2021

Albanian Association of Infectious Diseases

Cuts

3TC	Lanamodin
ABC	Abakavir
ADR	Unwanted reaction of the bar
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
ART	Antiretroviral Therapy
ARV	Combinations of Medications Used in Antiretroviral Therapy
AST	Transaminase aspartate
ATV/r	Atazanavir/Ritonavir
AZT	Zidovudina
BD	Twice a day
BMI	Body Mass Index
CM	Cryptococcal meningitis
CMV	Citomegalovirus
CNS	Central Nervous System
CPT	Preventive Therapy with Kotrimoxazole
CrAg	Cryptocoxic Antigen in Serum
CrCl	Cleaning creatinine
CTX	Kotrimoksazol
CYP450	Cytochrome P450
DAAs	Direct-acting antiviral therapies
DNA	Deoxyribonucleic Acid
DRV/r	Darunavir/ritonavir
DS	Dual power
DTG	Dolutegravir
EFV	Efavirenz
ETV	Etravirine
FDC	Fixed-dose combination
FTC	Emtricitabine
GT	Genotype HIV test
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
INH	Isoniazid
INSTI	Integrasa Thread Transfer Blocker
IPT	Preventive Therapy with Isoniazid
IRIS	Inflammatory Immune Reconstruction Syndrome
KS	Kapos' Sarcoco
LLV	Low-level virem
LP	Lumbar punctual
LPV/r	Lopinavir/Ritonavir
MSM	Men who have sex with men
NCD	Non-infectious disease
NNRTI	Non-nuclear reverse transcriptase inhibitor
NTI	Reverse transcriptase inhibitor
NVP	Nevirapinë
OD	Once a day
OI	Opportunistic infection
PCJ	Pneumonia Pneumocystis jirovecii
PCR	Polymerase chain reaction
PEP	Prophylaxis after Risk Exposure
PI	Protease Inhibitor
PLHIV	People living with HIV
PML	Multifocal progressive leukoencephalopathy

PMTCT	PThe transmission from mother to child
POC	PCare out
PrEP	Prophylaxis Before Risk Exposure
PWID	People who inject drugs
RAL	Raltegravir
RTV	Ritonavir
RNA	Ribonucleic acid
RPR	Plasma Rapid Reagina
IST	Sexually Transmitted Infection
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
VL	Viral load

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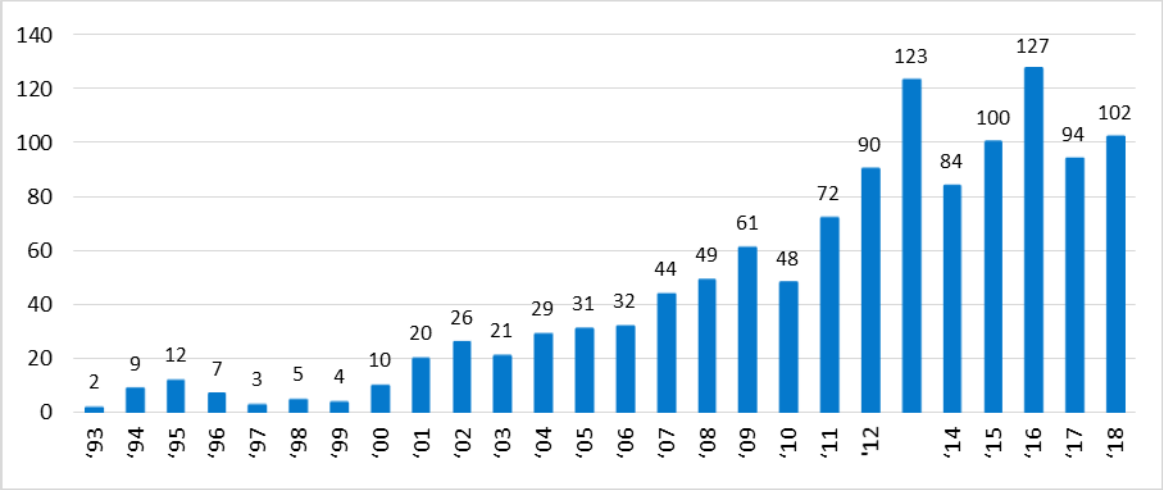
1. Home

The U.S. has a concentrated HIV epidemic. The first case of HIV was reported in 1993 and for many years the country's burden of HIV was low. By the end of December 2018, a total of 1205 cases of HIV had been reported. However, in recent years the number of new reported HIV cases has increased: while annual reported cases remained below 40 until 2006, between 2008 and 2018 annual HIV diagnoses increased more than twice from 49 cases (2008) to 127 cases (4.5 cases/100,000 - the highest rate) in 2016, the number of new cases reported in 2016 was 127 cases (4.5 cases/100,000) in 2016, and the 2016 total of 127 cases (4.5 cases/100,000) in 2016. 102 new cases in 2018 (Figure 1). The new cases tend to be young men and men having sex with men, which highlights the need to focus on new prevention technologies for this population.

Figure 1. Annual number of new HIV diagnoses, Albania, 1993-2018



Source: National AIDS Program, Annual Report 2018

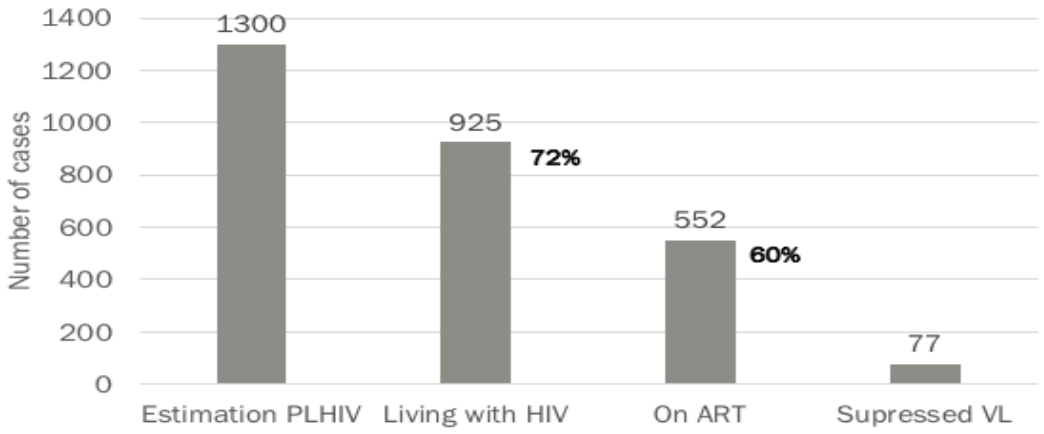
At the end of 2018, hiv prevalence was estimated at 0.04%, while the incidence was 3.6 per 100,000 people, but it is clear that these numbers are underestimated. Late diagnosis involves >60% of cases and the total volume of HIV testing is very low (45,760 in 2018) where most tests are carried out for blood safety issues.

Stigma and discrimination against HIV and sexual diversity make it difficult to work preventively, preventive communication strategies, and the acceptability of interventions such as community or perinatal testing. Mother-to-child transmission has been reported at 3.6%, with a minority of women receiving an HIV test before birth.

Specific populations concentrate relatively high prevalence of Hepatitis C, Hepatitis B virus, and HIV. The significant number of individuals using intravenous drugs puts them at serious risk for an explosive HIV epidemic and requires urgent implementation of testing and treatment strategies as well as combined prevention for controlling HIV and other communicable diseases such as HBV and HCV.

The cascade of care reveals deep gaps resulting from several factors that influence testing, referral, treatment and viral suppression. One of the most important are the continuous stockless residue of ARV drugs and viral load testing kits. However, other important factors such as deficits in HIV testing strategy and algorithms, lack of public campaigns to raise awareness of HIV status, lack of integration of HIV testing into other health interventions such as routine screening or prenatal care, and limited availability of human resources and infrastructure represent additional challenges for an effective response and seriously hinder the commitment to achieving goals. 90/90/90 in 2020.

Figure 2 HIV care continuation and targets 90-90-90 (2017)



Source: Buni R. HIV and AIDS in Albania

To improve the cascade of care and reduce the immunisation and mortality due to HIV, it is important to implement a series of interventions that should include:

a) Expand HIV testing through various approaches including provider-initiated testing, prenatal testing, community testing, and self-testing.

b) Implementing testing and treatment strategies, using new, effective and more tolerable drugs presented in combinations of fixed doses

c) Improve retention and support individuals to increase access to care

d) Reducing stockless waste and entity of individuals with 3-month supply in order to improve accession and reduce out-of-pocket costs for selected ARV drugs, especially those outside Tirana.

e) Implementing Point of Care diagnosis in the HIV clinic, especially for Viral Load (VL) testing. In addition to improving retention and facilitating access, this technology is cheaper than standard VL and offers results in 2 hours and can also be used for HIV confirmation in children and adults.

f) Simplification and optimization of ART options to gradually remove some older ARV drugs and move towards more effective and safer options in order to improve clinical outcomes and facilitate procurement.

g) Combined prevention implementation that includes extensive HIV testing, condoms, sexually transmitted diseases (STIs) and Post-Risk Exposure Prophylaxis (PEP). Furthermore, Pre-Exposure Prophylaxis (PrEP) should be implemented as an additional intervention to prevent HIV among individuals at significant risk of HIV.

2. Early link of HIV positive individuals for early initiating treatment

In order for communities to benefit from the impact of HIV interventions, in terms of reducing individual immunity and mortality, and for reducing HIV transmission, it is important to detect HIV individuals as soon as possible, i.e. to reduce late diagnosis (diagnosis of individuals when HIV disease has advanced), and to link as early as possible to the care for the identification and treatment of opportunistic infections (OI), the implementation of preventive interventions to reduce morbility and the rapid onset of antiretroviral therapy.

WHO Recommendation, Link to Care (Consolidated Guide 2016)[1]

Following an HIV diagnosis, a support interventions package should be offered to provide timely connections to care for all people living with HIV.
(Strong recommendation, moderate quality evidence)
The following interventions have demonstrated benefits in improving connectivity to care after an HIV diagnosis:
effective interventions that reduce the time between diagnosis and care engagement, including (i) improving the connection to case management; (ii) support for the detection of HIV; (iii) patient tracking; (iv) training staff to deliver multiple services, and (v) effective services; (*Evidence of moderate quality*)

- **Peer support and navigation access to connections; (*Evidence of moderate quality*); and**
- **Access to quality improvement using data to improve connectivity; (*Low-quality evidence*).**

Several publications have demonstrated positive results of rapidly starting antiretroviral therapy after the HIV diagnosis is confirmed. Studies conducted in the US and LMIC show that rapid onset is associated with more patient-initiation treatment, better resupply,[1] and higher rate of viral suppression than the standard approach.[2],[3]. Furthermore, faster viral suppression can reduce viral transmission. Therefore, early initiation, including the onset of ARVs on the same day of HIV infection is currently the WHO recommendation. This rapid access to ARV onset is particularly important for people with advanced HIV disease due to specific clinical benefits (decreased risk of mortality and immunodeficiency) and for individuals with acute HIV infection.
All efforts should be made to ensure that patients with a rapid HIV test, or an individual with suspected HIV infection, are linked early to HIV confirmation and treatment. Confirmation should be based on an established HIV testing algorithm that reaches at least 99% positive predictive value and uses a combination of tests with sensitivity ≥99% and specific ≥98%. This could mean using three different serological tests, or using a serological screening test (rapid test or ELISA) plus a molecular test such as HIV viral load (VL).

WHO recommendation, HIV confirmation 2019[4]

[1] Consolidated guidelines for the use of antiretroviral drugs for the treatment and prevention of HIV infection. Recommendations for a public health approach – Second publication, WHO, 2016. https://www.who.int/hiv/pub/arv/arv-2016/en/

[2] Koenig SP, Dorvil N, Dévieux JG, Hedt-Gauthier BL, Riviere C, Faustin M, Lavoile K, Perodin C, Apollon A, Duverger L, McNairy ML, Hennessey KA, Souroutzidis A, Cremieux PY, Severe P, Pape JW. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for people living with HIV: An unintrollable randomized trial. PLoS Med. 2017 Jul 25;14(7):e1002357. doi: 10.1371/journal.pmed.1002357.

[3] Pilcher CD, Ospina-Norvell C, Dasgupta A, Jones D, Hartogensis W, Torres S, Calderon F, Demicco E, Geng E, Gandhi M, Havlir DV, Hatano H. Effects of observed same-day initiation of antiretroviral therapy on HIV viral load and treatment outcomes in a public health setting in the U.S. J Acquir Immune Defic Syndr. 2017 Jan 1;74(1):44-51.

[4] WHO recommends countries to steer clear of the use of western blott and line immunoanalysis in HIV testing strategies and

Western blotting (WB) and immuno-line analysis should not be used in national HIV testing strategies and algorithms (*strong recommendation, low quality evidence)*

Various approaches can improve connectivity to care (Table 1) including: providing information, detection, addressing barriers to connectivity, creating systems to facilitate connectivity, coordination and integration of care, and use of a link registry.

Table 1: Interventions in Treatment Connectivity Improvement

Strategy	Action
Providing extensive information	Limiting extensive post-test counseling to those individuals with initial reactive HIV instead of all those tested for HIV. In this session, information about the nature history of the disease, the need to confirm hiv diagnosis and the change in outcomes with new drugs should be discussed. The benefits of instant assessment and early ARV initiation should be emphasized, in relation to the untransmittable concept, in order to reduce stigma and fear. From the first moment of diagnosis, physicians and patients should discuss ARV options and assess the willingness to start treatment immediately after sampling for viral load, without waiting for results.
Help identify when to disclose status to potential supporters	The counsellor should identify existing support from family or partners and provide means for disclosing their status, if it is clear during the discussion that this may contribute to retention and adulation. Facilitated partner notification should be provided.
Help overcome obstacles	Identify and address any obstacles to connectivity, especially due to distance, lack of transport, and explore ways to overcome such obstacles, refer to social workers.
Implement, monitor and audit standardized systems to facilitate connectivity	The provider providing the initial HIV diagnosis (even when it is not confirmed) is responsible for providing the link to care that begins the process on the same day of HIV diagnosis. If possible, for individuals tested in NGOs or other services, the link to treatment should be made through patient navigators or companions who have knowledge of how hiv clinic operates. If this is not possible, the institution that is giving the initial HIV test should book an appointment at the treatment center and provide the patient with reference information, referral form and contact details of the institution. In the centers, strong tracking should be implemented to ensure a successful connection, including gathering as much information as possible of the locator, SMS memory, phone calls and reaching friends, or community to accompany HIV patients for treatment. The national program should maintain a link registry for all HIV positive cases tested at various testing points. Centers must provide the patient with written related information (reference letter or folder). Information must be tracked, reported and audited periodically.
Ensure care coordination towards an integration of health care with primary care physicians	Where possible, coordinate and refer partners together, including mother-child couples. For individuals leaving the HIV clinic, discuss the existence of local resources to perform the routine test and provide direct contact between centers to ensure appropriate care and facilitate reduced stigma access. Identify online a service page, as well as printed materials, with open hours and facilitated meetings. Provide support to primary doctors in case of consultations for young HIV patients. Coordinate with local NGOs for facilitated referral, and for support services for key populations.

3. First assessment of individuals with HIV

To provide targeted services during initial evaluation, physicians must identify whether the patient is presenting with advanced HIV disease or if he does well (Table 2). Patients with advanced disease require more intensive evaluation for opportunistic infection identification and management (OI), and with the onset of antiretroviral therapy, they are at higher risk for developing inflammatory immune reconstruction syndrome (IRIS). In Albania, most individuals are diagnosed at the STAGE of AIDS (CD4 <200 cell/mm3). Therefore, it is important to carry out an initial exhaustive assessment because a significant number of these individuals will present, or develop, very early on during the ongoing follow-up an opportune infection. Advanced patients are also at higher risk of developing side effects (AEs) when

algorithms OSBH, 2019, https://apps.who.int/iris/bitstream/handle/10665/329915/WHO-CDS-HIV-19.30-eng.pdf

starting ARV and at higher risk for developing inflammatory immune reconstruction syndrome (IRIS).

3.1 Clinical assessment

All patients enrolling in HIV care should be taken a full medical history, offered a thorough physical examination and appropriate laboratory tests. Findings from this initial assessment should be documented in the health register to facilitate long-term patient follow-up. Table 2 summarizes important aspects of initial medical history and physical examination.

Table 2: Critical Elements to Address During Initial Evaluation for People Living with HIV

Rating	Description	Comments
Current and past medical history	The initial visit provides the possibility of establishing a meaningful relationship between the patient-care provider; The clinician should address concerns with open, non-judgmental and clear communication about sexual orientation and risk category. It is very important to discuss the benefits of being 'untransmittable', the untransmittable concept not only relieves individuals of fear of HIV transmission, but also reduces stigma and improves adulation during therapy.	
	Presenting current complaints/symptoms, including TB symptoms	Investigate about symptoms due to hiv-related and non-HIV-related co-existing diseases and co-diseases that will require immediate intervention Intensified Case Finding Instrument (ICF) Outcome
	First hiv positive test date Diseases of the past and present (p.sh. TB, hypertension, diabetes, kidney and liver disease, etc) Current drugs, including medicinal plants Allergies to drugs, especially allergies to sulfur History of ARV exposure History of hospitalizations Family history of chronic disease or cancer History of vaccination	Request written documentation of TB history Document past or current use of ARVs (including PMTCT, PEP, PrEP and ARV), in particular for migrants and individuals treated abroad. Accompanying medications (including prescription and natural products such as herbs and supplements) should be taken at each visit.
Psychosocial history	Drug and alcohol use, smoking. Diet, training. Education, employment, family, marital status History of depression or suicidal ideation; Current symptoms of depression Detection (opening to others for diagnosis) Social protection and welfare requirements (providing transportation for medicines, laboratories or clinical visits, food or shelter)	Drug and alcohol abuse can be a barrier to adulation. Depression and suicide may require urgent mental health evaluation and care. Encourage openness with trusted relatives/friends and sexual partners as this facilitates adulation and provides support. Providing and connecting with community support resources, including psychosocial support groups, peer mentors, harm reduction services for people who inject drugs, etc. Identify specific social support Check all these points during the tracking at least every year Take into account the need for care coordinated with toxicology or detoxification centers
Sexual and reproductive history	History and current symptoms of STIs Sexual practices. HIV partner status and sexual partner (s) disclosure If women: Pregnancy history, menstruation history, family planning and pregnancy plans History of cervical cancer detection	Give advice on safe sexual practices, advice on preventing STIs. Encourage partner testing and quick ARV initiation Discuss conception plans and effective contraception, in women who start Dolutegravir-based ARVs. Encourage contact tracing and HIV testing for sexual partners and all children of HIV-infected women.
Vital signs	Use oximetry if the patient complains of respiratory symptoms. Measure and record your weight, length, vital signs.	In adults, calculate BMI and monitor the growth curve for children. Unintentional weight gain is a recent side effect associated with ARV.

