EUROPE

1 Patient Evaluation and Antiretroviral Treatment for Adults and Adolescents

Clinical Protocol for the WHO European Region

Contents

I. Introduction **5**

II. Management of patients with HIV **6**
1. Initial patient evaluation 6
   1.1. Personal, family and medical history 6
   1.2. Physical examination 8
   1.3. Laboratory and other examinations 9
2. Counselling on issues related to living with HIV 10
3. Prevention of opportunistic and other infections 11
4. Antiretroviral treatment 11
   4.1. Initiation of ART 11
      4.1.1. Clinical and immunological considerations 12
      4.1.2. Considerations for viral load 12
      4.1.3. Considerations for drug resistance test 12
   4.2. First-line HAART regimen 13
      4.2.1. Considerations for NRTI component 13
      4.2.2. Considerations for NNRTI component 14
      4.2.3. Alternative 1st line HAART regimens 14
   4.3. Adherence to ART 15
      4.3.1. Barriers to high adherence and counteracting strategies 16
   4.4. ART success and failure 17
      4.4.1. Virological response 18
      4.4.2. Immunological response 18
      4.4.3. Clinical response 18
      4.4.4. Dissociated virological and immunological responses 18
   4.5. Second-line HAART regimen 19
      4.5.1. Considerations for NRTI component 19
      4.5.2. Considerations for PI component 19
   4.6. Salvage regimens 20
   4.7. Structured treatment interruption 20
5. Clinical monitoring of patients with HIV 21
   5.1. Monitoring of laboratory indicators before ART 21
   5.2. Monitoring of laboratory indicators in ART patients 21
   5.3. Immune reconstitution inflammatory syndrome 23
   5.4. Monitoring adherence 23
   5.5. Management of ARV toxicity and side-effects 24
   5.6. Drug interactions 26

III. Suggested minimum data to be collected at the clinical level **28**

Annex 1. Essential information on personal history of HIV/AIDS treatment and care **29**

Annex 2. Revised WHO clinical staging of HIV/AIDS for adults and adolescents **30**

Annex 3. Resistance tests **31**

Annex 4. Essential information about ARVs **32**

Annex 5. Tools for adherence monitoring **35**

Annex 6. List of antiretroviral drugs **36**

Annex 7. Glossary **39**

Annex 8. Beyond the horizon **40**

References **41**

I. Introduction

HIV/AIDS is chronic lifelong disease with no known cure, and therefore, people living with HIV (PLHIV) have to be followed medically for the rest of their lives *(1–3)*. The core component of treatment and care of PLHIV is provision of antiretroviral treatment (ART). Optimal ART increases the length and quality of life of HIV-infected patients, and reduces the onward transmission of the virus. WHO promotes a public health approach to ART *(4)*, which promotes the rational selection and sequencing of different drug classes into first and second-line regimens with salvage options; simplified and standardised clinical management; and standardised record keeping in order to preserve therapeutic options, minimize drug toxicity and side-effects, maximize adherence and to support the goals of ART.

The goals of ART are:
- clinical: prolongation of life and improvement of its quality;
- immunological: quantitative and qualitative immunological reconstitution, in order to prevent the onset of opportunistic infections;
- virological: maximum possible reduction of the viral load for the longest possible time, in order to halt the progression of disease and prevent and delay the development of drug resistance;
- epidemiological: reduction, ideally the prevention of onward HIV transmission *(5)*.

WHO has produced a series of guidelines to support ART delivery in national programmes and by treatment implementers, which are available on the WHO website http://www.who.int/hiv/universalaccess2010/en/index.html. Particular reference is made in this protocol to the guidelines and recommendations for clinical and immunological staging and to ART guidelines for ART in adolescents and adults.

Medical history, examination findings, exact history of ART, laboratory results, results of other medical procedures and social circumstances need to be documented for the entire treatment period, which may be years or even decades long. Such records are crucial for the individual patient as well as for retrospective analysis (for example, in endoscopic procedures, CT scanning, advanced microbiologic testing or viral load (VL) testing). For such purposes, an electronic record-keeping system is advisable, especially at the clinical level. Confidentiality of medical information should be ensured.

Optimal HIV-related treatment and care should be delivered by clinical teams. The core clinical team providing basic medical case-management of a patient should ideally consist of a physician (often an infectious disease specialist), a nurse and a social worker or a non-medical service provider. Each of the team members has distinctive roles in providing treatment and care, and their services should be complementary. A network of other specialists and self-help groups should be available in supporting PLHIV *(6)*.

II. Management of patients with HIV

Proper management of patients living with HIV is a comprehensive lifelong process focused on the patient's needs. It should include:
- initial HIV testing and confirmation of the result;
- appropriate counselling during the process of identifying HIV infection;
- clinical evaluation;
- patient counselling;
- monitoring patient health;
- initiating ART and its maintenance;
- prevention and treatment of opportunistic infections (OIs), other coinfections and comorbidities;
- psychological support;
- adherence support; and
- referrals to provide continuity of care.

Clinical evaluation of patients should include testing and counselling for health maintenance issues related to HIV as well as to other conditions that may interact with the management of HIV infection, especially potential interactions with ART.

1. Initial patient evaluation

The initial evaluation of a patient aims at determining the full status of his/her HIV infection, to develop a basis for further clinical management and for referral to non-medical services as appropriate.

Initial patient evaluation should include:
- confirmation of HIV infection status with potential time of infection established, if possible;
- a detailed personal, family and medical history;
- physical examination;
- laboratory and other examinations;
- specialist examinations, as appropriate; and
- clinical and immunological staging.

1.1. Personal, family and medical history

Patients newly diagnosed with HIV infection or patients who are transferred in, having had their long-term care and ART being initiated elsewhere, should provide a complete history before physical examination *(7)*. See Table 1.

Table 1.	Medical history information required at initial patient evaluation

General information:
- patient's name
- date of birth
- sex
- date of assessment

Testing information:
- date of first positive HIV test
- reason for being tested
- last HIV-negative test, if known

HIV exposure risk and transmission category (if known):
- injecting drug use
- sexual (heterosexual, homosexual, types of sexual contact: oral, vaginal, anal)
- blood or blood product transfusion, organ and tissue transplantation
- mother-to-child transmission
- occupational exposure (describe)
- unknown
- HIV status of sexual partner(s), if known
- risk factor of sexual partner(s), if known

Time and place (country) of infection most probable or known[a]

History of HIV treatment and care: (see Annex 1)
- time and place of previous treatment or HIV-related services, including treatment interruptions
- drug regimens
- side-effects
- adherence
- laboratory data (CD4 count, VL, electrolytes, liver function, renal function, full blood count, in chronological order for patients with longer infections (several years' duration) *(8)*)
- documented results of previous resistance tests (if performed)

HIV-related illnesses and conditions and HIV clinical staging:
- tuberculosis
- respiratory infections
- viral, other bacterial and fungal infections
- hepatitis C and B
- neoplasms
- other

Other illnesses and conditions:
- hospitalizations
- surgery
- mental health conditions (e.g. depression)
- kidney or liver diseases
- endocrinological disorders
- sexually transmitted infections (STIs)
- vaccinations
- allergies
- body changes
- current medications

Family medical history (diabetes, hypertension, skin disorders, malignancies, etc.)

Cardiovascular disease and disease risks (obesity, smoking, hypertension, etc.)

Exposure to tuberculosis (TB) (personal and household TB contacts)[b]

Current medications (including opioid substitution therapy (OST))

Substance use:
- illicit drug use (past and present)
- alcohol consumption

Reproductive and sexual health:
- contraceptive methods in female patients
- pregnancies (past, current, planned)
- sexual practices (oral, anal, vaginal)

Social history
- living situation (partners/spouses/family members, children, etc.)
- employment and occupation
- support networks (social and medical insurance, community groups, who knows of patient's HIV status, etc.)

[a] Useful for epidemiology, subtype of virus and possibly a drug resistance profile.
[b] For further evaluation on TB please refer to Protocol 4, *Management of tuberculosis and HIV coinfection*.

1.2. Physical examination

The physical examination should document presenting symptoms and signs and reproducible results so that other physicians can determine changes in status. A standardized history and examination questionnaire is preferable; see Table 2.

Table 2. Initial physical examination

General appearance: • height and weight • body morphology (lipodystrophy) • Karnowsky index or other standardized scale for general fitness
Vital signs: • blood pressure • temperature • pulse • respiratory rate
Lymph nodes
Skin (entire body): • in particular, assess for ◦ active or former herpes zoster ◦ liver disease ◦ Kaposi sarcoma ◦ seborrhoeic dermatitis ◦ injection sites in injecting drug users (IDUs) The documentation of skin disorders such as discoloured brown or dark patches is best made with photos; other possibilities include drawing the area of a patch on transparent foil, to be able to compare in future in examinations.
Oro-pharynx: • oral health and dental status • signs for: ◦ oral candidiasis ◦ oral hairy leukoplakia ◦ primary syphilis
Thorax and lungs: • signs (breathing, cough, dyspnoea) • form of thorax • control for risk of emphysema
Mamma examination (in female *and* male patients) to control for risk of carcinoma
Cardiac examination for baseline information when there may be higher risk for cardiovascular complications with ART *(9, 10)* or risk for endocarditis in IDUs
Abdominal examination (for baseline information for ART side-effects, especially in cases of chronic hepatitis, alcohol toxicity and cirrhosis): • consistency, size and shape of liver and spleen • bowel movement • tenderness • rigidity • nausea, vomiting, disphagia
Genital and anal region examination: • signs for: ◦ herpes simplex ◦ cytomegalovirus (CMV) ◦ syphilis ◦ Human papilloma virus (HPV), (condylomata acuminatae, anal carcinoma) *(11)*, other STIs ◦ erectile dysfunction
Legs (movement, mobility, lipodystrophy) to provide baseline information for ART side-effects
Neurological status (also signs of neuropathy)
Mental status
Eye and ear functions

1.3. Laboratory and other examinations

Table 3.	Laboratory testing

HIV-related testing:
- HIV serological testing (typically an enzyme-linked immunosorbent assay (ELISA) or rapid blood test), followed by confirmatory test (typically western blot) *(12)*
- CD4 cell count to determine the severity of immunodeficiency; in pregnant women CD4 *% (13, 14)*
- viral load testing by polymerase chain reaction (PCR), to determine level of viral replication[a]

Other infectious disease testing:
Routine testing:
- venereal disease research laboratory (VDRL) test for syphilis
- serological tests for hepatitis C and B viruses (HCV and HBV) – i.e. HCV antibodies and hepatitis B surface antigen (HBsAg)[b]
- toxoplasma immunoglobulin G (IgG) serological test and information about risk of infection if negative

If indicated:
- vaginal, penile or anal (as appropriate) swab for gonorrhoea and *Chlamydia trachomatis*
- *Cryptococcus* antigen titre when CD4 cell count is <200/mm^3 with clinical signs of cryptococcosis
- CMV antigenaemia (pp65 early antigen), when CD4 cell count is <100/mm^3.[c]

General laboratory testing:
- electrolytes (sodium, potassium)
- liver function (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase)
- bilirubin
- renal function (blood urea nitrogen (BUN), creatinine)
- lactate dehydrogenase (LDH) (general turnover of cells in lymphomas, signs of pulmonary infections, myocardial infarction, muscle damage, etc.)
- quick (international normalized ratio (INR) test or prothrombine time)
- full blood count with differential and platelets
- pregnancy test before initiating ART

If available:
- fasting glucose
- cholesterol (high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL))
- triglycerides
- lipase
- C-reactive protein (CRP)
- thyroid-stimulating hormone (TSH)

[a] Performance of tests by the same laboratory is preferable to rule out technical discrepancies.
[b] For further information on testing of hepatitis, please refer to Protocols 6 and 7, *Management of hepatitis C* and *HIV coinfection* and *Management of hepatitis B and HIV coinfection*.
[c] Very early detection of CMV infection is possible, and is a good marker for treatment response in CMV infection.

