

REPUBLIC OF RWANDA



MINISTRY OF HEALTH

**NATIONAL GUIDELINES FOR COMPREHENSIVE
CARE OF PEOPLE LIVING WITH HIV IN RWANDA**

4th Edition, 2011

PREFACE

Despite the many advances in the fight against and control of HIV/AIDS in the last decades, HIV/AIDS still remains a major health problem in developing countries. With about 200.000 people living with HIV/AIDS in Rwanda, the expansion of antiretroviral treatment to reach all patients who meet the eligibility criteria is one of the priorities of the Ministry of Health. There is evidence that starting eligible HIV-infected patients on ART alleviates their suffering and reduces the devastating impact of the pandemic. This also presents a good opportunity for an efficient response by involving persons living with HIV/AIDS, their families and the communities in the provision of care. This will strengthen prevention of HIV by increasing knowledge and the demand for counseling and testing as well as reducing stigma and discrimination.



However, the expansion of antiretroviral treatment is a real challenge that can only be overcome by the participation of all partners, both national and international. Apart from the financial support that is clearly essential, there is the supply of drugs and the monitoring of the mechanisms that have to be set up. Health care providers must be trained, the infrastructure must be set up or upgraded, education of the community and mobilization of the different persons involved in the fight against HIV/AIDS so that they can play their roles, must be carried out.

Human capacity strengthening should occupy an important place during the process of training and mentoring of social workers, nurses, doctors and other people involved in the fight against HIV/AIDS. This capacity strengthening must also motivate health care providers so that they are capable of offering quality care services to patients over a long time.

This guide presents new knowledge and guidelines on the provision of care to persons living with HIV/AIDS, in accordance with the last guidelines of the World Health Organization (WHO) published in 2006 and adapted to the Rwandan national context. It thus responds to the need by the Ministry of Health to improve the skills of the actors in the health sector as well as the quality of care and antiretroviral treatment offered in both public and private health facilities countrywide.

We are fully aware that in spite of the progress made, there is still a lot to be done in the domain of treatment and prevention in order to maintain hope for the eradication of the pandemic of HIV from our country. May this publication contribute to improve the knowledge on HIV/AIDS of all actors in the health sector and in improving the living conditions of our population.

The Ministry of Health is finally grateful to all the organizations and persons who contributed to the development and revision of the national guidelines for the management of persons living with HIV in Rwanda; please accept our heartfelt gratitudes.



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ACCRONYMS AND ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
DNA	Desoxyribonucleic Acid
AES	Accident d'exposition au sang
RNA	Ribonucleic Acid
ARV	Antiretroviral
AZT	Azidotymidin
CD4	Variety of lymphocyte (T4)
CDC	Center for Diseases Control and Prevention
CMV	Cytomegalovirus
CTM	Cotrimoxazole
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
EFZ	Efavirenz
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IDR	Intradermoreaction
IDV	Indinavir
NNRTI	Non Nucleosidic Reverse Transcriptase Inhibitor
NRTI	Nucleosidic Reverse Transcriptase Inhibitor
OIs	Opportunistic Infection
PI	Protease Inhibitor
M	Months
NFV	Nelfinavir
NVP	Nevirapine
WHO	World Health Organization
UNAIDS	Organisation des nations unies pour la lutte contre le SIDA
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother To Child Transmission
PLWHIV	People Living with HIV
RTV	Ritonavir
TDF	Tenofovir
FTC	Emtricitabine
VCT	Voluntary Counseling and Testing
HIV	Human Immunodeficiency Virus
VZV	Varicella Zoster Virus

CHAPITRE I. THE HOLISTIC MANAGEMENT OF PERSONS LIVING WITH HIV

1.1. Definition and Aims

Holistic management (HM) is the medical, psychological and social care that takes into consideration all of the problems of the patient so as to be able to lead him/her towards a normal family, social and professional life.

It aims at:

- Ensuring an adequate level of care to the concerned patients;
- Reducing the mortality and morbidity related to HIV-AIDS;
- Increasing the quality of life of the concerned patients;
- Promoting prevention through increasing access to screening.

1.2. Principles Guiding the Holistic Management of HIV

HM is a product of teamwork among many different professionals who must work together in a complementary and synergistic manner so as to meet the different needs of every patient.

The work of the different providers must be carried out with the highest degree of confidentiality so as to establish and maintain the confidence of the patient and without which there cannot be efficient patient care and management. The smooth implementation of HM requires creation of an appropriate operational framework that will permit free exchanges between the different stakeholders: programming meetings, staff meetings, etc.

HM must ensure a continuum of care within the health facility as well as beyond the boundaries of that structure. This continuity necessitates the participation in care of civic and community associations.

1.3. Practical accomplishment of medical care

This involves organization of team work within the health care facility:

- Definition of the objectives of the team work: Putting together and sharing information that will make it possible to improve the care provided to the patient, by looking at the patient in his entirety as an individual with responsibilities towards his family and society.
- Organization of the information exchange sessions: Create occasions for meetings and information exchange between the different care providers that play a role in the management of the patients

- Defining the rules that regulate the care team:
 - Trust;
 - Respect for confidentiality;
 - Non-stigmatization.

1.4. Components of Holistic Management of HIV

Psychosocial care

Psychosocial support and care signify the continuity of care to address psychological, social and spiritual problems of HIV-infected persons and their partners, families, and caretakers.

Three reasons justify the provision of psychosocial care to persons living with HIV-AIDS:

1. HIV/AIDS affects different aspects of the person's life;
2. Handling problems related to stigma and discrimination related to HIV/AIDS;
3. Ensuring adequate adherence to antiretroviral treatment and other drugs.

Medical Care

The medical management of HIV-infected people aims at ensuring stable clinical status to the patient.

It consists of a regular follow up to ensure prevention and management of Opportunistic Infections, WHO Clinical Staging, evaluation of eligibility to ARVs, the management of side effects related to drugs and the monitoring of treatment efficacy of the patient.

Nutritional Care and Support

Nutritional care and support for HIV-infected people consist of improving:

- Nutritional status and body composition including maintenance of weight and muscle mass,
- Immunity and prevent infections,
- Effectiveness and adherence to ARV treatment.

The nutritional management has three main components:

- Assessment of nutritional status by anthropometric measurements and dietary assessment;
- Nutrition interventions that include nutrition education and dietary supplements;
- Monitoring and evaluation to assess whether an improvement or not and establish sustainable strategies.

The Pharmacy and Drugs Distribution

The pharmacy nurse must organize and manage the appointments and must notify other members of the multidisciplinary team in cases of abandonment, poor adherence and lost to follow up in order for them to undertake the necessary follow up.

Data Entry and Filing

The filing system and data entry must be organized in such a way as to ensure patient confidentiality.

Important questions:

- Where is documentation on the patients kept?
- Who has access to these documents?
- Is the filing cabinet or filing room locked to avoid access by non-authorized persons?
- Who has access to the patients' database?

The patient information and service must be managed so as to be easily accessible by authorized users and operated in ways to improve the quality of care. The data should not be used for only reporting but also be used to help the system to take of patients.

1.5. Providing Care to the Multidisciplinary Team

The repeated exposure of health care personnel to the suffering and problems of patients infected by HIV has an impact on their psychological state. HIV/AIDS also has a psychological and social impact on the people surrounding the patient. They may be confronted by shock, despair, and the problem of stigma. The persons concerned by this issue include members of the care team, people who are close to or surround the patient, and the volunteers working in associations.

Objectives of care for the Multidisciplinary team:

- To guarantee the best strategy, whether for diagnosis or treatment, for the management of the patient based on a multidisciplinary approach;
- To offer an opportunity for mutual support among members of the multidisciplinary team;
- To give psychic energy to the care providers so that they may efficiently manage the patients' problems;
- To learn the methods of personal care (self care);
- To identify and operationalize the chain of clinical and para-clinical investigations;

- To improve patient flow in a framework of an expanded network of care;
- To encourage communication between different disciplines;
- To reduce interdisciplinary conflicts and avoid partisan decisions;
- To strengthen communication between different care and treatment partners that participate in the provision of holistic care for the patients;
- To participate actively in the processes for mastering the health expenses.

Approaches to care

The provision of care to the health care providers must be organized in different forms:

- Meetings of the psychosocial team;
- Supervision sessions;
- Brief therapy sessions and support groups for the care providers to prevent burn out.

Meetings with patients, their families and associations must be organized at least every 6 months to improve follow up and the mental and social well being of the staff.

CHAPTER II: PSYCHOSOCIAL CARE OF PLWHIV

2.1. The objectives of Psychosocial care

At each step of psychosocial care, one must remember the different objectives that will ensure the well-being of the individual patient. These objectives are:

- Provide support to the affected person regarding stress and psychosocial disturbances;
- Assist the affected person to adopt safe behaviors that are essential for prevention and control of the infection;
- Give correct information on HIV infection;
- Sensitize the community of the infected person in order to avoid stigmatization and discrimination;
- Contribute to prevention of HIV infection by making the affected person responsible for its control;
- Educate the patient's neighbors and family to support the patient in adhering to his/her antiretroviral treatment.

In brief, psychosocial care of persons infected by HIV/AIDS helps them to live positively.

2.2. Package of Psychosocial Care Activities

Psychosocial consultation

Preparatory psychosocial counseling

Following the disclosure of positive HIV results, patients may present in an emotional state that is not yet stable. They ask themselves many questions regarding antiretroviral treatment and their future. This counseling session offers an opportunity to respond to the different concerns and worries of the patient. The role of the counselor is to help the patient minimize as much as possible the factors that may hinder adequate adherence to antiretroviral treatment.

Psychosocial Evaluation

This is the psychosocial evaluation of the individual and his family, his resources and needs. In order to respond to these needs, we must also proceed to evaluate the community where the patient lives, religious or spiritual beliefs, social services, and legal resources.

Aspects to be evaluated:

- Evaluation of the patient's psychological state;
- Social evaluation;
- Positive behaviors of the patient.

Completing the Psychosocial Dossier

All the data collected from the patient during this session must be recorded in the psychosocial section of the patient's dossier.

Conclusions from the Session

At the end of the counseling session, the counselor must make conclusions regarding what he has heard and observed. The conclusions essentially concern:

- The psychological life of the patient vis-à-vis the infection, the disease and the treatment;
- The obstacles to treatment that are envisaged by the counselor;
- Specific problems that need follow up with the patient;
- The orientations to be done following the session.

Education and Treatment initiation sessions

A three-day session is necessary to discuss all of the issues related to treatment and the behaviors that underlie adherence to antiretroviral treatment.

The facilitation of the session should be supported by appropriate didactic materials (image boxes).

The subjects to be covered during the education and ARV initiation sessions are:

- Modes of transmission for HIV;
- Difference between HIV and AIDS;
- Modes of prevention for HIV;
- Antiretroviral treatment;
- Nutrition;
- Positive behavior.

2.3. Individual follow up counseling

Individual counseling sessions are important in the care program for persons living with HIV.

Aims of follow up individual counseling:

- To provide psychological support to the patient;
- To prevent opportunistic infections among persons infected with HIV/AIDS;
- To ensure follow up of the entire family/ family-based approach;
- To recall the modalities for taking the necessary examinations required for medical and biological follow up of the patient;
- To respond to the patient's questions;
- To help the patient during his social integration.

Group counseling or support groups

The group counseling is important as:

- It facilitates interpersonal relationships;
- It permits participants to become more expressive or open;
- It allows participants to know themselves and become more affirmative (self esteem);
- It allows each participant to share his/her own experiences.

During the group counseling the following aspects should be considered:

- Ensure free consent of each and every participant;
- Constitute groups: group patients with similar problems and in the same age categories;
- Respect the rhythm, the choice and the personality of each participant;
- Establish group regulations: (confidentiality, mutual respect, etc).

The counselor therefore plays the role of **Guiding- Facilitating- Supporting - Stimulating**.

2.4. Follow up at Home

Objectives of Home visits:

- To identify the residence of the patient: to verify and complete the information that was recorded earlier in the patient's dossier.
- Ensure a more intensive counseling (for example: failure to disclose HIV serostatus, refusal of testing by the partner).
- Assess the economic and social situation of the patients.
- Find patients who have missed an appointment or are lost to follow up.
- Catalyze participation of the family in the treatment process.
- Break the isolation of the patient.

Organization of home visits

- Identify cases that need home visits from consultation information, follow up registers, appointment diaries or databases.
- Plan the visits.
- Determine the personal objectives of each patient.
- Prepare the materials to be utilized: (vehicle, kits to be distributed, reporting forms, etc)
- Carry out home visits.
- Reporting: complete the home visit form and summarize the report in the patient's dossier. Give a verbal report during the staff meeting.

