodular or ulcerated lesions, which sometimes resemble acne, *molluscum contagiosum* or basal cell carcinoma.

Culture gives the final diagnosis. The causative agents are most commonly found in cerebrospinal fluid, sputum and urine, and hemocultures can be positive in severe infections, especially in AIDS patients. In disseminated cryptococcosis with meningitis, *C. neoformans* is often isolated from the urine culture, and pros-tasty foci of infection sometimes persist despite the successful removal of the pathogen from the CNS. The diagnosis is strongly indicated by the identification of encapsulated budding yeast smears in smears of body fluids, secretions, exudates or other samples. Enlarged proteins in cerebrospinal fluid and mononuclear pleocytosis are common findings in cryptococcal meningitis, and sometimes neutrophilia predominates. Glucose is often low. In case of isolated lung disease or urotrakta, fluconazole is given 400 mg PO 1×/day. For a more severe disease, fluconazole is given 400 mg PO 1×/day plus flucytosine 25 to 37.5 mg/kg 4×/day for 10 weeks. For meningitis, the standard regimen is amphotericin B plus flucletosine 25 mg PO for 6 to 10 weeks. Almost all AIDS patients need maintenance therapy for life. Fluconazole 200 mg PO 1×/day has an advantage, but itraconazole in the same dose is also acceptable. Also, IV can be given weekly doses of amphotericin B.

**HIV-related encephalopathy** – This brain disorder can occur as part of an acute HIV infection or may be due to chronic HIV infection. Its exact cause is unknown, but it is thought to be related to hiv infection and inflammation.

Although the specific symptoms vary from person to person, they can be part of a single disorder known as the AIDS dementia complex or ADC. Other names for ADC are HIV-related dementia and HIV/AIDS encephalopathy. Common symptoms include a decline in thinking or cognitive functions such as memory, thinking, judgment, concentration, and problem solving. Other common symptoms are changes in personality and behavior, speech and motor problems such as clumsiness and poor balance. When these symptoms are severe enough to interfere with daily activities, a diagnosis of dementia can be justified.

The AIDS dementia complex usually occurs when the CD4+ count drops to less than 200 cells/µL. This may be the first sign of AIDS. With the advent of ART, the frequency of ADC has declined. Art is not only able to...

to moan or delay the occurrence of the AIDS dementia complex in people with HIV, but can also improve mental function in people who already have ADC. The AIDS dementia complex is caused by the HIV virus itself, not by The OI that often occur in advanced HIV. Unlike almost all other forms of dementia, it usually occurs in younger people.

In dementia that is exclusively associated with HIV, subcortical pathological changes occur when infected macrophages or microglial cells infiltrate deep gray matter (i.e., basal gan- glia, thalamus) and white matter. The prevalence of dementia in the late stages of HIV infection ranges from 7% to 27%, but 30% to 40% may have milder forms. The incidence is inversely proportional to the cd4 number. Symptoms and signs of HIV-related dementia may be similar to those of other dementias . Early manifestations include slow thinking and expression, difficulty concentrating , and apathy. Motor movements are slowed down; Ataxia and weakness may be obvious. Abnormal neurological signs may include paraparesis, lower extremity spasticity, ataxia, and extension-zoro-plantar responses. Sometimes mania or psychosis is present. In acute exacerbation, clinical evaluation is necessary, which includes measuring cd4 cell count, HIV viral load, MRI and lumbar puncture. If patients who are known to have HIV infection have symptoms that indicate dementia, the general diagnosis of dementia is confirmed based on common criteria, including the following: Cognitive or behavioral (neuropsychiatric) symptoms interfere with the ability to function at work or perform normal daily activities. These symptoms represent a decrease compared to previous levels of functioning. An MRI should be done, with contrast and without it, to identify other causes of dementia, and if the MRI does not determine contraindications to lumbar puncture, a lumbar puncture should also be done. Late-stage HIV-related dementia findings may include non-amplifying diffuse white matter hyperintensities, cere-bral atrophy, and ventricular enlargement. Patients with HIV infection and untreated dementia have a worse prognosis (average life expectancy of 6 months) than those without dementia. The primary treatment for HIV-related dementia is ART, which increases CD4 counts and improves cognitive function.

Antimicrobial prophylaxis, along with ART, is also indicated in patients with severe immunosuppression and a resulting increased risk of OI. Antimicrobial prophylaxis can be safely discontinued when the CD4 cell count is >200/µL for more than six months after the onset of ART. The following table shows common organisms that cause opportunistic disease in HIV/AIDS patients below certain CD4 cell count thresholds.