Table 4.	Other examinations

- tuberculin skin test for those with no TB symptoms or no known TB exposure[a]
- sputum-smear microscopy and chest X-ray if signs and symptoms of active TB are present[a]
- ECG – optional (might be useful as a baseline for comparison due to greater risk for cardiovascular disease with ART) *(15)*

[a] For further information please refer to Protocol 4, *Management of tuberculosis and HIV coinfection.*

Other examinations may be necessary, depending on individual comorbidities, for example, in HCV/HIV or HBV/HIV coinfection, abdominal ultrasound to assess lymph nodes, size and shape of liver and spleen; or in presence of clinical signs of gastrointestinal (GI) tract disease, endoscopy of the upper and lower GI tract. Endoscopic findings should be documented with photos.

Table 5.	Specialist consultations if required
• neurological examination (for peripheral polyneuropathy) • ophthalmological examination (useful to repeat every three months for CMV retinitis when CD4 count is <100/mm^3) • gynaecological examination including a Pap smear every six months (for human papillomavirus-mediated (HPV-mediated) carcinoma)[a] • other specialist consultations as needed	

[a] There is no hard evidence to recommend routine rectal PAP smears at the time of writing this protocol. For more information please refer to Protocol 9, *Support for sexual and reproductive health of people living with HIV.*

2. Counselling on issues related to living with HIV

Patient counselling is an essential component of patient management strategy and patient-health care provider relationships. It should start with the assessment and discussion of the patient's social conditions, which may be predictors of cooperation during treatment. These include:

- partnership status and quality
- employment status, type of work and conditions
- people who are informed and should be informed of the HIV status
- people with whom health care workers can discuss the patient's health-related matters
- familial relationships
- availability of safe refrigerated storage for medications
- lifestyle factors that might interfere with treatment *(16–18)*.

Health care providers who counsel PLHIV should ensure that certain information is discussed and understood by the patient.

- Risk reduction (safe sex, injecting practices, etc.) must be explained, including the danger that unprotected sex with HIV-positive partners could lead to super-infection with another HIV strain and possible resistance to antiretrovirals (ARVs) *(19)*.
- Importance of disclosure to sexual partner(s), friends and family members for a few reasons:
  - obtaining psychological and treatment support
  - prevention of HIV transmission
  - testing of sexual partner(s).
- Availability of treatment, its benefits, preparedness to it, long-term consequences and importance of adherence should be discussed with every patient.
- Patients need to be informed about signs of possible OIs, and encouraged to have further evaluation. For further information, see Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS.*
- The importance of stopping illicit drug use needs to be discussed with users. If a patient is unable or unwilling to stop, the merits of harm-reduction measures should be discussed, including the merits of reducing drug use; not injecting; not sharing needles, syringes or other injecting paraphernalia; and drug dependence therapy (such as OST). For more information, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*
- Prevention of other infections should be discussed. Please refer to section 3 below.
- Based on the assessment of social conditions, healthy daily habits – sleep, nutrition, exercise – should be encouraged.
- Patients about to initiate ART should be counselled on:
  - adherence (see section II.4.3 below)
  - possible antiretroviral (ARV) toxicity (see section II.5.5 below)

  - drug interactions (see section II.5.6 below)
  - reliable contraception when the ARV regimen will contain efavirenz (EFV) (for further information refer to Protocol 9, *Support for sexual and reproductive health in people living with HIV)*
  - patient understanding of treatment process and related to it issues should be ensured by the health care provider.
- Patients should also be informed about legal responsibilities (if applicable) and their rights and be referred to other appropriate services.
- Patients should be informed of issues related to immunization (including travel) and occupational risks.

3. Prevention of opportunistic and other infections

- Prevention of active tuberculosis is among the first priorities. For more information on management of TB/HIV coinfected patients and prevention of active TB please see Protocol 4, *Management of tuberculosis and HIV coinfection.*
- As HBV/HIV and HCV/HIV coinfections are common and present further medical difficulties, their prevention must be emphasized. It is equally important to advise on reducing the risk of liver-related harm and preventing mother-to-child transmission (MTCT).[2]
- PLHIV should be immunized against hepatitis B and A and influenza. For further information, please refer to Protocol 12, *Immunization of people living with HIV and people at risk for HIV.*
- Every patient with a CD4 cell count less than 200 cells/mm^3 should be given prophylaxis against certain opportunistic infections, in particular *Pneumocystis jirovecii* pneumonia (PCP) and other infections. Co-trimoxazole should be given until the CD4 cell count is >200/ mm^3 for more than three months after initiating ART. For more information please refer to Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS.*
- In case of negative toxoplasma serology, the transmission route and ways to prevent infection should be explained (including risks associated with pets). For futher information see Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS.*

4. Antiretroviral treatment

4.1. Initiation of ART

The best point at which to start ART is under discussion *(20)*. A review of several cohort studies and guidelines shows a widespread view that clinical staging (stage 3 or 4) and CD4 counts are the best primary markers and viral load the secondary marker for this decision *(21–31)*. Prior to starting ART, support to ensure adherence should be initiated; see section II.4.3 below.

[2] For further information see Protocol 6, *Management of hepatitis C and HIV coinfection*, Protocol 7, *Management of hepatitis B and HIV coinfection*, Protocol 8, *Prevention of hepatitis A, B, C and other hepatotoxic factors in people living with HIV*, and Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants.*

4.1.1. Clinical and immunological considerations

WHO recommends initiation of ART using clinical and immunological criteria as per Table 6.

Table 6. Recommendations for initiating ART in PLHIV

WHO clinical stage[a]	CD4 cell count	Recommendation
1	<200/mm^3	Treat
	200–350/mm^3	Consider treatment[b]
2	<200/mm^3	Treat
	200–350/mm^3	Consider treatment[b]
3	200–350/mm^3	Treat
4	Regardless of CD4 count	Treat

[a] See Annex 2 for a description of the clinical stages.
[b] When the CD4 count is around 350 cells/mm^3, begin discussions with the patient on the advancing need for initiating ART and on preparations for starting.

The decision to initiate ART should be based on two different CD4 counts, ideally at least 7 days apart because of variability in the CD4 count itself and to rule out laboratory mistakes and other variances (for example, concurrent illnesses). In case of a concurrent acute illness, CD4 cell count should be repeated only after the illness is cured. Therapy should not however be delayed if a patient is unwell or if the second count cannot readily be performed. If the CD4 count is not available, the decision to initiate ART can still be made on clinical grounds alone – with clinical stage 3 or 4 illness.

Baseline CD4 count at the onset of ART (ideally determined when the patient is free from any active major opportunistic infection) is a critical value in determining prognosis, response to ART and for monitoring the subsequent immunological response to ART.

4.1.2. Considerations for viral load

Viral load is associated with loss of CD4 cells. Though on its own it is not a marker for initiating ART, in case of viral load >100 000 copies/ml (this can go as high as 1 million copies), the probability of rapid CD4 cell count decline is very high. Therefore, it is recommended to consider initiation of ART at CD4 cell count of 350/mm^3 if the viral load is higher than 100 000 copies/ml.

While viral load testing is more expensive and may be less accessible, it is important to have a baseline viral load if at all possible, as this value is relevant for monitoring ART. The absence of viral load data should not be a criterion for delaying the start of treatment, or used as a reason for treatment exclusion.

4.1.3. Considerations for drug resistance test

Prevalence of HIV drug resistance varies in different countries and is linked to several factors, including the duration of ART availability, history of treatment (mono- and dual therapy) and adherence. In western Europe, multicentric studies showed a 10% overall prevalence of resistance in newly diagnosed HIV-infected individuals between 1996 and 2002 *(32)*. A study of 40 cities in the United States revealed a resistance rate of 14% *(33)*. The highest results from these studies were 26% in Spain *(34)* and 19% in San Francisco *(35)*. In countries with a short or no history of ART, risk of HIV drug resistant virus transmission is significantly lower, and the first-line highly active antiretroviral treatment (HAART) regimen recommended below (section II.4.2) is effective for treatment of naïve patients. It is important to have population-based HIV drug resistance strategies in place to monitor for the appearance and spread of HIV drug resistance; and to act on the early warning indicators for drug resistance emergence in order to minimize its appearance and onward spread.

WHO does not recommend individual drug resistance testing prior to initiation of ART in settings where only one first-line regimen is provided in the public sector because any results will not influence ART. Instead, sentinel surveys that demonstrate resistance at population level above the threshold of 5% *(36, 37)* should be taken into consideration in adapting national recommendations for first-line ART. Refer to Annex 3 for additional information on resistance testing. Where resources permit, and the public sector provides more than one first-line regimen, then drug resistance testing at baseline may help determine the choice of optimal ART; cost and availability will likely limit the widespread use of this in many settings (*38–40)*.

4.2. First-line HAART regimen

It is recommended that two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) be combined in the first-line HAART regimen.

Table 7. Recommended first-line HAART

ARV drug classes	HAART regimens
2 NRTIs + 1 NNRTI	ZDV + 3TC + (**EFV**[a] or NVP) or TDF + FTC + (**EFV**[a] or NVP) or ABC + 3TC + (**EFV**[a] or NVP)

[a] EFV is highlighted as the preferred NNRTI.