Systemic examination	The hand and the palms of the hand for fading or jaundice; swollen lymph nodes (cervical, axiary, inguinal); mouth (for kaposi sarcoma (CS) leukoplakia, run-of-the-mouth, tooth decay); skin (for zoster herpes, dermatitis, papular itchy rashes (PPE), follicles, fungal infections, molluscrum and KS) Central nervous system (focal defects, retinal). Mental status examination (for mental status). The abdominal (for enlargement of the liver or spleen); Breathing (for percussion deafness; crackling or panting). Cardiovascular (for peripheral pulsations, edema, heart sounds). If there are specific symptoms: the genitourinary/anorectal system (for ulcers, discharges, warts and prostate examination for men aged ≥ 45). Speculum screening/screening for cervical cancer for women	This examination can guide advanced HIV disease and help identify the inter-current disease. Positive findings will need additional evaluations, such as needle aspiration cytology or biopsies for lymphadeopathies, or biopsies for skin injury. Cervical cancer screening should be repeated in women at least every year. cancer in men is controversial, but some guidelines recommend at least digital screening of the colon. Monitoring of developmental stages for children

3.2 Initial Assessment in the Laboratory of Individuals with HIV

Laboratory test results required during the initial visit are not a condition for initiation of treatment. Treatment can begin immediately after samples have been taken, especially in those with suspected advanced stage HIV disease, but carrying out these tests is important to have initial data about Viral Load, CD4 and resistance testing.
HIV should be confirmed and who recommends you to opt out of western blott use. Instead, viral loading can be used. POC-VL confirms HIV infection. If samples cannot be processed, they can be collected and raised/cooled for further processing. Table 3 summarizes the recommended initial laboratory studies for all people living with HIV.

Table 3 Laboratory Baseline Assessments for People Living with HIV (PLHIV)

	Test	Comments
Specific to HIV	HIV confirmation	The country must remove from the confirmation by Western Blott analysis. Confirmation should be made with a combination of 2 positive serological tests with different technologies (d.m.th. rapid test plus ELISA) or with a POC-VL. To avoid ART delay, the VL score should not be required to start treatment. VL can also be used for diagnosing babies.
	Number of CD4 cells	It is recommended first for all patients. Poc CD4 offers results in a few minutes. The lack of availability of CD4 should not result in delay of ART, especially in those subjects with symptomatic disease. Use the percentage for children ≤ 5 years) Repeat at least 6 months in individuals with initial CD4 below 350 cells/mm3 and annually in those individuals under treatment, undetectable viral load and >350 cells/mm3
	Viral Load (HIV-1 RNA)	The viral load score (VL) is not necessary for the start of treatment but should be taken at the outset if it has not already been received as confirmation of HIV. * POC VL offers results in less than 2 hours. Viral load should be repeated at least every 6 months in patients who are stable in treatment, and most often if the viral load is detectable and before arvv replacement.
	Hiv resistance or genotype (GT) test	GT can provide information on selecting third-line regimes. WHO surveys on resistance surveillance at national level should be implemented periodically. If available, GT should be performed to all individuals starting ARVs, pregnant women and children, given the lack of information regarding NNRTI resistance in the country. If not available immediately, samples can be taken and stored before treatment is started, and when patients have confirmed failure after 6-12 weeks of ARV with good adjective. *
	Serum cryptocoxic antigen (CrAg)	Take CrAg serum in all adults and adolescents with a number of CD4 cells ≤ 200 cells/mm3 or advanced disease. There are quick side stream analysis available. If positive, crAg in CSF should be required.
	Hematology	First, twice a year during the first year, then every year.
	Glucose	First, twice a year during the first year, then every year.
	Liver function	First, twice a year during the first year, then every year.

Other	Creatinine	First, twice a year during the first year, then every year. Calculate creatinine purification (CrCl) with each creatinine value. In those with CrCL ≤ 50 ml/min use alternative treatment (ABC-3TC or 3TC-DTG dual therapy). If HBsAg is positive, use the adjusted dose of TDF-3TC (every 48 hours if CLCR >50ml/m) or TAF-3TC or TAF-FTC.
	Lipids	TC, HDL-c, LDL-c, TG, at the beginning and every year.
	Pregnancy status	Pregnancy status should be determined for all women of reproductive age (based on the history of the last menstrual period, and if unsafe, irregular or delayed, then a urine pregnancy test should be performed)
	Urine analysis (for protein and glucose)	At the beginning and every year
	Hepatitis Serologies (A, B and C)	At the outset, to evaluate IgG HAV vaccination, HBV nucleus and AgHBs, and total HCV antibodies. Consider repeating each year if HCV is negative and the individual is at risk (intravenous street drug use, or positive HCV partners). If you are vaccinated for HBV, seek anti-HB.
	Toxoplasmosis IgG	First in those individuals who suspect CNS mass
	Syphilis Serology	VDRL or RPR, or quick treponemal test recommended for all PLHIV. It should be repeated periodically in sexually active individuals (every 6 months) with negative test at entry.
	Mantoux (PPD, TST) or IGRA	First and consider repeating it every year if the PPD is 0mm and the patient reports the risk of TB exposure. It is not recommended for individuals who have completed TB treatment. IGRA is more expensive and not easily available.
	Rx Chest	At first, for all individuals, especially if there are respiratory symptoms or advanced illness
	Gene Xpert MTB/RIF	For patients who present with respiratory symptoms and sputum production
* Samples of whole blood taken for viral load or HIV GT testing should be taken in EDTA tubes and should be centrifuged within 2 hours of being received. Samples should be left at room temperature (15-30°C) from the moment of receipt until centrifugation and separation. After separation, plasma samples should be maintained continuously at cooling temperature (4°C) until the parts are frozen (preferably used in sterile tubes1.5-2 ml, screwed polypropylene). Plasma for viral load and GT must be processed and raised to -20°C to -80°C (freezing at -80°C is preferable but -20°C is acceptable and not having a freezer -80°C is no barrier to preserving samples). If freezers are not available, then a protocol for DBS collection should be discussed and applied. [5],[6]		

Testing should be carried out at the nearest health centre for individuals living outside the city where the ARV delivery centre is located.

3.3 Identification and Care for Patients with Advanced HIV Disease

Patients who present with advanced disease may need a different level of care than those who present while still well clinically. All patients should be carefully evaluated to detect active opportune infections, which may require hospitalization in order to make assessments and arrive early on with a proper diagnosis.

All advanced individuals will require a closer follow-up during the initial period. This is important to prevent and detect opportunistic infections, early identification of inflammatory immune reconstruction syndrome (IRIS), support adherence, especially in individuals requiring multiple medications for the treatment or prevention of opportunistic infections, in addition to ART, and nutritional support for undernourished individuals.

Part of the intervention should also include evaluation of social support and referral to social services for providing resources that can facilitate the continued frequent meetings and access to other required drugs not provided by the programme.

WHO definition of Advanced HIV Disease [7]

[5] WHO/HIVResNet HIV Resistance Strategy in Laboratory, WHO, 2010
https://www.who.int/hiv/pub/drugresistance/hiv_reslab_strategy.pdf
[6] WHO Manual for Testing HIV Resistance to Grass Using Dried Blood Stain Samples, WHO, 2012,
https://apps.who.int/iris/bitstream/handle/10665/75829/WHO_HIV_2012.30_eng.pdf?sequence=1
[7] Guidelines for managing advanced HIV disease and rapid onset of antiretroviral therapy, WHO, 2017

or adults and adolescents and children older than five years of age, advanced HIV disease is defined as the umber of CD4 cells <200 cells/mm3 or who's stage 3 or 4 event.
ll children younger than five years old with HIV are considered to have advanced HIV disease

WHO recommendation for individuals with Advanced HIV

A package of interventions including the detection, treatment and/or prophylaxy for major opportunistic infections, rapid onset of ART and intensified adjective support interventions should be offered to all presenting advanced HIV disease. (*Strong recommendation, moderate quality evidence*)

Table 4: Additional Interventions for Individuals with Advanced HIV Disease

Screening, and prophylaxis for large opportunistic infections
• Intensive management of the appearance of disease and malnourishment. • TB-LAM in addition to Sputum GeneXpert sample, PLUS urine for individuals with fever, cough, weight loss or night sweating • Annual testing with Mantoux (PPD/TST) or IGRA if the base initial level is negative. • Serum Cryptooxic Antigen • Eye sink • Cotrimoxazole Preventive Therapy (CPT) • Priority for initiation of ART (caution if suspected or confirmed TB, TB meningitis, or cryptococcal meningitis) • Close monitoring for the development of IRIS

Some individuals may require domestic visits, or closer follow-up, especially for those taken out of hospital. People with advanced HIV who miss appointments should be tracked rapidly via phone or home visits. For advanced hospitalized patients, physicians should provide early interconnections and additional interventions to ensure retention, such as home visits by community health workers or peer navigators, or referral to primary care for closer follow-up.

https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/

4. Antiretroviral Therapy Goals in Children, Adolescents and Adults

The aim of ARV is to suppress viral replication with the aim of reducing the patient's Viral Load to unobtractable levels, achieving immunological recovery, to reduce the risk of advanced HIV disease, reduce immunodeficiency and mortality. With current therapeutic tools, viral suppression is an achievable target for all HIV individuals. As the virus integrates into human DNA, current therapies can suppress effective viral replication but cannot cure HIV infection. Therefore, hiv treatment should continue throughout life, and all efforts should be made to avoid hiv therapy interruptions, by patients and by the health system in case of stocking residue. Any interruption of receiving or offering arvatory treatment should be considered an emergency given the risk of HIV transmission to individuals presenting viral reversal. All patients should be advised of the benefits of ongoing treatment and health managers should ensure that pharmacies have at least 6 months of stock adjusted for the regimens in use, in order to cover eventual delays in ARV procurement.

Uninterrupted ARVs with constant strict adherance is essential to enjoy the social, community and individual benefits of Untransmittable. Maintaining untraceable levels of viral load is the best way to prevent damage to the body's immune system, recover and keep individuals in healthy condition, reduce sexual and vertical transmission of HIV and reduce the high cost of treating untreated HIV complications.

5. Entity and Time of Antiretroviral Therapy

All individuals with HIV should be offered Antiretroviral Therapy in order to reduce the viral load, recover immune damage caused by the virus, reduce morbility and mortality, and interrupt transmission of HIV.

WHO recommendation, when launching ARV (2016 guideline)

ARVs should be initiated in all individuals living with HIV, regardless of who's clinical stage and in any number of CD4 cells

(Strong recommendation and moderate quality of evidence for adults, pregnant women and infants, and recommendations with probation and low quality of evidence for children 1-10 years and adolescents 10-19 years.)

5.1 Arv Start Time

ArV initiation should follow the comprehensive principles of providing people-centered care. People-centred care should focus and organize around health needs, preferences and expectations of people and communities, maintaining individual dignity and respect, especially for populations in need, and should promote the engagement and support of people and families to play an active role in their care through informed decision-making.

WHO Recommendation on ARV Start Times

Early onset of ARV (<7 days from HIV diagnosis) should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical evaluation. (*Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)*

ArV initiation should be offered on the same day to people who are willing to start.
(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

In order to speed up the onset of ARV, initial consultation should be given on how to design an immediate adjective plan and how to recognize side effects. In subsequent counselling sessions during the first months on ARV, additional counselling sessions may be implemented to support treatment education, including the need for optimal lifetime adjective, as the ARV is monitored. For those customers who are not ready to launch on the same day, the preparation content of the ARV should be provided over the next seven days, taking into account the person's ability to travel to the clinic. Availability of point-of-care diagnostics for CD4 cell count, viral load, tuberculosis diagnosis and sidestream analysis of cryptococcal antigen (full blood, plasma or serum) may also support the programmatic implementation of the care package for people with advanced HIV disease, enabling such people to access appropriate prophylaxis or preventive treatment when this is indicated, and allow quick investigation for TB before arv's launch.

Table 5: Special Considerations for ARV Start Times

Population	Arv start time	Comments
Pregnant women	Initiate ARV as soon as possible, and the woman is ready to start it.	Intensive adulation counselling and close follow-up due to limited time for patient preparation
Patients with acute antiretroviral syndrome	Start the ARV once the individual is ready to receive it.	For every month after acute HIV infection there is a 10% risk of not recovering the normal number of CD4 during follow-up.
Babies (< 12 months)	Start the ARV once the individual is ready to receive it.	Intensive parental counselling is required and follow-up closely. In mothers who were not traceable during the birth activity, the babies' ARVs from birth should be taken into account.
Patients with motivation to start ARV immediately	Start the ARV once the individual is ready to receive it.	Intensive adulation counselling and follow-up close follow-up is required due to the limited time for patient preparation
Patients with TB have been diagnosed	Start anti-TB treatment immediately and start ARV as soon as anti-TB medications are tolerated, preferable within 2 weeks.	Close monitoring for IRIS
Patients with cryptococcal meningitis	Push arv until 5 weeks of CM treatment has ended and symptoms have resolved	Close monitoring for IRIS
Patients with tuberculosis meningitis	Push arv until 5 weeks of meningeal TB treatment has been completed and symptoms are resolved	Close monitoring for IRIS
All other patients.	Start ARV within 1 week of confirmation of HIV diagnosis in patients ready to start.	Adequate ARV preparation, and continuous monitoring of accession and support is recommended after starting ARV for all patients

6. WHO Recommends Frontline ARVs

As in all international HIV guidelines, WHO also recommends an integrassary inhibitor for first-line HIV therapy. In July 2019, WHO updated the global HIV treatment recommendation to include Dolutegravir and reduced dose of Efavirenz. Since EFV regimens should not be used in countries with national pre-treatment EFV resistance ratings of 10% or higher, and given that in Albania there is no recent data on HIV levels or resistance to ARV, young HIV patients should start a dolutegravir regimen until resistance studies can demonstrate whether EFV is still a suitable option for patients young. For children and newborns, who cannot use DTG, RAL is the preferred herd according to the WHO.

WHO recommendations for first-line ARV regimes

Dolutegravir (DTG) in combination with a nucleosid reverse transcriptase inhibitor (NRTI) is recommended as the first-line regimen preferred for people living with HIV starting ARVs
Adults and adolescents (*strong recommendation, moderately safe evidence*)
Infants and children with approved dosage of DTG (*conditional recommendation, low-security testing*)

6.1 The rationale for choosing DTG as preferred first-line therapy for adolescents and adults.

DTG is preferred in first-line ARVs in combination with two other ARVs for adolescents and adults, including women with birth potential. Recent studies show that this regimen is also preferred for pregnant women, based on better outcomes for pregnant women treated with DTG compared to other regimens. The DOLPHIN-2 study showed better virological suppression in pregnant women who receive DTG[8]. IMPACT 2010 (Vested Study) showed superior efficiency, faster viral suppression, and better fetal outcomes (less preterm birth and neonatal death) with DTG vs EFV-based regimens[9]. Women and adolescent girls who want to be pregnant or who are not using an effective method of contraception should be advised when starting DTG-based ARVs in relation to the potential increase in neural tube defects in children exposed to DTG during the first 8 weeks of pregnancy. DTG is well tolerated, has a high genetic barrier to resistance and fewer interactions between medications, and the benefit outweithe potential risks in these women.

Table 6, Choosing dolutegravir for ARV Optimization

Recommended DTG dosage
• ≥20Kg: DTG 50 mg QD, preferentially as a morning dose with or without food. • For patients taking rifampicin: increase the dose to DTG 50 mg twice daily up to 2 weeks after completion of TB treatment, then reduce again to DTG 50mg QD (2 weeks additional of the higher dose DTG is to counteract the ongoing effect of the liver enzyme induction of rifampicin, which continues for a short period after TB treatment has been completed) • For patients who fail a RAL-based regimen: use DTG 50mg twice daily
The most common side effects of DTG
The most common side effects of DTG are headache, nausea and mild insemonity. These side effects usually ease after continuous use for 1-2 weeks. It is essential to inform patients of these possible side effects and their temporary nature and to encourage them to continue ART and to consult again if they are concerned about continuing these effects. Two random selection experiments conducted in South Africa and Cameroon, and several group studies showed that, compared to EFV, DTG is associated with weight gain. This effect was most significant among women of African descent who were not taking tenofovir in the spinal cord. DTG may cause a small increase in serum creatinine levels, but this does not represent a real decrease in renal function.
Safety of DTG in pregnancy

[8] Kintu K, et al. Dolutegravir versus efavirenz in women who initiate HIV therapy in late pregnancy (DolPHIN-2): an experiment with casual, open-label selection. Lancet HIV. 2020 May;7(5):e332-e339.

[9] Chinula L et al. *Safety and efficacy of DTG vs EFV and TDF vs TAF in pregnancy: IMPAACT 2010 trial. Conference on retrovirues and opportune infections*, abstract 130LB, March 2020

DTG may be associated with increased risk of neural tube defects if taken around the time of conception. That potential risk is still under assessment. Data from the Tsepamo cohort observation showed that neural tube defect occurred in 4 births among women in DTG by conception, a small but significant increase compared to all other antiretroviral exposures. Although further studies showed a decrease from 0.94% (4 out of 426 exposures) to 0.30% (5 out of 1683 exposures), the prevalence gap, although low, remains statistically significantly higher than all other groups of ARV drug exposures. Botswana has no national fortification of food folate and no neural tube defects have been reported from countries with folate fortification. Data on birth outcomes, including neural tube defects, in pregnant women exposed to other integrase inhibitors are reassuring so far, although the number of future periconception exposures is limited. Continuous observation is needed to more definitively confirm or reject the neural tube defect signal and several studies are ongoing to address this.
DTG is considered safe after the neural tube closure, after 8 weeks of pregnancy, therefore, women who receive DTG identified after 8 weeks of pregnancy should not discontinue DTG.

Important interactions of drugs with DTG

Rifampicin lowers DTG levels: increase DTG to 50 mg twice daily for patients with rifampicin. There are no significant drug interactions between DTG and other anti-TB drugs currently used (including MDR-TB).
Mineral supplements, including: antacids containing calcium, zinc, magnesium or aluminum; iron supplements; prenatal vitamins (which contain iron and calcium) may decrease DTG absorption: administer DTG at least 2 hours before or 6 hours after taking any of these supplements. Dose separation is not required for calcium and iron supplements (including prenatal vitamins) if DTG is taken with a meal.
It is essential to educate patients about this important drug interaction, because many patients take these over-the-counter supplements and antacids without informing their healthcare provider.
Carbamazepine, phenobarbital, phenytoin: These anticonvulsants lower DTG levels: use a different anticonvulsant if available. If DTG is to be co-administered with these drugs then increase DTG 50 mg twice a day, although there is little data to guide this.
Metformin: DTG increases metformin levels; DTG levels are not affected: use a lower dose of metformin (often 50% of the usual dose) and monitor glycemic control. Use a maximum daily dose of metformin 1 g
For other drug interactions see www.hiv-druginteractions.org

6.2 The difference between Lamivudin and Emtricitabin

The totality of evidence to date, from pharmacological data to observational studies to direct and indirect comparisons in randomized trials, suggests that lamivudine (3TC) 300mg/day QD and emtricitabina (FTC) 200 mg/day QD are clinically and therapeutically interchangeable.

Three random selection experiments directly compared the safety and efficiency of 3TC and ftc against identical spinal regimens. Each of these experiments reported an insignificant difference in virological suppression, and when the results were merged, the overall difference was insignificant (1.03 relative risk, 95% confidence interval 0.96-1.10). These equivalence findings are further supported by indirect evidence from nine experiments with random selection comparing 3TC and FTC versus a similar spinal cord regimen of two different NRTI inhibitors (relative risk of virological suppression 0.99, 95% confidence interval 0.96-1.01). Data from observational studies are mixed. Overall, reported differences between 3TC and FTC in observational studies are often associated with changes in initial characteristics of treatment groups, particularly with respect to immunological and virological status, comorbidity, substance misuse, and pill burden.[10]

Therefore, the choice of FDC with 3TC or FTC should rely on programmatic and logistics aspects and costs.