CHAPTER III. OPPORTUNISTIC INFECTIONS

Regarding Cotrimoxazole prophylaxis, the national protocol recommends universal access, that is to say, systematically put all HIV-infected patients (adults or infants) on prophylaxis without taking into account the CD4 count.

Cotrimoxazole prophylaxis is maintained among patients on ARVs regardless of the trend in CD4 count levels.

3.1. Prevention of Opportunistic Infections

General preventive measures

Every patient who has been diagnosed with an OI must have health education on the following facts:

- **Information:** on the mode of transmission for HIV-AIDS so that he/she may avoid transmitting the infection to others (risky behavior, unprotected sexual intercourse, mother to child transmission, female contraception to prevent unwanted pregnancies, exposure to blood products and instruments contaminated by blood such as razor blades, re-use of syringes, instruments used in tattooing, etc.
- **Hygiene:** Immunosuppressed persons need to practice good hygiene to avoid diseases transmitted through the oro-fecal route.
- **The environment:** The work environment can constitute a risk. The HIV-infected health care worker is exposed to the risk of TB, particularly in developing countries where about 60% of patients admitted in medical wards are HIV-infected and have a high rate of HIV/TB co-infection. Animals are reservoirs for salmonella and cryptosporidia, and avoiding animal excreta is a useful preventive measure.

- **Nutrition:** The utilization of boiled water for drinking plays a key role in the prevention of infections. A balanced diet is recommended for all immunosuppressed patients, depending on their financial capacities. The consumption of alcohol and cigarettes is discouraged and money should be used to ensure a balanced diet.
- **Antiretroviral drugs and good adherence to treatment:** constitute the most important individual and group preventive measures.

3.2. Specific preventive measures

In order to know what one has to prevent, it is important to know what may happen.

Table 1:
Expected complications depending on the degree of immune suppression in HIV-infected patients:

CD4	Infectious complications	Non infectious complications
>500/mm ³	<ul style="list-style-type: none"> - Acute retroviral syndrome. - Candidal vaginitis. 	<ul style="list-style-type: none"> - Persistent generalized lymphadenopathy - Guillain-Barré syndrome. - Myopathy. - Aseptic meningitis.
200-500/mm ³	<ul style="list-style-type: none"> - Pneumococcal and other bacterial pneumonia. - Pulmonary tuberculosis. - Herpes zoster. - Oropharyngeal candidiasis (thrush) - Cryptosporidiosis. - Oral hairy leukoplakia 	<ul style="list-style-type: none"> - Cervical intraepithelial neoplasia - Cervical cancer. - B cell lymphoma. - Anemia. - Mononeuronal multiplex. - Idiopathic thrombocytopenic purpura - Hodgkin's lymphoma - Kaposi's sarcoma - Lymphocytic interstitial pneumonitis.
<200/mm ³	<ul style="list-style-type: none"> - <i>Pneumocystis jirovecii</i> pneumonia - Chronic disseminated Herpes simplex - Toxoplasmosis - Cryptococcosis - Disseminated histoplasmosis & coccidioidomycosis - Chronic cryptosporidiosis - Microsporidiosis 	<ul style="list-style-type: none"> - Wasting. - Peripheral neuropathy. - HIV associated dementia. - CNS lymphomas. - Cardiomyopathy - Vacuolar myelopathy - Progressive polyradiculopathy - Non-Hodgkin's lymphoma

	<ul style="list-style-type: none"> - Miliary and other forms of extrapulmonary TB - Progressive multifocal leukoencephalopathy (PML) - Candidal esophagitis 	
<50/mm ³	<ul style="list-style-type: none"> - Disseminated CMV - Disseminated <i>Mycobacterium avium</i> complex 	

The frequency of most complications increases as the CD4 count falls.

Certain conditions that are normally classified as non-infectious are associated with communicable microbes, e.g. lymphomas (Epstein-Barr virus - EBV) and cervical cancer (Human Papilloma Virus - HPV).

Chemoprophylaxis

- **Cotrimoxazole (Bactrim):** Protects against infections by toxoplasmosis and pneumocystis pneumonia. It also protects against other potential infections (Isospora belli and certain nocardias). The dosage is 960 mg once a day orally. The alternative in case of allergy is Dapsone 100mg once a day PO.
- **INH:** Currently systematic INH prophylaxis is not recommended in Rwanda and should only be used in the Reference hospitals for selected cases where active TB has been excluded.
- **MAC (Mycobacterium Avium Complex):** Prophylaxis is done with Azithromycin 1200 mg PO once a week. Prophylaxis can be stopped if the CD4 count is above 200 for more than 6 months and there are no signs suggestive of MAC. It should particularly be considered for patients that have Immune Reconstitution Inflammatory Syndrome (IRIS) *
- **CMV (CytoMegaloVirus):** Prophylaxis is indicated in case of secondary prophylaxis in a patient who has had CMV retinitis. The dosage is Ganciclovir 1000 mg PO. 3 times a day for 3-6 month after the patient initiates ARV treatment.*
- **Intestinal Helminthes:** Albendazole 400 mg PO once a year
- **Fungal Infections:** Prophylaxis is indicated in the case of secondary prevention against *Cryptococcus neoformans*, oral and esophageal candidiasis. The patient is provided with Fluconazole 200mg once a day PO. This treatment can be stopped when CD4 are maintained at above 100 for 6 month after initiating ARVs.

3.3. Vaccination

Vaccination should be postponed until CD4 increases or else there may be insufficient immunological response, especially if the CD4 are below 100.

The yellow fever vaccine, like all other live attenuated vaccines is contraindicated in symptomatic HIV patients and all persons whose CD4 count is below 200.

Pneumococcal vaccine

- The polysaccharide 23 variant vaccine is not recommended.
- The conjugated 7 or 9 variant vaccines should be given for the best results when available (very expensive) and is also indicated for children.

Hepatitis B Vaccine

Because of its high cost, this should be reserved for immunosuppressed persons, health care personnel and other groups at risk.

Tetanus and Diphtheria Vaccines

Both are recommended.

Others

- **Malaria:** Immunosuppressed persons are at an additional risk for contracting severe malaria. They should be very prudent in taking preventive measures, especially when it comes to HIV-infected pregnant women. For the preventive measures, please refer to the guidelines of the National Malaria control program.

3.4. Recommendations on cryptococcus neoformans infection

- Patients with advanced immunosuppression are at higher risk than others of having an asymptomatic or symptomatic cryptococcal infection; therefore, it is recommended to screen for cryptococcal disease in every patient with CD4 below 200, using cryptococcal antigen testing (CRAG) on plasma. Any patient with neurologic symptoms should have a CRAG performed on CSF after lumbar puncture for diagnosis.
- When the diagnosis is confirmed, the curative treatment will be fluconazole 800-1200mg/day/ 2 weeks as an induction phase for patients with asymptomatic cryptococcal infection (with antigenemia only). For CSF positive or symptomatic cases, use Amphotericin 0.7-1 mg/kg/day /2 weeks or Fluconazole 800-1200mg for induction. In consolidation phase, use Fluconazole 400mg OD for 10 weeks and complete with a maintenance phase of one year by

using fluconazole 200mg/day. For other adjuvant treatment and management of drug side effects, see the guideline for opportunistic infections of May 2010 page 43-44.

CHAPTER IV. THE PRINCIPLES OF ANTIRETROVIRAL TREATMENT

ARV treatment is an essential element of the care for PLWHA and it changes the natural evolution of HIV infection. It results in reduced morbidity and mortality.

4.1. The key factors in treatment

It should be noted that treatment hinges on 3 main factors, each of which will influence its success:

- The virus which may be more or less aggressive depending on the subtype and species of infecting virus;
- The patient, who will by and large determine the success of the treatment, depending on the associated pathologies (co-infection with TB, hepatitis B, etc), his/her capacity to adhere to treatment, his/her mode of life and the support s/he receives;
- The antiretroviral drugs, which ideally should be efficacious over a long time and with minimum side effects.

4.2. Mechanism of action of ARVs: the multiplication cycle of HIV

HIV is an RNA virus that must penetrate a CD4 cell in order to replicate. Inside the cell, it undergoes a series of transformations to give rise to new viruses.

ARVs act by blocking one of the stages during the replication cycle of HIV within the CD4 cell.

The key stages of the replication cycle are:

- Penetration of the virus through the membrane of the CD4 cell (by fusion with the aid of co-receptors);
- Transformation of viral RNA into DNA carried out by the enzyme reverse transcriptase;

- ✦ Integration of the DNA formed above into a foci of DNA within the CD4 nucleus, under the action of another enzyme: Integrase enzyme;
- ✦ The manufacture of viral RNA from the DNA;
- ✦ Formation of new viruses from that RNA and the synthesized proteins in the CD4 cell under the influence of the protease enzyme;
- ✦ Release of the reconstituted particles.

The main ARVs currently in use in Rwanda block the action of the two enzymes: Reverse transcriptase and Protease. Drugs capable of blocking entry of the virus into CD4 cells (co-receptor antagonists) and Integrase enzyme inhibitors are newly available in other countries.

4.3. The duration of HIV infection and the CD4 evolution during the course of the infection

HIV

When free and circulating in the plasma; the virus's life cycle is very short, with a half life of 6 hours.

A very small number of viruses can invade and penetrate reservoir cells or sanctuary cells (often macrophages) where they hide and can stay for several decades. These cells do not respond to treatment.

Given the very short half-life, the virus is reproducing continuously, and an infected person who is not on treatment can produce up to 10 billion new viruses every day, along with a high risk of mutations and drug resistance.

T- Lymphocytes (CD4)

An infected CD4 cell has a half life of 1.6 days (with a normal life cycle of several weeks), which means that the higher the number of infected CD4 cells, the more rapidly the body must manufacture new ones in order to maintain the normal number of T lymphocytes. Eventually the lymphatic system is depleted, and the number of T lymphocytes falls progressively, thus entering a state of immune deficiency.

The Effect of Treatment

By blocking viral replication, treatment will stop the production of new viruses (while the old ones die off very rapidly) which will make the amount of viruses in the blood (what we commonly call Viral Load) undetectable. However, there is no cure yet for HIV infection because there are still viruses that are hiding in reservoir cells.

When CD4 cells are no longer infected by new viruses, they resume their normal life cycle and their numbers increase progressively, thus improving the immunological situation.

Hence the aims of treatment are:

- Suppress the viral load to undetectable;
- Increase the number of CD4 cells so as to improve the immune reconstitution;
- Reduce the transmission of HIV;
- Minimize the risk of cross resistance;
- Minimize long term toxicity;
- Improve the clinical status of the patients;
- Improve the quality of life of the patient;
- Minimize the cost of care.

Qualities of a good treatment regimen that can result in good adherence

A good treatment regimen is one that combines drugs that are:

- **Potent:** capable of adequately blocking replication of HIV. To achieve this, it is important to combine at least 3 drugs (triple therapy). Such a combination is capable of blocking viral replication at different stages or at the same stage but using different mechanisms.
- **With prolonged action:** The association must block the replication for as long as possible.
- **Adherence:** Most therapeutic failures are a result of poor adherence to treatment. It is the first cause that should be investigated/considered in any case of treatment failure.

Given the importance of adherence to treatment success and the effect that psychosocial factors have on adherence, health personnel have the duty to go beyond the simple medical setting and ensure the comprehensive management of the patient.

This concept has been explained in the preceding chapter. For example, if a patient has depression, the health care worker should think about psychiatric illness, a side effect of EFV, a financial problem, a family dispute, etc. It is thus easy to understand the complicated nature of this approach; and it is for this reason that the multidisciplinary approach has been proposed.

In all cases, all of these factors should be taken into consideration so that an appropriate framework is set up to support the patient in following his/her treatment adequately.

4.4. Supporting a patient on ART

One must know that most treatment failures are due to poor adherence.

Thus successful treatment involves the following:

- Adequately prepare the patient before initiation of treatment: The patient should freely decide to accept the treatment, give informed consent and know the difficulties they may meet in follow up. A preparatory period is essential before initiating treatment. ARV treatment is never an emergency with the exception of AEB (accidental exposure to blood).
- Prescribe to the patient the drugs that are most suited to his/her mode of life; drugs with less frequent dosing are better respected than those with multiple daily doses (single daily dose is the ideal treatment).
- Adequately inform the patient on how he needs to take his/her drugs and any possible side effects. A lot of preparatory work must be done by the different categories of care providers to ensure adherence.
- Ensure that the patient has people around him/her who can act as treatment buddies to support him/her throughout his/her treatment; and if he wishes, ensure he gets group support from the community.

CHAPTER V. ANTIRETROVIRAL TREATMENT: FIRST LINE REGIMENS

5.1. Eligibility Criteria for ART Initiation

Not all HIV-infected patients need antiretroviral treatment immediately. In the period following the initial infection, the CD4 count and viral load attain a plateau for a variable period, usually several years. There is a state of equilibrium between the organism and the virus which keeps the body's immune system effective.