(For recommended dosages, please refer to Annex 4.)

4.2.1. Considerations for NRTI component

- The "backbone" of first-line ART is a combination of two NRTIs. One should be lamivudine (3TC) or emtricitabine (FTC); FTC is considered an equivalent drug to 3TC in both efficacy and toxicity *(41)*. The second is most often the thymidine analogue zidovudine (ZDV also known as AZT). A large body of data and provider experience is available for ZDV, as it was the first known ARV drug.
- Stavudine (d4T) is another thymidine analogue. It is available in several fixed-dose combinations (FDCs), is cheaper than ZDV and consequently widely used in many countries. However, it has a poor toxicity profile and recent studies have shown a higher rate of long term side-effects with d4T (*42–49)*. Many national and international recommendations are moving away from recommending it for initial therapy. It is increasingly being reserved as an alternative for ZDV (a within class substitution) when ZDV has to be substituted or changed for side effects or toxicity. The lower dose 30 mg is now recommended for all weights to reduce long-term toxicity.
- Other possible non-thymidine analogues for first-line are tenofovir (TDF) or abacavir (ABC) in combination with 3TC or FTC. Recently, one study has shown a slight superiority of TDF/FTC over ZDV/3TC when used in combination with EFV *(42)*, probably due to a lower rate of side-effects in the TDF arm. Further studies are needed. It should be noted that ABC has a risk of dangerous hypersensitivity syndrome; and, TDF can cause renal damage, so pre-screening for renal function is usually recommended.
- The advantage of TDF and ABC is their resistance profile, which potentially allows more NRTI combinations to support second-line protease inhibitors (PIs). The disadvantages are cost, avail-

ability and licensing, and the relative lack of programmatic experience and effectiveness data, which is less comprehensive than the data for the thymidine analogues *(43)*.

- NRTIs are available (or are likely soon to be prequalified and available) in the following FDCs, or one-pill formulations from originator and generic manufacturers:
  - ZDV + 3TC
  - TDF + FTC, TDF + 3TC
  - ABC + 3TC
  - d4T + 3TC
- An additional advantage of TDF/FTC and ABC/3TC is the availability of a once-daily regimen.

Other NRTIs and combinations are not recommended for first-line ART *(44)*. Certain rules pertain to the use of NRTIs.

- Do not combine "d-drugs" (ddI (didanosine), d4T).
- Do not give single d-drugs with pre-existing polyneuropathy.
- Do not combine ZDV and d4T.
- Do not combine 3TC and FTC.

4.2.2. Considerations for NNRTI component

- There are two NNRTIs, EFV and nevirapine (NVP), which are available and recommended for first-line ART. The effectiveness of NVP is comparable to that of EFV *(50)*. Both have important toxicities and side-effects which limit how they can widely be used.
- The best available data are for the regimen of ZDV + 3TC + EFV *(51–53)*. This three-pill combination is given in two doses per day. It is fast acting, the viral load falls rapidly in the first two weeks with EFV, the increase of CD4 count is comparable to other regimens and problems are limited.
- EFV should be avoided in patients with a history of severe psychiatric illness, in women of childbearing age who do not use effective contraceptives, and during the first trimester of pregnancy. NVP is an alternative option for these cases.
- NVP can cause severe hepatic toxicity which seems to be related to the level of immunosuppression *(54)* so its use is limited to female patients with CD4 count <250 cells/mm^3 and males with CD4 count <400 cells/mm^3. CD4 counts higher than these are associated with more risk of hepatic toxicity.
- NVP needs to be dose-escalated. There is a recommended 14-day lead-in period with 200 mg NVP once daily (OD) when starting this regimen, for better tolerance. After 14 days, the dosage should be increased to the standard regular 200 mg twice daily (BID).
- EFV is usually preferred when the patient is being co-treated for TB with rifampicin (see Protocol 4, *Management of tuberculosis and HIV coinfection* for further information).
- The combination of two NNRTIs with one NRTI is not recommended *(55)*.

4.2.3. Alternative first line HAART regimens

- Triple NRTI-based first-line regimens such as ZDV+3TC+ABC and ZDV+3TC+TDF can be recommended in specific circumstances where NNRTI is contraindicated or too complex to manage and have the advantage that they still preserve the PI class for second-line ART. These regimens can be used in the following circumstances:
  - intolerance or resistance to NNRTIs;
  - psychiatric disorders;
  - pre-existing liver disease – an increase of the ALT level by more than 3–5 fold–and established cirrhosis;
  - coinfection with HBV or HCV;
  - HIV-2 infection due to intrinsic resistance to NNRTI class; and
  - cotreatment of TB in women of child-bearing age and where adequate contraception cannot be guaranteed, and when NVP and boosted PIs cannot be used.

- ZDV+3TC+ABC has short-term inferior virological efficacy at least in patients with high initial viral loads but comparative immunological efficacy to ZDV+3TC+EFV regimen *(51, 56)*. ZDV+3TC+TDF is a promising regimen but there are limited data to date (see the following Protocols: 4, *Management of tuberculosis and HIV coinfection;* 6, *Management of hepatitis C and HIV coinfection;* and 7, *Management of hepatitis B and HIV coinfection*).
- Other triple NRTI-based regimens, such as ZDV+TDF+ABC or TDF+3TC+ddI have unacceptably high virological failure rates and high incidence of the K65R mutation *(57, 58)* and should not be used.
- Boosted PIs are usually reserved for second-line ART. They can exceptionally be used as part of first-line ART in combination with two NRTIs when triple NRTI regimen is not available or deemed inappropriate or when there are contraindications for NNRTIs (i.e. neither EFV nor NVP can be prescribed) including:
  - psychiatric disorders;
  - an increase of the ALT level by more than 3–5 fold;
  - cirrhosis;
  - pregnancy with CD4 count of 250–350 cells/mm^3, particularly in the 1st trimester of pregnancy (as EFV is contraindicated);
  - HIV-2 infection due to intrinsic resistance to NNRTI class; and
- If a first-line ART regimen containing a PI fails, there are very limited options for subsequent regimens at least within a public health approach and within the public sector in many countries. A failing PI regimen has, in consequence, more resistance patterns than a failing NNRTI regimen (point mutation in NNRTI class). In general therefore, it is recommended that PIs be left to second-line ART.

4.3. Adherence to ART

Optimal treatment benefits require strict adherence to ART. It is well recognized that when adherence is high, there is a dramatic reduction in HIV-associated morbidity and mortality *(59)*, whereas low adherence leads to rapid development of drug resistance *(60)*. Effective adherence levels have not been fully defined for ART (there being differences between a number of regimens), but levels lower than 95% have been associated with poor virological and immunological response, while levels of 100% seem to achieve even greater benefit than 95% *(61, 62)*. The most recent data show a correlation between drug resistance in various classes of ARVs and adherence *(63)*.

Low or insufficient adherence has consequences for patients, public health and national economies.

- Patients are in danger of developing significant viral resistance, treatment failure and disease progression *(64, 65)*. Changing to a new regimen after treatment failure results, in most cases, in more difficult adherence (more pills, side-effects, dietary restrictions, toxicity and dosing complexity).
- The increase in resistant viruses is likely to result in their transmission to newly infected individuals. Data from the United States *(66)* and Europe *(67)* suggest that such primary resistance is increasing, and that acquired resistance has a negative effect on ART response.
- Economically, the presence of resistant strains will result in increased use of second-line and salvage regimens, which are in general more expensive than first-line regimens.
- Low adherence also means a higher risk of disease progression, resulting in higher costs for treating opportunistic infections *(68)*.

4.3.1. Barriers to high adherence and counteracting strategies

Health care workers should identify possible factors which might lead to poor adherence to treatment and address it accordingly.

4.3.1.1. Patient factors and supportive methods

The role of patients themselves is fundamental. One cannot predict patients' adherence potential. Studies investigating the role of gender, race, age, mode of transmission and educational level as indicators of adherence have produced inconsistent results *(69)*. Individual adherence rates also vary over time *(70)*. Most PLHIV under treatment will exhibit low adherence at some time.

Barriers to adherence include:
- drug and alcohol use (may impair routine use of medication)
- poor diet due to poverty or due to other reasons
- religious beliefs *(71)*
- fear of disclosing HIV status through routine medications
- psychiatric conditions *(72)*
- fear of side-effects and doubts about the necessity of medication *(73)*.

Methods to support adherence include:
- education on the need for ART
- addressing patient misconceptions promptly
- regular evaluation of patient commitment to ART
- peer intervention (groups, friends, patient supporters)
- regular assessment of mental health problems
- assessing behavioral skills needed for adherence[3]
- contacting specialized social care services and other institutions.

4.3.1.2. Provider factors

Health care providers should clearly understand adherence and its role in resistance development when providing adherence support. Professionals working in the area of HIV/AIDS require continuous education in adherence issues. There are several strategies that health care workers should employ to increase adherence:
- Every HIV treatment centre should have a written and regularly reviewed adherence strategy.
- Health professionals need to be engaged in adherence support programmes *(74)*.
- Exploring patient preferences for involvement may act as a catalyst to adherence.
- Adherence services should be offered to all patients, taking into account the varying degrees of adherence that all patients show over the course of treatment.
- Adherence support should be continued for second-line and salvage regimens. Treatment failure is a key point for reinforcing adherence and support interventions *(75)*.
- As high adherence is a process and not a single event *(76)*, support must be offered when starting ART, changing ART and as a routine follow-up.
- Providers must ensure that patients have sufficient understanding of HIV, the relationship between adherence and resistance, the requirements of their regimen and potential side-effects. Verbal information should be supported by written information.
- Pill diaries, pill charts, medication containers, electronic reminders, and enlistment of family and friends as reminders can all be recommended by health care providers *(77)*.
- Adherence to ART is improved where patients view their relationship with their doctor and other health care providers positively *(78)*.

[3] These can be augmented by contacting people who can help (nurses, pharmacy, family), and by using timetables, pill boxes with clocks, pill-taking routines, strategies for travel and managing disclosure or discovery by others.

- Early follow-up should occur two days after initiating or changing a regimen, to evaluate whether the patient needs more information or has unregistered problems.
- The partnership between clinics and community-based organizations can improve the uptake of information, especially among hard-to-reach populations and some ethnic groups.