6.3 Use of Ritonavirus or Cobicistate with Protease Inhibitors

Ritonavirus, at doses of 100 mg once or twice daily, is effective in increasing the pharmacokinetic profile

[10] Technical update on treatment optimization: pharmacological equivalence and clinical interchangeability of lamiduvin and emtricitabin: a review of the current literature.
https://apps.who.int/iris/bitstream/handle/10665/70936/9789241503815_eng.pdf?sequence=1

of Protease Inhibitors (PI) through inhibition of CYP3A4 and P-glycoprotein (P-gp) intenstinal and hepatic, resulting in increased area under curve (AUC), maximum concentration (Cmax) and half-life of Protease Inhibitor (PI) allowing for less frequent dosing, Reduced pill burden, reduced impact of food on bio-availability, reduced variability of systemic drug exposure and improved treatment efficiency. Ritonavir is co-formulated with lopinavirus, and in generic forms with atazanavirus. Ritonavirus is available in oral presentation for individuals who cannot tolerate the pills.

Cobicista was approved as a pharmacokinetic growing agent in 2012 and is a potent inhibitor of CYP3A4 and P-gp as ritonavirus. However, there are important pharmacokinetic differences between cobicistate and ritonavirus, which can lead to clinically significant changes in drug interaction outcomes. Cobicista is co-formulated with darunavir and atazanavir IPs and the elvitegravir integrase inhibitor. When switching from ritonavirus to cobicistat, the lack of stimulating activity of enzymes with cobicistate should be taken into account. Concentrations of jointly administered drugs that are substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and UGT may be increased, and close monitoring with possible dose adjustments is recommended.

Similarly, when you switch from the kobicistat regimen- towards the regimen with adult ritonavir, the exposures of comedies that are substrates of these enzymes may decrease, and dose increases may be required to maintain the therapeutic effect. Clinicians should be aware of these important differences and differences when evaluating and managing potential drug interactions with retonavir-based regimens or cobicistas, especially in patients with multiple associated diseases and associated medications. Depending on the medications used together, additional monitoring and/or dosage adjustments may be required.[11]

As new interaction data is constantly emerging, clinicians are encouraged to use specific interaction sources of HIV drugs, such as www.hiv-druginteractions.org.

Taking into account a public health approach, prices and availability, ritonavirus is preferred over co-bibistate in countries where generic ritonavirus and PI/ritonavir co-formulation is allowed.

6.4 Tenofovir Alafenamidi vs. Tenofovir DF: advantages and disadvantages

Tenofovir-alafenamide (TAF) is a novel pro-drug formulation of tenofoviri with 6.5 times higher intraccelic concentration of tenofovir diphosphate phosphorylate, and 91% lower concentration in tenofovir serum, compared to TDF, resulting in non-inferior antiviral activity with 10% of the TDF dose. The bioekivalent dose at 300 mg TDF is 25mg, without amplifiers, or 10mg when used with pharmacokinetic enhancers such as ritonavirus (RTV) or cobicistate (COBI). This lower dose translates into reduced exposure of the drug in the kidneys and bones with potential improvements in tolerance. TDF is associated with renal or bone-on effects, although clinical trials showed that these effects are significant only when used with RTV or COBI. Conversely, when TDF is used with uncontested regimens, there were no clinically significant differences between TDF and TAF, according to a meta-analysis that evaluated 11 experiments with casual head-to-head selection involving 8,110 participants. Nine experiments compared TDF vs. TAF in HIV-positive people and two in people with hepatitis B. There were 4,574 participants who received booster agents (with both TDF and TAF) and 3,537 participants received non-reinforcing regimens. Participants treated with reinforced TDF had more bone fractures, lower bone mineral density, and more disruptions for unintended bone or kidney events. Conversely, there have been no significant differences in viral load suppression rates or endpoints of clinical safety (other than bone mineral density) between TDF and uncontaminated TAF.[12]

There are some concerns about TAF use: the lack of published data on TAF efficacy in patients confected

[11] Tseng A, Hughes CA, Wu J, Seet J, Phillips EJ. Cobicistat Vs. Ritonavir: Similar Pharmacokinetic Enhancers But Some Important Differences. Ann Pharmacother. 2017;51(11):1008–1022. doi:10.1177/1060028017717018

[12] Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide vs Tenofovir disoproxil fumarate: is there a real difference in efficiency and safety? J Virus Erad. 2018 Apr 1;4(2):72-79.

with TB as significant drug interaction based on pK modeling is predicted and there is no available data on TAF safety in pregnant women, placental or taf breast milk passage in humans. There was also a report regarding alopecia as the potentially occurring negative effect of TAF.[13]

Recently, WHO guidelines included TAF in recommended regimens under special situations, which includes pre-existing kidney or bone disease.

6.5 Frontline ARV for Teens and Adults

The table below shows the preferred and alternative frontline regimen for adolescents (≥ 15 years or >35 kg body weight) and adults. DTG in FDC with TDF and 3TC (or XTC) is a regimen that can be used in almost all populations, except for pregnant women in the first 8 weeks of pregnancy or planning to become pregnant. This combination required additional dosages of DTG in case of use with rifampicin. Alternative regimens include the use of EFV with TDF and 3TC (or XTC), or Protease Inhibitors such as ATV/r, LPV/r or DRV/r. **EFV should not be used as an initial regimen in countries with hiv>10% prevalence.**

Table 7: Adolescent & Adult ART Preferred Regimes

Favorite regime for all teenagers and adults	
TDF-XTC-DTG1 in one FDC 1 QD tablet (TDF-3TC-DTG 300-300-50 mg or TDF-FTC-DTG 300-200-50mg)	
Alternative regimes for all adolescents and adults	
• **TDF - XTC - EFV** (TDF-3TC-EFV 300-300-600 mg or TDF-FTC-EFV 300-200-600mg) • **TDF - XTC+ATV+RITO** (TDF-3TC 300-300mg QD or TDF-FTC 300-200mg QD+ATV 300 mg QD+RITO 100mg QD) • **TDF - XTC+RAL** (TDF-3TC 300-300mg QD or TDF-FTC 300-200mg QD+RAL 400 mg BD) • **TAF2 - XTC+DTG** (TAF-FTC 25-200mg QD or TAF-3TC 25-300mg QD+ DTG 50mg QD)	
Other scenarios	
Women planning to be pregnant	TDF-XTC+ ATV+ RITO(TDF-3TC 300-300mg QD or TDF-FTC 300-200mg QD+ATV 300 mg QD+RITO 100mg QD), **or** TDF-XTC-EFV (300-300-600mg) **or** TDF-FTC-EFV (300-200-600mg) QD before bed or 2 hours before dinner. TDF-3TC-DTG 300-300-50 mg or TDF-FTC-DTG 300-200-50mg **can be** considered as an alternative option, as small but significant increase in risk of infant NTDs when taking dolutegravir (DTG) around the time of conception is discussed. **Use EFV only if resistance testing is available and does not show resistance-related mutations**.
Individuals with tuberculosis	TDF-3TC double-dose of DTG: (TDF-3TC-DTG 300-300-50 mg or TDF-FTC-DTG 300-200-50mg) am QD **plus** DTG 50mg 12 hours distance up to 2 weeks after rifampicin discontinus, **or** TDF-XTC-EFV (TDF-3TC-EFV 300-300-600mg or TDF-FTC-EFV 300-200-600mg) QD at bedtime or 2 hours before dinner. **Use EFV only if resistance testing is available and does not show resistance-related mutations.**
Individuals with renal disease	DTG+3TC5(3TC 300 mg QD **plus** DTG 50mg QD), **or**

[13] El Zein S, Tabaja H, Kanj A, Richmond D, Veltman J. Alopecia After Switch to Tenofovir Alafenamide ne 6 African American Women. Open Forum Infect Dis. 2019. Jun 6;6(7):ofz278. doi: 10.1093/ofid/ofz278.

(ClCr <50ml/m)[4]	TAF-FTC + DTG (TAF-FTC 25-200 mg QD **plus** DTG 50mg QD)

[1] XTC stands for interchangeable use of Emtricitabin or Lamivudin.

[2] TAF can be used in individuals with renal or bone disease.

[4] HBsAg positive individuals should continue TDF with a regulated dose or use a TAF-based combination.

[5] Dual therapy with 3TC-DTG can be considered in individuals without 3TC resistance and with HBsAg negative

6.6 First Line ARV for Babies and Children

These recommendations apply to patients who start ARVs for the first time. All patients must have their weight documented at each visit. Children and adolescents should have the correct dose of weight-based ARVs confirmed at each visit. Babies and children depend on their caregivers for adherence to medication. Caregivers should be adequately prepared for their role in managing ARVs to infants and children, including addressing anticipated challenges such as tasting grass. Stewards should always be shown how to measure and administer ARVs and then required to demonstrate that they understood. This should be done at the time of the description of the ARV (by the clinician) and at the time of the distribution of the ARV (ideally by the pharmacist). Table 8 shows favourite frontline regimes.

Dolutegravir is the preferred medication for infants and children over the age of four weeks and more than 3 kg, although lopinavirus or raltegravir are acceptable alternative regimens if DTG formulations are not available, given the superiority over regimens based on the non-nucleoside reverse transcriptase inhibitor (NRTI).[14] In addition, all non-recommended regimens should be optimised as children grow older and while there are better formulations available, using the DTG-based regimen, which showed it was more robust and easier to administer[15]. Children weighing 30 kg or more should simplify on a single ARV pill consisting of TDF-XTC (3TC or FTC)-DTG.

Table 8: First Line Preferred ARV Regimens and Dosages in Children

Age	Favorite first-line regime	Alternative first-line regime
The Neonations	AZT/3TC/RAL1	AZT/3TC/NVP See table 9 below for dosage
Children 3-30 kg	ABC + 3TC + DTG2	ABC + 3TC + LPV/r or RAL3 TAF+3TC(or FTC)+DTG4 See table 9 below for dosage

[1] Newborns who begin antiretroviral therapy with a RAL-based regimen should switch to a rigid LPV/r formulation as soon as possible.
[2] Children weighing 20 kg or more should take 50 mg dolutegravir QD. See the dosage in Table 9.
[3] RAL should be used as an alternative regimen only if solid LPV/r formulations are not found.
[In] Europe, TAF is approved for use in children older than 12 years old or weighing more than 35 kg.

Table 9 shows the recommended doses revised and confirmed by the WHO's PEDIATRIC ARV Working Group on June 19, 2020.[16]

Table 9: ARV Dosing for Children from 0-4 Weeks

[14] Hill AM, Hughes S, Liew Z, Pozniak A. Meta-analysis of dolutegravir for 7340 patients in 13 randomized trials: effects of current HIV RNA suppression on efficacy and safety. 4th Joint Conference of BHIVA and BASHH, 17–20 March 2018, Edinburgh, United Kingdom.
[15] Switching to new antiretrovirals in HIV programs. Geneva: World Health Organization; 2017 (found in https://www.who.int/hiv/pub/toolkits/transition-to-new-arv/en).
[16] Consideration for the introduction of new formulations of antiretroviral drugs for children. Policy Summary, 1 July 2020 (available at https://www.who.int/publications/i/item/9789240007888)

Formulation	3–5.9 kg		6–9.9 kg		10-13.9 kg		14-19.9 kg		20–24.9 kg		25–29.9 kg		≥30 kg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC 120/60 mg scored dispersible tablet	1		1.5		2		2.5		3		1 adult tab (600/300 mg)		1 adult tab (600/300 mg)	
LPV/r 40/10 mg pellets (capsules)	2	2	3	3	4	4	5	5	6	6	—		—	
LPV/r 40/10 mg granules (sachets)	2	2	3	3	4	4	5	5	6	6	—		—	
LPV/r 100/25 mg tablets	—	—	—	—	2	1	2	2	2	2	3	3	3	3
4-in-1 ABC/3TC/LPV/r 30/15/40/10 mg (capsules)	2	2	3	3	4	4	5	5	6	6	—	—	—	—
DTG 5 mg dispersible tablets[a]	1		3		4		5		—		—		—	
DTG 10 mg scored dispersible tablet	0.5		1.5		2		2.5		—		—		—	
DTG 50 mg tablet	—		—		—		—		1		1		1	
TDF/3TC (or FTC)/DTG 300/300 (or 200)/50 mg tablet	—		—		—		—		—		—		1	

Dispersable tablet – melting tablet; Pellet/pill; granules /grains

7. When arv is changed

There are several reasons that support arv changing in individuals treated for HIV. This includes:

a) Optimizing or simplifying treatment for patients with untrained viral loads
b) Changing ARVs for patients in failure
c) Change in ARV due to toxicity

7.1 Optimization Therapy for Patients With Untrained Viral Loads

Optimization implies altering an ARV regimen, even when the patient is virally suppressed or currently tolerates his regimen well and there are no interactions between medications that require an immediate change.

The most common reasons for optimization include:

- Accommodate age/weight crossings between children and adolescents
- Avoid even mild unwanted events that can affect adversity
- To adapt to recommended new regimes
- To simplify a regimen to one with fewer pills or doses
- To prevent long-term toxicity or risk of interactions
- To reduce the risk of post-stock residue or interruptions
- Improve the efficiency and cost-effectiveness of the program
- Simplify follow-up, monitoring and scaling

All People Living with HIV Who Receive a Non-Recommended Regimen Should Be Considered for Optimisation

Decisions on modification of the regime should be discussed internally, agreed with the management team and discussed with the patient to understand the benefits of intervention. Some patients may feel afraid to change a regime that is working. The short and long-term benefits of optimizing the regimen and potential risks should be discussed with patients. It is always possible to return to the previous regime in case of intolerance or new side events. Typically, patients who take more than one dose a day, and those with mild side events only realize the benefits after switching to the new regimen.

Always discuss with the patient the possibility of new side effects when changing to a new ARV, especially common side effects for all ARVs (headache, nausea, diarrhea) and any side effects specific to the new ARV. Reassure patients that most side effects are mitigated with continued use after 1-2 weeks.

Table 10: Regimens That Can Be Optimized for Adults That Are Virally Printed

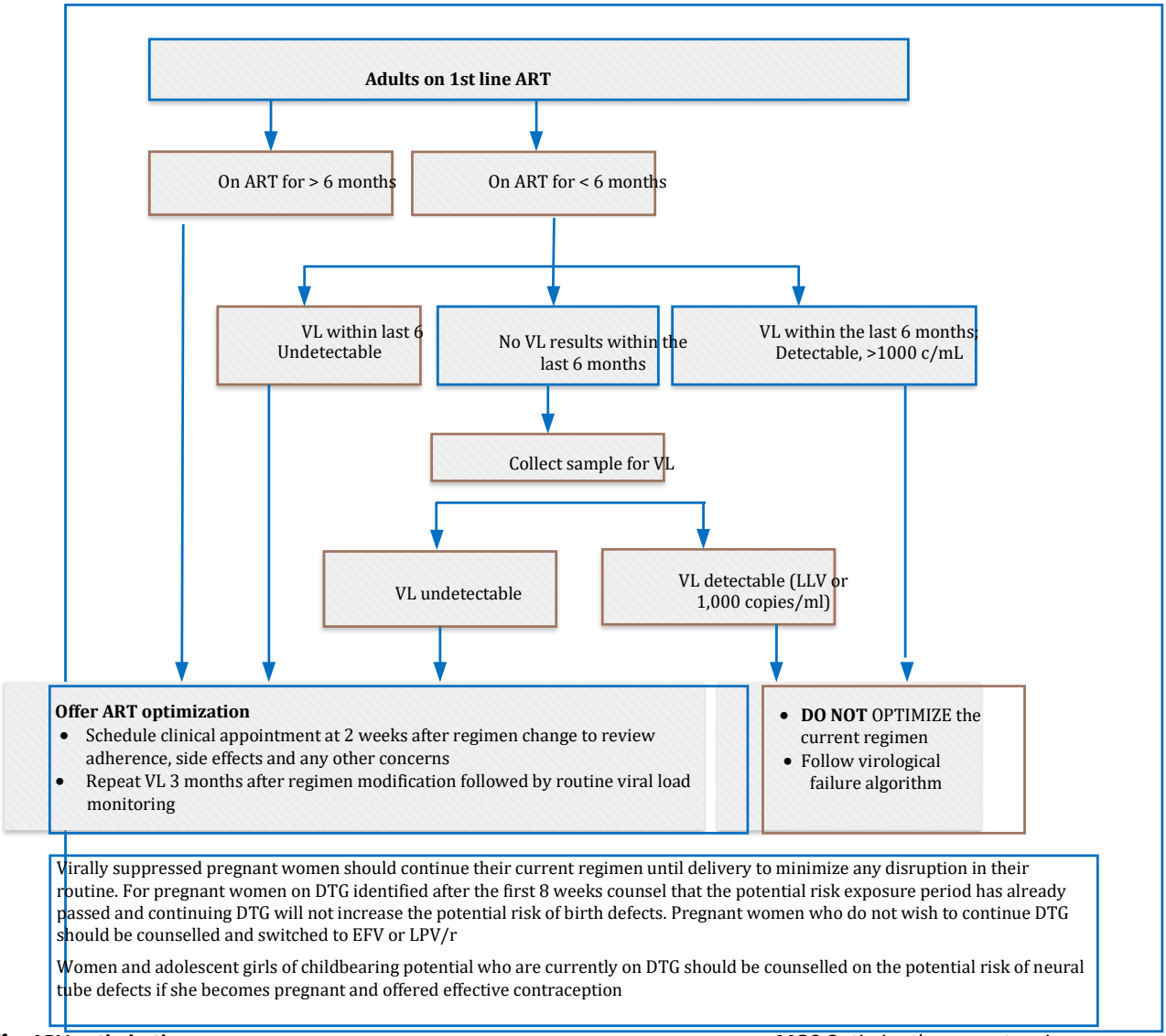
Current regime	Optimized preferred regime	Comments
First line EFV/TDF/FTC	DTG/TDF/3TC, Or continue with EFV/TDF/FTC	Switch to DTG regimen patients who report neurological symptoms, cognitive problems or who present work restrictions for EFV use. If women, make sure they receive adequate counseling and effective contraception.
First line EFV + TDF/FTC	DTG/TDF/3TC Or continue EFV/TDF/FTC	Switch to the DTG regimen patients who report neurological symptoms, cognitive problems or who present work restrictions for EFV use. In women transitioning to DTG provide adequate counseling and effective contraception
First line EFV + AZT/3TC	DTG/TDF/3TC	If women, provide adequate counseling and effective contraception.
First line LPV/r +TDF/FTC	DTG/TDF/3TC	If women, and plan a pregnancy, DO NOT switch.
Second line	DTG/TDF/3TC	If AZT/3TC is being used due to failure during a TDF/3TC regimen, consider

LPV/r or ATV/r +AZT/3TC	or DTG + AZT/3TC	continuing if toxicity is not visible.
Second line LPV/r or ATV/r +ABC/3TC	DTG + TDF/3TC	Avoid using ABC because you need HLA-B51 testing.
Second line RAL +ABC/3TC	DTG + TDF/3TC	Avoid using ABC because you need HLA-B51 testing.

- Women and adolescents with birth potential who require DTG; it is not recommended for women and adolescent girls with birth potential who are not on effective contraception due to the potential risk of birth defects when DTG is used around the time of conception.
- TDF can be used with renal dose adjustments (see table 15) in HBsAg+ patients or it can be passed on to TAF.