However, in due time and with the occurrence of intercurrent infections, HIV replicates progressively, infects more and more CD4 cells, and breaks the existing equilibrium. It is from this stage that there is a progressive increase in the viral load and a regular decline in CD4 cells. It is at this stage that it becomes necessary to suppress viral multiplication.

Initiation of ARV treatment depends on three patient-related criteria: the clinical stage, the immunological state, and the social status (especially given the importance of this aspect on adherence).

With the help of an accurate history taking and a complete examination of the patient, the clinician stages the patient based on the WHO classification criteria. This classification is based on two types of findings which permit the

determination of the clinical stage: retrospective/historical findings and other findings noted during the clinical examination. Given the importance of the clinical stage in the decision regarding the treatment of the patient, historical /retrospective findings must be taken with a lot of caution.

For example, it is possible for the patient to declare having had 2 episodes of pneumonia in the last 6 months, while actually he is interpreting 2 severe episodes of bronchitis as pneumonia; this mistake will significantly affect the decision-making of the clinician.

5.1.1. Criteria for clinical and immunological eligibility (Adult)

Confirmed HIV seropositivity and one of the following two criteria:

- Any patient >15 years with WHO Stage 3 and 4 regardless CD4 cell count
- Any patient >15 years in WHO Stage 1, 2 with CD4 < 350/mm³
- Any patient >15 years with HIV-TB coinfection regardless CD4 cell count
- Any patient with HIV-Hepatitis B coinfection
- Any HIV-Positive Sex partner in discordant couple regardless CD4 and WHO stage

5.1.2. Mandatory Social Criteria

- Having a fixed residence in the catchment area of the nearest HF
- Being enrolled in HIV Care program in an authorized HF (accreditation)
- Having disclosed his/her HIV serostatus to a family member or someone close.
- Acceptance of home visits by a health care worker.
- Accept to take medication over the whole lifetime.
- Be supported by someone trusted in order to improve adherence; this person is called a treatment buddy.
- Commit him/her self to having only protected sexual intercourse.
- Not receiving antiretroviral drugs from another program.
- Accept to make financial contribution if not in possession of a certificate of neediness.

5.2. Initial Pre-ART Check up

Every patient eligible to ART should benefit from a complete initial check up intending to assess his/her status before ART treatment. This will guide the choice of appropriate ARV regimen. This assessment will also help in strategies and decision making for immediate or future management of the patient.

5.3. Clinical Assessment

It consists of :

- A systematic screening for active TB
- A systematic screening for STIs
- Clinical history and full clinical examen to exclude possible OI

5.4. Biological Assessment

This assessment intends to explore the function of different organs:

Organs	Test
Liver	Liver Tests (ALAT, ASAT), HEPATITIS B
Kidney	Creatinine and Clearance
Immunity	CD4

5.5. Psychosocial Assessment

Since the adherence of the patient is the key to success of ART, it is recommended to make thorough evaluation sessions of pre-ARV counselling before initiating antiretroviral therapy. At the end of the counseling, the counselor must make conclusions in relation to what he/she heard and observed. These conclusions are mainly related to:

- The psychological experience of the patient vis-à-vis the infection, disease and treatment;
- Barriers to adherence anticipated by the counselor;
- The specific problems which need to be focused on during the patient follow up ,
- The guidance made after the session

5.6. Recommendations on different first line ART molecules in Rwanda

Overview on different ART classes and principles of ARV treatment

ARVs and Mechanism of Action

There are three main ARVs classes used in first line regimen in Rwanda:

- Nucleoside reverse transcriptase inhibitors (NRTIs) that competitively block reverse transcriptase (analogues).
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) which block reverse transcriptase in a non competitive manner.

- Protease Inhibitors (PI) which inhibit the Protease enzyme.
The choice of ARVs

At the national level, the choice of ARV is decided by RBC/IHDPC/HIV Division, based on extensive research and review of treatment guidelines agreed upon by experts. These guidelines take into consideration several factors such as efficacy, tolerability and cost of the drug regimen. For these reasons, generic and combination drugs have been preferentially selected.

At the international level, Rwanda receives support from several bilateral and multilateral donors.

At the national level, treatment initiatives supervised by the Ministry of Health through RBC/IHDPC/HIV Division in accordance with the national treatment plan. Today, these initiatives have allowed equal access to ARV treatment to all eligible Rwandan population.

5.7. Main ARV Combinations

- 2 NRTI + 1 NNRTI or 2 NRTI + 1 PI according to the case
- The association of 3 NRTIs is possible but because of the reduced potency should not be considered except in cases of extreme necessity or after expert opinion.

The recommended first line regimen

There are four options recommended in first line regimen (Adult)

	NRTI	NNRTI
1	Tenofovir (TDF) + Lamivudine (3TC) or FTC	Efavirenz (EFV)
2	Tenofovir (TDF) + Lamivudine (3TC) or FTC	Nevirapine (NVP)
3	Abacavir (ABC) + Lamivudine (3TC) or FTC	Efavirenz (EFV)
4	Abacavir (ABC) + Lamivudine (3TC) or FTC	Nevirapine (NVP)

FTC: Emtricitabine

NB:

- Give NVP in case of allergy or contraindication to EFV
- Give ABC in cases TDF is contraindicated (renal insufficiency with CrCl < 50ml/min).
- The combination of ART including TDF+FTC+EFV (Atripla) is accepted and depending on financial capabilities to procure it .

Specific dosage of 1st line drugs

Molecule	Dosage
Lamivudine (3TC)	150 mg twice a day or 300mg once a day
Emtricitabine(FTC)	200mg once a day
Abacavir (ABC)	300 mg twice a day or 600 mg once a day
Efavirenz (EFV)	600 mg once a day.
Nevirapine (NVP)	200 mg once a day for 14 days and then, 200 mg twice a day
Tenofovir (TDF)	300 mg once a day
Kaletra (LPV/r)	400/100 mg twice a day (2 tablets twice a day)

ARV regimens are based on the list of generic and branded drugs that are currently available in Rwanda:

Treatment regimen: TDF + 3TC + EFV

Evening (1) TDF 300mg + 3TC(2)300mg + EFV 600mg

NB: (1) Encourage taking drugs in the evening because of the side effects due to EFV
 (2) Give the formulation of 3TC 300mg to facilitate once daily dosage.

Treatment regimen: TDF + 3TC + NVP

Initial phase 15 days	TDF 300mg + 3TC 300mg /FTC 200mg + NVP 200 mg	=	Tenofovir+ Lamivudine (1 tablet) or Emtricitabine (1 tab) + Nevirapine (1 tablet of 200 mg)
*Maintenance phase	TDF 300mg + 3TC 300mg/FTC 200mg) 1x/ + NVP 200 mg twice daily	=	Tenofovir + Lamivudine (1 tab) or Emtricitabine (1 tab) + Nevirapine (1 tab of 200 mg/twice a day)

Treatment regimen: ABC + 3TC + EFV

Evening (1) ABC (2) 600mg + 3TC 300mg + EFV 600mg

NB: ⁽¹⁾ Encourage taking drugs in the evening because of the side effects due to EFV

⁽²⁾ Give the formulation of ABC 600mg to facilitate once daily dosage.

Treatment regimen: ABC + 3TC + NVP

*Initial phase 15 days 1OD (single dose)	ABC(2)600mg + 3TC 300mg + NVP 200 mg
*Maintenance phase	ABC 600mg + 3TC 300mg 1 a day + 2 a day NVP 200 mg

⁽²⁾Give the formulation of ABC 600mg to facilitate once daily dosage

5.8. Recommendations for HIV-TB co-infection

Overview on HIV-TB co-infection

Tuberculosis is the leading cause of death in people infected with HIV in Africa. Systematic detection of TB in persons living with HIV and early treatment is among the most effective ways to prolong their lives.

In Rwanda the incidence of TB has more than doubled over the past decade due to TB-HIV co-infection. During the year 2010, 98% of TB patients were tested for HIV and 32% were HIV positive. On the other hand 3.5% of HIV patient newly enrolled into care and treatment services in Rwanda from August 2010 to August 2011, were diagnosed TB.

HIV infection causes progressive destruction of the immune system and promotes opportunistic infections, including TB.

People infected with HIV are at 10 to 50 times higher risk of developing active TB than those not infected. Indeed 50% of co-infected individuals will develop TB during their existence (in the absence of ARV treatment) while this percentage is only 5 to 10% for those not infected with HIV.

Just as HIV infection promotes the rapid passage of TB infection to TB disease, it accelerates the progression of HIV infection (increasing viral load).

Consequences of HIV on Tuberculosis control

- Increase in the number of cases of TB linked to HIV;
- Late diagnosis because patients with TB symptoms consult late due to the fear of the stigma attached to both TB and HIV;
- Difficulty in diagnosis given the different clinical presentations of TB linked to HIV. Increase in the number of cases of extra-pulmonary TB and sputum negative pulmonary TB (common presentations in advanced stages of immune deficiency);

- Difficulties in treating a single patient with two diseases at the same time, in two separate clinics;
- Difficulty in attaining a satisfactory success rate given the high mortality during treatment as well as the numerous treatment defaulters (often linked to the side effects from the drugs);
- High rate of relapse;
- Risk of nosocomial infection/transmission;
- Heavy workload in TB and HIV clinics.

Screening of co-infection TB-HIV

Screening of TB-HIV co-infection has the following objectives:

- To ensure timely provision of care to co-infected patients;
- To monitor trends in HIV infection among TB patients as well as TB prevalence among people infected with HIV.

In practice, the screening of co-infection will be organized as follows:

- Explain to every new TB patient that the 2 diseases are frequently linked and the advantages of HIV screening;
- Systematically offer and perform an HIV test except in the case of refusal by the patient. Results are always confidential.

Advantages of HIV screening

- The patient will have a better understanding of the risky behaviors and the precautionary measures that he has to undertake in order to avoid transmission of the infection.
- In case of a positive result, timely follow up will be instituted and the patient will receive the necessary treatment (prevention of opportunistic infections, ARVs, etc.). S/he will receive psychological support that will enable him to manage the anxiety linked to the disease and make important decisions for example regarding reproduction.

Active screening of tuberculosis in HIV-positive patient

- In countries with a high prevalence of HIV infection, TB may be the first sign of HIV infection. Often the disease manifests itself at an early stage of the HIV infection and presents in the form of sputum positive pulmonary TB.

- However, when HIV infection is at an advanced stage, the diagnosis of TB is more difficult because sputum smears are often negative for mycobacterium, and the clinical and radiological features may be atypical. Sputum negative and extra pulmonary forms of TB are hence more common in severely immunosuppressed patients.
- The characteristics of TB depend on the degree of immunosuppression at the time the disease develops.

Characteristic	Early phase of HIV infection	Late phase of HIV infection
Clinical forms	Pulmonary TB	<ul style="list-style-type: none"> ➤ Disseminated or extra-pulmonary TB; ➤ Sputum negative pulmonary TB; ➤ Predominance of generalized/ systemic signs (fever, wasting).
Microscopy	Often positive	Positive or negative
Xray	Cavities more frequent	Opacities, infiltrations without cavities
CD4	< 500 / mm ³	< 100 / mm ³

- Sputum examination remains the key and an invaluable exam in the diagnosis of TB because of its capacity to detect contagious sputum positive cases.
- The differential diagnosis of sputum negative TB and other pulmonary pathologies linked to HIV is difficult and must follow the National algorithm for TB diagnosis.

Management of HIV-infected patients with tuberculosis

The treatment of Tuberculosis is a priority and must be supervised (DOTS)

- The treatment regimens for TB are the same as for HIV negative patients. The response to treatment is the same and sputum becomes negative as quickly as in the case of non HIV-infected TB patients.
- However, HIV-infected TB patients have a higher risk of drug-related toxicity.
- Mortality during treatment is higher.
- Relapse and reinfection are more common.
- Given the frequency of gastrointestinal disturbances in HIV-infected patients, malabsorption should be considered as a possibility in cases where TB persists in the presence of adequate treatment.

- In cases of second line treatment, use a sterile needle and syringe for each streptomycin injection.

Antiretrovirals

All HIV-positive patients with confirmed TB co-infection are eligible for ARVs regardless of CD4 count and clinical stage.

In co-infected patients, the priority is to treat TB first. It is reasonable to start HAART at the end of the second week of treatment for TB but on the basis of clinical status this time can go up to eight weeks.