4.3.1.3. Regimen factors and strategies

- Dosing more than two times a day is associated with lower adherence levels *(79)*, while there is probably no adherence difference between one or two daily doses *(80)*. In regimens with single or double daily dosing, more of the doses are taken at a time. Taking the dose later than prescribed has been associated with treatment failure in multivariate analysis *(81)*.
- A low pill burden is associated with the likelihood of having a viral load below 50 copies/ml after 48 weeks *(80)*.
- Adherence levels are not correlated with any ARV class. However, conflicting dietary rules for different drugs can be a problem *(82)*.
- Harmful drug interactions and side-effects can influence adherence. Doses can be missed due to vomiting or diarrhoea, and fatigue can cause patients to sleep past doses *(83)*.

Methods to support adherence include:

- evaluating lifestyle factors like eating, sleeping and working patterns and adjusting the regimen accordingly;
- assessing individual preferences for regimen characteristics such as pill size, formulation, burden, dietary restrictions, etc.;
- showing patients the pills prior to regimen selection;
- education about side-effects, prompt palliation of them and information about support;
- dispensing medication in small amounts at frequent intervals, which can facilitate:
  - opportunities to address adherence problems before they lead to resistance;
  - limiting treatment disruptions and misuse;
- utilization of once-daily options and FDCs, which can lower the pill burden and be beneficial early in treatment; and
- directly observed treatment (DOT), particularly in hospitals.

4.4. ART success and failure

All patients should be regularly monitored by skilled clinicians. Ideally all should have access to both immunological and virological tests. Successful ART can be defined by clinical, immunological or virological criteria (see Table 8).

Table 8. Criteria for treatment success

	Virological		**Immunological**	**Clinical**
Marker	Viral Load		CD4 cell count	Clinical stage
Time[a]	24 weeks	48 weeks	24–48 weeks	By 12 weeks of treatment initiation should be asymptomatic or have few symptoms
Suggested ranges[a]	<400 copies/ml	<50 copies/ml	Increase from baseline by at least 50-100 cells/mm^3	Stage 1 or 2[b]

[a] Time and suggested ranges should not be seen as absolute and strict numbers.
[b] Please see section II.5.3 below for more information on immune reconstitution inflammatory syndrome (IRIS).

Failure of first-line ART can be defined and identified in three different ways: clinically, immunologically and virologically. The three may reflect different aspects of failure. Further, it is proving difficult in the absence of good clinical end-point data on the subsequent durability of second-line responses, to know which is the best indicator of when to switch and what value or level should be used. There are differing views about whether a patient with a "failing" regimen, regardless of

criterion used, should switch to second-line ART, and when to do so. There is no clear consensus globally on the definition of treatment failure. Currently, different biological end-points are used to represent virological, immunological and clinical failure in different settings.

4.4.1. Virological response

- VL is the earliest indicator of treatment success or failure, followed by CD4 cell count approximately a month later. In rare cases, a paradoxical reaction of virological response and immunological failure occurs; consequently, VL should be seen in combination with CD4 cell count.
- Failure to decrease viral load to <400 copies/ml by week 24 of treatment or <50 copies/ml by week 48 means incomplete virological response.
- When the viral load has already decreased to an undetectable level, but two measurements are >400–1000 copies/ml in 4 to 8 weeks, it means there is a risk of virological failure *(84)*.[3]
- "Blips" are slight elevations of viral load, from under the testing threshold to around 50–200 copies/ml. They may happen without the development of resistant virus strains (laboratory errors), but should be an indicator for a discussion of adherence *(86)*. In this situation, therapeutic drug monitoring (TDM) may also be helpful, if available. Any blip should be controlled within four weeks.
- If no reason is found for virological failure (poor adherence, suboptimal drug levels, drug–drug interactions, etc.), a second-line regimen should be discussed.

4.4.2. Immunological response

- CD4 cell count response on its own can be used as an indicator of treatment failure or success.
- On average, a CD4 cell increase of about 150 cells/mm³ occurs in the first year in treatment-naive patients *(87, 88)*. Failure to increase CD4 cell count more than 50 cells/mm³ during the first year of ART is considered immunological failure.
- If the CD4 cell count does not increase for six months, adherence to treatment should be reassessed and ensured.

4.4.3. Clinical response

- Patients will usually reverse their clinical stage and become asymptomatic (stage 1) or have minimal or minor HIV-related signs and symptoms (stage 2).
- Some stage 3 or 4 OIs can recur and the prognostic significance of oral and oesophageal candida in particular is not always clear-cut.
- Usually however, presentation of a new or recurrent stage 3 or 4 event (OI or other HIV-related illness) after initiation of ART is an indicator of clinical failure.

4.4.4. Dissociated virological and immunological responses

Despite the persistence of low but detectable viremia (VL suppressed to less than the natural set point), CD4 cell count may remain stable or even increase in some patients taking HAART *(89–91)*. In a large intercohort analysis even in those people who had experienced 3-class virological failure and continue to take HAART, viremia less than 10 000 copies/ml or suppression of at least 1.5 log copies/ml less than the pretherapy value, was not associated with a decline in CD4 cell count *(92, 93)*.

[4] WHO headquarters notes that the optimal viral load value at which ART should be switched has not been defined. However, values of more than 10 000 copies/ml have been associated with subsequent clinical progression and appreciable CD4 cell count decline. In resource-limited settings, WHO, at the global level, has provisionally opted for 10 000 copies/ml, as an interim recommendation for switching to second-line HAART, if the VL indicator is used as a criterion *(85)*.

4.5. Second-line HAART regimen

- When failure of the first-line regimen has been identified, it is recommended that all drugs are changed and then the patient switches to second-line treatment.
- Second-line ART is the next regimen used in sequence immediately after first-line ART has failed. The PI class is reserved for second-line use. Ideally, ritonavir-boosted PIs are recommended, supported by two agents from the NRTI class. See Table 9 for second-line ARV regimens.

Table 9. Recommended second-line HAART for adults and adolescents

First-line HAART regimens	Second-line HAART regimens after treatment failure
ZDV + 3TC + (EFV or NVP)	**LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ABC or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + TDF + ABC or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + TDF + (ZDV + 3TC)[b]
TDF + FTC + (EFV or NVP)	**LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ABC or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ZDV
ABC + 3TC + (EFV or NVP)	**LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ZDV or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ZDV + TDF (+ 3TC)[b]

[a] LPV/r is listed as the preferred RTV-boosted PI in this table, but other boosted PIs can be substituted, based on individual programme priorities. ATV/r, SQV/r, FPV/r and IDV/r are all possibilities. In the absence of a cold chain, NFV can be employed as the PI component, but it is considered less potent than an RTV-boosted PI.

[b] ZDV + 3TC are listed here for strategic use since resistance to both is predicted following failure of the listed first-line regimen. ZDV may prevent or delay the emergence of the K65R mutation; 3TC will maintain the M184V mutation, which may decrease viral replicative capacity as well as induce some degree of viral resensitization to ZDV. It must be stressed that the clinical efficacy of this strategy has not been proven.

(For recommended dosages of ARVs, please refer to Annex 4.)

4.5.1. Considerations for NRTI component

- Minimum changes for a second-line regimen are two new NRTI drugs. Never change only one drug in cases of suspected resistance.
- If the first-line ART included ZDV + 3TC, then ABC in combination with ddI (or TDF with dose-adjusted ddI and close monitoring) may be an option *(94)*.
- Patients who began with TDF or ABC may now benefit from ZDV *(95)*, due to the higher likelihood of resistance. For instance, the K65R mutation promoted by TDF and ABC increases susceptibility to ZDV *(96, 97)*.
- 3TC is also useful in cases of 3TC resistance, as the regularly acquired 184V mutation reduces viral fitness and also increases susceptibility to ZDV *(96)*.

4.5.2. Considerations for PI component

- With a first-line regimen containing a NNRTI, second-line ART should include a PI.
- In the PI class, the majority of drugs are boosted with a low dose of RTV, itself a PI, 100 mg BID – except nelfinavir (NFV), which is boosted not chemically but with food. The means of boosting is ritonavir's inhibition of the cytochrome P450 (CYP) 3A4 isoenzyme. Subsequently, the drug levels of the main PIs (except NFV) are increased *(98)*. RTV is used only for boosting other PIs and is not effective as a stand-alone ARV.
- The differences among the PIs lie in the number of mutations needed to develop resistance and in the profile of their side-effects.
- One of the highest genetic barriers for resistance is documented for LPV/r *(99)*.
- The resistance profiles of ritonavir-boosted atazanavir (ATV/r), fosamprenavir (FPV/r), indinavir (IDV/r) and SQV/r show slight differences that have little or no clinical impact.

- NFV seems to be inferior to the other PIs, but it is well documented in pregnant women. In case of failure, the D30N mutation is usually selected; it does not encode for cross-resistance for other PIs *(100, 101)*.
- LPV/r is the PI of choice due to its well-documented potency *(102)*, availability as a FDC and relatively low pill burden and good tolerance. A new tablet formulation of LPV/r has been approved in Europe requiring two pills BID and no refrigeration *(103)*.
- Recent studies *(104, 105)* showed similar efficacy of SQV/r and FPV/r to LPV/r, but in ARV naive patients. The pro-drug formulation of amprenavir (APV) in the form of FPV, the once-daily PI ATV and the new formulation of SQV (500 mg tablets) have not been directly tested against LPV/r. Therefore, only indirect data are available. Further studies with head to head comparisons among boosted PIs in ARV experienced individuals are needed.
- Possible side effects, comorbidities, drug interactions and individual preferences should influence the choice of PI.
- If first-line ART regimens containing PIs fail, the choice of a second-line regimen is mainly based on resistance profiles. If resistance profiles are not available, then resistance to the PIs contained in the first-line regimen must be assumed to be the cause of the regimen's failure (see section II.4.4 above for success and failure criteria).
- Possible options in the event a first-line regimen with a PI fails:
  - ZDV + 3TC + PI/r → ABC + ddI + NNRTI
  - or one of the salvage options (see section II.4.6 below).

4.6. Salvage regimens

In case of confirmed second-line ARV treatment failure (using virological, immunological or clinical criteria), a salvage regimen should be considered. Salvage regimens are combinations of drugs that will probably work even against viruses that are partly drug resistant. Every regimen after second-line treatment is complicated and requires a high level of ART knowledge and skill on the part of the healthcare provider. Performing a resistance test in these circumstances is highly desirable. It is at times better to wait several months before initiating salvage treatment, although this strategy can be dangerous, particularly if the CD4 cell count is low.