Figure 3. Optimizing ARV regimens for Adolescents and Adults (≥15 years old) of the Front Line ARV

Figure 3: Optimizing ART Regimens for Adolescents and Adults (≥ 15 years) on First Line ART



Offer ARV optimization

• Schedule clinic appointment 2 weeks after regime change to review adulation, side effects and any other concerns

• Repeat VL 3 months after modification of followed regime

Routine monitoring of viral loads

-MOS Optimize the current regime

- Follow the algorithm of dThe Virological

Virally-dominated pregnant women should continue their current regimen until birth to minimize any disruption to their routine. For pregnant women in DTG identified after the first 8 weeks, advise that the potential period of risk exposure has already passed and the continuation of DTG will not increase the potential risk of birth defects. Pregnant women who do not wish to continue DTG should be consulted and switched to EFV or LPV/r

Women and adolescent girls with childbeasting potential who are currently on DTG should be advised of the potential risk of neural tube defects if she becomes pregnant and are offered effective contraception.

7.2 Change in ARVs due to treatment failure

It requires viral load to identify response to treatment, monitor adulation, and identify treatment failure.

Below are the most common indications for viral load:

- As a confirmatory HIV test in children born to women with HIV.
- As a diagnostic test for suspected acute retroviral HIV syndrome (in individuals with hiv negative test and unexplained fever or neurological symptoms, or rash/rash and lymphedeopathy)
- As a monitoring test to assess response to treatment: This test should be repeated every 6 months in all treated populations. A VL at 3 months after starting treatment may provide early information about the response to treatment.
- Additional VL testing may be necessary in a situation where treatment failure is suspected (in individuals taking ARVs for more than 6 months who present virological relapse). VL should be performed after an adulation intervention and after providing adequate ARV for 8-12 weeks.
- As a requirement before you replace a drug in patients with more than 6 months in therapy, due to unwanted events, or before making the switch for simplification of treatment.

Interpretation of Viral Load Results and Treatment Failure Definition

The goal for the ARV is to achieve sustained viral suppression defined as below the Detection Limit (LoD), which is considered "unobtrable." The specific LOD depends on the analysis used to measure viral load.

Non-compliance or discontinuation of treatment is the most frequent cause of traceable VL. Therefore, **adhesive issues and the continuation of supply of ARVs should be addressed before requesting a new VL to confirm the failure of treatment.** With the old intolerance of ARVs, the number of pills and undesirable events were the main cause of poor adversity and single agent switches were common practice. With the new generation of ARVs, and with dolutegravir, tolerance is significantly better, and the risk of virological failure due to the appearance of resistance is extremely rare. Proper counselling can identify people at risk of non-adage, d.m.th. those who do not adjust to HIV diagnosis or have mental health problems, drug abuse, or depression.

Inadenation vs failure: any traceable VL score in individuals who do not receive at least 90% of ARVs at the time of conducting the study should be considered an adjecence issue and should not promote ARV regime change until ARV failure is confirmed. An adulation intervention should be provided and patients should be advised to take ARVs adequately, and a new test should be repeated after 8-12 weeks.
Two VL ≥ 1,000 copies/ml after at least 6 months of ARV use in adhering individuals confirms virological failure. To confirm virological failure, attention should be devoted to addressing poor adherence, drug interactions, absorps, or other potentially treatable reasons before repeating VL. Virological failure requires GT and immediate arv change.

Blip/temporary deviation: traceable values below 200 copies/ml in individuals who had previously achieved unwoven VL may be a temporary deviation. This does not require a change in ARV. To confirm a temporary deviation, a new viral load should be required and the result must be untitled. If the second VL is traceable and under 1,000 copies/ml, it should be considered low-level viremia.

Low-level viremia (LLV) is determined to have at least two consecutive VLs above LoD but < 1,000 copies/ml. Most guidelines define LLV as a stable traceable VL, but below 200 copies/ml. Therefore, most experts suggest non-reversal of ARV treatment in these patients as under 200 copies/ml there is not enough data to confirm a higher risk of virological failure, resistance accumulation or clinical trials

supporting change. Less clear is what to do with patients with VL between 200 and 1000 copies/ml, as the results of the various studies are more conflicting. Who recommends not changing ARVs until the viral load is higher than 1,000 copies/ml, but other studies suggest these patients are at an increased risk of treatment failure. These patients should have closer follow-up, to receive an adulation intervention and repeat VL after 6-12 weeks of taking ARV with good adulation. If VL is still traceable, the decision should be made based on the level of VL. Values higher than 1,000 will require GT and change of handling, but values below 200 copies can be closely monitored. The decision of regime change in individuals with VL between 200 and 1,000 should be taken into account factors such as possible adversity of the future regimen, number of future options available, risk of viral transmission, stage of HIV infection, etc. Cases should be discussed in an interdisciplinary team which should assess the barriers the individual may have to pursue treatment and propose interventions. GT should be required to all individuals, the possibility to amplify will depend on the value of VL, but almost all samples with VL > 500 copies/ml will be amplified

Figure 4: Monitoring of Patient Viral Load in ARVs (Line 1 and Line 2)

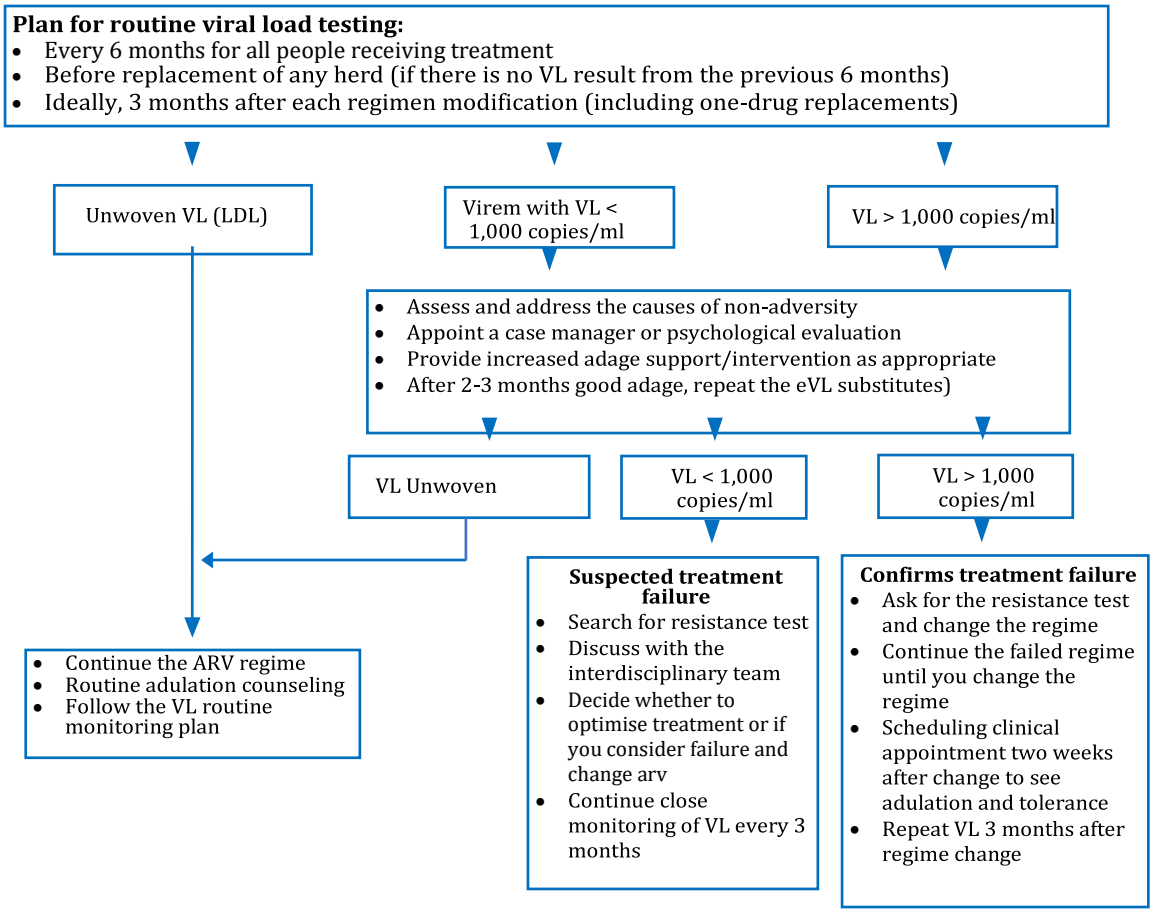


Table 11: Recommended Second-Line ARV Regimens in Infants, Children, Adolescents & Adults

Age/scenario	ArVe Frontline	Second line ARV
Children and babies	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG Alternative: AZT (or ABC) + 3TC + RAL
	ABC + 3TC + NVP (or RAL)	AZT + 3TC + LPV/r
	AZT+ 3TC+NVP	ABC + 3TC + DTG (alternative LPV/r or RAL)
	ABC/3TC + DTG	AZT +3TC + LPV/r until it reaches 30 kg.
	3TC+EFV	AZT (or ABC) + 3TC + DTG Alternative: AZT (or ABC) + 3TC + LPV/r

Table 12: Third-Line ARVs in Children, Adolescents & Adults

	Possible 3rd Line Regime	Comment
Children	RAL (or DTG) + DRV/r + 3TC	DTG should be replaced with RAL in children after pediatric DTG formulations are available and weight-based doser generations are determined. The NNRTI should be chosen based on arv history, GT and weight. In children >2 years and more than 10kg, weight-adjusted ETV can be used.
	RAL (or DTG) + DRV/r + DRV/r + 3TC + other/e NRTIs	
	RAL (or DTG) + DRV/r + 3TC + NNRTI	
Adults	DTG + DRV/r + 3TC among those who have not previously been exposed to DTG and DRV/r and GT fully susceptible to these drugs	The final regime should be adapted based on the results of arv and GT history to provide at least 2 fully active regimens, ideally 3. In patients naive to NNRTI EFV would be as effective as ETV. If you have previously been exposed to EFV or NVP, use GT to establish the use of **Doses:** DTG 50mg BID in case of earlier exposure to DTG or RAL, or 50mg QD among those who have never been exposed to RAL or DTG. DRV/r: 600/100 mg BID ETV: 200 mg BID
	DTG + DRV/r + 3TC + other/n NRTI based on GT	
	DTG + DRV/r + TDF/3TC/EFV (or ETV) (use EFV if the individual is naive to NNRTI and ETV if already received EFV or NVP)	

Indication for HIV genotype resistance testing: GT, if available, should be required for all naive individuals who initiate ARVs, all children infected before initiating therapy, all pregnant women with traceable VL, and all patients with virological failure after confirming VL after 6-12 weeks of taking ARV with good adjective. If the test is not available, samples must be taken and stored for further processing.

7.3 Support adulation to prevent treatment failure

Psychosocial support for people living with HIV and their families is essential to their well-being and good health outcomes. HIV affects virtually every aspect of someone's life, as well as the lives of those close to them. People living with HIV need psychological and social support to cope with various issues that are

common to chronic diseases, as well as those that are unique to HIV. These include stigma, grief, self-image, loss of earning capacity, life skills and chronic diseases, among others. Providing psychosocial support involves identifying the needs they may have and addressing them. In some cases, some of these needs can be anticipated and addressed even before they come to the fore in the individual's life.

Not all individuals require support, therefore, discriminating against individuals seeking psychological support is essential to providing patient-centered care.

Health education is important and can support adulation. Patients should have information about hiv's natural history, how ARV works and the clinical implications of non-adulation. Address the side effects of drugs and how to avoid them, recognize and manage them, such as misconceptions and beliefs about HIV and ARV. Discuss alcohol and drug use, and how to prevent these from affecting the treatment plan. Make clear the connections between CD4, viral load and transmission should be highlighted, reinforcing the untransmittable = untransmittable concept.

Support groups: Encourage the patient to join a peer support group. Support groups provide opportunities for counseling and sharing experiences and give confidence and promote a positive attitude towards HIV status.

Family and social support: Ask about relationships and family in a non-judgmental way and respecting the patient's privacy and confidentiality. Discuss the role of openness to close family members/trusted friends in promoting accession and offer to facilitate opening up. Encourage identification of a treatment supporter/friend who may remind the patient to take the medication and obtain patient consent to contact the treatment supporter if necessary.

Routines and reminders: Explore the patient's routine and encourage the patient/caregiver to set a specific time of day to take the ARV and link the ARV time to a specific event/t in his or her daily schedule. Discuss how to manage missed doses. Encourage the patient/guardian to set an alarm on their phone. Discuss whether stigma interferes with taking medicine on time or holding clinic appointments.

ADVICE ON IMPROVING ACCESSION

Individuals who present Traceable Viral Load after being unsightly, or who discontinued ARVs should have access to an adulation increase counseling session. The goal is to assess potential adjective barriers in a non-judgmental manner and help the patient build an adage plan with concrete objectives. It is important not to focus only on knowledge of HIV and ARV, but also to review psychological, emotional and socioeconomic factors that can contribute to poor adulation. In addition, exploring the patient's motivation for taking medication often highlights the reasons for poor adulation. Usually, this consultation requires at least three sessions, and components include:

- Review understanding of Viral Load and discuss why patient VL is high
- Review the cognitive, behavioral, emotional and socioeconomic barriers of adulation
- Education about treatment
- Knowledge about medications: dosage, timing, storage, side effects
- Discuss risk reduction (p.sh. for substance abuse)
- Motivation, support system, referral needs
- Screening mental health for depression, cognitive problems or substance abuse
- Help prepare, review and adapt an adage plan to address identified issues
- Discuss VL advancements and further results

In some attitudes, this intervention is not sufficient and a case manager, who coordinates a multidisciplinary patient management case management, tracks holding appointments for their patients, arranges patient notification, ensures proper tracking of the defaulter (person not adhering to adherence), or coordinates home visits to their patients.

In order to be effective, it is important that clinics have the ability to implement systems to identify those individuals who miss appointments, and to identify those individuals who have lost VL monitoring, or who file viral returns.

7.4 Alteration of ARV due to side reactions of the drug

Staff should be educated about the risk of possible interactions and side effects of all antiretroviral therapies in use, and all other prescribed drugs, including prophylaxin for opportunistic infections, or associated medications commonly used in individuals HIV for non-contagious diseases such as statins or diabetes drugs.

All individuals who start ARVs should be informed about what to expect, what are the most frequent side effects, and when to consult in the emergency room. The patient should have an appointment between 2-4 weeks after starting treatment to assess tolerance and adhesiveness. VL, if available, may be required after 3 months of therapy for confirmation of virological suppression.

Side reactions can have a significant impact on the patient's adulation staff and patients should be able to recognize and manage. Physicians should discuss with patients the advantages of new ARVs, in particular their better efficacy and their safer profile, evidenced by a lower rate of ADRs.

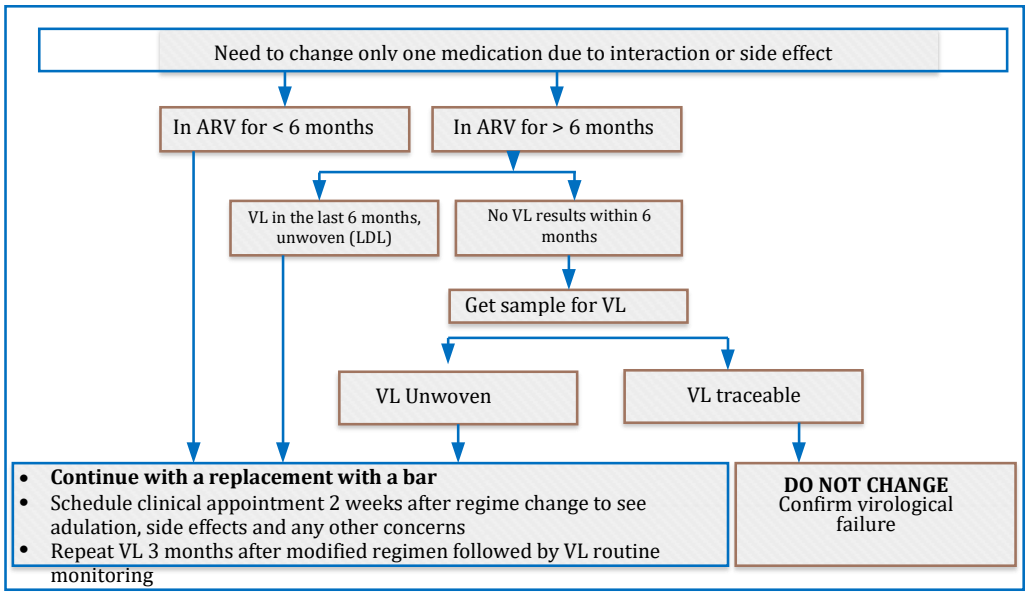
Table 13: Common Significant Side Reactions of Grass

ARV Agent	Side reaction of the bar	Comments
NRTI (reverse transcriptase inhibitors)		
ABC	Reaction of overeatence to ABC	**To avoid this, all individuals should be tested for HLA-B5701 before using ABC. If the HLA-B5701 test is positive, never expose this individual to the drug.** The reaction of superstability to ABC is rare but potentially fatal. Symptoms usually worsen within a few hours after each dose of ABC. **Within 8 weeks of starting an ABC-containing regimen**, the patient develops every 2 of the following symptom groups simultaneously • Fever • Erythematous rash and/or pruritus rash (itch) • Respiratory symptoms (shortness of breath and/or sore throat and/or cough) • Gi symptoms: nausea and/or vomiting and/or diarrhoea • Extreme fatigue and/or body pain preventing normal AND activities • there is no more likely alternative explanation for the symptoms **Management:** Stop the ABC immediately and replace it with the other NRTI. The patient should NEVER be challenged again with ABC - a single dose can result in a fatal over-estee response.
AZT	Anemia, neutropenia	Do not use AZT if Hb <9.5 g/dL. Risk factors: CD4 number < 200 cells/mm3; BMI < 18.5 (or body weight < 50 kg); Anemia at first. Parallel use of other drugs with similar ADR (cotrimoxazole, gancyclovir, ribavirin). If HB ≤ 8.5 g/dL or neutrophils ≤ 1.0 x 109/L switch from AZT to another NRTI.
	Lactic acidosis	Risk factors: pregnancy; obesity. Change immediately.
	Lipoatrophy	Risk factors: Low CD4 number.
TDF	Kidney dysfunction	Risk factors: Hidden kidney disease; age > 60 years; BMI <18.5 (or body weight <50 kg); diabetes; hypertension; We use the protease inhibitor, or nephrotoxic bar, the number of CD4 <200 cells/mm3. Follow up with urine and creatinine analysis in the serum and calculate creatinine clearance (CrCl). Switch off TDF in those with ClCr<50ml/min or use adjusted TDF dosage.
NNRTIs (non-nuclear reverse transcriptase inhibitors)		
All NNRTIs, including ETR	Rash /overeatness (NVP>>EFV>ETR)	Risk factors: for NVP overeating, women with CD4 count> 250 cells/mm3, men with CD4 count> 400 cells/mm3
EFV	CNS side effects	Risk Factors: Pre-existing psychiatric disorder
	Gynecomastia	Switch from EFV to an alternative, and consult Gynecology if gynecomastia doesn't improve
NVP	Severe	Avoid using this bar.

	hepatotoxic toxicity	Risk factors: HBV or HCV co-infection; simultaneous use of hepatotoxic drugs; women with CD4>250 cells/mm3; men with CD4>400 cell/mm3 number
PIs (Protease Inhibitors)		
All PIs are reinforced with RTV	GI Intolerance (LPV/r>DRV/r>ATV/r)	Diet, antiemetics. Change if this is affecting adulation.
	Dislipidemia (LPV/r>DRV/r>ATV/r)	Risk factors: obesity; Sedentary lifestyle; Diet rich in saturated fats and cholesterol
ATV/r	Hyperbilirubinemia	This ADR requires replacement of the drug only if the cosmetic effect of jaundice is likely to interfere with patient adhesive
DRV/r	Rash / overconsuction	Risk factors: allergy sulfa. Treat it with antihistamine evaluation and close up. Stop if fever, mouth ulcers or strong, progressive rashes appear.
INSTI (Integrasa Wire Transfer Blockers)		
DTG	Insomnia	And then you will be given it in the morning. If there is no improvement, then try to give it with a low-fat meal or on an empty stomach
	Weight gain	Higher with second generation INSTI (similar effect observed with bictegravir)

Most of the time it is easy to identify the grass that is causing the negative effect. If the reaction is not life-threatening, and the patient is stable, the doctor can decide whether to continue the same treatment, as most of them resolved in 1 month, waiting for the side effect to be resolved, or if the reaction is severe enough to change the medication. Most of the time, side effects appear a few weeks after the onset, but occasionally, they can develop several months or years into treatment. Among those who take ARVs for less than 6 months, the risk of developing an ARV mutation is very low and the drugs can be replaced without additional procedures.