**Infections Opportunistic Infections**

| Sumarne preporuke profilakse oportunističkih infekcija za HIV u SAD-u (JAMA 2018.320.379) | | | |
|---|---|---|---|
| **CD4** | **Oportunistička infekcija** | **Profilaksa** | **Kriterij za D/C** |
| Bilo koji broj CD4 | Influenza, HAV, HBV, HPV, VZV, *S. pneumo*, TB | Vax: Gripa, HAV, HBV, HPV, PCV 13, PPSV23 nakon 8 sedm; bez živog uzročnika sa CD4<200; latentna TB: INH/B6 x 9 mj | nema |
| < 200 | *Pneumocystis jirovecii* (ili kandidijaza) | TMP-SMX DS QD (preferirano) ili 1 SS QD *ili* dapson 100 mg QD *ili* atovakon 1500 mg OD | CD4>200 x 3 mj. |
| < 150 | *Histo* (samo ako je endemska; ne u MA) | Itrakonazol 200 mg PO QD | CD4>150 x 6 mj. |
| < 100 | *Toxoplasma* | TMP-SMX DS QD *ili* dapson 50 mg QD + pirimetamin 50 mg qWk + leukovorin 25 qWk | CD4>200 x 3 mj. |
| < 50 | *Mycobact. avium complex* (MAC) | Ppx više nije preporučen ako je započet ARV | CD4>100 x 3 mj. |

| Treatment of OI in adults with HIV/AIDS – also see "Invasive fungal infections" | | |
|---|---|---|
| **Pathogen** | **Diagnosis** | **First-line drug treatment** |
| **MAC** | Cx (krvi/sputuma/bronha/srži/tkiva), AFB bojenje | Azitro 600 mg qdan ili Claritro 500 mg BID + etambutol 15 mg/kg QD |
| ***Pneumocystis jirovecii*** | Tipično inducirani sputum (osj 50-90%) ili BAL ispiranje (osj >90%) za dx; Cx nije pouzdan | TMP-SMX (15-20 mg/kg/dan TMP IV) x 21 dan, ±steroidi ako PaO2<70 ili A-a >35 |
| ***Toxoplasmosa gondii*** | CT/MRI: povećanje prstena, najviše bodova ima IgG+ ali ne IgM+, Bx mozga ako je Rx neuspješan (r/o CNS limfom) | Pirimet 200 mg x1; onda po težini + sulfadiazin + leukovorin x 6 sedm. |
| **Herpes simpleks virus (HSV)** | Oralni/genitalni: DFA, PCR, virusni CX<br>CNS: LP + CSF PCR | Acikl. 400 PO q8h ili valacikl. 1g PO q12h x5-10d; CNS: acikl. 10mg/kg IV q8h x3 sedm. |
| **Citomegalovirus (CMV)** | Retinitis: pregled; Kolitis/ezofagitis: bx; PNA: bronha; Neuro: LP sa PCR, Bx mozga, Krv: PCR | Općenito: ganiciklovir ili foskarnet IV, prebaciti na PO sa poboljšanjima |
| **PML** | MRI: ne-povećavajuće lezije, LP sa JCV PCR | Samo tx koji modificira bolest je ARV |
| **Kriptokokoza (rijetka u dijelovima SAD-a)** | Serum i CSF CrAg, serum ili/i CSF kultura, ↑ tlak otvaranja CSF | Ambisome + flucitozin x 2 sedm. →zatim visoka doza fluc x 8 sedm. →zatim niska doza x 1 god. |
| **Mukokotana kandidijaza (ezofagalna/oralna)** | Klinički dx. Bijeli plak uklonjen depresorom za jezik +KOH; EGD + Bx | Oralno: fluc 100 mg PO x7-14d vs nistatin S&S; Eso: fluc 100-400 mg PO/IV x14-21d) |

*Account created for the MGH Internal Medicine Housestaff Manual „White Book“ https://stk10.github.io/MGH-Docs/WhiteBook-2019-2020.pdf*

U pojedinim je slučajevima indicirana profilaksa specifičnih OI. Uspješni dugotrajni ART rezultira postepenim oporavkom broja CD4 T-ćelija i poboljšanjem imunološkog odgovora i repertoara T-ćelija (prethodno izgubljeni odgovori antigena mogu se obnoviti). Broj perifernih T-ćelija se početno povećao nakon što je terapija započela, ali to predstavlja preraspodjelu aktiviranih T-ćelija iz centara replikacije virusa u limfnim čvorovima umjesto stvarnog povećanja ukupnog broja CD4 T-ćelija. Mjere za sprečavanje OI su efikasne kod mnogih PLHIV. Osim poboljšanja postojećih bolesti, liječenje ART-om smanjuje rizik od razvoja dodatnih OI. Odrasli i adolescenti koji žive s HIV-om (čak i na ART-u) bez dokaza o aktivnoj tuberkulozi u okruženjima sa visokim opterećenjem tuberkulozom trebaju primiti preventivnu terapiju izonijazidom (IPT), a kao pomoć pri odlučivanju se može koristiti i tuberkulinski kožni test. Vakcinacija protiv hepatitisa A i B se preporučuje svim osobama izloženim riziku od HIV-a prije nego što se zaraze; međutim, može se dati i nakon infekcije. Preporučuje se trimetoprim/sulfametoksazol profilaksa u dobi između 4 i 6 sedmica i prestanak dojenja novorođenčadi HIV-pozitivnih majki. Također se preporučuje osobama da se spriječi PCP kada je CD4 ispod 200 ćelija/µl i kod onih koji imaju ili su ranije imali PCP. Osobama sa značajnom imunosupresijom se također savjetuje da dobiju profilaktičke terapije za toksoplazmozu i MAC. Odgovarajuće preventivne mjere su smanjile stopu ovih infekcija za 50%. Vakcinacija protiv gripe i pneumokoka se preporučuje kod osoba s HIV/AIDS-om.