The recommended regimens for adults are:

TDF + 3TC + EFV or ABC + 3TC + EFV

The recommended regimens for pregnant women only:

TDF + 3TC + Kaletra or ABC + 3TC Kaletra (1st Quarter)

TDF + 3TC + EFV or ABC + 3TC + EFV (2nd and 3rd Quarter)

- Refer to PMTCT pregnant women infected with HIV, for preventive therapy of HIV transmission to the child.
- If EFV is administered together with rifampicin, the usual dose of EFV does not change and remains at 600mg.
- If a patient is treated with a regimen containing NVP and develops tuberculosis, NVP will be replaced by EFV.

How to do this?

The patient will take:

TDF + 3TC + EFV 600mg

ABC + 3TC + EFV 600mg

- NVP is stopped and then we can start anti-TB drugs safely.
- The combination of PI to TB treatment is not recommended and dose adjustment may be required after specialist advice.
- For the prevention of HIV transmission, we should inform all TB patients about prevention of HIV infection:
 - Abstinence;
 - Faithfulness (reducing the number of sexual partners);
 - Condom use (have a stock for patients with tuberculosis);
 - Treatment of sexually transmitted infections (STIs);
 - Use of disposable syringes for all injections.

Patients infected with HIV will receive comprehensive care including:

- The correct clinical management;
- Direct supervision of TB treatment;
- All necessary care;
- Counseling and psychosocial support

The comprehensive management will be organized by levels and should incorporate an active participation of the community and families.

TREATMENT OF TB/HIV COINFECTED PATIENTS	
SITUATION	RECOMMENDATION
Patient co-infected with HIV and TB	<p>✦ Initiate anti-TB treatment. Start the administration of an association of ARV below between 2-8 weeks after starting TB treatment.</p> <p>TDF + 3TC + EFV ABC +3 TC + EFV</p> <p>✦ For pregnant women only: In the first quarter: TDF + 3TC + Kaletra * After the first quarter TDF + 3TC + EFV</p>

3TC: Lamivudine; EFV: Efavirenz; ABC: Abacavir; TDF: Tenofovir;
*The dose of Kaletra will be adjusted by increasing because coadministration with rifampicin decreases much plasma levels of Kaletra. We propose the following: Add to Ritonavir Kaletra for a ration of 1:1 (often 300 mg ritonavir) or double the dose of Kaletra. Always monitor these patients closely because of increase of side effects. It is preferable to seek for expert advice.

ARV treatment in children being treated for Tuberculosis

Begin ARV early after initiation of anti TB (2-8 weeks)

If <10 kg:

2 NRTIs + NVP * or 3 NRTIs (AZT or d4T) + 3TC + ABC.

*: The dose of NVP will be doubled given the combination with rifampicin. It will be imperative to monitor patients' liver function (GPT to 2 weeks, 1, 3 and 6 months).

These children will be monitored in a reference center.

After the end of anti TB, if it was 3 NRTIs pass to EFV or NVP according to the weight of the child

If > 10 kg:

2 INRTIs + EFV. The dose of EFV was increased by one third considering the combination with rifampicin (eg if the normal dose is 300mg => give 400mgr).

If there are formal contra indications of NNRTI, one can give two NRTIs + LPV / r * or 3 NRTIs during the treatment of tuberculosis. Remember to readjust the ARV treatment after the end of TB treatment.

✓ LPV / r: Lopinavir / ritonavir (Kaletra): The dose will be doubled with regular monitoring because there is an increase in side effects of Kaletra, always seek the advice of an expert.

- NRTI: nucleoside reverse transcriptase inhibitor (AZT, 3TC, D4T, DDI, ABC, TDF).
- NNRTI: Non-nucleoside reverse transcriptase inhibitor (EFV and NVP)

All patients with TB-HIV will be followed in the TB service (ONE STOP TB / HIV SERVICE) where they will receive:

- The anti TB drugs
- Cotrimoxazole prophylaxis
- Blood sample for monitoring CD4 and biological assessment
- Medical consultation for enrollment and follow-up
- Nutritional assessment

Health centers with no ART service, co-infected TB / HIV patients will be referred to an accredited ARV treatment site.

Co-infected patients (TB-HIV) who develop peripheral neuropathy should receive 1 tablet of Pyridoxine 25 mg daily and 100 mg for patients coinfected MDR-TB/VIH. This medication is available in the program.

Certain patients develop an immune reconstitution syndrome (IRIS) after initiating ARV treatment, with deterioration in the clinical state and signs such as high fever, increased severity of respiratory symptoms and increased lymphadenopathy.

This syndrome is due to an inflammatory response to an opportunistic infection and should not be considered clinical failure. Anti-TB treatment should be maintained and the patient referred to the doctor in charge of ARV treatment for appropriate treatment.

5.9. Recommendations on HIV-Hepatitis B Coinfection

The hepatitis B virus (HBV) is a double-stranded DNA virus having hepatocyte as the main target.

This virus is found in the blood and body fluids and is more "infectious" than HIV (100 times or more)

The main routes of transmission are:

- Blood
- Sex
- Mother to child

The natural history of HBV infection is highly variable. It is influenced by:

- The degree of viral replication
- The presence of mutations
- The age of the host
- Gender
- The immune response
- Co-morbidities (alcohol, viral co-infections)

Terminology commonly used in HBV infection

- **HBs antigen:** HBV surface antigen (indicating active infection)
- **HBc antigen:** HBV core antigen (evidence of past infection)
- **HBeAg:** if positive, evidence of active HBV infection (absent or rare in patients with mutations in precore and core)

Relation between HIV and hepatitis B

- The risk of passing from acute hepatitis B to chronic hepatitis is increased;
- HBV reactivation in inactive carriers of HBV is more common;
- The spontaneous seroconversion of HBsAg and HBeAg are less frequent;
- Progression to fibrosis is faster;
- The risk of hepatocellular carcinoma is higher
- However, HIV infection is not influenced by HBV infection.

Principles of screening for hepatitis B

The prevalence of co-infection with HBV in people with HIV is high. The therapeutic management of HBV infection should take into account the necessity to treat HIV infection and integrate anti-HBV and HIV in a comprehensive strategy. Given the prevalence of HIV / HBV co-infection and prognosis of hepatitis B, it is recommended to screen for hepatitis B in every HIV + person who is not yet initiating ART (pre ART population) or receiving ART non TDF/3TC based regimen ; it is also recommended to vaccinate all HIV+ population who will be HepB negative after screening.

Health care workers in close contact with PLWHA should also receive Hepatitis B vaccine.

The main therapeutic goal: stopping the replication of HBV

Obtaining a HBs seroconversion is more rare.

Treatment should also aim to reverse fibrosis, prevent complications of cirrhosis and the occurrence of a carcinoma.

The therapeutic strategy related to whether or not antiretroviral therapy

In case an HIV treatment is necessary, the inclusion in the regimen of **tenofovir** in combination with **lamivudine** or **emtricitabine** is recommended.

In Rwanda, it is recommended to start antiretroviral treatment in any patient with HIV-HBV co-infection, regardless of CD4 count or WHO clinical stage.

The recommended ARV regimen is **TDF-3TC-EFV**

5.10. Recommendations on monitoring of patients on first line ARV

It is important to make a close follow up of patients during the first month to optimize adherence and detect early side effects due to ARVs.

It is recommended to make a systematic clinical follow up every three months and CD4 count control every six months. The Viral Load will be done every twelve months for patients on ART.

Recommendations for clinical and biological follow up of patients on ARVs

Date	Clinical	Labo
Pre-ARV	+	CD4, ALAT, Creatinine (Clearance)
D 15	+ adherence	
M 1	+ adherence	Creatinine (Clearance) if TDF
M 2	+ adherence	None
M 3	+ adherence	Creatinine (Clearance) if TDF
M 4	+ adherence	None
M 5	+ adherence	None
M 6	+ adherence	CD4, Creatinine (Clearance) if TDF
After 6 Months		
Monthly for one year + adherence		<ul style="list-style-type: none">• CD4 : every 6 months• Viral Load every 12 months• Creatinine if TDF
Note: FBC, ALAT and amylsema will be done if clinically indicated		

After 1 year of treatment in the absence of any problems, a medical visit every 3 months is sufficient. It is also recommended to plan a visit to the counselor at least every 3 months (adherence assessment, and follow-up counseling).

5.11. When and how to change the treatment regimen in first line?

There is no reason for modifying treatment systematically; any modification must be decided on based on the biological and clinical information of the particular patient. An efficacious and well tolerated drug is not changed except in the case of very special circumstances (e.g. stock out).

The first ARV treatment regimen given to the patient must be active and durable. If adherence is adequate, the clinical and immunological benefits will be long-lasting. ARV drugs should only be changed with caution and after thorough consideration of the reasons for changing.

Knowing the history of the sequence of ARVs taken can influence the treatment decisions depending on the information known about resistance and cross-resistance. In addition, premature changes in the treatment regimen can consume all of the options that would have been available in the future.

The clinician can change the treatment regimen in 5 main situations:

- Toxicity: a severe side effect;
- Treatment failure;
- Pregnancy;
- Drug interactions.
- TB-HIV Co-infection

In this chapter, we discuss changing treatment due to toxicity; and drug interactions. Other causes such as TB drug interaction, pregnancy and treatment failure have been discussed in other chapters or sections.

This chapter is divided into 4 parts:

- A- Side Effects and Toxicities
- B- Switching ART due toxicity
- C- Biological Criteria to switch treatment ;
- D- Drug-Drug Interactions

Switching ART due to toxicity or side effects

Introduction

At the initiation of treatment, opportunistic infections constitute the main problem to cope with, but side effects to ARVs very quickly become the major concern in the provision of care to PLWHIV.

Side effects can be detected through symptoms or through biological examinations. Some symptoms are minor or transient, while others need symptomatic treatment or close clinical follow up.

If a serious toxicity due to a specific ARV drug appears, it is possible to just replace the single drug. In this chapter, we explain the common side effects of drugs from the same group of ARVs, and then discuss in detail each drug that is in use in Rwanda. Table 1 below summarizes the major side effects of first line drugs as well as the drugs proposed for substitution.

Principles on the management of side effects:

1. Know the drugs: The health care worker must know each and every drug and know when each side effect commonly appears.
2. Patient information: if the patient is informed of the major side effects of the drugs s/he is taking, s/he can come for consultation in a timely manner in case of severe side effects.
3. As much as possible avoid combining drugs that have similar side effects (e.g. D4T and DDI).
4. Only change the drug that is causing the side effect: this is the most commonly applied rule. However, it is sometimes difficult to know which particular drug is causing the side effect. As a reminder, changes must not be taken lightly since in Rwanda; there are a limited number of drugs to choose from.
5. Describe, in the patient dossier and in as much detail as possible, each side effect. This information is essential in determining the new drug that the patient will eventually be given as well as to avoid giving the same drug again in the future.
6. Be attentive and accessible: the health care provider must ask the patient about any eventual occurrence of side effects and ensure that the patient has constant access to the health services.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

Side effects of the group:

Lactic acidosis can occur with any nucleoside drug, although it is more common in patients treated with stavudine (D4T) and made worse by the combination of DDI + D4T. Symptomatic lactic acidosis is rare (less than 0.1%), but up to 5% of asymptomatic patients on NRTIs can have elevated levels of blood lactate. Even though it is relatively uncommon, health care workers must be familiar with the syndrome because of its potential severity.

Symptoms present as fatigue, abdominal pain, nausea/vomiting, dyspnea and weight loss.

Laboratory analyses show a high level of lactic acid with or without metabolic acidosis. An increased anion gap ($\text{Na} - (\text{Cl} + \text{CO}_2) > 16$), creatinine-phosphokinase (CPK), transaminases, and LDH are also common findings. Hepatic steatosis may be revealed by imagery of the liver (CT scan, ultrasound).

The best response is to stop the offending antiretroviral drug (special attention should be paid to D4T and DDI). Lactic acidemia will dissipate in 3 to 6 months. Restarting ARV drugs usually requires consultation with an expert, because the possibility of re-introducing NRTIs without risk has not yet been proven.

Lipodystrophy is defined as the loss of peripheral subcutaneous fat and accumulation of fat in the abdominal area, the upper part of the back, the chest and certain subcutaneous tissues. It is a common finding and is more frequent in patients on D4T, D4T/DDI combination, and to a lesser extent AZT, and following long periods of treatment (see point C). The treatment options are limited to physical exercise and to changing the ART regimen. There is little data on this option but a timely replacement of D4T with TDF or ABC will at least halt the progression of the problem.

Anemia is most common with AZT, usually macrocytic; it often occurs within the first 3 months of therapy and may lead to blood transfusions and hospitalization.

Pancreatitis is most common with ddl + d4T (and also with AZT) and can present with abdominal pain, nausea and vomiting. The clinician must also ask about alcohol use (a common cause of pancreatitis).