Figure 5: Management of an ARV drug replacement



In those who take ARVs for more than 6 months, it is important to confirm that the individual has viral suppression. If the patient has long-term disapproval due to side effects or intolerance, mutations of resistance to some of the regimen's drugs may have appeared, and changing a drug without evaluating this situation could mean "virtual monotherapy". Therefore, it is indicated to perform a VL before a single drug is replaced, and if VL is untraceable, the patient may switch without additional intervention. Conversely, if VL is traceable, viral failure should be considered and acted upon accordingly.

Table 14: Changing a Single Frontline ARV for Children and Adolescents

Age	Impacted script and ARV	Alternative ARV to use
< 4 weeks	NVP: Develops supersedibility reaction	Use RAL

	AZT: Baby Hb < 9.5 g/dL	Push ARV to 4 months, then start ABC+3TC+LPV/r
4 weeks - < 6 years old	ABC: Develops ABC supersedibility reaction	Use AZT (if Hb ≥ 9.5 g/dL).
	LPV/r: Unable to tolerate LPV/r	Use RAL
	LPV/r: Develops TB	RAL at x2 dose twice daily based on standard weight up to 2 weeks after TB treatment, then continued with standard weight-based RAL dose twice daily (BD)
6 to 14 years (between 20-35 kg body weight)	ABC: Develops ABC supersedibility reaction	Use AZT (if HB ≥ 9.5 g/dL)
	DTG: severe insomnia	Use LPV/r
	DTG: develops TB	DTG 50 twice daily until 2 weeks after TB treatment followed by standard DTG dosage

Table 15: Grass Regulation in Renal Impairments and Hepatitis in Adults

Grass	CrCl (ml/min)		Hemodialysis	Severe liver damage	Comments
	10-50	<10			
ABC	No change			AVOID serious hepatic injury	
AZT	No change	300 mg/day	300 mg/day	Reduce dosage by 50% or double administration interval to moderate to severe injuries	The drug is used only in exceptional situations based on genotype information
TDF	Every 48 hours.	1 pill every 7 days	1 pill every 7 days	An alteration	Do not stop with patients with HBsAg+. If available, consider using TAF in those with>10ml/m.
TAF	No change	No data	No data	No change	
3TC	150 mg OD	50 mg OD	50 mg first dose, then 25 mg daily	No change	Some experts recommend against being based on adjustment/adaptation.
TDF-FTC or TDF-3TC	Every 48 hours.	1 pill every 7 days	1 pill every 7 days		
TAF-FTC or TAF-3TC	Do not use	Do not use	Do not use	No change	
LPV RTV ATV .DRV	No change			No change, use carefully in moderate to severe damage	
DTG	No change			Use it carefully in serious injury.	
EFV	No change			Use it carefully in mild to moderate liver damage, AVOID in serious injury	
NVP	No change			AVOID	Grass should phase out in adults
ETV	An alteration			Use it carefully in severe liver damage.	
CTX	CrCl 15-30 ml/min uses 50% of the normal recommended dose; AVOID if CrCl < 15ml/min			Use it carefully in mild to moderate liver damage, avoid in serious injury	
Fluconazole	If crCl ≤ 50 ml/min then use 50% of the normal recommended dosage			Use it carefully	Monitor hepatotoxicity in older adults and accompanying TB therapy

8. Monitoring of individuals in ARVs

Follow-up involves planned clinical and laboratory appointments, but patients or physicians may need to plan additional clinical evaluations and tests for patients with concerns/complaints, or abnors who need close observation, especially during the following weeks after therapy commences, and with more care in those patients with advanced disease, which present a higher degree of complications. These patients should be monitored for the development of side reactions of the drug, and the barriers to IRIS

adversity and development should be identified and addressed. As a general guideline, it is recommended to monitor patients after 2 weeks and 4 weeks of treatment start, and then monthly until viral suppression.

Patients with confirmed viral suppression can be followed every 3-6 months based on the patient's preference and clinician judgment, and the availability of sufficient supply of drugs to avoid remaining stockless. It is important to carry out the work in such a way that patients do not come to the clinic every month, or even more often.

The table below shows the recommended appointment schedule. Clinicians and patients should be encouraged to schedule additional appointments as needed, whenever an acute issue arises. If an individual does not live near the clinic, doctors should discuss where he/she should seek care in case of acute symptoms or complications, and, ideally, coordinate care with the local provider.

All meetings should include counselling and ongoing adulation support (initiated at the initial visit), evaluation of adulation and correct retention of drugs, assessment and management of early side effects of the drugs and patient counselling on the same visit.

Vital signs and weight must be measured and recorded at each visit. In children and adolescents, length must also be measured and ARV doses confirmed at each visit

Table 16: Clinical and Laboratory Monitoring Summary for People Living with HIV1

	ARV launch	**Weeks (after ARV)**		**Months (after ARV)**					**Every 6 months**	**Comments**
Visits	Day 0	J 2	J 4	m2	m3	m4	m5	M6		
History and physical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adage and support	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Presence of TB symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓	Ask about fever, cough, bad mood, weight loss or night sweating
HIV genotype test	✓	*	*	*	*	*	*	*	*	If available at the beginning and in case of viral failure
CD4 number	✓				✓			✓	✓	Consider 3 months in those with less than 200 CD4s at the start. Patients with CD4>50/mL can be screened annually
Viral Load	✓				✓				✓	In 3 months, >1 reduction of a log-in (BSL) is expected. Additional viral loads may be needed to confirm failure, or after switching.
Pregnancy status	✓	*	*	*	*	*	*	*	*	* At each visit ask about the date of the last appointment and request additional pregnancy tests as needed.
Urine analysis (protein & glucose)	✓				✓			✓	✓	
Routine: hematology, liver function, creatinine, glucose	✓				✓			✓	✓	
Lipid Profile: HDL, LDL, TG, Col T.	✓								✓	
Syphilis (VDRL, TPHA, or RPR)	✓								✓	STIs should be evaluated every six months in sexually active people.
PAP, colpo, mammogram	✓									Repeat every year.

Viral hepatitis serology	✓									In the beginning (BSL) HBsAG, HCV, HAV total IgG. During the follow up, look for antiHBsAg. Repeat HCV in those at risk.

8.1 Identifying individuals at risk of non-adage or requiring special follow-up

Some patients are easily identified as potential non-adhesives based on their previous history of missed appointments, not taking ARV from pharmacy or DIScontinusing ARV for many different reasons. However, when starting ARVs in naive patients, it is important to identify those who may have a higher risk of termination, in order to offer closer follow-up to facilitate early identification and provide additional support. The following individuals may represent a non-exhaustive list of individuals who may usually require additional support to ensure good adulation:

- Individuals with depression or other serious associated illnesses that affect quality of life
- Problematic use of alcohol or drugs
- Age <20
- Unstable housing and lack of social or family support

8.2 ARV reboot

People who re-engage in care after discontinuation of treatment with advanced HIV disease should be offered a comprehensive clinical assessment and a similar package of interventions as advanced naive individuals.

When considering resuming treatment in an individual who presented several interruptions in an NNRTI (non-non-non-non-nonleoside reverse transcriptase inhibitor) is taken– the regimen provider should consider that the likelihood of drug resistance may be high and patients may require more intensive virological monitoring. These patients can switch to the second-line regimen, even when the individual meets the criteria for 2 VL>1,000 copies/ml due to missed lab appointments or lack of access.

8.3 Refilling ARV Prescriptions for Stable Patients

For stable patients, prescription drugs should be made sure to last until the next clinic visit, along with future laboratory requirements in order to avoid unnecessary clinical visits.
ARVs, CPTs and condoms (and ideally any other medication, such as oral contraceptive pills or statins) should be given for 1 month after initiation (to monitor tolerance) and then every 3 months. The clinic should have a system to track ARV intake to identify those who do not adhere to ARV recompletion for active tracking or individuals.

The program should ensure that there is sufficient stock to cover all patients' medicines corresponding to the time a new procurement may last (6 months).

9. Inflammatory Immune Reconstruction Syndrome (IRIS)

Definition: Inflammatory Immune Reconstruction Syndrome (IRIS) is a paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started ARV with reconstruction (improved functioning) of their immune system. The immune system, once it has recovered some functions, is now able to respond against foreign antigens. IRIS represents up to 32% of advanced individuals starting ARVs**.**

Rating:

Unmasked IRIS: the appearance of a previously undiagnosed opportunistic infection (OI) after starting ARV (or switching ARV to a suppressive regimen)

Paradoxical IRIS: exacerbating a previously diagnosed disease after arv onset (or switching ARV to an oppressive regimen)

Risk Factors for IRIS:

- Advanced immunosupression (WHO Phase 3 or 4, or CD4 cell count 200 cells/mm3 (or CD4% ≤ 25% for children ≤ 5 years))
- Patients with an opportunistic infection diagnosed as TB, MAC, CMV and PCP
- Low initial CD4 (CD4 count ≤ 50 cells/mm3 or %CD4 ≤ 10%)
- High initial viral load
- Substantial increase in the number of CD4 and decrease in viral load after arv onset

IRIS diagnostics: IRIS should be suspected every time a patient has clinical deterioration several weeks to months after starting ARV (or switching to an ARV suppressive regimen). Clinical deterioration usually occurs within 4-8 weeks of onset or arv changing (but it can be months after). IRIS has different clinical presentations due to the numerous possible pathogens to which the immune system may respond and various immune system reactions; Generally there are clinical manifestations consistent with an inflammatory condition

A high level of suspicion is required when assigning an IRIS diagnosis, which is usually with exception. It is necessary to exclude the possibility of drug reaction, patient disregard in the treatment of opportunistic infections, continuously active infection and/or resistance of the drug to treatment of opportunistic infection.

The most common conditions associated with IRIS include

Table 17: IRIS, Signs and Symptoms

IRIS Signs /Symptoms	
Main presentations	
Tuberculosis (TB)	Patients responding to TB treatment may have worsening of pulmonary symptoms, X-ray results suggesting worsening of TB disease, enlargement of lymph nodes causing blockage of the airways, or meningeal symptoms. Tuberculome or pericardial effusions are prescribed
	TB-IRIS can also result in hepatotoxicity, which can be difficult to distinguish from the toxicity caused by drugs
	TB-IRIS may occur in undiagnosed MDR (multi-drug resistant) TB-TB patients
***Mycobacterium avium complex* (MAC)**	It can be presented as pulmonary disease or systemic inflammation that is not distinguishable from active MAC
	Atypical appearances may occur, such as localized lymphadenitis or endobronic mass lesia; Osteomyelitis is a late atypical manifestation
	Patients with MAC-IRIS may not have bacteria and may not have known history of MAC diagnosis
Cryptococcal meningitis	It is commonly presented as worsening of meningitis symptoms including possible rapid hearing loss and/or vision, ataxia and/or elevated intracranial pressure

Cytomegalovirus Retinitis (CMV)	It is presented as retinite, vitride or uveit (variable timing, with the average vitritis time of immune reconstruction 20 weeks after arv onset in a study)
	Retinitis is inflammation that is usually at the site of previous CMV retinitis
	Uveitis and vitritis are the presence of inflammatory cells in the eye as a result of IRIS and may help distinguish IRIS from the active cmv retinitis [Karavellas et al. 1999]
	CMV-IRIS in the eye can cause rapid and permanent vision loss
Hepatitis B or C virus	Transient increases in transaminases can occur after ARV starts with immune reconstruction and can be difficult to distinguish from hepatitis caused by drugs.
	Hepatic flare-ups are usually mild and self-limited, but can result in decomposition in someone with preexisting cirrhosis
Progressive Multifocal LeukoencePhalopathy (PML)	PML lesions can be exposed or worsened and may appear as new focal neurological deficits or lesions in MRI
Sacroma Kaposi (KS)	It is a deterioration of KS.
	The cube is the most common appearance. Other signs include lymphedema and oral, gastric, lung, genital or conjunctitive lesia
	Fatal cases of KS-IRIS have been reported
Cerebral Toxoplasmosis	It can present as cerebral abscess (also known as toxoplasmosis encephalitis) or, rarely, diffused encephalitis or corioretinitis
Autoimmune diseases	Existing sarcoidosis may get worse
	Late presentations of Gravet's disease are reported 8 to 33 months after arv onset
Small presentations	
Simple herpes virus (HSV) and zoster varicella virus (VZV)	HSV and VZV can be reactivated after ARV onset, even in patients without the previously diagnosed disease
	Presentations are usually similar to non-IRIS diseases; However, IRIS can worsen a patient's symptoms
Non-specific dermatological complications	A number of dermatological manifestations, such as foliculitis and oral and genital warts, may appear or worsen during immune reconstruction

Patient Assessment: Since IRIS is an exclusionary diagnosis, it is important to carry out all possible assessments to rule out active opportunistic infections or other possible explanations that may justify the symptoms.

Individuals should be assessed and the following data should be recorded in any case of doubt IRIS of the presence of systemic specific symptomatology and time association with ARV initiation, adjective to the ARV regimen, and in particular the base level CD4 and VL. If individuals have a more recent VL and Cd4, a rapid reduction of VL and a significant increase in CD4 may indicate IRIS.

Data regarding the diagnosis and treatment of opportunistic infections are also important to try to identify the lack or adequate response (as an alternative to IRIS diagnosis), resistance or occult OI. Co-infection with TB and a systemic fungal infection, such as cryptococcal disease, is not uncommon. This option should be considered before labeling that the participer presents IRIS.

Table 18: IRIS Management

The severity of IRIS	Definition	Management
Soft	Resolved over time in most patients Symptomatic treatment is often enough	Treat OI and manage accompanying symptoms **Treat inflammation associated with IRIS:** • NSAIDS for mild inflammation/fever • Steroids inhaled for bronchospasm or cough **Surgical intervention:** • Draining of abscesses • Cutting hot and painful lymph nodes

Rough	Threatens a patient's functional condition Causes permanent disability Potentially leading to death **Examples:** Decreased pulmonary capacity from TB or MAC infection Neurological Complications from Cryptococcocal Infection Loss of vision from CMV retinitis infection	Treat OI and manage accompanying symptoms **Manage inflammation associated with IRIS:** • If there is no cryptococcal meningitis or KS: give 1 to 2 mg/kg of prednisone for 1 to 2 weeks. Follow up with a period of individualized dose reduction • Do not use corticosteroids for management of CM or CS-associated IRIS • Closely monitor patients on corticosteroid therapy for: o Hyperglycemia o Hypertension o Changes in mental status o Avascular necrosis o Exacerbating an existing infection o Predisposition to a new infection (p.sh. TB and CMV)

10. Showing and Preventing Specific Infection Opportun

10.1 Prevention and Treatment of Pneumocystis Jiroveci Pneumons

All people living with HIV, children after 6 weeks, adolescents, pregnant women and adults, who have a CD4 number lower than 200 CD4 mm/3 should take (medication) to prevent Jirovecii Pneumonia Pneumonia pneumonia, *Toxoplasma Gondii* encephalitis and other bacterial diseases, unless they have an allergy to sulphate drugs or develop CPT toxicity. For HIV-infected infants, CPT should begin at 6 weeks of age.

Table 19: Daily Dose of Cotrimoxazole Preventive Therapy

Weight (kg)	If you use oral suspension (240mg per 5ml)	If you use a tablet with a single-fold power 480	If you use a dual-power tablet 960 mg
1 – 4	2.5ml	1/4 SS tab	--
5 – 8	5ml	1/2 SS tab	1/4 DS tab
9 – 16	10ml	1 SS tab	1/2 DS tab
17 – 30	15ml	2 SS tabs	1 DS tab
> 30	20ml	2 SS tabs	1 DS tab
Adult (any weight)		2 SS tabs	1 DS tab

Note: If crCl 15-30 ml/min then use 50% of the recommended normal dose; If CrCl <15 ml/min then CTX should be avoided

MANAGEMENT OF PATIENTS WITH ALLERGIES TO COTRIMOXAZOLE

Rash/rash is the most common side event associated with CTP, and occasionally severe. The rash usually develops 7-14 days after the onset of CPT, and is often a mild maculopapular rash with or without pruritus/itching. Rarely, rashes can appear with fever, systemic symptoms, mucus involvement, severe skin exfoliation, and Stevens-Johnson syndrome.

Table 20 Management of Herediti-Bound Skin Rash

Severity	Features	Action
Soft	said; erythym +/- small popules; pruritus; It affects < 50% of the body's surface area.	Continue CTX; Close monitoring; Symptomatic treatment with antihistamy +/- local steroids (NO oral steroids)
Average	said; erythym +/- small popules; pruritus; It affects ≥ 50% of the body's surface area.	Stop CTX; symptomatic treatment with antihistammin +/- local steroids (NO oral steroids); evidence of decreased sensitivity after symptoms are fully resolved
Rough	Severe mucus involvement; bubbles; companion fever; Every percent of the body surface	Stop CTX; hospital admission for supportive management (IV fluids, wound care, pain control, infection control, super-infection monitoring); **The patient should never be re-challenged with CTX or other drugs containing sulphes**. document and report adverse events and issue patient alert/alert card

Decreased sensitivity is effective in most patients with mild to moderate rash and should be proven after the individual recovers fully from the episode of the skin rash.

Table 21: Cotrimoxazole Standard Regimen for Desensitization (8 days)

Day	Dose of TMP/SMX Suspension (40/200 mg per 5ml)
Day 1	0.5ml
Day 2	1ml
Day 3	2ml
Day 4	3ml
Day 5	4ml
Day 6	5ml
Day 7	1 SS tablet
Day 8	2 SS tablets/1 DS tablet per day
Note: For children, continue until they reach the recommended weight-based dose	

Table 22: Rapid Cotrimoxazole Regimen for Desensitization (6 Hours)

Hours	Dose of P/SMX Suspension (40/200 mg per 5ml)
0 hour	0.5ml
Hour 1	1ml
2 hour	2ml
3 a.m.	3ml
4:00	4ml
5 p.m.	5ml
6 hour	1 SS tablet
Note: The rapid desensitization protocol should not be used for children because cumulative dosage will be too high	

DAPSONE AS A SUBSTITUTE FOR CPT

In situations of severe allergy to cotrimoxazole or when desensitization is not successful, dapsone can be used instead of CPT. It is primarily effective as prophylaxis against PJP but does not prevent toxoplasmosis. Dapson causes haemolytic anemia in some patients and can exacerbate anemia, so patients should be monitored every 1-2 weeks for the first two months.
The dose of Dapsone in adults is 100 mg QD and in children 2 mg/kg QD (maximum dose: 100 mg) OR 4 mg/kg once a week (maximum dose: 200 mg) CPT and dapsone may be discontinued after CD4 reaches >200 cells/mm3.