Strategije za sprečavanje oportunističkih infekcija HIV/AIDS-om: Prevencija OI kod HIV/AIDS-a podrazumijeva multidisciplinarni pristup koji uključuje ljekare u primarnoj zdravstvenoj zaštiti, agense zaraznih bolesti i socijalne radnike za podršku. Rano započinjanje ART-a je i dalje najefikasnija metoda za sprečavanje OI. Dodatne metode uključuju primjenu nekoliko strategija, uključujući vakcinaciju, skrining na koinfekcije, izbjegavanje izloženosti, edukaciju pacijenta i antibiotsku profilaksu.

Postoji malo ili nimalo dokaza koji ukazuju na kliničku korist pokretanja antimikrobne profilakse protiv sljedećih organizama: 1. Histoplazma kapsulirana; 2. Kompleks *Mycobacterium avium* (MAC); 3. *Bartonella spp*; 4. Citomegalovirus (CMV); 5. Kriptosporidij; i 6. *Candida spp*. Ti organizmi imaju malu učestalost kod bolesnika s HIV/AIDS-om i postoji mogućnost za značajne interakcije lijekova s ART-om ako se istovremeno započne s profilaksom. Stoga se smatra da pravovremeno započinjanje ART-a i naknadno poboljšanje broja CD4+ ćelija pružaju odgovarajuću prevenciju bolesti.

| Organizam | Bolest | Broj CD4 pod rizikom | Profilaksa |
|---|---|---|---|
| *Mycobacterium tuberculin* | Plućna ili ekstrapulmonalna TB | Bilo koji broj, ako je skrining test pozitivan ili bolesnici imaju prethodnu historiju aktivne TB | Ako je skrining test pozitivan, prvi je korak isključiti aktivnu bolest kroz RTG grudnog koša.<br>Ako je negativan, započeti liječenje izoniazidom tijekom 9 mjeseci. |
| *Coccidioides* sp. | Kokcidioidomikoza | < 250 ćelija/microL<br>I iz endemskih regija jugozapadnih Sjedinjenih Država | Flukonazol za bolesnike s pozitivnim serološkim testovima |
| Pneumocystis *jirovecii* | Pneumocistična pneumonija | < 200 ćelija/microL | Trimetoprim-Sulfametoksazol<br>Alternativni agensi: Dapson, atovakon ili pentamidin u obliku aerosola |
| *Toxoplasma gondii* | Toksoplazmoza | < 100 ćelija/microL | Trimetoprim-Sulfametoksazol<br>Alternativni agensi:<br>Dapson + pirimetamin + leukovorin<br>Atovakon + pirimetamin. |

Jednom kada je započeto liječenje MAC-a i postoje naznake da se stanje poboljšava i lijekovi dobro podnose, treba započeti ART. Standardni postupak podrazumijeva započinjanje ART-a 4-6 sedmica nakon početka liječenja MAC-a. Nakon šest mjeseci s poboljšanim imunološkim odgovorom (broj CD4 >100 ćelija/mm$^3$), treba smanjiti liječenje MAC-a ili ga zaustaviti i upotrijebiti sekundarnu profilaksu. Zaustavljanje sekundarne profilakse je moguće kad je imunološki sistem stabilan i reaguje duže od 3-6 mjeseci. Liječenje MAC-a ili sekundarnu profilaksu treba primjenjivati šest mjeseci da bi se osiguralo uspješno liječenje i izbjegao recidiv. Važno je započeti s liječenjem MAC-a da bi se izbjegla zabuna oko toga dolaze li neke nuspojave od MAC-a ili ART-a.

| Liječenje netipične mikobakterioze | | | | |
|---|---|---|---|---|
| **Antibiotik** | **Doza** | **Učestalost** | **Način** | **Trajanje** |
| ***Liječenje prvom linijom lijekova (15,16)*** | | | | |
| Klaritomicin | 500 mg-1000 mg | BID | PO | 6 mjeseci; odlučiti na osnovu kliničkih procjena. |
| + | | | | |
| Etambutol | 15 mg/kg | OD | PO | 6 mjeseci; odlučiti na osnovu kliničkih procjena. |
| + | | | | |
| Rifabutin | 300-450 mg | OD | PO | 6 mjeseci; odlučiti na osnovu kliničkih procjena. |

| | | | | |
|---|---|---|---|---|
| ***Drugi lijekovi aktivni protiv MAC[a]*** | | | | |
| Azitromicin | 500-1200 mg | OD | PO | 6 mjeseci |
| Ciprofloksacin | 500 mg | BID | PO | 6 mjeseci |
| Amikacin | 15 mg/kg/dan ili | OD | IV | Ne duže od 4 sedmice |
| | 7.5 mg/kg/dan | BID | IV | |