- If possible two effective drugs should be added, for example the fusion inhibitor enfuviztide (ENF) *(106)*, which is administered twice daily with subcutaneous application, and the new boosted PIs TPV/r *(107, 108)* or boosted darunavir (DRV/r) *(108–112)*.
- The genetic barrier of TPV/r seems to be even higher than that of LPV/r, and data show its efficacy to be comparable or better than the latter's *(113)*. This PI is presently used only for salvage regimens.
- Another option is a combination of two PIs *(114–117)*, except boosted tipranavir (TPV/r), which is not to be combined with any other PIs.

(For recommended dosages, please refer to Annex 4.)

4.7. Structured treatment interruption

Most ART providers are opposed to planned interruptions, but there are conditions that may justify them. For example, constant CD4 count >500 cells/mm^3 with completely suppressed virus for years may offer such an opportunity. Although it is not necessary to interrupt, it is better to do so than to face poor adherence followed by the development of resistant strains. During structured treatment interruption, the CD4 cell count normally falls rapidly to pre-ART levels; thus, it is imperative to monitor monthly counts during the first three months, then once every three months. Some patients continue to maintain satisfactory CD4 cell count (usually >350 cells/mm^3) with a low VL (1000–5000 copies/ml) for months and years. The scientific investigation of this issue is continuing *(118–122)*, and involves discussions particularly among the self-help groups and ART providers. However, a recent multicentric trial conducted in the United States demonstrated that this strategy can be associated with an increased risk of HIV disease progression, occurrence of non-AIDS re-

lated complications (kidney, liver and cardiovascular disease) and death *(123)*, which motivated the interruption of the specific arm study using the structured treatment interruption strategy. Because of these results and the lack of definitive evidence of the benefits of structured treatment interruptions strategies in other studies, WHO does not recommend this approach outside clinical trials.

5. Clinical monitoring of patients with HIV

Once a person has been diagnosed with HIV infection, a continuum of care and monitoring should be ensured.

5.1. Monitoring of laboratory indicators before ART

- CD4 cell count
  - Repeat every six months, unless there are unexpected results (rapid fall of CD4 cells count or diagnosis of opportunistic infection).
  - If starting ART is under discussion (CD4 count is 350 cells/mm^3 or less), repeat CD4 count every three months. Statistically, every patient has a median average loss of 50 CD4 cells/mm3 per year, but they can also drop very quickly, especially with concomitant infection.
- Viral load
  - Although viral load testing is expensive, the costs of unmonitored ART are much higher (useless drugs, hospital admission in case of failure), as well as bringing a much higher risk for further transmission of HIV due to higher infectivity from an elevated viral load.
  - If possible, viral load should be monitored in the same interval as CD4 cell count. The result gives a hint about the intensity of viral replication; low viral load (1000–5000 copies/ml) indicates slow progression, high viral load (>100 000 copies/ml) indicates a high risk for rapid progression.
- The general laboratory testing panel (see Table 3 above) should be repeated every six months if there are no changes with regard to initiation of ART or other circumstances (comorbidities, pregnancy, etc.).

5.2. Monitoring of laboratory indicators in ART patients

Successful ART is first reflected by the decrease of viral load; immunological response is a result of viral load, and thus occurs later. ART monitoring is best done with viral load and CD4 count both.

- Viral load
  - VL should be measured after 4–8 weeks for assessment of whether the regimen is successful. Viral load usually falls below the assay's limits of detection within 16–24 weeks.
  - Subsequent monitoring of viral load should be done in intervals of three to four months.
  - Once viral load is below the testing threshold which is <50 copies/ml (or 60 or 70 copies/ml, depending on the available test), it should remain there.
- CD4 cell count should be repeated every six months, except in case of clinical failure.
- The general laboratory testing panel (see Table 3 above) should be repeated every six months if there are no changes in ART or other circumstances.
- Depending on specific ARVs used, the frequency for laboratory testing might differ. See Table 10.

Table 10.	Frequency of laboratory testing, generally and with specific ARV use							
	Baseline	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48**
Viral load	X			X		X	X	X
CD4 count	X			X		X	(X)	X
Complete blood count	X		X	X	X (ZDV)	X	(X)	X
Liver Function Test (LFT)	X	X (NVP)	X	X (NVP, ZDV, PIs)	X (NVP, PIs)	X	(X)	X
Cholesterol triglycerides	X (PIs)				X (PIs)			X (PIs)
Renal function test	X	X (TDF)	X (TDF, IDV)			X	(X)	X

X: laboratory tests to be performed irrespective of the ARVs being administered; **X (ARV)**: laboratory tests to be performed if an ARV in parentheses is being administered; (**X**): optional test.

5.3. Immune reconstitution inflammatory syndrome

IRIS happens after initiating ART, more often with CD4 counts <100 cells/mm^3. If a dormant opportunistic infection is not diagnosed because of missing clinical symptoms, there may be an inflammatory reaction after initiating ART, due to an improved and activated immune system, leading to diagnosis of the OI *(124, 125)*. This may occur in up to a third of persons with TB who initiate ART *(85)* (for further information on IRIS in TB/HIV coinfected patients, refer to Protocol 4, *Management of tuberculosis and HIV coinfection*). The OI often presents differently than usual, for example, in abscesses with *Mycobacterium avium-intracellulare* (MAI) or curious chest X-rays with PCP. The incidence of IRIS is probably about 10%. MAI and CMV are the most common OIs, but worsening of a treated PCP may also occur *(126)*. In principle, ART should be continued along with treatment of the OI. Low-dose prednisone or prednisolone (20–60 mg/day) may help. ART should be discontinued if irregularly taken due to side-effects of OI treatment or if there is pain with oesophagitis (CMV, herpes, candidiasis).

5.4. Monitoring adherence

Every patient's adherence to ART should be measured and recorded during routine clinical visits. While there are tools for monitoring adherence (see Annex 5), the preferred method is a standardized questionnaire for 14 days or one month.

Viral load rebound should always prompt physicians to discuss adherence behavior with their patients. The use of open questions that acknowledge customary low adherence is more likely to elicit full responses.

Optimizing adherence in the first four to six months of treatment is crucial to ensuring long-term immunovirological success *(127)*. Several interventions are possible, but priority should be given to interventions aimed at improving adherence in the early months of ART *(127–131)*.

Staff should provide individualized support to adherence, based on the needs of each patient at any time during treatment. At every patient visit, health care providers have to ensure that every patient:

- has emotional and practical living support
- fits the drug regimen into a daily routine
- understands that non-adherence leads to resistance
- recognizes that all doses **must** be taken
- feels comfortable taking drugs in front of others
- keeps clinical appointments

- understands ARV interactions and side-effects
- knows alarm signals and when to see a doctor about them *(132, 133)*.

Once a patient is already on ART, additional issues may arise which also need to be addressed in a timely fashion:
- treating depression to enhance adherence and improve long-term outcomes *(134)*; and
- management of drug interactions and dosages.

5.5. Management of ARV toxicity and side-effects

Side-effects are common with ARVs, especially PIs. See Table 11.
- LPV/r and NFV can cause severe diarrhoea.
- LPV/r is associated with hyperlipidaemia (especially high triglycerides).
- Problems with lipid metabolism can occur with nearly all PIs.
- Long-term studies of side-effects and increased risk for cardiovascular complications are needed.

Toxicity might be a reason for substitution of prescribed ARV to another ARV drug within the same regimen. Switching to another treatment regimen due to toxicity is not recommended.

Table 11. Documented toxicity of ARVs and suggestions for management

ARV	Toxicity	Management
Hepatic necrosis (life-threatening)		
NVP	• Fever, rash (50%), nausea, vomiting, eosinophilia, elevation of ALT/AST • Usually in first 6–18 weeks, rare after 48 weeks • 1–2% of all NVP treated individuals, higher if CD4 count >250 in females and >400 in males	• Monitor LFT at weeks 2, 4, 8 and 16, and then every three months. • Treatment is symptomatic. • Hepatic necrosis is life threatening; in severe clinical situations, stop drugs at once.
Lactic acidosis (life-threatening)		
From highest to lowest risk: • d4T with ddI • ddI • d4T • ZDV	• Nausea, vomiting, wasting, fatigue, pancreatitis, multiorgan failure, acute respiratory distress syndrome (ARDS) • 1–10 per 1 000 patients/year for ddI and d4T	• Monitor lactic acid clinically. If suspected, look for early indicators (creatine kinase (CK), HCO_3). • The symptomatic treatment is bicarbonate against acidosis. • Change to ABC, TDF, 3TC, FTC.
Hypersensitivity (life threatening in case of re-exposure: anaphylactic shock)		
ABC	• Nearly always fever and rash, also fatigue and nausea • 5%, rare after six weeks	• Monitor skin, do not start together with other rash-producing drugs. • Stop ABC, do not use again if diagnosis is firmly suspected. • Change to ZDV, TDF or d4T.
Stevens–Johnson syndrome, toxic epidermal necrolysis		
NVP Less with EFV	• Fever, rash with blistering, myalgia • NVP: 0.3%, EFV: 0.1%	• Monitor skin. • Administer antibiotics and intensive care of wounds, perhaps in a burns centre.
Pancreatitis		
From highest to lowest risk: • d4T with ddI • ddI • d4T	• Pain, high levels of lipase • ddI 1–7%, less with dose adjustment	• Monitor lipase level. • The symptomatic treatment is pain medication, parenteral nutrition, drug stoppage. • Change to ZDV or TDF or ABC.