TREATMENT OF PJP

The preferred therapy is CTX in dose 2 DS tablets every 8 hours for 21 days. If the disease is critical, use IV (at 5/25 mg/kg every 8 hours of TMP/SMX). Add prednisone if PaO2<10kPA or <70 mmHg. Prednison should be added 30 min before starting CTX treatment.

Alternative therapy is Primaquine 30 mg every 6 hours + clindamycline 600-900 every 8 oral or IV hours.

10.2 The emergent, prevention and treatment of cryptococcal meningitis (CM)

WHO recommendation:
Cryptococcal meningitis

Diagnosis

For adults, adolescents and children living with HIV suspected to have a first episode of cryptococcal meningitis, immediate lumbar puncture with CSF opening pressure measurement and rapid analysis of cryptococcal antigen as the preferred diagnostic approach is recommended.

(Strong recommendation, moderate-security evidence for adults and adolescents; low-security evidence for children)

Prevention and Depistration

It is recommended the sequestration for cryptococococcal antigen followed by preliminary antifunction therapy in people with antigen-positive cryptococococcal to prevent the development of invasive cryptococcal disease prior to arV onset or reset for adults and adolescents living with HIV who have a number of CD4 cells <100 cells/mm3 (Strong recommendation; evidence of moderate certainty) and can be considered at a higher CD4 cell count threshold of <200 cell/mm3 (conditional recommendation; moderate proof of safety)

All individuals with symptoms of chronic encephalitis (headache, confusion) should undergo lumbar punctures, and geneXpert CSF for TB should be performed simultaneously, as well as TB-LAM urine. All adults and adolescents living with HIV with a baseline CD4 number of 200 cells/mm3 or advanced HIV infection, should be screened for cryptococcal infection. In addition, all individuals with clinical suspicion of C should perform a cryptococcal check. Asymptomatic people living with HIV with CrAg positive should be offered a lumbar puncture to determine if they have cryptococcal meningitis. If the crAg in the serum is positive but CSF is negative, extrameningeal infection is confirmed and the individual should receive pre-treatment with fluconazole 800 mg/day for two weeks followed by 400 mg/day for eight weeks, followed by fluconazole 200-mg/day maintenance therapy.

If CrAg is CSF positive, CM is confirmed and combination antifungeal therapy should be initiated immediately. Liposomal amphotericin B is preferred over amphotericin B deoxychollate, since liposomal amphotericin B has demonstrated equivalent efficacy and better safety compared to conventional amphotericin B deoxychollate form. However, access to liposomal amphotericin B is limited due to its high cost.

WHO Recommendation: Treatment of Cryptococcal Meningitis
Induction
Preferred induction regime: • For adults, adolescents and children, a short-coursed (one week) induction regimen with amphotericin B deoxycholine (1.0 mg/kg/day) and flucitosis (100 mg/kg/day, divided into four doses per day), followed by 1 week fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents, up to a maximum dose of 800mg per day), is the preferred option for treating cryptococococcal meningitis in people living with HIV (strong recommendation, moderate safety evidence for adults, low-security evidence for children and adolescents) **Alternative options depending on the availability of the bar:** Two weeks of fluconazole (1200 mg per day for adults, 12 mg/kg/day for children and adolescents) + flucitosin (100 mg/kg/day, divided into four doses per day) (strong recommendation, evidence of moderate safety). • Two weeks of amphotericin B deoxychools (1.0 mg/kg/day) + fluconazole 1200 mg per day for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg per day (strong recommendation, evidence of moderate safety).
Consolidation
Fluconazole (800 mg per day for adults, 6-12 mg/kg/day for children and adolescents up to a maximum of 800 mg per day) is recommended for the consolidation phase (for eight weeks after the induction phase) (strong recommendation, low-security test).
Maintenance
Fluconazole (200 mg per day for adults, 6 mg/kg/day for adolescents and children) is recommended for maintenance phase (strong recommendation, high-security evidence)
Arv start time
It is not recommended to start arvarians for adults, adolescents, and children living with HIV who have cryptococcal meningitis due to the risk of adult mortality and should be postponed 4-6 weeks from starting antifungal treatment. (Strong recommendation, low-risk testing for adults and very safely test children and adolescents)

The toxicity of the drug and side effects from amphothyricin B therapy, especially hypochalemia, nephrotoxicity and anemia, are frequent. Hydration, electrolyte supplementation and hematological and kidney monitoring is required when using Amphotericin. Therapeutic lumbars are a critical component of CM management and the procedure should be performed daily for patients with symptomatic CM. Lumbar punctures should aim to decrease 50% daily and continue daily until they reach values less than 20 cm for 3 consecutive days.

10.3 Prevention, diagnosis and treatment of tuberculosis

All PLHIV should receive counselling on the risk of taking tuberculosis, strategies for reducing TB exposure, recognizing clinical manifestations of TB and seeking care promptly. All individuals should be trained on the cough label for reducing the risk of transmission of tuberculosis to others and on the need to achieve adequate intake of preventive tuberculosis therapy.

Healthcare settings present adequate conditions for TB transmission, especially in vulnerable individuals such as people living with HIV. All healthcare facilities should develop and implement TB infection control guidelines to reduce the risk of TB transmission among patients, visitors and staff.

TB SCREENING FOR PEOPLE LIVING WITH HIV (PLHIV): INTENSIFIED CASE FINDING (ICF)

Tuberculosis screening and prevention services should be provided to all patients at every clinical visit and all household contacts of active TB patients. Tuberculosis-based symptom-based detection in children includes cough, fever, lack of vitality, or poor weight gain, lethargy, less mood than usual, and in adults coughing of any duration, fever, visible weight loss and night sweating.

Who's Recommendations: Tuberculosis
The exception of active TB
Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of actual cough, fever, weight loss or night sweats are unlikely to have active tuberculosis and should be offered preventive treatment, regardless of their status on arv. (Strong recommendation, moderate quality evidence.) Chest X-rays can be offered to persons living with HIV and ARV and preventive treatment given to those who have no abnormal X-ray findings. (Recommended conditional, low quality evidence.) Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of actual cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases that cause the symptoms. (Strong recommendation, moderate quality evidence.) Infants and children living with HIV who have poor weight gain, fever or actual cough or who have a history of contact with a TB case should be evaluated for TB and other diseases that cause such symptoms. If the assessment does not indicate TB, these children should be offered preventive treatment, regardless of their age. (Strong recommendation, low quality evidence.)

Regardless of the above, all HIV individuals in close contact with a TB case should be evaluated for active diseases. If TB is excluded, and latent TB is confirmed, all individuals should be evaluated for preventive therapy with izoniazid (IPT). Given the low incidence of TB in Albania, it is considered that latent tuberculosis infection (LTBI) should be documented before initiating IPT using a Skin Tuberculosis Test (TST, PPD or Mantoux) or interferon-gamma release analysis (IGRA). Terthary cutting for PPD should be considered 5mm. It is important to take into account the high incidence of anergy among those with advanced disease, therefore, these studies should be repeated after arvings are started periodically.

Revised IGRAs (QuantiFERON-TB® Gold In-Tube and T-SPOT®). TB) does not provide strong evidence that these tests should be preferred over TST. The benefit of IRRs is to receive samples at the same time as testing for viral loads or other lab-based studies. TST is less expensive but requires a cold chain, two healthcare visits and training in carrying out and reading this intradermal injection.

Who's Recommendations: Tuberculosis
Testing for latent tuberculosis infection

An TST or IGRA can be used to test for Latent TB Infection (LTBI). (Very good advice, very low quality evidence.)

People living with HIV who have proved LTBI positive benefit more from preventive treatment than those who have come out negative for LTBI; LTBI testing may be used, where possible, to identify such individuals. (Strong recommendation, high quality evidence.)

LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or in the family contacts of children aged <5 years. (Strong recommendation, moderate quality evidence.)

TUBERCULOSIS (TB) PREVENTION:

Isoniazid-based therapy is the most common treatment used in the treatment of Latent TB Infection, but the WHO also considers alternative regimens.

Who's Recommendations: Tuberculosis
Treatment of Latent TB Infection
Monotherapy with aziazid for 6 months is recommended for the treatment of LTBI in both adults and children in high and low TB incidence. (Strong recommendation, high quality evidence.) 9 months of izoniazid, or a three-month regimen with rifapantin every week, plus izoniazid, or 3-4 months of zozoazid plus rifampicin, or 3-4 months only rifampicin may be considered as alternatives. (Strong recommendation, high quality moderate evidence.) IPT should also be given regardless of the degree of immunosupression, history of prior TB treatment and pregnancy. (Recommended conditional, low quality evidence.) In selected high-risk home contacts of patients with multi-drug resistant tuberculosis, preventive treatment can be considered based on individualized risk assessment and a sound clinical justification. (Recommended conditional, very low quality evidence.)

Indications for Isoniazid Inhibitory Therapy (IPT): IPT should be provided to patients in whom TB is excluded and meets the acceptance criteria to initiate IPT:

- All people living with HIV over the age of 12 months (children and adults including pregnant and breastfeeding women) with TST>5mm and whose control proves negative for active TB
- All children under 5 years of age, regardless of HIV status, who have had close contact recently with positive swp tuberculosis disease, without any evidence of active TB
- Prisoners who are negatively tested for active TB (regardless of their HIV status)

Contraindications to IPT: Patients with the following should not receive IPT until the underlying problem is addressed

- Active tuberculosis disease
- Active hepatitis B or C
- Symptoms of peripheral neuropathy
- Poor clinical appointment adjecence or CTP, ARV.
- He has completed a full IPT course.
- Exposure to MDR or XDR TB

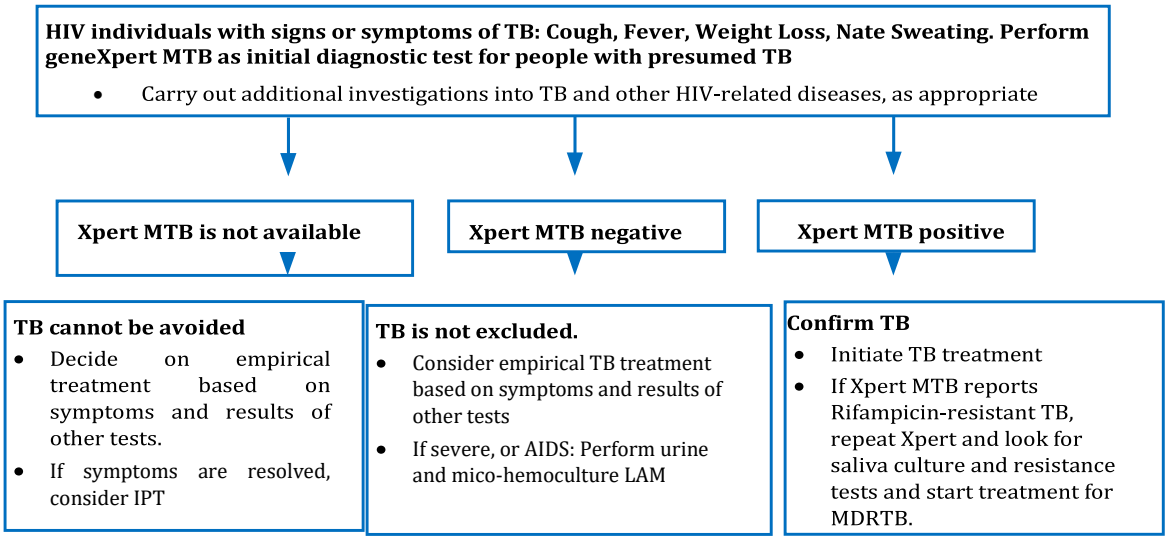
Dosage and duration of Isoniazid: IPT should be administered once in a lifetime for 6 calendar months. The dose is 5mg/kg/day, for adults and children older than 5 years. In children under 5 years of age, 10mg/k/d (range 7.5-15) should be used. Children using IPT should be weighed at each visit and correct weight-based dosing confirmed. Pyridoxin should be added daily to reduce the risk of developing peripheral neuropathy.

Patient Adherence to IPT: Patients should be looked at monthly to identify hepatotoxicity and to review/reinforce adherence. At each visit, ask about TB symptoms and monitor for INH side effects, including gastrointestinal symptoms, hepatitis, rash, and peripheral neuropathy. IPT should be immediately discontinued if symptomatic with liver enzymes >3ULN, or if it is asymptomatic with liver enzymes >5ULN. Monitor each week until it is resolved.

DIAGNOSIS OF TUBERCULOSIS

For People Living with HIV who have presumed TB, gene Xpert MTB/Rif analysis is the preferred testing platform to confirm diagnosis, with TB-LAM being used as an additional bedside test for critically ill patients or with advanced HIV infection.

Figure 6: Diagnosis of tuberculosis



[Additional] tests include chest X-rays, TC, TST or IGRA scans and depending on symptoms, thin needle aspiration of lymph nodes, pleur effusion analysis, ADA, sputum smear analysis for rapid bacil acid, and culture.
[B] TST positive or IGRA in individuals with fever or detection in X-ray or TC scans should promote empirical treatment and assess the response after 2 months.

WHO recommendations: TB diagnosis

Xpert-MTB [17]

Xpert MTB/RIF should be used in place of conventional microscopy, culture and DST as initial diagnostic tests in adults suspected of having MDR-TB or HIV-related TB (strong recommendation, high quality evidence).

Xpert MTB/RIF should be used in excess of conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (strong recommendation, very low quality evidence).
Xpert MTB/RIF can be used rather than conventional microscopy and culture as the initial diagnostic test in all adults suspected of having TB (conditional recommendation acknowledging resource implications, high-quality evidence).
Xpert MTB/RIF can be used more than conventional microscopy and culture as the initial diagnostic test in all children suspected of having TB (conditional recommendation acknowledging resource implications, very low quality evidence).
Xpert MTB/RIF may be used as a follow-up test for microscopy in adults suspected to have TB but are not at risk of MDRTB or HIV-associated TB, especially where further testing of sputa-negative specimens (conditional recommendation recognising resource implications, (High quality evidence).

[17] Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of TB and resistance to rifampicin: Xpert MTB/RIF analysis for diagnosis of pulmonary and extrapulmonary TB in adults and children https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf?sequence=1

Xpert MTB/RIF should be used in preference to microscopy and conventional culture as initial diagnostic test for CSF samples from patients suspected of having TB meningitis (strong recommendation given the urgency of rapid diagnosis, very low quality testing).
Xpert MTB/RIF may be used as a replacement trial for common practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory samples (lymph nodes and other tissues) from patients suspected of having TB outside the lungs (conditional recommendation, very low quality evidence).

LAM[18]

In hospital settings, WHO strongly recommends the use of LF-LAM to help diagnose active tuberculosis in HIV positive adults, adolescents and children:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) (strong recommendation; moderate safety in trials) or
- with advanced HIV disease or who are seriously ill (strong recommendation; moderate safety in evidence); or
- despite the signs and symptoms of TB and with a CD4 cell number less than 200 cells/mm3 (strong recommendation; moderate safety in the trials).

In outpatient settings, WHO suggests using LF-LAM to help diagnose active TB in HIV-positive adults, adolescents and children:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (conditional recommendation; low safety in trials) and
- despite the signs and symptoms of TB and with a CD4 cell count less than 100 cells/mm3 (conditional recommendation; very low safety in the trials).

In outpatient settings, WHO recommends that LF-LAM should not be used to help diagnose active tuberculosis in HIV positive adults, adolescents and children

- without evaluating TB symptoms (strong recommendation; very low certainty in evidence about the accuracy of the test)
- no TB symptoms and unknown number of CD4 cells or no TB symptoms and number of CD4 cells greater than or equal to 200 (strong recommendation; very low evidence evidence for accuracy of the test) and
- no TB symptoms and with a CD4 cell count of 100-200 cells/mm3 (conditional recommendation; very low certainty in the evidence about the accuracy of the test)

TREATMENT OF TUBERCULOSIS SENSITIVE TO THE DRUG

In patients with HIV and drug-sensitive pulmonary TB, the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen. It is preferable to use fixed-dose tablets (FDC) over specific drug formulations and daily doses remain the frequency of preferred doses.[19]

ARV FOR ASSOCIATED TB/HIV INFECTION

As with all individuals with HIV, those diagnosed with TB/HIV co-infection should start ARV once anti-TB medications are tolerated, preferable within 2 weeks. For TB meningitis consider postponing ARV 5 weeks after starting TB treatment. All patients should be monitored for the development of IRIS and monitored closely for toxicity. MDR-TB should be managed in environments with experience in managing these cases.

Individuals may receive:

- EFV-based HIV treatment (plus 2 NRTI) without requirement adjustments

[18] Analysis of side flow of lipoarabinomanane of urine (LF-LAM) for the diagnosis of active tuberculosis in people living HIV Policy update (2019).
https://apps.who.int/iris/bitstream/handle/10665/329479/9789241550604-eng.pdf?sequence=1&isAllowed=y&ua=1

[19] Guidelines for treatment of herb-sensitive tuberculosis and patient care UPDATE 2017
https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1

- DTG plus 2 NRTI plus using an additional dose of dolutegravir (DTG 50mg BD) to offset the induction effects of CYP450 enzymes from rifampicin.
- Regimen based on Ritonavir or Cobicistat plus a rifabutin-based anti-TB therapy (rather than rifampicin). Rifabutin should be at 150mg/QD dose.

Rifampicin should not be used with ritonavir, cobicistat or TAF. Raltegravir and dolutegravir can be used by adjusting the dosage (RAL 800mg BD and DTG 50mg BD).

Table 23: ARV Replacement for TB Treatment

Current regime	Age	Recommended Replacement
Based on - RAL	All ages	Give double the standard dose of RAL up to 2 weeks after completing rifampicin-based TB treatment, then reduce to the standard weight-based dose, or switch to DTG BID.
Based -DTG	All ages	Give TDF/3TC/DTG FDC am + DTG 50mg pm for the duration of treatment of rifampicin-containing TB treatment and for 2 weeks after TB treatment has ended, then return to TDF/3TC/DTG FDC OD
Based on PI	< 3	Reinforce LPV/r with additional RTV (additional with ritonavir up to 1:1 ratio) After completing TB treatment return to the recommended **first-line regimen (ABC + 3TC + LPV/r)**
	3 years – 5 years (and < 20 kg body weight)	Reinforce LPV/r with additional RTV (extra with ritonavir up to 1:1 proportion) After completing TB treatment return to the recommended **first-line regimen (ABC + 3TC + LPV/r)**
	≥ 6 years old (**or** ≥ 20 kg body weight)	Switch from PI/r to DTG and continue this regimen even after completion of TB treatment (give DTG 50 mg BD for the duration of the treatment of tuberculosis containing rifampicin, then reduce to DTG 50 mg QD 2 weeks after the tuberculosis treatment has ended) For women and adolescent girls with birth potential continue PI/r (with rifabutin-based anti-TB treatment) instead of DTG
EFV-based	Every age	Continue the same regimen for the duration of TB treatment. Take into account for optimizing the regimen with DTG after the completion of TB treatment
NVP-based	< 3	Change NVP to LPV/r.Reinforce LPV/r with additional RTV. After completing TB treatment switch to **the recommended first line regimen (ABC + 3TC + LPV/r)**
	≥ 3	Switch to EFV If ≥ 6 years old or ≥ 20 kg switch from NVP to DTG and continue this regimen even after completion of TB treatment (give TDF/3TC/DTG FDC am + DTG 50mg pm for the duration of the treatment of tuberculosis containing rifampicin and for an additional 2 weeks after tuberculosis treatment has ended, then return to TDF/3TC/DTG FDC OD)

Always assess for hiv treatment failure in patients who develop TB after being on ARV for ≥6 months. If the patient is on the front line, with detectable VL and history of non-adversity, an early transition to a second-line DTG-based regimen is recommended.