[a] *Rimfapicin nije efikasan protiv MAC.*

Nakon pokretanja ART-a, moguće je prekinuti primarnu profilaksu ako je broj CD4 porastao preko odgovarajućeg nivoa indikacije tokom 3-6 mjeseci (npr. PCP: >200 ćelija/mm$^3$, toksoplazmosis: >100 ćelija/mm$^3$, MAI: >50 ćelija/mm$^3$). Prekid sekundarne profilakse bi također trebao biti moguć u istoj situaciji uz pomno praćenje. Uvijek je indicirano ponovo pokrenuti profilaksu kada broj CD4 padne ispod nivoa indikacije. U narednoj tabeli su sažete najnovije preporuke za strategiju profilakse.

| **Profilaksa OI za pacijente inficirane HIV-om** | | | |
|---|---|---|---|
| **Patogen** | **Indikacija** | **Prvi izbor** | **Alternative** |
| *Pneumocystis jirovecii* | Broj CD4 <200 ćelija/mm$^3$<br><br>ili<br><br>orofaringealna kandidijaza | TMP-SMZ<br>(kotrimoksazol) tableta dvostruke jačine PO[a] OD[b] | TMP-SMZ tableta jednostruke jačine PO OD (1)<br>TMP-SMZ tableta dvostruke jačine PO TIW[c] (ponedjeljak, srijeda i petak)<br>Dapson 50 mg PO BID[d]<br>Dapson 100 mg PO OD (2)<br>Pirimetamin 50 mg + dapson 50 mg + folinska kiselina 15 mg OD<br>Inhalacija pentamidinom 300 mg svake 3 sedmice (3)<br>Također moguće: klindamicin ili atovakon (4, 5) |
| *M. tuberculosis* | Pročišćeni proteinski derivat (PPD) reakcija ≥5 mm<br><br>ili<br><br>nedavni kontakt sa slučajem aktivne TB | Isoniazid (INH) 300 mg PO + piridoksin 50 mg PO OD tijekom 6 mjeseci (6) | Potrebna su dalja istraživanja za razvoj alternativnog profilaktičkog liječenja tuberkuloze u područjima s visokom prevalencom otpornosti na INH. |
| *Toxoplasmosa gondii,* primarna | Broj CD4 <100 ćelija/mm$^3$ | TMP-SMZ<br>tableta dvostruke jačine PO OD | TMP-SMZ tableta jednostruke jačine PO OD (7, 8)<br>Dapson 50 mg PO OD + pirimetamin 50 mg PO QW[e] + folinska kiselina 25 mg PO QW |

| | | | |
|---|---|---|---|
| *Toxoplasmosa gondii,* sekundarna | Broj CD4 <100 ćelija/mm$^3$ | TMP-SMZ tableta dvostruke jačine PO OD | Dapson 50 mg PO OD + pirimetamin 50 mg OD + folinska kiselina 15-25 mg OD |
| *M. avium complex* | Broj CD4 <50 ćelija/mm$^3$ | Azitromicin 1200 mg PO QW | Klaritromicin 500 mg PO BID (9, 10) |
| *Cryptococcus neoformans* | Broj CD4 <50 ćelija/mm$^3$ | Flukonazol 100-200 mg PO OD (11) | |

[a] *PO: per os.*

[b] *OD: jednom sedmično*

[c] *TIW: tri puta sedmično*

[d] *BID: dva puta sedmično*

[e] *QW: jednom sedmično*

*HIV/AIDS TREATMENT AND CARE CLINICAL PROTOCOLS FOR THE WHO EUROPEAN REGION*

Terapijska efikasnost ili imunogeni potencijal vakcine nisu u potpunosti utvrđeni kod bolesnika s HIV/AIDS-om. Vakcinacija se snažno potiče u ovoj populaciji; potencijalna je korist u ublažavanju težine i smrtnosti od bolesti koju je moguće spriječiti vakcinom. Generalno, inaktivirane vakcine se uglavnom preferiraju nad živim vakcinama zbog potencijalnog rizika od bolesti povezanih s vakcinom. Ako postoji bilo kakva sumnja u vezi s imunogenošću ili naknadno testiranje ne pokaže odgovarajući odgovor na antitijela, preporučuje se revakcinacija nakon što se postigne broj CD4+ ćelija >200/µL. Sljedeće vakcine se rutinski preporučuju bolesnicima s HIV/AIDS-om:

- Sezonski oblik vakcine protiv gripe koji se inaktivira godišnje;
- Tetanus, difterija, acelularni hripavac (TdaP): Preporučuje se svim pacijentima starijim od 11 godina i još ga nisu primili, nakon čega slijedi pojačana doza protiv tetanusa i difterije (Td) svakih 10 godina.
- Humani papiloma virus (HPV): Generalno se primjenjuje tokom adolescencije od 11 do 12 godina, ali se kod HIV bolesnika preporučuje do 26 godina. Primjena ove vakcine čak i nakon 26 godina starosti se preporučuje pacijentima s visokorizičnim seksualnim ponašanjem.
- Pneumokokna vakcina: Pacijentima starijim od dvije godine se preporučuje uzimanje konjugirane vakcine protiv pneumokoka (PCV13 ili Prevnar) s bilo kojim brojem CD4+ ćelija, a zatim slijedi pneumokokna polisaharidna vakcina (PPSV23 ili Pneumovax) nakon najmanje osam sedmica. Preporučuje se da se ovaj pojačivač daje nakon što se broj CD4+ ćelija poveća na >200/µL. Dalja doza PPSV23 se preporučuje nakon pet godina od prve primjene PPSV23.
- Vakcina protiv hepatitisa A i hepatitisa B: Primjenjuje se pacijentima za koje se utvrdi da nisu imuni tokom rutinskog pregleda. Preporučuje se provjera odgovarajućeg odgovora na antitijela nakon mjesec dana od primjene vakcine. Ako se primijeti loš odgovor, preporučuje se primjena vakcine nakon broja CD4+ ćelija na >200/µL.
- Vakcina protiv meningokoka: Primjena konjugirane vakcine protiv meningokoka sa serogrupama A, C, W, Y se preporučuje kod bolesnika starijih od dva mjeseca. Usto, vakcina protiv serogrupe B se preporučuje bolesnicima s asplenijom, nedostatkom komplementa i tokom meningokoknih izbijanja koja uključuju serogrupu B.

Određene vakcine se preporučuju kada pacijenti ispunjavaju određene indikacije, kao što su:

- *Haemophilus influenza b*: indicirano samo za djecu u dobi od 5 do 8 godina ili za odrasle kod kojih postoji rizik od širenja hemofilnih infekcija poput asplenije ili nedostatka komplementa.

- Ospice, zaušnjaci, rubeola: Pacijentima bez ozbiljno oslabljenog imunološkog stanja (broj

CD4 <200 ćelija/μL kod odraslih ili manje od 15% kod djece mlađe od 5 godina) preporučuju se dvije doze MMR vakcine u razmaku od 28 dana ako nemaju bilo koji dokaz o prethodnom imunitetu. Za nekoga ko ima jasnu historiju prethodne imunizacije, laboratorijskog nalaženja imunološkog odgovora ili rođenja prije 1957. godine, vakcinisanje nije potrebno.

Pravovremeno uvođenje ART-a i poboljšanje broja CD4+ je najefikasnija metoda smanjenja rizika od OI. Korištenje ART-a može, međutim, dovesti do IRIS-a zbog upalnog odgovora nakon što se uoči poboljšanje broja CD4+ ćelija i postigne imunološki odgovor. Prikaz IRIS-a može biti nespecifičan i zavisi od vrste OI, mjesta i ozbiljnosti upalnog odgovora. Zbog nespecifičnog prikaza, teško ga je razlikovati od aktivnih infekcija (npr. upale pluća stečene u bolnici), napredovanja prethodno dijagnosticiranih OI ili nuspojava povezanih s lijekovima. Nastavak ART-a i simptomatsko liječenje su osnova upravljanja IRIS-om. Korištenje steroida je rezervisano za teške oblike IRIS-a.

Neliječeni HIV pacijenti su skloni višestrukim OI zbog progresivnog snižavanja CD4+ T-ćelija. Zbog visokog morbiditeta i smrtnosti od ovih infekcija, treba učiniti da ti pacijenti imaju dovoljno sredstava za ranu dijagnozu HIV-a i pravovremeno započinjanje ART-a. Tim bi pacijentima trebao upravljati multidisciplinarni tim koji uključuje specijalistu za zarazne bolesti, internistu, medicinsku sestru, farmaceute i socijalne radnike. Također im je potrebno redovno praćenje laboratorijskih pretraga da bi se procijenili poboljšanje broja CD4+ ćelija, nuspojave povezanih s lijekovima i pojava OI. Pacijenti s HIV-om se često suočavaju sa socijalnom stigmom zbog svojih infekcija. Tim mora dodatno osigurati odgovarajuću socijalnu i finansijsku podršku i rehabilitaciju za intravenske korisnike droga, zajedno s edukacijom pacijenta o sigurnim seksualnim praksama i izbjegavanju visokorizičnog ponašanja.