ARV	Toxicity	Management
Nephrotoxicity		
TDF	• Renal failure and Fanconi syndrome • More frequent in individuals with baseline renal dysfunction *(135)*	• Monitor creatinine, history of renal failure. • Treatment is symptomatic. • Eventually try again with dose adjustment of TDF (creatinine clearance is needed: TDF every second day). • Change TDF to ZDV, ABC or d4T.
Anaemia		
ZDV	• Anaemia and neutropenia (slight decrease is normal with ZDV) • 1–4%, dose dependent	• Monitor blood count after 2, 4, 8 and 12 weeks. Macrocytosis with light anaemia (haemoglobin up to 10 g/dl or 100 g/litre) is common. • Treatment is a transfusion of erythropoetin (very expensive) or changing ZDV to another NRTI (TDF, ABC or d4T).
Peripheral neuropathy		
d-drugs: ddI, d4T	• Pain/paraesthesia of extremities • 10–30%, also after years	• Monitor peripheral nerves, warn patient. • Treatment is pain management, change of ART. Stop d-drug, change to another NRTI (ZDV, TDF, ABC).
Fat atrophy		
d4T and other NRTIs	• Reduced buccal fat and extremity fat • Common with long use (mitochondrial toxicity)	• Monitor and compare to previous pictures. • Change d4T to TDF or ABC. If atrophy is irreversible, plastic surgery is indicated.
Fat accumulation		
PIs	• Increased abdominal fat ("crixi belly"), breast size, buffalo hump • 20–80%	• Measure and compare to previous pictures. • Change to NNRTI if lipodystrophy/lipoatrophy is not tolerable. Plastic surgery may be indicated.
Rash		
NNRTI > APV/FPV > ABC	• Maculopapular itching • 15% NNRTI, APV ~20%, ABC 5%	• Monitor fever, LFT, CK in close visits. • Think of other allergenic drugs (sulfamethoxazole/trimethoprim and other antibiotics, prophylaxis). Rashes sometimes resolve spontaneously with continued ART. • Change NVP to EFV or vice versa. If no improvement, try a new regimen.
Elevation of transaminase		
NNRTIs (all) and PIs (all)	• Otherwise unexplained elevation of LFT • 8–15% with PI and NNRTI • More frequent in patients with chronic HBV or HCV	• Monitor ALT every three months, look for other reasons (drugs, hepatitis). • Elevation often resolves with continuation of NNRTI or PI. • Discontinue NNRTI or PI.
Gastrointestinal intolerance		
PIs (all), ZDV, ddI	• Nausea and vomiting, diarrhoea • Common	• Rule out other reasons (IRIS with CMV colitis, cryptosporidiosis, microsporidiosis, also weeks after initiating ART). • Treatment is loperamide if there is no other reason for diarrhoea; metoclopramide, Zofrane for nausea and vomiting.

ARV	Toxicity	Management
Central nervous system (CNS) toxicity		
EFV	• Nightmares, impaired concentration, depression (risk of suicide) • 50%	• Warn patient, take psychiatric history, refer to psychiatric consultation. • Treatment usually not necessary, resolves in 5–21 days.
Insulin resistance		
PIs (all but ATV), especially IDV	• Elevated glucose tolerance, elevated glucose with morning fasting • 5%	• Monitor fasting blood glucose. • Treatment is via diet and exercise, metformin or Glitazone. • Change PI to NNRTI.
Hyperlipidaemia		
d4T > PIs (all but ATV)	• Increased lipids, increased LDL, cholesterol, triglycerides (for the last, d4T is particularly prominent) • % varies	• Monitor fasting lipid levels at initiation of ART and every six months. • Treatment is per lipid, cholesterol and triglyceride guidelines. • Use statins and fibrates. Be careful with interactions (no simvastatin, no lovastatin).
Hyperbilirubaemia		
ATV > IDV	• Elevation of bilirubin (harmless; possible itching, no prolonged liver damage, reversible) • Frequency varies	• Monitor bilirubin and clinical symptoms. • Stop drug only if not tolerated. Change PI.
Nephrolithiasis		
IDV	• Abdominal pain, haematuria, renal colic • 10–20% per year, less with >3 litre fluid/day	• Monitor urinalysis, creatinine. • Treatment is the same as for nephrolithiasis.

Source: *Bartlett (136).*

5.6. Drug interactions

Drug interaction can be a severe problem in ART. PLHIV need to take a good deal of different agents due to concomitant diseases or manifestation of HIV and AIDS.

Though some drugs are genuinely contraindicated, most drugs that show interactions can still be given in combination; however, the probability of side-effects is then greater, and they should be closely monitored. The effectiveness of contraceptives could also be jeopardized. (See also Protocol 9, *Support for sexual and reproductive health of people living with HIV.*) Tables 12 and 13 illustrate interactions of drugs with NNRTIs and with PIs.

Table 12. NNRTI interaction with selected drugs

NNRTI (drug A)[a]		With … (drug B)	Effect	Significance [b]
EFV	NVP			
+		Ergotamine	↑ level of B	++(avoid)
	+	Antiarrhythmics: lidocaine, amiodarone, others	↑ and ↓ level of B	++(caution)
+	+	Anticonsulvants: carbamazepine, phenytoin, phenobarbital	↓ level of B and/or A; use gabapentin instead	++
(+)[c]	+	Itraconazole, ketoconazole	(–)[c] level of B	+
	+	Cyclosporine, tarolimus, Rapamycin	↑ level of B	++
	+	Calcium channel blockers	↑ level of B	++
+	+	Sildenafil, vardenafil, tadalafil	↑ level of B	++
	+	Fentanyl	↑ level of A	++
+	+	Methadone	↓ level of B	++
+	+	Contraceptives	↑ and ↓ level of B	++
+	+	Rifampin, rifabutin	↑ and ↓ level of B, ↓ level of A (caution)	++
+	+	St John's wort	↓ level of B	++
+	+	Warfarin	↑ level of B	++

[a] + *or* ++ under drug A shows the drug strength in changing the level of drug B.
[b] Significance: + probable importance, ++ definite clinical importance.
[c] (+) or (–) indicates inconsistent results.
Sources: Sande & Eliopoulos; Gilbert, Moellering & Eliopoulos; Antoniu & Tseng *(137–139)*.

Examples of how the tables should be read are as follows.
1. In Table 12 line 6: EFV strongly increases the levels of midazolam, alprazolam and triazolam while NVP does so less strongly. The significance of this is that there is a definite clinical importance; however, these drugs can still be coadministered.
2. In Table 13 line 4: APV, IDV LPV, NFV, RTV and SQV all increase the levels of carbamazepine, clonazepam, phenytoin and phenobartial while these drugs in turn decrease the levels of the those PIs. The significance of this is that there is definite clinical importance. The combination of any of these should be avoided.

Table 13. Protease inhibitors interactions with selected drugs

Protease inhibitor (drug A) [a]							With … (drug B)	Effect	Significance [b]
APV	ATV	IDV	LPV	NFV	RTV	SQV			
					+		Fentanyl, tramadol, hydrocodon	↑ level of drug B	+
			+		+		Codeine, morphine, methadone	↓ level of drug B	+
+	+	+	+	+	+	+	Amiodaron, lidocaine, flecainide	↑ level of drug B	+
+		+	+	+	+	+	Carbamazepine, clonazepam, phenytoin, phenobarbital	↑ level of drug B ↓ level of drug A	++(avoid)
+	+	+			+		Tricyclic antidepressants	↑ level of drug B	+
	+				+		All other antidepressants	↑ level of drug B	+
					+		Loratadine	↑ level of drug B	++

Protease inhibitor (drug A) [a]							With … (drug B)	Effect	Significance [b]
APV	**ATV**	**IDV**	**LPV**	**NFV**	**RTV**	**SQV**			
			+				Atovaquone	↓ level of drug B	+
+	+	+	++	+	+	++	Benzodiazepine	↑ level of drug B	++
					+		Beta blockers	↑ level of drug B	+
+	+	+	+	+	+	+	Calcium channel blockers	↑ level of drug B	++
	+				+	+	Clarithromycin, erythromycin in renal impairment	↑ level of drug B	+(caution)
+		+		+	+	+	Clarithromycin, erythromycin	↑ level of drug B and drug A	+
	+		+	+	+		Contraceptives	↑ level of drug B	++
+			+		+	+	Corticosteroids	↑ level of drug B ↓ level of drug A	+
+	+	+	+	+	+	+	Cyclosporine	↑ level of drug B	+
+	+	+	+	+	+	+	Ergot derivatives	↑ level of drug B	++(avoid)
+	++	+	+	+	+	+	Proton pump inhibitors (PPIs)	↓ level of drug A	+(caution) (++, ATV-avoid)
+	++	+	+	+	+	+	H_2 antagonists	↓ level of drug A	++ (caution) (++, ATV-avoid)
+	+	+	+	+	+	+	Lovastatin, simvastatin	↑ level of drug B	++(avoid)
	+						Irinotecan	↑ level of drug B	++(avoid)
+		+	+	+		+	Ketoconazole, itraconazole	↑ level of drug B ↑ level of drug A	+
+	+	+	+	+	+	+	Pimozide	↑ level of drug B	++(avoid)
+	+	+	+	+	+	+	Rifampin	↑ level of drug B ↓ level of drug A	++(avoid)
+	+	+	+	+	+	+	Rifabutin	↑ level of drug B ↓ level of drug A	+(caution, dose adjustment)
+	+	+	+	+	+	+	Sildenafil	Some ↑, some ↑ level of drug B	++
+	+	+	+	+	+	+	St John's wort	↓ level of drug A	++(avoid)
	+						Tenofovir	↓ level of drug A	++(add RTV)
		+	+		+		Theophyline	↓ level of drug B	+
+	+		+		+		Warfarin	↑ level of drug B	+

[a] + *or* ++ under drug A shows the drug strength in changing the level of drug B.
[b] Significance: + probable importance; ++ definite clinical importance.
Sources: Sande & Eliopoulos, Gilbert, Moellering & Eliopoulos, Antoniu & Tseng *(137–139)*.

III. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to treatment and its success. Such indicators assist managers in decision-making on ways to strengthen and expand these services to all who need them.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV patients "seen for care" (seen at least once in the previous 12 months);
- number of HIV patients seen for care who are eligible for ART (CD4 <350 cells/mm^3);
- number of HIV patients seen for care initiating HAART;
- number of HIV patients seen for care receiving first-line HAART;
- number of HIV patients on HAART changing from first-line HAART to second-line HAART;
- number of HIV patients on HAART changing from second-line HAART to salvage HAART;
- number of HIV patients interrupting ART treatment, including the reason (e.g. death, toxicity/side effects, loss to follow-up, ARVs not available, etc.);
- number of patients who died while on HAART, including cause of death (e.g. HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide);
- number of HIV patients who died within the first 12 months of initiating HAART; and
- number of deaths among all HIV patients including cause of death (e.g. HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

Annex 1. Essential information on personal history of HIV/AIDS treatment

Table 14.	Essential information on personal history of HIV/AIDS treatment					
Date	CD4 cells/ mm^3	%	VL copies/ml	Current ART	Resistance (genotype or phenotype)	Previous ART regimens, reasons for changing

Annex 2. Revised WHO clinical staging of HIV/AIDS for adults and adolescents

(Interim European Region version for people aged ≥15 years with positive HIV antibody test or other laboratory evidence of HIV infection)

Acute HIV infection
- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1
- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Clinical Stage 2
- Seborrhoeic dermatitis
- Angular cheilitis
- Recurrent oral ulcerations (two or more episodes in six months)
- Herpes zoster (extensive zoster across one dermatome)
- Recurrent respiratory tract infections (two or more episodes in any six-month period of sinusitis, otitis media, bronchitis, pharyngitis, tracheitis)
- Fungal nail infections
- Papular pruritic eruptions

Clinical Stage 3
- Oral hairy leukoplakia
- Unexplained chronic diarrhoea for longer than one month
- Recurrent oral candidiasis (two or more episodes in six months)
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Clinical Stage 4a
- Pulmonary tuberculosis
- Extrapulmonary tuberculosis (excluding lymphadenopathy)
- Unexplained weight loss (more than 10% within six months)
- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia (two or more episodes within one year)
- CMV retinitis (±colitis)
- Herpes simplex virus (HSV) (chronic or persistent for at least one month)
- HIV-associated encephalopathy
- HIV-associated cardiomyopathy
- HIV-associated nephropathy
- Progressive multifocal leukoencephalopathy (PML)
- Kaposi sarcoma and HIV-related malignancies
- Toxoplasmosis
- Disseminated fungal infection (e.g. candida, coccidomycosis, histoplasmosis)
- Cryptosporidiosis
- Cryptoccocal meningitis
- Non-tuberculous mycobacterial infection or disseminated mycobacteria other than tubercle bacilli (MOTT)

[a] Possibly to be included in Stage 4 if supported by sufficient evidence: anal cancer and lymphoma (T-cell Hodgkin lymphoma).
Source: WHO Regional Office for Europe *(140).*

Annex 3. Resistance tests

Resistance testing needs a minimum of 500–1000 copies/ml; it is not possible with completely suppressed virus.