Impaired renal function is most common with TDF, though it is not a common side effect (i.e. < 3%). When prescribing TDF, it is important to calculate the creatinine clearance:

Creatinine Clearance Calculation:

If Creatinine machine reports in mg/dL:

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{creatinine (mg/dL)}} \quad \times 0.85 \text{ for a woman}$$

or

If Creatinine machine reports in $\mu\text{mol/L}$:

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{0.81 \times \text{creatinine } (\mu\text{mol/L})} \quad \times 0.85 \text{ for a woman}$$

The normal creatinine clearance should be > 90 mL/minute.

Interpretation of Renal Creatinine Clearance:

≥ 90 ml/min. = Normal

60-89 mL/min = Mild Renal insufficiency

30-59 ml/min = Moderate Renal insufficiency

≤ 29 mL/min = Severe Renal insufficiency

Note:

- If clearance > 50 mL/min, OK for TDF; if clearance < 50 mL/min, give alternative - ABC
- If at creatinine control 3 or 6 months, decrease in clearance or increase in creatinine by ≥ 15%, consider possible TDF toxicity and switch to ABC.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Nevirapine and Skin Rash

The most common side effect due to NVP is skin rash, found in 20% of patients (especially black women); it occurs more commonly in the first 8 weeks after initiating treatment. Usually the rash is minor or moderate but it may necessitate interruption of treatment in 5-7% of patients. Potentially fatal reactions have been reported. Patients with rash should always be assessed for hepatotoxicity

Table 2 shows the different stages of the severity of the reaction while the treatment algorithm for managing the dermatological toxicity is found in the annex. Note that NVP must be stopped if the reaction reaches stage 3.

Dermatological toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Erythema, pruritis	Widespread maculopapular eruptions of dry desquamation	Appearance of blisters or humid desquamation or ulceration or association with fever or pain	Appearance of the following signs: affecting the mucosa, Stevens Johnson syndrome, Erythema multiforme, necrosis, or exfoliative dermatitis.

Nevirapine and Hepatotoxicity

Hepatotoxicity is also common, occurring most frequently in the first 6 weeks but at times up to 18 weeks after initiation of treatment. The risk factors are female gender, abnormal baseline hepatic enzymes, co-infection with Hepatitis B/C, and high CD4 levels (CD4 > 250 for women and CD4 > 400 for men).

- Usually minor, hepatotoxicity can be fatal and health care providers should always remember to monitor the liver function of their patients in case of any anomaly or pain in the right hypochondrium at the initiation of treatment and as often as they judge it necessary. Table 2 describes the different stages of the severity of the toxicity while the treatment algorithm for managing hepatic toxicity is found in the annexes. NVP must be stopped completely if stage 3 toxicity is reached (transaminase levels > 5 times above the normal limit)

Hepatotoxicity

	Normal	Grade 1	Grade 2	Grade 3	Grade 4
ALAT (SGPT) (UI/l)	< 40	50-100	100-200	200-400	>400

- NVP lowers the plasma concentration of estrogen-containing hormonal contraceptives. Alternative or additional methods of family planning should be used.

Efavirenz (EFV)

Efavirenz and Skin Rash

Occurs in 15 to 25% of patients. The rash is usually minor to moderate but may require interruption of treatment in 2% of patients. Potentially fatal reactions have been reported. The algorithm for managing dermatological toxicity is found in the annexes.

Efavirenz and Central nervous system side effects

Occur in at least 50% of patients and can include nightmares, vertigo and insomnia. It is therefore preferable to take the drug just before going to bed at night. The side effects usually disappear after one month of treatment and do not require treatment interruption except in about 2 to 5% of patients.

Efavirenz and Hepatotoxicity

Is less common and less severe than with NVP but elevation in liver function enzymes to 5 times the normal levels has been noted in 2 to 6% of patients. The algorithm for the management of hepatotoxicity is found in the annexes.

Efavirenz and Teratogenicity

EFV is teratogenic in cynomolgus monkeys and must not be prescribed for pregnant women during the first trimester. Pregnancy category D. If a woman becomes pregnant while on EFV and does not present until the second or third trimester, there is no indication to change the drug.

Important notice:

NNRTIs remain in blood for a very long period after stopping the drug. It is therefore advised that on stopping EFV or NVP the patient should continue with their 2-NRTI base regimen (e.g. D4T + 3TC) for 5 to 7 days after stopping the NNRTIs in order to avoid creating a situation of monotherapy and increasing the likelihood of resistance.

Protease Inhibitors (PIs):

Side effects of this category

Insulin resistance occurs in 30 to 90% of patients on PIs and results in overt diabetes in 1-11% of patients. It usually occurs in the first 2 to 3 months of treatment and at the latest by the end of the first year. To monitor for its occurrence, it is important to measure blood glucose at least every 3 months during the first year.

Two solutions are open to clinicians in case of overt diabetes: either to prescribe oral anti-diabetic drugs or interrupt treatment. In the latter case, since PIs are used in second line treatment, an expert opinion should be sought first because such patients will usually be resistant to other drugs.

Hyperlipidemia (increase in cholesterol and triglycerides) is a side effect reported for all PIs and ritonavir in particular. This has the effect of increasing the risk of cardiovascular disease and pancreatitis. Given the prohibitive cost of statins, management is often limited to advice on diet and healthy living (nutrition and physical exercise).

Lipodystrophy presents as loss of peripheral sub-cutaneous fat and its accumulation in the abdomen, the upper part of the back, the chest and certain subcutaneous tissues. In some patients, it is associated with hyperlipidemia and hyperglycemia.

Over long periods of treatment, it is observed in many patients (20 to 80%); with the risk increasing if a PI is combined with D4T, D4T/DDI and to a lesser extent AZT. In this case also, the treatment options are limited to physical exercise or to changing the ARV treatment regimen.

Hepatotoxicity is a side effect common to all ARVs, PIs are no exception with ritonavir being more often implicated.

Biological examinations required when considering changing treatment due to toxicity.

Parameters	Grade 3 toxicity
Hematologic	
Hemoglobin	< 6,9 g/dL
Neutrophil count	< 749/mm ³
Platelets	< 49 999/mm ³
Biochemistry	
Sodium	< 122 mmol/L or > 159 mmol/L
Potassium	< 2,4 mmol/L or > 6,6 mmol/L
Bilirubin	> 2,5 x higher than normal values
Creatinine	See CrCl
Glucose	< 0.39 g/L or > 2.51 g/L (non diabetic fasting)
ASAT (SGOT)	> 5x higher than normal values
ALAT (SGPT)	> 5x higher than normal values
Alkaline Phosphatase	> 5x higher than normal values

* In case of gastrointestinal signs or abdominal pain.

Major side effects of first line regimens and the recommended substitution drugs

Regimen	Toxicity	Alternative drugs
TDF+3TC/ FTC + NVP/EFV	<ul style="list-style-type: none"> ✦ Renal toxicity due to TDF ✦ Severe hepatotoxicity due to NVP ✦ Rash due to NVP that puts the patient's life in danger (Stevens Johnson syndrome) ✦ Persistent CNS toxicity due to EFV 	<ul style="list-style-type: none"> ✦ Change TDF -> AZT ✦ Change NVP -> EFV (except during 1st trimester of pregnancy) ✦ Change NVP -> LPV/r ✦ Change EFV -> NVP
ABC+3TC +NVP/EFV	<ul style="list-style-type: none"> ✦ Hypersensitivity reaction due to ABC ✦ Persistent gastrointestinal intolerance: (nausea, vomiting, malaise, diarrhea, headaches or anorexia) due to ABC ✦ Severe hepatotoxicity due to NVP ✦ Persistent CNS toxicity due to EFV 	<ul style="list-style-type: none"> ✦ Change ABC -> AZT ✦ Change ABC -> AZT ✦ Change NVP -> EFV (except during 1st trimester of pregnancy) ✦ Change EFV -> NVP

Drug Interactions

General information

Drug combinations used in treating HIV infection are susceptible to various interactions that may manifest as a reduction or a potentiation of the therapeutic effect or adverse drug reactions of other drugs.

Drug interactions are:

- Pharmacokinetic: A drug affects the absorption, the distribution, the metabolism, or the excretion of the other.

or

- Pharmacodynamic: Two drugs may have an antagonist additive or synergistic action.

These two interactions may be combined thus making the situation even more complex:

- Interactions may be exacerbated by a pre-existing pathological state: renal or hepatic insufficiency, abnormal digestive absorption, kidney medulla deficiency, etc.
- Interactions are studied two by two but the final outcome of a multidrug administration are often little known; interactions with illicit products have been even less studied.

The absorption of drugs through the digestive system may also be affected by certain foods and even affect the daily dosages.

Hepatic metabolism and the hepatic cytochrome systems

Most drugs and food substrates are hydrophobic and thus cannot be excreted (through the urinary or biliary route) until after they have been transformed into water soluble metabolites.

This metabolism mainly occurs in the liver and involves several enzymes.

Induction of cytochrome enzymes

It is their increase in the system that leads to the acceleration of the oxidation reactions, that may result in a reduction in the action of the drug or an increase in the toxicity due to its toxic metabolites.

Inhibition of cytochrome enzymes

The action of the inhibitor drug on the cytochrome may be non-competitive (if it is not metabolized there) or competitive (if it is metabolized from there). In the

latter scenario, the result of the reciprocal inhibition will vary depending on the respective affinities of the substrate for the cytochrome.

Reminder of the major drug interactions

Summary of main interactions between ARV drugs and others drugs commonly used in Rwanda.

Drug interactions

	Nevirapine	Efavirenz	Lopinavir /rit	Nelfinavir	Indinavir
Ketocazole Fluconazole	Keto ↓63%; No effect; Fluconazole		LPV ↓13%; Keto ↑ x 3	Dosage does not change	IDV ↑68%; Reduce dose to 600 mg 3 X a day
Rifampin	NVP ↓37% ; Do not use. ↑hepatotoxicity!	EFV ↓25%; EFV to 600 mg/j	LPV ↓75%; Do not use. If inevitable, seek specialist opinion first:	NFV ↓80%; Do not use	IDV ↓89%; Do not use
Macrolides : Clarithromycin, Erythromycin, Azithromycin	NVP ↑26%; Clarithro ↓30%; Dose does not change	Clarithro ↓39%; Use Alternative			Clarithro ↑52%; dosage does not change

	Nevirapine	Efavirenz	Lopinavir/ritonavir	Nelfinavir	Indinavir
Oral contraceptives	Estradiol \searrow 20%; Use alternative methods	Estradiol \nearrow 37%; Use alternative methods	Estradiol \searrow 42%; Use alternative methods	Estradiol \searrow 47%; Use alternative methods	Estradiol \searrow 37%; Use alternative methods
Anticonvulsants: (Phenobarbital, Phenytoin, Carbamazepine)	Effect not known	Effect not known	Effect not known. May reduce the effect of PI.	Effect not known May reduce the effect of PI.	Effect not known May reduce the effect of PI.
Antihistamines: (Astemizole, Terfenadine)		Do not use	Do not use	Do not use	Do not use
Psychotropic drugs*: (Triazolam, Midazolam)		Do not use	Do not use	Do not use	Do not use
Gastroenterology drugs: Cisapride		Do not use	Do not use	Do not use	Do not use
Anticoagulants: Warfarin		Risk of bleeding \searrow Warfarin and monitor!			
Theophylline			Theophylline \searrow 47%; Adapt the dose of Theo.		

Garlic supplements must not be taken during treatment with NVP.

Lopinavir/r potentiates the effect of Diazepam. A smaller dose should therefore be prescribed. Certain products taken by patients (St. John's wort) may have interactions with ARVs: always verify this during follow up.

Note: In case of side effect or toxicity, change the causing molecule but not the whole regime

CHAPTER VI: CHANGING ARV TREATMENT BECAUSE OF TREATMENT FAILURE

6.1. Introduction

Successful ARV therapy results in clinical and immunological improvement due to suppression of viral replication.

It is reasonable to expect a symptomatic patient to show clinical improvement within three months after initiating ARV treatment.

After six months of ARV treatment, CD4 cells generally increase by at least 50 cells/mm³ although the significance of this increase depends on the baseline CD4 at the time of ARV treatment initiation.

Treatment failure is usually associated with poor adherence to treatment (see chapters on adherence and provision of care to the patient), and it is important to assess adherence to ARV treatment before changing drugs.

6.2. Definitions of treatment failure

Treatment failure can occur at 3 levels:

- ✦ **Clinical failure:** Occurrence of a new opportunistic infection or a malignancy that reveals clinical progression of the disease (new WHO Stage 4 condition). Recurrence of a previous opportunistic infection.

Progression towards a higher clinical stage after ruling out immune reconstitution syndrome. (The recurrence of TB may not represent progression of the HIV disease as it may be a case of re-infection.)