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## 6.8 Tuberkuloza i HIV

Tuberkuloza i HIV infekcije predstavljaju svaka za sebe ozbiljan problem. Udružene, one posta- ju još opasnije po zdravlje svake individue. Tuberkuloza (TB) je najčešća koinfekcija s HIV-om. Procjenjuje se da je rizik od razvijanja TB 16-27 puta veći kod osoba koje žive s HIV-om od osoba koje nemaju HIV infekciju. HIV infekcija može znatno utjecati na progresiju TB i dovesti također do prelaska iz latentnog u oblik aktivne TB. Osoba koja živi sa HIV-om i kod koje je dokazana latentna tuberkuloza (LTBI) ima daleko veće šanse da oboli od aktivne TB nego osoba bez HIV-a. Naravno, kako HIV utječe na progresiju TB, dešava se i obratno, da TB može dovesti do brže progresije HIV-a.

WHO je proklamovala strategiju "Tri 'I' " za kontrolu TB:

1. Izoniazid prevencija (IPT) gdje je indicirana,
2. Jačanje napora u cilju otkrivanja aktivne TB (eng. intensified case finding - ICF),
3. Kontrola TB infekcije (IC).

Tri "I" bi trebali biti dio HIV njege i liječenja u cilju jačanja ART-a.

Ono što je važno naglasiti odmah na početku je da se liječenje aktivne TB provodi na istim principima bez obzira da li se radi o koinfekciji sa HIV-om ili ne. Druga nesporna činjenica je da se kod svih oboljelih od aktivne TB, a koji su uz to inficirani sa HIV-om, liječenje TB provodi obavezno po principima direktno kontrolisanog kratkotrajnog liječenja (DOTS). DOTS se preporučuje za cijelo vrijeme liječenja TB, a najmanje u početnoj fazi. Ključno pitanje koje je stalno prisutno u brojnim raspravama je kada je optimalno vrijeme za uključivanje ARV terapije kod oboljelih od TB sa HIV koinfekcijom. Nažalost, odgovor ostaje kao i ranije da to nije poznato. Preporuke su da se liječenje HIV infekcije odloži ako je to ikako moguće za 2-8 sedmica od početka liječenja TB. Neki autori vrijeme odlaganja određuju u odnosu na broj CD4 ćelija/mm$^3$. Odlaganje je poželjno jer u prvom redu smanjuje rizik od nastanka IRIS-a, a sa druge strane olakšava liječenje i adherenciju oboljelog, izbjegava interakcije antiretrovirusnih lijekova i antituberkulotika, te izbjegava pojačanu toksičnost lijekova, uključujući hepatotoksičnost i neuropatije koje karakterišu obje grupe.

**Procjena stanja**

Svaku HIV-om inficiranu osobu treba obavezno ispitati na TB, čak i ako nemamo jasne anamnestičke podatke (kontakt sa TB inficiranim, respiratorna simptomatologija i sl.). Ako je osoba inficirana sa *Mycobacterium tuberculosis*, važno je ustanoviti da li se radi o aktivnoj ili latentnoj TB. Po definiciji WHO-a, latentna tuberkuloza se definiše kao stanje perzistentnog imunog odgovora na stimulaciju sa *Mycobacterium tuberculosis* antigenom, ali bez dokaza o klinički aktivnoj TB. Za procjenu se koristi tuberkulinski test ili *interferon gamma release assay* (IGRA). Ako se otkrije da osoba ima latentnu TB (koja nije ranije liječena, a ispitivanjem se utvrdi da se ne radi o aktivnoj TB), koju možemo definisati tako da je TKT ≥5 mm induracije ili postoji pozitivna reakcija u IGRA testu, treba započeti preventivni tretman.

WHO preporučuje u preventivnom tretmanu za odrasle i djecu u zemljama sa visokom ali i niskom incidencom TB monoterapiju sa izoniazidom u trajanju od 6 mjeseci. Za zemlje sa visokom incidencom TB se preporučuju i opcije kratkotrajnog tretmana. Rifampicin plus izoniazid dnevno u toku tri mjeseca treba biti ponuđen kao alternativa za 6-mjesečnu monoterapiju sa izoniazidom kao preventivni tretman za djecu i adolescente <15 godina u zemljama sa visokom incidencom TB (jaka preporuka, nizak kvalitet dokaza – **Nova preporuka)**

Rifapentin i izoniazid jednom sedmično u toku 3 mjeseca mogu se ponuditi kao alternativa za 6-mjesečnu monoterapiju izoniazidom, kao preventivni tretmani za odrasle i djecu u zemljama sa visokom incidencom TB (uslovna preporuka, umjereni kvalitet dokaza – **Nova preporuka**).