10.4 Viral Hepatitis A

Hepatitis A is a liver disease caused by the hepatitis A virus (HAV). The virus primarily spreads when a non-immune person (unvaccinated or uninfected before) receives food or water contaminated with the faeces of an infected person. The disease is closely related to unsafe water or food, inadequate hygiene, poor personal hygiene and oral-sex. Unlike hepatitis B and C, hepatitis A does not cause chronic liver disease and is rarely fatal, but can cause depletive symptoms and full hepatitis (acute liver failure), which is often fatal. In Albania, serology for HAV is very high among the general population and several outbreaks have been reported. Globally, some reports indicate that HAV disproportionately affects MSM individuals. Therefore, all MSM individuals with HIV should be assessed to identify their immune status and vaccinated if there is no evidence of infection in the past. All individuals with HIV with associated HBV and HCV infection should also be vaccinated.

10.5 Viral Hepatitis B

HIV and HBV have a common pathway to transmission. HIV infection has a profound impact on almost every aspect of the natural history of HBV infection. Acute HBV infection in HIV positive people is associated with increased risk of chronic disease, decreased chances of spontaneous cleansing, higher replication and reactivation rates, and therefore increased incidence of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). Furthermore, HIV/HBV co-infection has been associated with rapid HIV disease progression and poorer HIV treatment outcomes. Other complications of HIV/HBV co-infection include increased incidence of drug-related hepatotoxicity, and ARV-related immune reconstruction hepatitis. In Albania, HBV vaccination programs in newborns and people who inject drugs (PWID) began in 2000, with a significant impact on reducing new cases in children and adolescents. In the 2005 BIO BSS survey the prevalence of HBsAg+ among MSM was 17%, but the country reported a significant and steady decrease in new hepatitis cases.

Checkup: All adolescents and adults living with HIV (plus children who did not perform routine immunisations in childhood) should be screened at the first visit for HBV infection, using HBsAg (which is also available as a rapid test), as part of the initial assessment. If available, HB and anti-HB punctuation can also be used for identifying previous infection or immunity. In addition, while following individuals with HIV with signs of liver disease (jaundice, ascites, abnormal liver at touch, other signs of cerosis) or unexplained and persistent alt-alt uptension should also be screened for HBV as part of their work.

Prevention: all non-immune HIV individuals (anti-HBs <10 UI) should receive HBV vaccination. If anti-HBs is not available, all individuals with negative HBsAg should be vaccinated. As a strategy to reduce the population-level burden of HBV infection, HIV prevention and treatment facilities should integrate HBV prevention through vaccination. Thus, HBV vaccination is also recommended for high-risk groups like MSM, incarcerated individuals, individuals with HCV, healthcare workers, drug users, sex workers, infants and young children, domestic and sexual contacts. General infection prevention measures adopted for people living with HIV and in healthcare settings are effective in preventing HBV transmission. These include hand hygiene, personal protective equipment in the healthcare environment, adequate management of medical waste including the safe disposal of sharp tools used, disinfection and sterilization, harm reduction counseling and services for people who inject drugs, and safer sexual practices.

ARV therapy for individuals with HBV: the same recommendations for treatment preparation, counseling for accession and support and monitoring of ARV are applied to these patients. However, all HBVs should take TDF/3TC (or FTC) as a backdrop, as single 3TC will result in rapid resistance display. Therefore, before starting a regimen with ABC-3TC plus a third bar or a dual therapy with DTG+3TC it is necessary to confirm that patients do not have chronic HBV. In case of kidney damage (as assessed by creatinine clearance), the dose of TDF and 3TC should be adjusted and/or considered taf use. TDF or TAF should be continued in case the patient has to switch to the second or third coming.

Follow-up monitoring: Hepatic eruptions (AST> 5 times normal value) can occur, often in the initial 3 months such as IRIS, and these erections can be tolerated as long as the patient is not severely symptomatic, remains stable without progression and there is no evidence of synthetic dysfunction (normal INR, normal glucose, normal albumin). Laboratory monitoring after initiation should be performed every six months. Patients should be advised and supported not to consume alcohol. The appearance of hepatitis can also occur in the event of stopping TDF or TAF, therefore these patients should be advised against discontinusing arv. TDF achieves 86% HBV suppression in 3 years.

Who's Recommendations: Hepatitis B[20]
Monitoring
It is recommended that the following be monitored at least every year: • Alt (and AST levels for APRI), HBsAg, HBeAg, antiHBe and HBV DNA levels) • Non-invasive tests (APRI or FibroScan result) to assess the presence of cirrhosis, in those without cirrhosis at first; • The adage should be monitored regularly and at every visit. (Strong recommendation, moderate evidence quality)

The most frequent monitoring (every 3 months) is indicated in persons with advanced disease (compensated or decompensated cirrhosis); during the first year of treatment to assess the response and adulation of treatment; where access to treatment is disturbing; and people after discontinus of medication. Decomposed cirrhosis is determined by the development of portal hypertension (ascites, varicular hemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice).

10.6 Accompanying viral hepatitis C infection

In Albania, there is little information about the prevalence of HCV. In the 2011 BIO BSS survey conducted among people who inject drugs the prevalence of HCV was 26.5% suggesting a dramatic increase compared to previous years. The general population also sees a prevalence of 2.8. The genotypes circulating in Tirana are 1b (50%), 2c (18%), 4a (14%), 3a (8%) and 1a to 6%[21].

Hiv/HCV is associated with rapid progression of liver fibrosis, higher risk of liver disease worsening even in the presence of controlled HIV disease, worsening hepatotoxicity as a result of ARV and other drugs used in the treatment of associated diseases. Thus, HIV positive persons at risk of HCV-accompanying infection should be identified and offered HCV treatment. The recent introduction of direct-acting antiviral therapies (DAA) for the treatment of HCV has simplified the management of HIV/HCV associated infection; enabling safe management of uncomplicated HIV/HCV infection.

Prevention: Provide access to harm reduction programs for people who inject drugs and educate on the risk of needle separation, injection tools during recreational drugs and/or steroid use. However, advocate for safer sex and provide accurate, accessible and tailored information to increase awareness and knowledge of HCV on HCV transmission routes and clinical complications. Provide accessible HCV testing for people at risk and connect with appropriate care for those infected with HCV to reduce ongoing HCV transmission.

Screening: HCV testing, with lab-based serology or rapid testing, should be offered to all individuals with HIV. HIV-negative individuals should be screened based on risk, in particular:

- People who currently or in the past inject any kind of drug, including steroids and psychoactive substances.
- People who exchanged sex for money, goods or favors
- People with a history of needle injury where the source was known to have hepatitis C or injected drugs.
- Men who have sex with men who have additional risk factors including the ratio of

[20] Guidelines for prevention, care and treatment of people with chronic hepatitis B infection. https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf;jsessionid=F4AC9A7231410650FF09CD06F5AA408A?sequence=1

[21] Haldeda M, Baume J, Tamalet C, Bizhga M, Colson P. Hepatitis C Genotips in Tirana, Albania. Int J Infect Dis. 2014 Jan;18:90-3. doi: 10.1016/j.ijid.2013.08.015. Epub 2013 Oct 2. PUBMed PMID: 24169401.

traumatic sexual practice (p.sh. punching), diagnosis of venereum lymphognuloma or syphilis, hepatitis C infection resolved or previously treated, involvement in 'chemsex'.
- Recipients of suspected unsafe blood products (p.sh. before 1990)
- Current and past prisoners.

Confirmation and monitoring: RNA is necessary for confirmation of HCV infection among individuals with reactive serology or rapid HCV test.

Who's recommendation: Hepatitis C[22]

Viraemic infection detection
Directly after a reactive result of the HCV antibodies serological test, it is recommended to use quantitative or quality NAT for detecting HCV RNA as the preferred strategy to diagnose viraemic infection. (Strong recommendation, moderate/low quality of evidence)

Evaluation of HCV treatment response
Nucleic acid testing for qualitative or quantitative detection of HCV RNA should be used as a cure test at 12 or 24 weeks (d.m.th. sustained virological response [SVR12 or SVR24]) after the completion of antiviral treatment. (Conditional recommendation, moderate/low quality of evidence)

Evaluation of liver fibrosis and cirrhosis rate
In limited-resource areas, it is suggested that the aminotransferase/platelet ratio index (APRI) or FIB-4 tests be used to evaluate hepatic fibrosis than other non-invasive tests requiring more resources such as elastography or fibroTest. (Recommended conditional, low quality of evidence)

Hiv/HCV companion infection treatment: HCV treatment evolved quickly and currently, there are several possibilities that achieve HCV healing.

Table 24: Recommended DAA for HCV Treatment (Based on WHO and EACS Guidelines)

Genotype	DaA regime*	Duration of treatment		
		Non-cirrotic	Compensated cirrotic	Decompensated Cirrotic
1 & 4	Glecaprevir (GLE)/Pibrentasvir (PIB)	8 weeks	12 weeks	Not recommended
	Sofosbuvir (SOF)/Velpatasvir (VEL)	12 weeks	12 weeks	12 weeks + RBV
	SOF/Daclatasvir (DCV)	12 weeks +/- RBV	12 weeks + RBV	12 weeks + RBV
2	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/VEL	12 weeks	12 weeks	12 weeks + RBV
	SOF/Daclatasvir (DCV)	12 weeks	12 weeks	12 weeks + RBV
3	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/VEL+/- RBV	12 weeks	12 weeks + RBV	12 weeks + RBV
	SOF/Daclatasvir (DCV)	12-24 weeks	24 weeks + RBV	24 weeks + RBV
5 & 6	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/VEL	12 weeks	12 weeks + RBV	12 weeks + RBV
	SOF/Daclatasvir (DCV)	12-24 weeks	12 weeks + RBV	24 weeks + RBV

[22] Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection. Geneva: World Health Organization; 2018. https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ay_ua=1

Factors such as cirrhosis, prior treatment or the existence of NS5A mutations require that The RBV is added to most scenarios. If rbv cannot be used, otherwise, it can Longer treatment is required. Genotype 3 may require increasing the duration of GLE/PIB treatment to 16 weeks and 24 months SOF/DCV. The main goal of treatment is the sustained virological response (SVR) at 12 weeks after the end of therapy. Patients should continue surveillance for HCC (hepatocellular carcinoma).

11. Maintenance of Health

11.1 Immunisations

All children, regardless of HIV status, should be immunized following the national plan, with some exceptions for babies with severe immunosupression.
Adolescents and adults should check their vaccination card to ensure they have full coverage of Hepatitis A, Hepatitis B, Neumokokal disease, Influenza, HPV (before 26 years) and diphthria (DT).

Table 25: Vaccinations in HIV-Living Children and Adolescents and Adults

Infection	Planning	Use in children with HIV	Comments
BCG	East;	No	Among those exposed, wait until the second PCR excludes HIV before establishing vaccination.
DT	6 years;	Yes	Every 10 years in adults
DTP	2 years;	Yes	

DTePHibHepB	2, 4, 6 months;	Yes	
HepB	birth;	Yes	Make sure everyone is immunized.
IPV	2, 4 months;	Yes	
MMR	1, 5 years;	According to CD4	Use only in those with CD4>15% or>200 cells/mm3 in those aged 5 .
OPV	6 months; 2, 6 years;	No	It is contraindicated in children HIV and domestic contacts. Use IPV
Rotavirus	2, 4, 6, months;	?	Limited data available
Td	14, 18 years;	Yes	
Hepatitis B	East, complete 3 do	Yes	Check the status in all adults with HIV and show the full series if it is not immunocompromised
Pneumococcal conjunction 13	2, 4, 6 months	Yes	3 separate doses >8 weeks apart
Pneumococcal polysaccharide 23	1000	Yes	1 dose >8 weeks of PCV13
Human Papillion Virus (HPV)	Before sexual debut	Yes	Three doses are given for 6 months in 11 years (before sexual debut) to 26 years if they have not been vaccinated before.
Influenza	After 6 months	Yes	Every year. Do not use weakened live vaccines. Use the inactivated vaccine. In <9 years, use 2 doses separated by at least 4 weeks.
Hepatitis A	12 months or later	Yes	2 doses
Yellow fever	Travel	On request	Contraindicated for children <6 months and AIDS. Use only in patients <60 years old and CD4> 200 cells/mm3

11.2 Detection for children and adolescents

Current evidence presents mixed findings on the impact of detection, with some studies showing benefits, others risks, and yet others showing no mental health differences among young people who know and do not know their diagnosis. However, there is evidence that secrets kept in a family are associated with unhealthy adaptations, and there is a very strong clinical consensus that patients and their families benefit from disclosure (open diagnosis). Carers are the primary reason for not being disclosed, because of concern that disclosing them would be a burden, lead to depression and fear about the questions this might cause.[23] One study showed that hiding diagnosis was associated with increased internal behavioral problems and psychological adjustment problems in children as well as increased psychological distress of the caregiver[24], and another study that children who knew their diagnosis reported significantly lower scores on measures of depression and anxiety than children who did not know their[25] diagnosis.Diagnosis is available when children are "ready". The concept must move from a binary static moment to the idea of participating in a dialogue, and an evolving discussion process that should reflect a child's developmental understanding of illness and health. Partial detection is often seen as appropriate when children are younger and the specific name of the disease may not make sense to them, or be important enough to help them face their fears about symptoms and drugs. Full disclosure should be finalised pre-teen and sexual debut in order to allow them to make informed decisions and choices. This could have public health implications, as many perinatally infected adolescents live with multi-drug resistant viruses, the result of inadequate adherence and years of partially suppressive therapy creating the potential for transmission of ARV-resistant strains of the virus to others. Making decisions about sexual behavior and respecting complex lifestyle-

[23] Flanagan-Klygis E, Ross LF, Lantos J, et al. Detection of HIV diagnosis in pediatrics. J Clin Ethics. 2001 Summer;12(2):150–157.
[24] Bachanas PJ, Kullgren KA, Suzman Schwartz K, et al. Predictors of psychological adaptation in school-aged children infected with HIV. J Padiatr Psychol. 2001; 26: 343–352. Creo que me voy a salir más a mi hermano usted **** madre mi hermana se no se debe pensar que yo y me quiero sacar a mi hija encima yo creo que estoy bien tranquila podrías verte viejo y sin nada o sea una realidad
[25] Riekert KA, Wiener L, Battles HB. Predicting psychological distress in school-aged children with HIV. Child health care. 1999;28:201–220.

disrupting regimes can be a difficult challenge for anyone, but especially for young people.

Table 26: Suggested Time Period and Actions for Diagnostic Detection

Age	Phase	Action
0 - 4 year old	Not to diagnose	Reinforce the importance of adulation
5 - 8 year old	Partial diagnosis detection	Partial disclosure is the term used to describe situations in which children are given little but not all information about their illness. They may be informed of the need to take medicines in order to keep their virus or disease away; Without learning that their virus or "disease" is called HIV or AIDS. For example, a child may be told that he/she needs to take pills so that blood soldiers are more efficient at fighting germs." When full disclosure occurs, children are told the name of the disease (HIV and/or AIDS), disease-specific information (p.sh., how the virus works, how it is transmitted) and how they contracted the disease.
9 to 12 years old	Gradually move on to full disclosure. Change the idea of discovery from a single event to an individualized, dynamic and gradual process of communicating information about health, disease and lifestyle.	Before supporting families to move on to full disclosure: • Guide carers with specific considerations about a child's ability to understand information and cope with the knowledge they are infected with HIV. • Assess the caregiver's abilities to cope with the stress of disclosure, the ability to seek help when needed, and the ability to discuss other stigmatized family secrets that may be related to revealing a child's HIV diagnosis. If a child or caregiver is simultaneously experiencing significant stressors unrelated to the disease, it may not be the best time for detecting a diagnosis. Caregivers in severe depression or anxiety may need to address their mental health needs before they can begin the discovery process. • Help families rehearse and prepare for actual discovery: Role-playing for a discovery scenario with a counseling professional, when medically appropriate, and being able to communicate a sense of hope and optimism about their child's prognosis and future has been found helpful. Other families who have been through this situation can help. • Connect them to sources of support as this is linked to better results. Each family will need to turn to other important people in their lives for continued support. Encourage them to maintain a constant open communication. Follow the next stages in the discovery process. The provider can assist in the process that assists the caregiver in: • Evaluation of the child's social support system to ensure the availability of sufficient support once the disclosure is completed • Evaluate a child's previous knowledge about HIV, including information provided to school, any myths and misunderstandings. Providing or reinforcing accurate information • Using an imaginative exercise or story to assess a child's response to discovering HIV status • Finally, tell the child about their HIV status. Support parents to find out about the infection and explain the way the infection is. Addressing immediate reactions and concerns a child may have
	After the discovery (1-2 weeks after full disclosure)	Find out if they have noticed anything after discovery, p.sh. behavioral change. Encourage your child to tell his story and come out as a hero (a comic book can be helpful). Connect your child to a support group or an older child whose diagnosis has been revealed.

11.3 Family Planning and Pre-Conception Counseling

The purpose of pregnancy should be determined for all women of reproductive age and their partners in order to ensure proper family planning or pre-conception counselling. At each visit, pregnancy status should be determined (based on the history of the last menstrual period, and the urine test if necessary).
For patients who do not have an immediate desire to become pregnant, double contraception should be provided immediately with follow-up appointments planned to ensure non-stop in the provision of contraception.
For patients who intend to become pregnant, the main pre-conception messaging and services are displayed in the Tablet.

Table 27: Key Advocacy Messages and Pre-Conception Services

Script	Key messages of counseling	Pre-conception services
All couples who want to conceive	Delaying pregnancy until it is confirmed that viral suppression reduces the risk of vertical transmission to the baby, improves baby outcomes and reduces the risk of transmission to the sexual partner. Untransmittable = Untransmittable. Partners with HIV require a 6 month period after starting treatment and confirming unwoven VL to engage in unprotected sexual activity.	ARV for all PLHIV, including those intending to get pregnant: Initial investigations Syphilis control Cervical cancer screening Controlling STI symptoms Evaluation, counselling and nutrition support Folic acid supplement Standard VL after 6 months on ARV to confirm viral suppression
Additional Messages for Discord couples: male HIV+ partner	Postpone unprotected sex until viral suppression is confirmed in the PARTNER. Discuss using PrEP for hiv-negative partner for the first 6 months after arv onset. In situations where viral suppression is challenging, consider referring to a specialist for additional options like sperm washing and artificial fertiation.	
Extra messages for discordant couples: female PARTNER HIV+	Postpone unprotected sex until viral suppression is confirmed in the PARTNER. Discuss using PrEP for hiv-negative partner for the first 6 months after arv onset. Discuss self-insemination during the peri-ovulation period, when appropriate/as preferred. In situations where viral suppression is challenging, consider referring the specialist for additional options like p.sh.artificial insemination with sperm washing.	

11.4 Prevention and Control of Non-Infectious Diseases

Control, prevention and management of specific non-communicable diseases should be a regular component of HIV care due to their associated immunity and mortality. HIV individuals are at higher risk for cardiovascular, liver and kidney diseases due to chronic inflammatory condition associated with HIV infection itself and other viruses such as HCV or HBV, microbial dislocation, incompetent immune reconstruction.