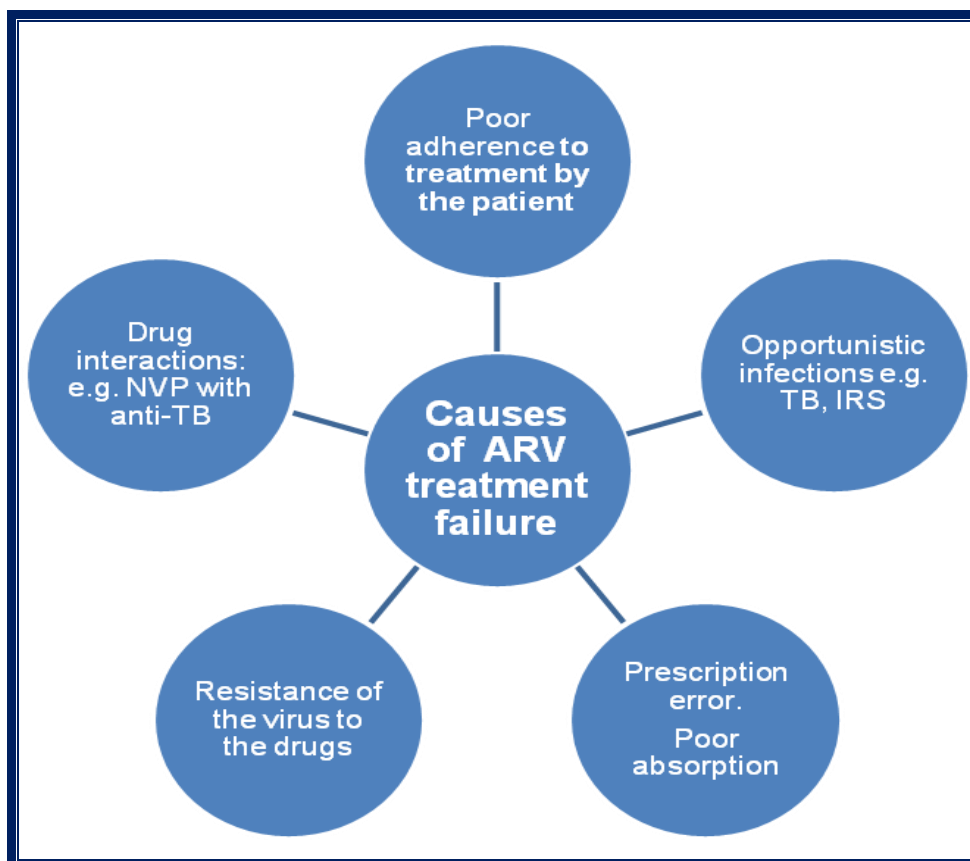
- ✦ **Immunological failure:**

- A return of CD4 counts to the pre-treatment baseline or below (in the absence of any concomitant infection that is liable to cause a transient reduction in CD4).
- A fall of more than 50% in the CD4 below the peak value ever obtained after initiating ARV treatment (in the absence of any concomitant infection that is liable to cause a transient reduction in CD4).

Virological failure: Detectable viral load (VL > 1,000) after 6 months of treatment in a patient with good adherence to ARV treatment.

- Viral load will help to decide where there is doubt regarding changing treatment from first to second line. VL will be the final determinant for treatment failure.

6.3. Causes of treatment failure



6.4. Management of treatment failure: What to do in case of suspicion of treatment failure?

- Given the cost of 2nd and 3rd line regimens, their frequent side effects, the high number of tablets that need to be taken and especially the limitation in the number of alternatives currently available in Rwanda, clinicians often hesitate to change treatment even though the criteria are very clear. From now onwards, it is strongly advised to be systematic in making decisions on ARV treatment.
- Establish trust with the patient, verify the patient's adherence in a precise manner (how many doses did you forget in the last 3 days, last week) and in a

more general manner (the patient should evaluate the percentage of pills s/he took in the last months using a visual analogue scale), verify at what time the patient has been taking his/her drugs.

- Verify if there is no intercurrent opportunistic infection that may be causing a transient decline in CD4 cells (e.g. TB). If there is TB, then treat it and check CD4 after the intensive phase and at the end of TB treatment and decide accordingly.
- Rule out any drug interaction problems in the past.
- Rule out any problems with absorption (e.g. vomiting or frequent diarrhea).
- Repeat CD4 the following month. Counseling must be strengthened to ensure optimal adherence during the waiting period before the next test. It is important to redo the test in order to rule out any laboratory error; however do not allow more than 3-4 weeks to pass in case the failure is real.
- Once immunological failure is confirmed, and after identifying the cause, discuss all the cases of failure with the care team; do not hesitate to seek a second opinion by internet or telephone. The doctor (or nurse) should never take the decision to change from 1st to 2nd line alone. A treatment committee at each health facility should review these cases of suspected treatment failure before the regimen is changed. If the failure is confirmed, the whole regimen must be changed. The choice of new ARV drugs must take into consideration cross-resistance with ARVs that have been used earlier.

What to do in case there is dissociation between the 3 causes of treatment failure?

- If a patient shows evident clinical improvement in spite of a disappointing immunological evolution (increase in CD cells $< 50/ \text{mm}^3$ after 6 months), continue treatment with the initial regimen, and verify adherence and CD4 count 3 months later. If the patient has obvious immunological failure, it is suggested to check a viral load (VL) to confirm the failure: if detectable, change treatment; if undetectable continue with the current treatment. It should be noted here that treatment is changed if VL is >1000 copies/ml after 6 months of treatment following the strengthening of adherence.
- If a patient shows good clinical and/or immunological improvement in spite of virological failure: if evaluation reveals good adherence, change the patient to second line treatment. If adherence is poor, continue with the current treatment, institute measures for improving adherence and check CD4 and VL after 3 months.
- Immune Reconstitution Inflammatory Syndrome (IRIS) is characterized by the appearance of signs of an OI a couple of weeks or months following the initiation of ARV treatment in a patient with advanced immune suppression

(usually CD4 < 50-100). It is an inflammatory response to a pre-existing subclinical OI. It is also possible that this reconstitution leads to the development of atypical presentations of certain OIs. An increase in the severity of the OI is one of the possible outcomes of the disease during ARV treatment and should not be considered as clinical failure.

Detailed recommendations for the changing from 1st to 2nd line regimen.

3TC (lamivudine) and FTC (emtricitabine) are interchangeable because they have nearly the same structure, share the same pharmacological properties as well as the same resistance profile. 3TC should be maintained in the second line regimen because it has a residual effect on the virus by maintaining pressure on the M184V mutation, resulting in increased sensitivity to AZT or TDF.

N.B.: Indinavir/r is a good alternative in case of intolerance to LPV/r (Kaletra) (refer the patient to a referral center). In the cases where the patient has had resistance tests carried out, the second line treatment could be adapted based on the efficacy of each ARV drug - expert consultation should be sought for interpretation of any genotyping data.

Recommended Combinations for Second line in Rwanda

First line Regimens	2 nd Regimens
TDF (Tenofovir) + 3TC / FTC (Lamivudine or Emtricitabine) + NVP (Nevirapine)/EFV (Efavirenz)	AZT (Zidovudine) + 3TC (Lamivudine) + Lop/rit (Kaletra).
ABC (Abacavir) + 3TC (Lamivudine) + NVP (Nevirapine)/EFV (Efavirenz)	AZT (Zidovudine) + 3TC (Lamivudine) + Lop/rit (Kaletra).
AZT(Zidovudine)/D4T(Stavudine)+3TC (Lamivudine)+NVP (Nevirapine)/EFV (Efavirenz)	TDF (Tenofovir)+3TC (Lamivudine) + Lop/rit (Kaletra)

Recommended Combinations for third line regimen in Rwanda

Regimen recommended after failure of the 2nd line regimen

In Rwanda, the 3rd line regimen combination is: TDF/3TC/RAL/ETV/DRV/r

Molecule	Dosage
Lamivudine (3TC)	300mg once a day
Tenofovir (TDF)	300 mg once a day
Raltegravir	400 mg twice a day
Ritonavir	100 mg twice a day
Darunavir	600 mg twice a day
Etravirine	200 mg twice a day

The 3rd line regimen must only be given upon expert consultation and usually with the assistance of genotyping test. Virological failure (VL > 1,000) is the primary determinant of 2nd line failure. Before prescribing 3rd line therapy, the patient MUST undergo extensive additional adherence counseling and should have a treatment partner involved with assisting in adherence. 3rd line regimens will only be prescribed at referral centers.

The rationale for maintaining TDF and 3TC in the 3rd line regimen is that studies have shown that continuing NRTIs in salvage regimens produces better virological outcomes than if they were discontinued. Renal function should continue to be monitored while on TDF.

CHAPTER VII. ADHERENCE TO DRUGS AND IMPLEMENTATION STRATEGIES

- a) Adherence to medication is the term used to describe the fact that the patient takes his/her drugs correctly in terms of dosage, frequency and timing.
- b) The patient participates in adherence by deciding either to take or not take the drugs.
- c) Observance means that the patient does what the doctors/pharmacist tells him/her to do.
- d) Both adherence and observance are important factors for the success of treatment.

- e) Poor adherence results in virologic failure, the development of drug resistance, immunological failure and eventually clinical failure.
- f) Compliance means that the patient conforms to and totally respects the directives guiding the prescribed drugs.

7.1. Factors that influence adherence

Factors linked to the patient

- Forgetfulness.
- Preparation and motivation of the patient.
- Negligence.
- Being far from home.
- Life styles (alcohol abuse, etc.).
- Depression.
- Cultural issues (stigma).
- Socio-economic issues (isolation, sufficient support, employment, work pace, nutrition deficiency, etc.).

Factors linked to the health care provider

- Preparation of the health care provider (knowledge, skills).
- Counseling the patient.
- Education of and communication with the patient.
- Other providers reinforcing the doctor's message, e.g. showing when to take the drugs with tables or diaries.
- Adherence support team.
- Support to the health care provider.

Factors linked to treatment and the drugs.

- Number of different drugs prescribed.
- Number of doses in a day.
- Side effects.
- Food restrictions.
- Drug interactions
- Stock outs.
- Taste of the drug.
- Cost of treatment and follow up.

7.2. Intervention strategies in the domain of adherence

It is important to counsel the patient properly before initiating ARVs. This involves clinicians, nurses, pharmacists, social workers, and others, i.e. the entire treatment team. It is important not to initiate treatment during the patient's first visit. You should counsel the patient on adherence to treatment in order to ensure the best adherence.

Once treatment is started, you should monitor and provide steady support for adherence. The strategies include:

- Prepare and motivate the patient, provide basic information on the drugs, discuss the importance of adherence, when to take the drugs, drug interactions, etc.
- Simplify treatment whenever possible.
- Adapt the treatment to the patient's life style where possible.
- Manage side effects and prepare the patient for them.
- Set up a team responsible for adherence (see PART A CHAPTER 4).
- Tailor management of the patient based on the circumstances of each person's life.
- Provide support aids that can help to increase adherence (IEC materials).
- Utilize a person to serve as a home link to the patient (treatment buddy) to support adherence.

Note: Adherence counseling requires the capacity to be able to transmit the technical aspects of adherence and the skills to make the patient feel relaxed, so that s/he can feel free and trust the health care provider. The latter may require a significant time investment.

7.3. Measures of adherence

- ✦ Discussion and self evaluation of the patient: a practical and cost-effective way is to count pills (labor intensive).
- ✦ Discussion with the treatment buddy.
- ✦ Pharmacy dossier/monitoring of prescription renewals.
- ✦ Directly observed treatment (DOT): theoretically leads to 100% adherence. It is labor intensive and less practical outside of institutional settings.
- ✦ Evaluation of treatment response (clinical response, CD4): This is not the first evaluation of adherence; it is a proxy marker; it can be useful if used together with the patient's self evaluation. We can also use viral load if available.

CHAPTER VIII. PROVISION OF CARE TO THE PREGNANT WOMAN

8.1. Background

In April 1999, with support from UNICEF, TRAC established the PMTCT Program in Rwanda at a pilot site in Kicukiro (City of Kigali) with the goal of proving the feasibility of a PMTCT program in Rwanda.

When the program was launched, Zidovudine was chosen as the prophylaxis to be given to pregnant women starting in the 28th week of pregnancy, and women were hospitalized throughout the period of prophylaxis until they gave birth.

But, as the Zidovudine regimen was very expensive (\$800 per woman) and the follow up of women was difficult, it gave way to the HIVNET 012 regimen, which called for a single 200mg dose of Nevirapine (NVP) to be given to the mother at the beginning of labor and a single 2mg/kg dose to be given to the baby within 72 hours of delivery.