Sljedeće opcije se preporučuju za tretman latentne TB u zemljama sa niskom incidencom TB kao alternative za 6-mjesečnu monoterapiju sa izoniazidom: 9 mjeseci izoniazida, ili 3-mjesečni režim jednom sedmično rifapentin i izoniazid, ili 3-4 mjeseca izoniazid plus rifampicin ili 3-4 mjeseca rifampicin sam (jaka preporuka, umjereni do visokokvalitetni dokazi – **Postojeća preporuka**)

U područjima sa visokom incidencom i prenošenjem TB, odrasli i adolescenti koji žive sa HIV-om, a ne zna im se status ili imaju pozitivan tubekulinski kožni test, te nije vjerovatno da imaju aktivnu TB, trebali bi dobijati izoniazid najmanje 36 mjeseci bez obzira na to da li dobijaju ART. Izoniazid bi takođe trebalo davati bez obzira na stepen imunosupresije, historije o prethodnom liječenju TB ili trudnoći (uslovna preporuka, nizak kvalitet dokaza – **Postojeća preporuka**)

Za razliku od WHO-a, CDC preferira kratkotrajne režime u odnosu na 6 ili 9-mjesečnu terapiju sa izoniazidom.

Restitucija imunog sistema usljed ARV terapije može izmijeniti sliku, tj. može biti praćena konverzijom iz negativnog u pozitivni tuberkulinski kožni test, a isto tako i ako se radi o IGRA-i. Preporučuje se da se nakon procjene stepena oporavka imunog sistema pod ART-om ponovi test (TKT ili IGRA, ako su prethodno bili negativni). Najlakši način provjere ovog oporavka je praćenje broja CD4 ćelija i kada broj CD4 ćelija poraste iznad 200/mm$^3$, treba ponoviti test ako je prethodno bio negativan.

**Moguće opcije**

Još jednom je važno naglasiti činjenicu da se liječenje aktivne TB provodi na istim principima bez obzira da li je osoba HIV pozitivna ili negativna.

Ako je osoba HIV pozitivna, a TB dijagnosticirana kada je već pod ARV režimom, treba pažljivo procijeniti režim, uz mogućnost prilagođavanja doza, a naročitu pažnju posvetiti ARV lijekovima i njihovim interakcijama sa rifamicinom.

Ako osoba nije na ARV liječenju, treba što prije započeti liječenje TB, a ARV terapiju odgoditi ako je moguće za najmanje 2-8 sedmica. Ukoliko se radi o HIV-om inficiranoj osobi sa aktivnom TB koja nije bila nikada pod ARV režimom, neki autori se rukovode brojem CD4 ćelija. Ukoliko je broj CD4 ćelija niži, terapija počinje ranije, ali ne prije 2 sedmice od početka liječenja TB, izuzev ako broj padne ispod 50 ćelija/mm$^3$, a ako je viši ili visok, vrijeme između početka liječenje TB i početka ARV liječenja se produžava.

Tako npr., američki *web* sajt clinical info HIVgov navodi da bi svi pacijenti sa HIV-om i aktivnom tuberkulozom koji nisu na ARV liječenju (ART) trebali započeti ART po sljedećoj šemi:

1. **CD4 ćelije<50 /mm$^3$**, započeti ART što je prije moguće, ali unutar 2 sedmice od početka liječenja TB,
2. **CD4 >50 ćelija/mm$^3$**, započeti ART unutar 8 sedmica od početka liječenja TB.
3. **U toku trudnoće**, bez obzira na broj CD4 ćelija, započeti ART što je prije moguće,
4. **S tuberkuloznim meningitisom** kada se ART započne rano, pacijenti bi trebali biti stalno nadzirani i praćeni zbog visokog procenta neželjenih učinaka i smrti u randomiziranim eksperimentima.

*(Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf,K-14, 2019 )*

Kod HIV-pozitivnih osoba sa tuberkuloznim meningitisom, WHO preporučuje da se početak ART-a odloži do završetka intenzivne faze liječenja TB.

Kod HIV inficiranih osoba sa dokumentovanom *multi-drug* rezistencijom (MDR) ili ekstenzivnom *drug* rezistencijom (XDR), ART bi trebalo početi 2-4 sedmice od utvrđivanja TB rezistentne na lijekove i započinjanja druge linije liječenja TB.

Uska saradnja infektologa koji liječi osobe koje žive sa HIV-om i pulmologa je presudna u svim ovim okolnostima.

**Liječenje tuberkuloze**

Već je spomenuto da se liječenje nerezistentne TB kod osoba koje žive s HIV-om ne razlikuje od osoba bez HIV infekcije. Aktivna TB se liječi prema standardnim vodiljama, tj. kratkotrajnim režimom koji se sastoji od davanja rifampina (RIF) ili rifabutina (RFB) sa izoniazidom (INH), pirazinamidom (PZA) i etambutolom (EBM) koji se daju u toku 2 mjeseca, a potom nastavlja izoniazid sa rifamicinima (rifampin ili sl.) još 4 mjeseca. Ako HIV inficirana osoba ima broj CD4 ćelija manji od 100/mm$^3$, preporučuje se – bez obzira na sve – najmanje tri sedmice liječenja rifamicinom (ako se daje kraće, izaziva u visokom procentu rezistenciju na rifamicin). Uprkos neželjenim interakcijama lijekova, rifamicin treba svakako uključiti u terapiju aktivne TB kod HIV inficiranih osoba, uz prilagođavanje doze ako je potrebno.