Traditional risk factors for cardiovascular disease include: tobacco use and exposure to tobacco products, arterial hypertension, dyslipidemia, diabetes, obesity, physical inactivity, family history of cardiovascular disease, older than 45 for men and 55 for women. Lifestyle modifications are always the first line of prevention and management of hypertension, diabetes mellitus and dyslipidemia. These are recommended for all patients to prevent cardiovascular disease and should be integrated into routine HIV treatment and prevention. For comprehensive guidelines on prevention, diagnosis and management of non-communicable diseases, refer to the National Guidelines on Non-Communicable Diseases or the 2019 EACS Guideline.

Table 28: Life Style Modifications to Prevent and Manage Cardiovascular Disease in PLHIV

Smoking Cessation
For individual smokers, assess at each visit the willingness to quit. Tobacco addiction treatment and cessation programs should combine behavioral/counseling support with pharmacotherapy treatment. Inform the patient that smoking cessation has numerous short and long-term benefits, including • Reduce premature aging/skin wrinkles • Improved fitness and faster recovery from common infections • Lowering risk of respiratory infections and chronic lung disease • Lowering the risk of high blood pressure, diabetes, kidney disease, heart disease and stroke • Improved infant outcomes (for pregnant women who smoke) • Reducing cancer risk: lungs, bladder, breast, mouth, throat, esophagus • Reduce the risk of TB or death from TB
Dietary Changes and Weight Loss

Advise the patient to maintain a healthy BMI, drink 1.5-2 liters of water a day and other healthy nutrition advice: • Reduce/abstain from alcohol • Reducing sugar intake • Reducing red meat • Reduced consumption of fatty foods, fats for flavorings and fried foods • Increased whole grains, vegetables, fruits and beans • Increased fish intake • Consume less than 5 g (under one teaspoon) of salt per day
Physical activity
Advise engaging with an active lifestyle with moderate intensity physical activity: 30 minutes of aerobic activity such as brisk walking, at least 5 days a week

Every year all individuals with HIV should be tested for creatinine, glycemia, lipids (HDL, LDL, General cholesterol and triglycerides).

11.5 Cancer detection

Cervical cancer is a leading cause of cancer death for women and greatly reduces with the use of HPV vaccination. Without the HPV vaccine, the disease and mortality from cervical cancer can be reduced through early detection with routine screening. All women >21 years old must have annual PAP screening. Mammograms should be recommended in women 50-70 years of age. Colon cancer should be investigated in all adults 50-80 years of age. Annual faeces occult blood or sigmoidoscopy every 5 years can help reduce cancer mortality.

Hepatocellular carcinoma is most common in HIV individuals with cirrhosis due to HCV or HBV. The abnegation and alpha-fetoprotein are proposed every six months in order to perform early diagnosis and improved ability for surgical eradication.

12. Preventing Transmission from Mother to Child of HIV

Routine prenatal care (ANC) provides an important opportunity to provide high quality combined HIV prevention through targeted health education and counselling; HIV testing for your wife, partners and family members link to hiv prevention and treatment; and to discuss and plan for future contraception needs.

WHO recommendation[26]:
Testing pregnant women
All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)* at least once and as soon as possible *(syphilis: strong recommendation, moderate quality evidence; HBsAg*: strong recommendation, low quality evidence).* * Especially in environments with a seroprevalence ≥2% HBsAg in the general population. The hiv/syphilis (RDT) double rapid diagnostic tests could be the first test in HIV testing strategies and algorithms in the ANC.
Re-testing pregnant women in low HIV burden settings
Retest pregnant women with unknown status or HIV-negative who are in serodisclosure relationships, where the partner is not virally suppressed on ARV, or have any other known ongoing risk of HIV in late pregnancy - on a visit to the third trimester. If either the first test or retesting is lost or delayed, testing of "to know the current situation" is necessary.

[26] Consolidated Guides on HIV Testing Services for Changing The Epidemic, WHO 2019. https://www.who.int/publications-detail/consolidated-guidelines-on-hiv-testing-services-for-a-changing-epidemic

An additional retesting for women with unknown status or HIV-negative in the postnatal period may be considered in women from key populations, or who have HIV partners who are not virally suppressed. Countries may also consider an additional postnatal test in specific districts or provinces with high hiv burden or incidence.

Table 29: Essential Prenatal Care Package

The intervention	Recommendation/Description
Counselling	Include information on the importance of at least 4 ANC visits, birth to the institution, and postnatal care. Women who have been newly diagnosed with HIV and/or have just started ART may need more intensive advisory and education on HIV. Pregnancy risk signs: offer information about returning to the ANC as soon as possible in case they develop a fever, lower abdominal pain, severe headache, sore legs, convulsions. During pregnancy, you should provide iron, folate and multivitamins. Monitor for anemia, advise on adequate calorie intake. All pregnant women should receive information about risk reduction, including breast replacement. Postpartum contraception: advise on methods of contraception and help the patient develop a plan for effective contraception to avoid unplanned pregnancies.
PHDP, IPV and HIV education/counselling	For HIV positive women, encourage and support hiv status disclosure, partner/family testing, condom use, contraception after birth, STI surveillance, prevention and treatment, adversity counselling and support, Intimate Partner Violence Assessment and Prevention (IPV) and ongoing HIV education/counselling
Clinical assessment	History - including medical, obstetrics and psychosocial history. Use of drugs including medicinal plants, drug allergies. TB screening: All women presenting at the ANC should be screened for TB infection Reproductive tract infections: depisto for STIs (non-normal genital discharge, genital ulcers and history of pelvic inflammatory disease). Physical examination – perform obstetric examination including vital signs, breast examination, abdominal and fetal examination, speculum and bimanual examination, cervical cancer screening, STI screening
Other	Immunization of mothers, iron, folate and multivitamin, STI detection and treatment, ART for HIV+

12.1 ARV for HIV-positive pregnant women and prophylactics in babies

The aim of ARV for HIV-positive pregnant women is twofum: to restore and maintain maternal immune function and therefore overall health, and secondly, prevent hiv transmission in the womb, during birth and delivery activity.

Table 30: Recommendations for Managing Pregnant Women with HIV

Recommendations from mothers	
Script	
Pre-conception planning for women already on ARVs (not yet pregnant)	Maintain an ARV if a specific ARV has not contraindicated in pregnancy (d.m.th. DTG is not recommended in women seeking to become pregnant due to the potential risk of neural tube defects). Replace DTG with other permitted ARVs.
In ARV at the time of pregnancy confirmation	If a woman is on DTG at the time of pregnancy identification and the pregnancy has more than 8 weeks, she should continue the same regimen unless there is any other reason to switch after the teratogenicity period has already passed.
Not in ARV at time of pregnancy confirmation	Prepare the patient and start with ARV as soon as possible with a non-DTG regimen, if it is less than 8 weeks. It is recommended to start on the same day that HIV infection is confirmed. Perform VL 3 months after starting ARV
Appearance in birth activity not in ARV	Start art immediately. Ensure zidovudin IV during birth activity.

Managing birth and birth activity	Minimize vaginal examinations, use aseptic techniques to perform childbirth, avoid artificial membrane rupture, monitor birth activity and avoid prolonged birth activity with the use of partography, avoid unnecessary trauma to the genital tract. Recommend IV zidomudina and elective cesarean section if VL after 36 weeks of pregnancy is ≥ 1,000 copies/ml. If viral load is unwound, recommend vaginal birth and zidovudine IV is not required

Table 31: ARV Prophylaxis for HIV-Exposed Infants

The Babies Scenario	Baby Prophylacsia
Low-risk exposed infant (mother on ART with unwoven VL)	Prophylaxy of babies with AZT 4 weeks
High-risk infants (mothers who did not take ARV drugs, antepartum or intrapartum, or who had traceable viral load near the time of birth, or who were sero-converted during pregnancy)	AZT 8 and 3 doses of NVP (prophylactic dose, with dosages given within 48 hours of delivery, 48 hours after the first dose and 96 hours after the second dose) Or Empirical HIV therapy using either ZDV, 3TC and NVP (treatment dosage) or ZDV, 3TC and RAL administered from birth to age 6 weeks.

13. Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis (PEP) is short-term use of antiretroviral treatment to reduce the likelihood of HIV infection after potential exposure and should be included as part of combined prevention tools. People may be accidentally exposed to HIV through work in healthcare or because of exposures outside the healthcare environment, for example, through unprotected sex or sexual assault. Health workers are at increased risk of HIV exposure through contact with contaminated blood and other bodily fluids containing HIV, through injury from syringe and other sharp objects, or through the skin and mucous membranes. To avoid exposure to HIV, precautions should be taken when treating potentially contaminated body fluids using appropriate protection such as gloves, aperitifs and glasses; You should be careful with sharp tools including minimizing blind surgical procedures and proper treatment and disposal of these tools; safe storage of contaminated waste; cleaning of dirty sheets/clothing; Adequate disinfection procedures and universal hepatitis B vaccination of at-risk non-immune groups including health staff, police, prison staff and rescue workers. PrEP should always be offered as soon as possible (and within 72 hours) after a high-risk exposure. A three-drug regimen course for 28 days is the preferred pep regimen. For occupational exposure, immediate care of the exposure site includes: wash the site with soap and water and allow the wound to bleed for a few minutes (but do nothing that will increase tissue damage, such as squeezing, hard cleaning, or further cutting the site)

Table 32: Prophylaxis After Exposure

Considerations

Exposure	• Take into account the exposures that have occurred within the last 72 hours • High risk: mucus meth; unspoiled skin, or percutaneous injury, or unprotected receptive sexual exposure or sexual assault • Material: blood or blood-based body fluids; Breast milk; sperm; vaginal secretions; synovial fluids, pleural, pericardial, amniotic; CSF, or; HIV cultures in the laboratory • SOURCE OF HIV positive or unknown in high-prevalence environments (drug users, etc.)	
Initial contact management	Offer PEP as soon as possible. Advise on reducing the risk of transmission, including sexual contact and breastfeeding. Offer rapid HIV testing for exposed and sourced individuals. Review hepatitis B vaccination status (if not previously immunised and & HBV positive unknown). Look for basic creatinine, hematology, liver function, HCV, antiHBs and HBsAg and EIA for HIV. Consider tetanus toxin for any physical damage to the skin or mucus if they are not vaccinated. If the source is HIV negative, stop PEP. Report and document the episode at the clinic.	
ARV regime for pep at work or non-work or sexual assault	**Adults:** TDF + 3TC + DTG (consider EFV or LPV/r as an alternative for women and adolescent girls with birth potential who do not use contraception) **≥ 6 years** (or ≥ 20 kg body weight): TDF+3TC+DTG **0-6 years** old and < 20 kg: ABC + 3TC + LPV/r	AZT can be used as an alternative when TDF or ABC cannot be used For children who cannot tolerate LPV/r: use RAL or DRV/r
Start time	As soon as possible after exposure, but no later than after 72 hours	
Duration of PEP	28 days (Emergency rooms should offer treatment until the next ID appointment). All healthcare centers should have PEP kits in pharmacies with at least 5 days of treatment	
Follow up continuously	Week 1: Assess and manage side effects due to PEP. Check the basics. Assess HBV vaccination. Week 4 and 12: HIV testing.	
Other services for sexual exposure and sexual assault.	Prophylactic STI treatment in case of sexual assault. Emergency contraception for non-pregnant women Documenting clinical evidence of the attack and collecting forensic evidence. Mental health support.	

14. Pre-exposure prophylaxis (PrEP)

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by an uninfected person at high risk of contracting HIV infection to prevent hiv infection.

Who Recommendation Pre-Exposure Prophylaxis[27]

PrEP Indiscrete

Oral prEP (containing TDF) should be offered as an additional preventive choice for people at substantial risk of HIV infection as part of combination prevention approaches.
(High quality evidence, strong recommendation)

The significant risk of HIV infection is determined by an incidence of HIV infection in the absence of PrEP that is sufficiently high (>3% incidence) to make prEP provision potentially costly (or cost effective). Providing PrEP to people at significant risk of HIV infection maximizes the benefits in terms of risks and costs.

PrEP does not eliminate the risk of HIV infection and does not prevent STIs or unintended pregnancies. Therefore, it should be offered as part of a combined preventive package that includes risk reduction counseling, HIV testing, condoms and lubricants, STI detection and treatment, contraception, needle exchange and opioid replacement therapy.

Regime: Pre-exposure prophylaxis should be provided after you have determined the suitability, readiness for effective use, ongoing follow-up and lack of contraindications to the

[27] https://apps.who.int/iris/bitstream/handle/10665/186275/9789241509565_eng.pdf?sequence=1

regimes described below.

Table 33: PrEP Regimens

Favorites	Alternative
TDF/FTC (300 mg/200 mg) as FDC QD	TDF/3TC 300 mg/300 mg as FDC QD
Dosage: PrEP: 1 pill daily (indicated for heterosexual, MSM and transgender individuals). Event Drive PrEP pre-exposure prophylaxis (for MSM only) use 2 pills between 24 and 2 hours before sex, 1 pill 24 hours after sex, and another pill 48 hours after sex. If more sexual intercourse occurs, continue taking 1 pill a day until after 48 hours of the last sexual activity.	

Pre-exposure prophylaxis promoted by the event may be offered as an alternative to daily PrEP dosing for MSM. Data from randomized selection trials, open label extension studies and implementation studies show that event-induced pre-exposure prophylaxis (ED-PrEP) is as effective at preventing HIV infection as daily PrEP among MSM, but we do not have data among transgender individuals or women.[28] Common side effects include nausea and vomiting, often mild, self-limiting and occur during the first 1-2 months. It may need symptomatic treatment (anti-emetics such as metoklopramide). Tenofovir can cause a transient increase in creatinine, and rarely protein and Fanconi syndrome (presents as polyuria, bone pain and weakness). It usually resolves after treatment is discontinued. Creatinine should be measured before the onset of PrEP and every six months after the onset of PrEP. More frequent creatinine monitoring can be guaranteed if there are associated disease conditions that can affect kidney function, such as diabetes mellitus and uncontrolled hypertension. Protection is achieved after 7 doses of PrEP.

Pre-exposure prophylaxis (PrEP) should be offered to all individuals at high risk of HIV infection, defined as hiv incidence greater than 3 per 100 persons years. Typically, this incidence is identified among several groups of men who have sex with men, transgender women in many settings, and individuals who have sexual partners with undiagnosed or untreated HIV infection. Examples of individuals at significant risk include:

- Hiv sexual partner not on AVT, or in ARVs <6 months, either with poor ARV adjective, or with VL is traceable
- Individuals engaged in transactional sex
- Recent Sexually Transmitted Infections
- Repeated use of post-exposure prophylaxis for sexual exposure
- History of sex while under the influence of alcohol or recreational drugs as a habit
- Non-condomless or non-condom use during sex with people with unknown HIV status
- Needle and syringe separation for injection for drug use

Criteria for starting prophylaxis before exposure:

- HIV confirmed negative, DHE
- There is not an actual or recent disease (within the last one month) consistent with acute HIV infection (fever, sore throat, muscle or joint pain, swollen glands, diarrhoea or headache) following a high-risk exposure for HIV, ET
- Ready to adhere to PrEP and ready to participate in periodic HIV testing and follow-up assessments. There is no contraindication to the use of TDF+/- FTC (or 3TC)

Contraindication to oral PrEP:

- Confirmed or suspected HIV infection in potential user
- Impaired renal function (rated creatinine clearance <50 ml/min)
- Unable or unwilling to adhere to the specified prophylaxis schedule prior to exposure or follow-up

[28] How much is 2+1+1? Event-driven pre-exposure oral prophylaxis to prevent HIV for men having sex with men: Update the WHO recommendation for pre-oral exposure prophylaxis. WHO, 2019. https://www.who.int/hiv/pub/prep/211/en/

Table 34: Substantial Risk Assessment Questions Examples

In the last six months:
• Have you had more than one sexual partner? • Have you had sexual contact where neither you nor your sexual partner had a condom? How many of your sexual partners were HIV positive or with unknown HIV status? • Have you had sex with HIV-positive partners or people with unknown HIV status without a condom? Have you been treated for a sexually transmitted infection? • Have you injected drugs? If so, have you used syringe, needles or other drug preparation equipment that had already been used by another person? • Have you had sex while under the influence of alcohol or drugs? • Is your partner HIV? Is he/she unsealable?

Prophylaxis before periconceptual exposure: Pre-exposure prophylaxis is usually required for serodissquil couples trying to conceive to avoid using in vitro fertility methods or sperm washing techniques. In this case, HIV negative individuals should be cautioned for the lack of risk of HIV transmission among heterosexual serodisscurdent individuals when the infected partner is not traceable.[29]. However, when the partner with HIV has not been able to achieve viral suppression or when the status of viral suppression is unknown, it is recommended to administer PrEP to partner without HIV to reduce the risk of sexual transmission of HIV. In this case, an individual who does not have HIV should start oral PrEP every day starting 1 month before conception is attempted and continue for 1 month after conception occurs.[30]

Monitoring: WHO provides a series of modules to support the implementation of PrEP among a range of populations in different environments that are available online[31]. Oral prEP is an opportunity to connect with individuals around sexual health, particularly the management of bacterial and viral STIs. The status of HIV-negative antibodies must be verified before the onset of PrEP, but samples for laboratory tests suggested in addition to HIV testing (including creatinine, hepatitis serology, and syphilis) can be taken and sent to the laboratory and the PrEP user can be contacted if the test results require additional action, confirmation, or treatment.

When to terminate PrEP: PrEP should be terminated if these situations occur:

- The prEP user becomes HIV positive. These individuals should be referred immediately for HIV and ARV confirmation. Sometimes, confirming HIV can be challenging in those cases.
- Kidney failure with creatinine clearance below 50 ml/min
- Report that there is no current risk of HIV

Table 35: Summarization of Initial Assessment and Follow-up Following

Procedure	Frequency
HIV test	First, first month and then every three months.
Symptoms of acute HIV	on every visit. If present at first, push PrEP until you rule out acute HIV
Creatinine	First and every six months. More frequent monitoring of individuals older than 50 years of age or with a concomitant disease
HBsAg	At the beginning. If you vaccinate negatively. If positive, refer to your hepatologist and advise against stopping PrEP due to the risk of inflaming hepatitis.
HCV	At the beginning. Repeat it every year, or more frequently among people who inject drugs.
VDRL or RPR	First, and repeat every six months.
CT/NG	Depending on availability, at the beginning and every 6 months (rectal PCR, tampon and urine).
Review vaccinations	First (focus on HBV, HPV, HAV, DT)

[29] Del Romero J, Castilla J, Hernando V, Rodríguez C, García S. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross-sectoral and future cohort study. BMJ. 2010 May 14;340:c2205. doi: 10.1136/bmj.c2205.
[30] CDC. Prophylaxis of Preexistence Exposure for Prevention of HIV Infection in the United States 2017. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

[31] WHO implement tool for pre-exposure prophylaxis of HIV infection. https://www.who.int/hiv/pub/prep/prep-implementation-tool/en/

Counselling	As needed: To assess whether the client is at significant risk of HIV. Discuss prevention needs and provide condoms and lubricants. Discuss desire for PrEP and readiness to take PrEP. Develop a plan for effective use of PrEP, sexual and reproductive health. Assess fertility goals and provide safer contraception or advice for conception. Assess intimate partner violence and gender based violence. Assess substance use and mental health issues
Tolerance, adulation and side effects	At every visit.
Pregnancy or breastfeeding	Pregnancy and breastfeeding are not contraindications to prEP provision. Pregnant or breastfeeding women whose sexual partners are HIV positive, or who are sex workers can benefit from PrEP as part of the combined prevention of HIV infection.
Remind PrEP users that it takes 7 doses of pre-exposure prophylaxis to achieve adequate arv levels in the tissue to be effective. During these days, safer sexual practices should be encouraged (including abstination and condoms).	