In December 2005, in the wake of problems of resistance to the monotherapeutic use of NVP and with a desire to increase the efficacy of the prophylaxis by combining several antiretroviral drugs, the regimen was changed and a triple therapy protocol for PMTCT was adopted. In November 2009, new WHO recommendations were published, and these insist on breastfeeding protected by antiretroviral. Each country should adapt its PMTCT protocol accordingly. That is why Rwanda also revised its protocol.

The number of sites offering PMTCT services increased from 1 site in 1999 to 366 sites in December 2009.

8.2. ARV treatment in pregnant women

There are three particularities of provision of ARV care to pregnant women:

- Adverse side effects are more common and may influence the choice of the ARV drugs (e.g. risk of severe rash with NVP treatment is seven times higher than for men).
- Lactic acidosis and hepatic steatosis are more common when using nucleoside analogues (83% of the first 107 cases that were reported).
- The possibility of an as-yet unknown pregnancy while under treatment.

Nonetheless, ARV treatment of women including those that are pregnant remain a priority.

HIV-infected women should be counseled on family planning.

There are three possibilities relating to pregnancy regarding antiretroviral treatment among women:

- ARV for the woman in the reproductive age group.
- ARV for the pregnant women who meets the criteria for initiation of ARV treatment (eligible for ARVs).
- ARV for the woman who is already on triple therapy who becomes pregnant.

8.3. ARVs for the woman in the reproductive age group

There is a dual problem:

The problems related to the association of contraception to ARVs:

Several ARVs (PIs and NNRTIs) modify the metabolism of hormonal contraceptives and need special precautions when this mode of contraception is utilized in conjunction with ARV treatment.

The following table shows the interactions between ARVs and hormonal contraceptives:

ARV	Effect on the plasma concentration of ethinyl - estradiol	Adaptation of dosage
NRTI	No effect	
Nelfinavir	Reduction of 47%	↑>30µg ethinyl - estradiol
Lopinavir/r	Reduction of 42%	↑30 µg ethinyl - estradiol
Nevirapine	Reduction of 19%	↑ 30 µg ethinyl - estradiol
Efavirenz	Increase of 37%	↓15 or 20 µg ethinyl - estradiol

In the case of difficulties in using Ethinyl Estradiol, it is essential to recommend another mode of contraception:

- ✦ Either utilization of progesterone only pills: some interactions with ARVs exist in the form of reduction in the plasma concentrations of progesterone.
- ✦ Or use an intrauterine device (IUD), but keep in mind the increase risk of infections in the case of severe immune deficiency.

In all cases, the utilization of condoms (male or female) is recommended because they have an important role in preventing re-infection with HIV in case the partner is HIV-infected, and protection against infection if the partner is HIV negative.

Problem of the choice of ARVs

The choice of ARVs for women in the reproductive age group is similar to that for men; however, we should try to avoid drugs that are potentially teratogenic (EFV). EFV can be used by any woman provided that she uses contraception and is informed of the necessity to immediately inform her doctor in case she becomes pregnant. The doctor should then modify the treatment regimen by replacing EFV with NVP during the first trimester.

8.4. Pregnancy desire

This phenomenon is very frequent and remains the hardest to manage. In principle, pregnancy in an HIV-infected woman should not be encouraged, even in the presence of PMTCT.

The doctor together with his patient should therefore manage this desire as best as he can. Similarly each woman in the reproductive age group should be adequately counseled before she decides to become pregnant.

Each PMTCT site should also offer effective family planning services.

The first issue concerns the partner; and here there are 3 possibilities:

- ✦ **Either he is HIV-infected:** It is obvious that there is a need to counsel this couple on condom use in order to avoid re-infection but it will also be an opening to determine the right moment for conception while at the same time reducing the number of unprotected sexual encounters as much as possible.

- **He is HIV negative:** In this case there is a risk of eventual transmission through unprotected sexual encounters. Here, we should encourage protective techniques such as insemination of the partner with sperm using a syringe or a condom.
- **Or his HIV status is not known:** in this case, the situation may be further complicated by two scenarios:
 - The woman conceals her HIV serostatus from her partner. In this case, it is very likely that the woman undertakes frequent and unprotected sex and pregnancy desire increases the risk of transmission.
 - The partner refuses to check his HIV status and it is necessary to reduce the risk to the two partners by limiting, if possible, the number of unprotected sexual encounters.

The second issue is the clinical and immunological status of the woman. In this case, it is important to evaluate the clinical state of the woman and her CD4 count. If the status is poor (poor clinical status, low CD4), then it is necessary to analyze the cause of treatment failure.

In summary, the points to be evaluated when a woman on ARVs wishes to become pregnant are:

The partner's HIV serostatus

- Is the disease stable?
 - Good evolution in CD4 (check it if necessary).
 - Good clinical evolution.
 - No intercurrent opportunistic infections.
- What is the social support that the patient is receiving?
- Is the ARV regimen the ideal one?
- Information on the risks that the mother, baby and the partner face.

The desire to become pregnant is often a major issue of concern for most HIV-infected women. The importance of this desire may vary in time. The woman may forget this desire at the initiation of treatment, and then later, as she begins feeling better she may begin to want to have children again.

The failure of the doctor to be open-minded or to freely discuss the issue with patients may result in problematic situations. It is therefore necessary to regularly discuss this subject with patients during follow up because most patients will not talk about it spontaneously.

8.5. Guidelines for the administration of antiretroviral drugs in HIV positive pregnant women and exposed infants

It is recommended that any HIV+ pregnant woman, already on ARV or not, receives all care including ARV respecting the PMTCT protocol into force in the same health facility. This will be possible since the ministerial instruction of delegation of powers (task shifting) of physicians to the nursing staff was signed. The district hospital must do the maximum to oversee this approach especially for non-ARV sites.

A clinical evaluation (Stages WHO) and a biological assessment including the CD4 count, hemoglobin, liver function and the renal function must be made before the start of the ARV prophylaxis in PMTCT.

Indeed, pregnant or not, an HIV positive woman should be put on antiretroviral on medical indications. In a pregnant woman, it is appropriate to begin this treatment from the beginning of the second quarter (end of the period of early embryogenesis with teratogenic high risk). Which means from 14th week of amenorrhea for the women with the number of CD4 count below 350/mm³. If this date is past, the treatment has to be started as earlier as possible.

The following situations are possible among pregnant women:

HIV-positive pregnant women eligible for ARV treatment

- Any woman with a CD4 count < 350 regardless of her WHO clinical stage and any woman with a WHO clinical stage of 3 or 4 regardless of her CD4 count are eligible for ART. The treatment should begin as early as possible no matter how advanced the pregnancy.

The regimen is composed of Tenofovir 300mg + Lamivudine 300mg + Nevirapine 200mg: **TDF + 3TC + NVP**.

Any woman with impaired renal function or likely to have impaired renal function will receive Abacavir 300mg + Lamivudine 150mg + Nevirapine 200mg: **ABC + 3TC + NVP**

Note: This is a lifelong treatment.

HIV-positive pregnant women with CD4 counts between 350 and 500

- Any HIV-positive pregnant woman with a CD4 count between 350 and 500 will be considered in PMTCT as a woman eligible for ARV treatment for life. This is to avoid a discontinuation of ARV therapy in a woman who would be eligible or who could even conceive again sometime later and restart ARV treatment. They will receive triple therapy from the 14th week.

The ARV regime is Tenofovir 300mg + Lamivudine 300mg + 600mg Efavirenz: **TDF + 3TC + EFV**

Note: This is a lifelong treatment.

HIV-positive pregnant women with a CD4 count > 500 (non eligible for Arv treatment)

- Any woman with a CD4 count > 500 is non-eligible for ARV treatment, but the women will continue the treatment for life to avoid a discontinuation of ARV therapy in a woman who would be eligible or who could even conceive again sometime later and restart ARV treatment.
- They will receive triple therapy from the 14th week of gestation and they will continue the treatment for life not one week after the cessation of breastfeeding as it was recommended before

The ARV regime is Tenofovir 300mg + Lamivudine 300mg + Efavirenz 600mg: **TDF + 3TC + EFV**

HIV-positive pregnant women with prior exposure to single-dose Nevirapine

- All HIV-positive pregnant women who were exposed to single-dose Nevirapine during their previous pregnancy will receive Tenofovir 300mg + Lamivudine 300mg + Lopinavir/Ritonavir (Kaletra) 250mg: **TDF +3 TC + Lop/r**

Note: The single dose of NVP means:

- A single tablet that was taken by the woman just after the beginning of the labor and this tablet were taken alone without another tablet either before or after.
- Women who have taken a regime which includes the single dose of NVP but with AZT before or AZT/ 3TC after; the latter are not part of this category.

HIV-positive pregnant women with impaired renal function

- Any woman with impaired renal function or likely to have impaired renal function will receive Abacavir 300mg + Lamivudine 150mg + Efavirenz 600mg: **ABC + 3TC + EFV**
- Women with impaired renal function or likely to have impaired renal function who were exposed to single-dose Nevirapine during their previous pregnancy will receive Abacavir 300mg + Lamivudine 150mg + Lopinavir/Ritonavir (Kaletra) 250mg: **ABC + 3TC + Kaletra**

However the monitoring of renal function is important.

Note: ARV prophylaxis will not be stopped one week after the cessation of breastfeeding.

HIV-positive pregnant women arriving late: after 34 weeks of gestation

All HIV-positive women arriving after 34 weeks of gestation need to begin **TDF + 3TC + EFV** treatment after a renal assessment (Creatinine) without waiting for the results of the CD4 count.

HIV-negative pregnant women in a serodiscordant couple

- An HIV-negative woman in a sero-discordant couple (i.e., the partner is HIV-positive and the woman HIV-negative) will need to be tested for HIV every three months, as well as at the onset of labor.
 - If she is shown to be HIV-positive: refer to the section on care for HIV-positive pregnant women (see above).
 - If she remains HIV-negative, she will receive during labor
 - a single dose of **TDF + 3TC + EFV** and continue with **TDF + 3TC** (one combined tablet per day) for one week after delivery.
- Prophylaxis in children:
 - The child must take daily NVP syrup until the cessation of breastfeeding unless the mother turns positive during breastfeeding period.

If the mother is shown to be HIV-positive at the time of breastfeeding, she should be put on ARV triple therapy, and the child should continue taking NVP for six weeks after the initiation of the mother's triple therapy.

Note: For a woman eligible already under trithérapie for life > don't change the regimen except in case of side effects. The woman should continue the same regimen

SPECIAL RECOMMENDATION FOR THE SERODISCORDANT COUPLES

It is currently recommended to treat the HIV+ partner using ART in serodiscordant couples regardless neither the number of CD4 nor the clinical stage.

ARV prophylaxis for children exposed to HIV (children born to HIV-positive mothers)

All children born to HIV-positive mothers, whether the mothers breastfeed or not, will receive Nevirapine (NVP) syrup during the first six weeks of life.

Postnatal consultation for the mother-child couple

The follow up of the mother-child couple will be done by the following services:

- Breastfeeding
- Vaccination;
- Growth monitoring (monitoring of exposed children);
- FP

Breastfeeding

- Advice on diet should be discussed when the results are announced and gone into in more detail throughout the pregnancy and during the postpartum period. The recommended feeding method is as follows:
 - **Exclusive** breastfeeding until **six months**;
 - **Introduction** of healthy, balanced, and appropriate complementary food at six months and continuation of breastfeeding **without exceeding the maximum recommended duration of 18 months**;
 - Weaning should be done **gradually over a period of one month** (advice and nutritional support are necessary during this period);
 - Advice on a healthy and balanced diet for the child and the mother must be given continuously to the mother;
 - Regular clinical follow up of the mother and child will continue;
 - ARVs should be given during the entire period of breastfeeding and the week following the cessation of breastfeeding;
 - If a mother wishes not to breastfeed, make sure that safe and adequate replacement food is available, give appropriate advice on substitute milk to use and healthy and balanced complementary foods to offer starting at six months, and tell her that she must continue to give milk.
 - If the mother chooses replacement feeding, the child must be fed exclusively by replacement feeding and not breast milk during the first 6 months.

From 6 months up to 24 month, compliment the milk meals with adequate complementary foods that are locally available.

The success of artificial feeding depends on:

- The quality of the counseling that was given; the issue of infant feeding should be discussed as early as possible following the disclosure of seropositivity.
- The facilitation that is provided by the PMTCT program towards this feeding: supply of free milk and feeding bottles for the first six months. It is important to give clear explanations on how to clean the feeding bottles or cups and how to sterilize them using boiling water. Access to clean water is an important factor and must be evaluated before considering artificial feeding.
- The family and/or community support received by the mother.
- The quality of mother infant follow-up done by the health care team.