DOTS je obavezan u liječenju aktivne TB kod HIV inficiranih osoba.

**Liječenje HIV infekcije kod koinfekcije s tuberkulozom**

Posljednje ažuriranje preporuka za prvu i drugu liniju režima antiretroviralnih lijekova koju je sačinio WHO 2019. godine zasniva se na najnovijim dokazima o sigurnosti i efikasnosti pri korištenju dolutegravira i efavirenca 400 mg kod trudnica i osoba sa koinfekcijom TB. Rifamicini su nezaobilazni u liječenju TB.

Oni, međutim, predstavljaju snažne induktore jetrinog citohroma P-450 (CYP450), P-glycoproteina (P-gp ) i UGT1A1 enzima. Rifabutin i rifapentin su snažni induktori CYP3A4. Kao snažni enzimski induktori, oni ubrzavaju metabolizam lijekova, snižavajući dužinu izlaganja antiretroviralnim lijekovima. Najviše su pogođeni proteaza inhibitori ali i neneukleozidni inhibitori reverzne transkriptaze (efavirenc, nevirapin), te i integraza inhibitori i antagonist CCR5- lijek maravirok. Većina nukleozidnih inhibitora reverzne transkriptaze, inhibitor fuzije – enfuviritid, te ibalizumab nemaju tako važne interakcije sa rifamicinima. Tenofovir alafenamid (TAF) je P-gp supstrat i njegova primjena sa rifamicinima se ne preporučuje dok se ne provedu detaljna istraživanja.

Kada se primjenjuju dolutegravir, raltegravir ili maravirok, preporučuje se povećanje doza. Ukoliko se moraju primijeniti inhibitori proteaze, preporučuje se upotreba rifabutina. Neki autori to preporučuju i za inhibitore integraze.

WHO preporučuje da se započne ART kod osoba koje su pod tuberkulostaticima sa jednim od režima prve linije (1$^{st}$-line).

**Tenofovir dizoproksil fumaratom (TDF) + emtricitabin (FTC) + raltegravir 400 ili 800 mg 2x dnevno**

**TDF/FTC/EFV** ili **TDF/3TC/EFV** (pratiti koncentracije lijeka nakon 2 sedmice)

**TDF/FTC/Dolutegravir 50 mg dvaput dnevno** sa rifampicinom

**TDF/FTC/ bustirani PI** (umjesto rifampicina koristiti rifabutin 150 mg 1x dnevno)

Kao preferirani drugi režim (2$^{nd}$-line) ako se koristi rifampicin

**Optimizirani režim sa NRTI + dolutegravir 2x50 mg dnevno, ili**

**dvostruka doza lopinavir/ritonavir (800 mg/200 mg) 2x dnevno**

Ili ako se koristi rifabutin

**Optimizirani NRTI režim + dolutegravir ili bustirani PI u standardnoj dozi**

IRIS se može pojaviti nakon započinjanja ART-a, pa se u tom slučaju liječenje TB i ART ne prekidaju nego se istovremeno tretira IRIS (jaka preporuka, slab nivo dokaza - ekspertno mišljenje). Kod liječenja aktivne TB, kod HIV inficiranih osoba se može pojaviti sa ili bez ART-a, ali u daleko većem procentu uz primjenu ART-a, dobro poznati IRIS. Ovaj sindrom se ispoljava povišenom temperaturom, groznicom, uvećanjem limfnih čvorova, pojavom plućnih infiltrata ili izljeva. IRIS može znatno doprinijeti pojavi veće smrtnosti kod HIV-om inficiranih na ART u toku prve godine liječenja. Mnogo veća vjerovatnoća za pojavu IRIS-a su broj CD4 ćelija manji od 50/mm$^3$, teži oblici TB i ako započnemo liječenje sa ARV lijekovima manje od 30 dana od početka liječenja TB. Zato se preporučuje, kada god je to moguće, odgoditi početak ART liječenja za 2-8 sedmica od

početka liječenja aktivne TB, jer to može smanjiti učestalost pojave i težinu kliničke slike IRIS-a.

Ukoliko se IRIS ipak javi u blažoj ili srednje teškoj formi, potrebno je nastaviti i ART i liječenje TB uz dodavanje režimu nesteroidnih antiupalnih lijekova. U teškim oblicima IRIS-a potrebne su visoke doze kortikosteroida (prednizon 1 mg/1 kg tjelesne težine u toku 1–4 sedmice).

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