Genotypic resistance testing is based on the analysis of RNA mutations. The amplified genome is sequenced. Known mutations are encoded for changed susceptibility of the virus. It is an indirect proof of drug resistance. The resistant virus population has to be higher than 20% of the whole population.

Virtual phenotypic resistance testing uses computer-based algorithms of genotypic tests connected with large data banks for interpreting results.

Phenotypic resistance testing, like microbiological susceptibility testing, examines the ability of viruses to replicate in cell culture in the presence of different agents. It is compared to the same ability of wild-type virus. The 50% inhibitory concentration (IC50) is a marker of drug potency. The results of the test show different grades of susceptibility.

Which resistance test to use

All tests are presently very expensive. Genotypic tests cost €400, phenotypic tests cost €800 (2005). The time between taking the sample and achieving results can be weeks. Basic genotypic testing should show enough evidence for further planning of regimens. First- and second-line regimens do not require the more expensive phenotypic test. When there is a confused ART history, with a lot of already known mutations or an inexplicable treatment failure, a phenotypic test might be justified. For all tests, the individual has to continue taking the failing regimen; otherwise, wild-type virus will overgrow the resistant strains. There are no standardized recommendations for the use of either phenotypic or genotypic resistance testing.

Annex 4. Essential information about ARVs

Table 15. Essential ARV drug information

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile (major and minor)
NRTIs						
Abacavir	ABC	300 mg	300 mg tablet BID or 600 mg OD	No re-exposure if history of hypersensitivity reaction.	Hypersensitivity reaction (fever, rash, and influenza-like symptoms such as GI and pulmonary symptoms)	65R, 74V, 115F, 184V/I
Didanosine	ddI	250 mg 400 mg	Patients ≥60 kg: 400 mg tablet OD Patients <60 kg: 250 mg tablet OD	Two hours after meal, dose reduction with TDF; not in combination with ribavarin.	Peripheral polyneuropathy, pancreatitis, lactic acidosis	65R, 74V
Emtricitabine	FTC	200 mg	200 mg capsule OD		Same as 3TC	65R, 184V/I
Lamivudine	3TC	300 mg 150 mg	300 mg tablet OD or 150 mg tablet BID		Rare diarrhoea	65R, 184V/I
Stavudine	d4T	30 mg	30 mg capsule BID	Not with ZDV.	Peripheral neuropathy, lipodystrophy, elevation of ALT/AST	41L, 67N, 70R, 75T/M/S/A, 210W, 215Y/F, 219Q/E
Tenofovir	TDF	300 mg	300 mg tablet OD	Dose reduction of ddI, not in combination with d4T; careful with renal insufficiency (dose reduction).	Renal insufficiency	41L, 65R, 210W
Zidovudine	ZDV	300 mg	300 mg tablet BID	Not with d4T; better susceptibility when 65R and 184V.	Anaemia, GI, headache	41L, 67N, 70R, 210W, 215Y/F, 219Q/E
ABC + 3TC	KVX	600 mg ABC, 300 mg 3TC	1 tablet OD			
TDF + FTC	TVD	300 mg TDF, 200 mg FTC	1 tablet OD			
ZDV + 3TC	CBV	300 mg ZDV, 150 mg 3TC	1 tablet BID	Higher (historical) dose of ZDV (higher risk of side-effects).		
ZDV + 3TC + ABC	TZV	300 mg ZDV, 150 mg 3TC, 300 mg ABC	1 tablet BID	Not once daily.		

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile (major and minor)
NNRTIs						
Efavirenz	EFV	600 mg	600 mg tablet OD	Start in the evening.	Dizziness, sleeping disorders, psychiatric disorders (depression, risk of suicide)	100I, 101E, 103N, 106A/M, 108I, 181C, 188L, 190A/S, 225H, 230L
Nevirapine	NVP	200 mg	200 mg tablet BID	First 14 days 200 mg OD, then 200 mg BID.	Rash, liver enzyme elevation	100I, 101E, 103N, 106A/M, 108I, 179D/E, 181C/I, 188C/H, 190A/S, 230L
Delaverdine	DLV	200 mg 100 mg	200 mg × 2 tablets TID or 100 mg × 4 tablets TID	Not used in Europe.	Rash, GI symptoms, diarrhoea	K103N/S, Y181C/I, P236L, G190A/S/E/Q/C, Y188L/H/C, V106A/M, K101E/P, M230L, K238T/N, F318L, V179D/E
PIs						
Atazanavir	ATV	300 mg	300 mg capsules OD plus 100 mg capsules RTV OD	Dosage for treatment experienced patients. Use with RTV.	Bilirubin elevation (harmless)	24I, 33F/I/V, 36I/L/V, 46I/L, 50L, 54V/L/M/T, 82A/F/T/S, 84V, 88S, 90M
Fosamprenavir	FPV	700 mg	700 mg tablet BID plus 100 mg capsule RTV BID	Dosage for treatment experienced patients. Use with RTV.	Rash, headache, diarrhoea, dyslipidaemia	32I,47V, 50V, 54L/M, 82A/F/T/S, 84V
Indinavir	IDV	400 mg	400 mg capsules BID plus 100 mg capsule RTV BID	Use with RTV.	Kidney stones, dyslipidaemia	24I, 32I, 36I, 46I/L, 54V, 82A/F/T/S, 84V, 90M
Lopinavir/ritonavir fixed combination	LPV/r	133 mg/33 mg 200 mg/50 mg	(133 mg/33 mg) × 3 capsules BID or (200 mg/50 mg) × 2 tablets BID	Old formulation required refrigeration; new formulation does not; once daily under discussion.	Diarrhoea, meteorism, dyslipidaemia	10I/R/V, 20M/R, 24I, 32I, 33I/F/V, 46I/L, 53L, 54V/L, 63P, 71V, 82A/F/T, 84V, 90M
Nelfinavir	NFV	250 mg 625 mg	625 mg × 2 tablets BID or 250 mg × 5 tablets BID	With meal, resorption increases 270%; no booster with RTV.	Diarrhoea, meteorism	30N, 36I, 46I/L, 54V/L/M/T, 82A/F/T/S, 84V, 88D/S, 90M
Ritonavir	RTV	100 mg	Only as a booster		Dyslipidaemia, liver enzyme elevation, diarrhoea	
Saquinavir	SQV	500 mg	500 mg × 2 capsules BID plus 100 mg capsule RTV BID	New 500 mg tablets; was in 200 mg tablets until 2004. Use with RTV.	Diarrhoea and other GI symptoms, dyslipidaemia	48V, 53L, 54V/L, 82A/F/T, 84V, 90M
Tipranavir	TPV	250 mg	250 mg × 2 capsules BID plus 100 mg × 2 capsules RTV BID	Dosage for treatment experienced patients. Do not combine with other PIs. Use with RTV.	Dyslipidaemia (severe), liver enzyme elevation, diarrhoea	13L/V, 20M/R/V, 33F/I, 35D/N, 36I, 45R, 46I/L, 47V, 54A/M/T/V, 58E, 66F, 69K, 71I/K, 74P, 82F/L/T, 84C/V, 90M, 91S

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile (major and minor)
Fusion inhibitors						
Enfuvirtide	ENF	90 mg	90 mg/ml subcutaneous injection BID	No oral formulation.	Skin reaction (itching, swelling, pain)	gp41 single point mutation or gp 41 double and triple point mutations between positions 36 and 45; gp 41 mutation outside of position 36-45

Sources: Adapted from Sande & Eliopoulos, Gilbert, Moellering & Eliopoulos, Antoniu & Tseng, IAPAC *(137–139, 141)*.

Annex 5. Tools for adherence monitoring

Self-reporting is a good adherence marker, but it is not perfect. It seems to overestimate ART adherence more than other methods *(142)*. To be effective, the patient must be willing to disclose problems, particularly face to face. This method may be important in reinforcing the central role of patients in managing their own adherence, as opposed to provider-controlled methods.

Provider estimates of adherence have been demonstrated to be poor *(143)* and are not advisable.

Drug-level monitoring is expensive and not yet possible for all ARVs. It is not a method for routine control of adherence, and can only reveal a snapshot of the time the sample is taken *(144)*. In case of low plasma drug levels, adherence has to be discussed. Laboratory markers like mean corpuscular volume of erythrocytes might show adherence to ZDV and to a lesser extent d4T.

Medication Event Monitoring System (MEMS) is frequently used in research settings. An electronic device fitted to pill boxes records the removal of the cap. It is associated with predictable virological response to ART *(145)*. It is not possible with blister packs.

Pill counts and pharmacy records may be seen as an unwelcome attempt of health care providers to police adherence. They are time-consuming and require patients to bring their medication with them.

Pill identification test (PIT) is a novel method that correlates with validated self-reporting measures *(146)*. Patients are invited to distinguish the pills of their regimen from a display of ARVs, including two "twin pills", which are similar but not identical to their own.

The use of **surrogate markers** is reliable but too late when poor adherence is revealed. Individuals with virological failure on a PI-containing regimen had low PI blood levels, low adherence levels by pill count and an absence of genotypic resistance to PIs, suggesting their treatment failure had been caused by low adherence *(147, 148)*. Providers have to be careful with interpretation of these markers, however, because of other possible reasons for low drug levels *(145)*.

Annex 6. List of antiretroviral drugs[5]

Table 16. Antiretroviral drug list

International non-proprietary name (INN)	Proprietary name	Pharmaceutical company
NRTIs		
Abacavir (ABC)	Epzicom *US*, Kivexa *United Kingdom* (lamivudine/abacavir) Trizivir *Europe, United Kingdom, US* (zidovudine/lamivudine/abacavir) Ziagen *United Kingdom, United States*	*GlaxoSmithKline*
	Abavir	*Genixpharma*
	Virol Virol LZ (abacavir/lamivudine/zidovudine)	*Ranbaxy*
Didanosine (ddI)	Videx, Videx EC	*Bristol-Myers Squibb*
	Dinex EC Odivir Kit (didanosine/lamivudine/efavirenz)	*Cipla*
	Aviro-Z Virosine Viro-Z	*Ranbaxy (India)*
	Divir	*Thai Government*
Emtricitabine (FTC)	ATRIPLA (efavirenz/emtricitabine/tenofovir)	*Bristol-Myers Squibb and Gilead Sciences*
	Emtriva Truvada (tenovovir/emtricitabine)	*Gilead Sciences*
Lamivudine (3TC)	Combivir *United Kingdom, United States* (lamivudine/zidovudine) Epivir *United Kingdom, United States*, Zeffix *United Kingdom* Epzicom *United States*, Kivexa *United Kingdom* (lamivudine/abacavir) Trizivir *United Kingdom, United States* (zidovudine/lamivudine/abacavir)	*GlaxoSmithKline*
	Lamivox Stavex-L (lamivudine/stavudine) Stavex-LN (lamivudine/nevirapine/stavudine) Zidovex-L (lamivudine/zidovudine) Zidovex-LN (lamivudine/nevirapine/zidovudine)	*Aurobindo*
	Duovir (lamivudine/zidovudine) Duovir-N (lamivudine/nevirapine/zidovudine) Lamivir Odivir Kit (didanosine/lamivudine/efavirenz) Triomune (lamivudine/nevirapine/stavudine)	*Cipla*
	Heptavir Lamistar 30, Lamistar 40 (lamivudine/stavudine) Nevilast (lamivudine/nevirapine/stavudine) Zidolam (lamivudine/zidovudine)	*Genixpharma*
	Virolam Virocomb (lamivudine/zidovudine) Virolans (lamivudine/nevirapine/stavudine) Virolis (lamivudine/stavudine) Virol LZ, Abac-ALZ (abacavir/lamivudine/zidovudine)	*Ranbaxy*

[5] This list is a compilation of those ARVs that are widely used, and should not be construed to be exhaustive. It was accurate as of 31 July 2006. ***Disclaimer:*** The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.

International non-proprietary name (INN)	Proprietary name	Pharmaceutical company
Stavudine (d4T)	Zerit, Zerit XR	*Bristol-Myers Squibb*
	Stavex Stavex-L (lamivudine/stavudine) Stavex-LN (lamivudine/nevirapine/stavudine)	*Aurobindo*
	Stavir Lamivir-S (lamivudine/stavudine) Triomune (lamivudine/nevirapine/stavudine)	*Cipla*
	Lamistar (lamivudine/stavudine) Nevilast (lamivudine/nevirapine/stavudine) Stag	*Genixpharma*
	Stavir	*GPO (Thailand)*
	Avostav Triviro-LNS (lamivudine/nevirapine/stavudine) Virolans (lamivudine/nevirapine/stavudine) Virolis, Coviro (lamivudine/stavudine) Virostav	*Ranbaxy*
Tenofovir (TDF)	Truvada (tenofovir/emtricitabine) Viread (tenofovir)	*Gilead Sciences*
	ATRIPLA (efavirenz/emtricitabine/tenofovir)	*Bristol-Myers Squibb*
Triple nuceoside (TRZ)	Trizivir *United Kingdom, United States* (zidovudine/lamivudine/abacavir)	*GlaxoSmithKline*
Zidovudine (ZDV or AZT)	Combivir *United Kingdom, United States* (lamivudine/zidovudine) Retrovir *United Kingdom, United States* Trizivir *United Kingdom, United States* (zidovudine/lamivudine/abacavir)	*GlaxoSmithKline*
	Zidovex	*Auribindo*
	Zidovir Duovir (lamivudine/zidovudine)	*Cipla*
	Zido-H (zidovudine)	*Genixpharma*
	Antivir	*GPO (Thailand)*
	Aviro-Z Virocomb (lamivudine/zidovudine) Virol LZ (abacavir/lamivudine/zidovudine) Viro-Z	*Ranbaxy*
NNRTIs		
Delavirdine (DLV)	Rescriptor	*Pfizer, Inc*.
Efavirenz (EFV)	Sustiva *Europe, United Kingdom*, Stocrin *Australia, Europe, Latin America, South Africa* ATRIPLA (efavirenz/emtricitabine/tenofovir)	*Bristol-Myers Squibb*
	Viranz	*Aurobindo*
	Efavir	*Cipla*
	Estiva	*Genixpharma*
	Efferven	*Ranbaxy*

International non-proprietary name (INN)	Proprietary name	Pharmaceutical company
Nevirapine (NVP)	Viramune	*Boehringer Ingelheim*
	Nevirex Stavex LN (lamivudine/nevirapine/stavudine)	*Aurobindo*
	Duovir-N (lamivudine/nevirapine/zidovudine) Nevimune Triomune (lamivudine/nevirapine/stavudine)	*Cipla*
	Nevilast (lamivudine/nevirapine/stavudine)	*Genixpharma*
	GPOVir	*GPO (Thailand)*
	Nevipan Triviro LNS (lamivudine/nevirapine/stavudine) Virolans (lamivudine/nevirapine/stavudine) Zidovex-LN (lamivudine/nevirapine/zidovudine)	*Ranbaxy*
Fusion inhibitors		
Enfuvirtide, T-20	Fuzeon *United Kingdom, United States*	*Roche Pharmaceuticals & Trimeris, Inc.*
Protease inhibitors		
Amprenavir (APV)	Agenerase *United Kingdom, United States*	*GlaxoSmithKline*
Atazanavir (ATV)	Reyataz *Europe, United States*	*Bristol-Myers Squibb*
Fosamprenavir (FPV)	Lexiva *United States*, Telzir *United Kingdom*	*GlaxoSmithKline and Vertex*
Indinavir (IDV)	Crixivan	*Merck & Co.*
	Indivex	*Aurobinda*
	Indivir	*Cipla*
	Indivir	*Genixpharma*
	Virodin	*Ranbaxy*
Lopinavir/ritonavir combination (LPV/r)	Kaletra	*Abbott Laboratories*
Nelfinavir (NFV)	Viracept	*Pfizer, Inc., Roche Pharmaceuticals*
	Nelvex	*Aurobinda*
	Nelvir	*Cipla*
	Nelfin	*Genixpharma*
	Nefavir	*Ranbaxy*
Ritonavir (RTV)	Norvir	*Abbott Laboratories*
	Ritovir	*Hetero/Genix*
Saquinavir (SQV)	Fortovase *Europe, United Kingdom, United States* Invirase *United Kingdom, United States*	*Roche Pharmaceuticals*

Annex 7. Glossary

Adherence is patient ability to take ARV drugs as prescribed at specific time. High adherence is defined as taking over 95% of doses; low adherence is anything under this level.

Backbone is the part of ARV treatment, usually consisting of two NRTIs which are used in combination with an NNRTI or a PI or a PI and fusion inhibitor. “Optimized backbone” means an adjusted combination of probable working NRTIs based on results of resistance testing.

Genetic barrier is a description of the number of mutations needed for the virus to be resistant to a drug. Resistance with 1 mutation means a low genetic barrier; resistance with 10 mutations means a very high genetic barrier, though this characterization is subject to change.

Major mutations are the changes in viral RNA that encode for resistance to particular ART drugs or ART classes.

Minor mutations work in combination and can lead to resistance or counteract disadvantages of other major or minor mutations.

Nucleoside analogue mutations (NAMs) reveal cross-resistance for most NRTIs.

A **point mutation** is one change in the RNA code resulting in resistance to a drug or class of drugs. For example, in ART treatment mutation 103 means a resistance to all NNRTIs, resulting from changes in virus at specific point.

Resistance is the result of changing amino acids in the RNA strain of the virus. This happens due to the poor replication abilities of HIV. Most changes lead to the death of the virus; other changes are viable, and the resultant virus has the ability to survive the mechanisms of ART. In most cases, resistance leads to poorer viral fitness, meaning a slower HIV replication rate. Though a benefit for the patient at the beginning, it will result in total resistance and high replication rates of the less fit viruses. However, several combinations of resistance patterns can balance this disadvantage, so that some resistance patterns result in a fitter virus in the end.

Thymidine analogue mutations (TAMs) are usually a result of ZDV treatment.

Annex 8. Beyond the horizon

Research on ART continues. New viral mutations and drug resistance occur regularly – as do new understandings of the interactions between drugs and the virus. The following are some of the latest ARVs to be approved or to be pending approval, along with new combinations of older drugs.

- A once-daily fixed-dose combination of TDF + FTC + EFV has been recently developed and appears to be slightly more effective than the standard ZDV + 3TC + EFV combination *(42)*.
- TMC125 (etravirine) is a new NNRTI that has potencies despite existing mutations which encode for NNRTI class resistance *(149)*.
- DRV (darunavir) is a new PI with an even higher genetic barrier than LPV/r. Development of resistance is slower than with NFV, APV or LPV/r in vitro. TMC114 is available through an expanded access programme (EAP) *(150)*. It has been recently approved by the US Federal Drug Administration (FDA).
- AG1549 (capravirin) is also a second-generation NNRTI, which is effective despite classical NNRTI mutations.
- New coreceptor inhibitors in the fusions molecule are coming. CXCR4- and CCR5-expressing viruses are being fought with drugs that can inhibit one or both of them. New tests for the coreceptor expression of the virus are needed for this treatment. Side-effects are limited for now, though initial experience with this new class has revealed cardiotoxic effects. On August 6, 2007, FDA granted accelerated approval to Selzentry (maraviroc) for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral Replication and have HIV-1 strains resistant to multiple antiretroviral agents.

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