Follow up schedule

The first appointment is after six weeks (child: vaccination, PCR, Cotrimoxazole, growth monitoring, monitoring of psychomotor development), and monitoring will

continue every month following the vaccination schedule. After the vaccinations, monitoring will continue every month until 18 months, and for at-risk cases (non-cessation of breastfeeding at 18 months, malnutrition, HIV infection, etc.), it will be prolonged and overseen by the relevant services.

The appointment at six weeks is crucial. The identification of exposed children in the vaccination service will be facilitated by the immunization card integrating information about the mother's HIV and interventions in the PMTCT program.

It is important to harmonize follow-up appointments of the child with those of the mother to avoid multiple visits.

Biological follow up

- Children born to HIV-positive mothers will be closely monitored, clinically and biologically, in order to diagnose and provide early treatment to those needing ARVs before 18 months.

PCR

- The first direct test (PCR 1) is done at six weeks or during the first visit after six weeks for all children born to HIV-positive mothers, or at any time if the exposed child shows suspicious symptoms (poor growth, long-term unexplained fever, long-term diarrhea despite treatment, recurring infections, signs of malnutrition, recurring thrush).
 - If the PCR 1 is **negative**, continue to monitor and do a serology test at nine months.
 - If the PCR 1 is **positive**, confirm with a second PCR but at the same time start giving ARVs (as the second PCR test result can take time).
 - If the confirmation PCR is **negative**, do a third PCR to reconfirm the result:
 - If the third PCR is **negative** (because of error in the PCR 1), stop the pediatric care already initiated and do the serology test at nine months.
 - If the third PCR is **positive**, continue the pediatric care already initiated and refer to the ARV pediatric program.
 - If the confirmation PCR is **positive**, continue the pediatric care already initiated and refer to the ARV pediatric program.

SEROLOGY

If a child has a negative PCR or if the PCR test is not available, a serology test will be done according to the national algorithm:

The serology test at nine months:

- If the serology is positive, confirm with a PCR (because of the possible presence of maternal antibodies). If the confirmation PCR is positive, refer for pediatric care.
- If the serology is negative, continue the ongoing care and do a final serology test at 18 months—or one month after the cessation of breastfeeding.

The serology test at 18 months

- If the serology is positive, confirm with a PCR. If the PCR is also positive, the child is considered HIV-positive and transferred to pediatric care.
- If the serology is negative and the child is no longer breastfeeding, he is directly declared HIV-negative and moved out of the program.

Note: For children who are breastfed beyond 16 months, the serology will be made a month and a half (6 weeks) after the complete stop of breastfeeding.

Growth monitoring and evaluation of nutritional status

The first two years of life are a period of rapid growth in children. The child's weight at birth is about 3kg. The child doubles his birth weight after six months and triples it after one year. At two years, he weighs about 12kg.

The size of the child is about 50cm at birth. It increases to about 75cm after one year and 85cm after two years. Head circumference is between 33cm and 36cm at birth. It increases to about 45cm after one year and 47cm after two years.

The anthropometric parameters most commonly used for growth monitoring of children are as follows:

- **Weight:** The naked or lightly dressed (without shoes) child is weighed with a well calibrated scale by, if possible, the same person each time. The scale should be recalibrated every morning.
- **Height:** Children under two years should be measured lying down; older children should be measured upright. Never use a tape measure.
- **Head circumference:** This should be measured in all children under five years every time they have contact with the health center. A tape measure should be used and should be passed around the frontal and occipital bones.

Regular growth monitoring can allow for early detection of weight, height, and head circumference abnormalities, the exact cause of which will be sought to undertake appropriate treatment and allow the child to realize his full growth and development potential.

Completing growth charts: At each consultation, the weight, height, and head circumference should be recorded on the growth chart in the child's file.

- All children born to HIV-positive mothers should be completely examined (weight, size, neurological development, suspicious signs of infection) every month until they reach 18 months.
- If the child shows growth or neurological problems, or suspicious signs of infection (fever, impaired general condition, dyspnea, etc.), he will be immediately referred to a doctor.
- Assess nutritional status monthly, and interpret the results to offer appropriate advice and nutritional care given that exposed children are at risk of malnutrition.

Medical care

- Cotrimoxazole should be systematically given to every child born to an HIV-positive mother from six weeks of life. At the same time, the child should also be given his first PCR (DBS) and second vaccination. The length of treatment will depend on confirmation of the negative result of the PCR or on serologic HIV in the child.
- If the result is confirmed positive, the child will be referred to the pediatric care program.

CHAPTER IX: POST EXPOSURE PROPHYLAXIS

Introduction

Every person who has been a victim of accidental exposure to blood/body fluids or rape must have access to an early evaluation of their risk of HIV infection and antiretroviral prophylaxis if indicated. This is why it is necessary to have functional services that work 24 hours a day. It has been shown that initiating prophylaxis early diminishes the risk of HIV infection by about 80%.

9.1. Accidental exposure to blood (AEB)

The risk of HIV infection following exposure to blood is less than the risk related to HBV and HCV. Nonetheless, it is important to determine if the exposed person needs ARV prophylactic treatment.

It is the duty of the employer to train his staff on prevention of accidental exposure, provide personal protection methods, and set up the necessary safety measures. Any accident must be declared as soon as possible (< 48 hours) in accordance with the existing guidelines.

An HIV serology test should be carried out on the exposed health care provider as soon as possible (ideally within 4 hours of exposure). If it is negative, a follow up serology will be done after the third month and before the end of the sixth month.

9.2. Criteria for prophylactic ARV treatment

The actual risk for a given patient must be evaluated by one of the health care providers from the health facility. This evaluation includes:

- The severity of the exposure, which is directly linked to the depth of the wound and the type of needle that was responsible for the injury.
- Venipuncture needle > needle for injection > non sharp instrument.
- The risk is even less following external contact of secretions with the skin or mucosa (splash).
- The risk is higher with blood than with any other body secretions (amniotic fluid, serous fluid).

The patient from whom the exposure originated should be considered:

- His HIV serostatus.
- His clinical and immunological status vis-à-vis HIV infection.
- His earlier HIV treatment regimens.

If his HIV status is not known, it is important to establish it with his free consent (testing without the knowledge of the patient or forcing him to consent under duress is prohibited). In any case, if the HIV status of the patient cannot be obtained within 4 hours, prophylaxis should be started immediately in accordance with the criteria in Table 1. If eventually the person from whom the exposure arose is proven to be HIV negative, then ARV prophylactic treatment should be stopped.

9.3. Prophylactic treatment

Always clean the exposed area immediately.

Needlesticks or skin injuries

- Clean the wound immediately with clean water and soap.
- Rinse with antiseptic: Dakin solution of Bleach 12° 1:10 dilution, or if impossible use 70% alcohol or povidone iodine dermal solution (Betadine).
- Contact time at least 5 minutes.

Splash on the mucous membranes (particularly the conjunctiva):

- Rinse for at least 5 minutes with copious amounts of water or preferably physiological saline.
- Do not apply disinfectant on the mucous membranes.

Recommendations for ARV prophylaxis depending on the degree of exposure and the HIV serostatus of the source of the exposure.

Source	Exposure		
	Massive	Moderate	Minimum
HIV + with low CD4 or OI	Recommended	Recommended	Recommended
HIV + Asymptomatic	Recommended	Recommended	Discuss
HIV status unknown, but risk factor for HIV (≥ 1 risk factor)	Recommended	Recommended	Discuss
HIV status unknown or unknown source without risk factors	Recommended	Discuss	Discuss

9.4. ARV treatment

This depends on the HIV serostatus of the source and the degree of exposure.

Evaluation of the degree of exposure:

- Massive exposure = deep penetrative wound with intravenous devices of IV or intra-arterial needle, prick with materials used to draw laboratory specimens.
- Moderate exposure = cut with a lancet through gloves, superficial prick with an IV or intra-arterial needle.
- Minimum exposure = Superficial bruise with a plain needle (suture) or small caliber needle (IM or SC), contact with mucosa or skin, prick with an abandoned syringe.

Maximum delay in implementing prophylaxis

In order to ensure maximum benefit from prophylaxis, treatment should start as early as possible, within the first **6 hours** following the exposure, without waiting for results of HIV serology of the source person. A limit of **48 hours** is reasonable in seeking maximum efficacy.

Duration of treatment

Treatment is for **4 weeks (28 days)**. An initial prescription of 1 to 2 weeks and weekly consultations enable close monitoring and psychological support so as to strengthen adherence to treatment.

Choice of drugs

The new recommended therapeutic regimen is:

TDF (Tenofovir) + 3TC / FTC (Lamivudine or Emtricitabine) + LPV/r (Kaletra)
 TDF (Tenofovir) + 3TC/ FTC (Lamivudine or Emtricitabine + EFV (Efavirenz)

If there is no TDF or a contraindication: AZT (Zidovudine) + 3TC (Lamivudine) + LPV/r (Kaletra).

N.B: Never give EFV to a pregnant woman.
NVP should never be given for PEP.

The treatment regimens described in this document are based on the recent recommendations of the WHO (New PEP guidelines) and regimens based on TDF are highly recommended.

Follow up

The person should be informed of:

- The risk of side effects due to the treatment;
- The importance of adherence;
- The need for prevention.

S/he must give informed consent for the prophylaxis.

A pregnant woman should be informed of the risk of transmitting HIV to her child and those related to taking antiretroviral drugs (it is recommended to seek the opinion of a referral doctor). A pregnancy test should be proposed to each and every woman.

Confidentiality should be strictly respected.

Avoid unprotected sexual intercourse during this period.

Bilan de suivi et d'évaluation

Date	Person not on prophylaxis	Person on prophylaxis
Initial assessment during the first 4 hours	HIV serology	- HIV serology - FBC - Pregnancy test
2 weeks		- FBC (If AZT)
At M1	Between 3 and 6 weeks after the exposures: - HIV serology	Between 3 and 6 weeks after the exposure: - HIV serology At the end of treatment: - FBC (if AZT)
At M2		1 month after completing the treatment: - FBC (if abnormal at M1) - HIV serology
At M6	- HIV serology	- HIV serology

Rape

Although there is less information on the efficacy of prophylaxis following sexual exposure than for exposure to blood, available data suggests that prophylactic treatment may reduce the risk of acquiring HIV infection. Prophylactic treatment should be routinely provided to rape victims.

Evaluation of the risk of infection

The following questions should be asked:

- ✦ What was the nature of the exposure? For example, what was the nature of the sexual attack? Was there a significant exposure (vaginal or anal penetration)?
- ✦ Is the HIV status of the source person (the rapist) known or not?
 - Is he HIV-infected? If yes, is he on ARV treatment?
 - Is the source person (rapist) available for the HIV test? If yes, does he accept to be tested?
- ✦ Is the exposed patient (rape victim) already infected with HIV? If the HIV status of the patient is not known, a rapid test must be performed systematically.

9.5. Indications and prophylactic regimens

If an HIV negative person is raped by someone who is known to be HIV-infected, post exposure prophylaxis must be given immediately or as soon as possible. The victim should be tested for HIV as soon as possible. There are, however, several circumstances that still remain vague. This is the case when the HIV status of the rapist is not known.

Prophylactic treatment is similar to the one used in the case of exposure to blood. In this case there is a need to add on prophylactic treatment for STIs.

9.6. What to do in case of rape

HIV status of the source person (rapist)	HIV status of the exposed person (rape victim)	Recommendation
Positive or negative	Known positive	No prophylaxis is indicated
Known positive*	Known negative	Immediate prophylaxis indicated
Known positive	Not known	Immediate HIV Rapid test done on the victim. - If HIV negative, give prophylaxis S - If HIV positive, stop prophylaxis and refer victim to HIV treatment clinic.
Not known but accepts HIV test	Known negative	Immediate HIV Rapid test done on the rapist Give prophylaxis as you wait for the results. - If the rapist is HIV negative, stop prophylaxis - If rapist is HIV positive, continue with prophylaxis
Not known but accepts HIV test	Not known	Immediate HIV Rapid test done on the rapist and the victim Give prophylaxis as you await the results If the rapist is negative, stop the prophylaxis - If the victim is positive, stop prophylaxis and refer her to the HIV care and treatment clinic.
Not known and either refuses the test or is not available	Known negative	Counsel the victim and inform her of the risks and benefits of prophylaxis and explain the options; then give prophylaxis if the victim accepts.
Not known and either refuses the test or is not available	Not known	Immediate HIV Rapid test done on the rape victim If the victim is HIV negative, then give prophylaxis Counsel the victim and inform her about the risks and benefits of prophylaxis and give options.

* If the rapist is HIV-infected and on ARV treatment, consult an expert for advice.

Follow up

Follow up is similar to post exposure prophylaxis in case of exposure to blood.

CHAPTER X : MANAGEMENT OF HIV-INFECTED CHILDREN

Children are also affected by HIV/AIDS. Data from UNAIDS in December 2006 showed that 2.5 million (between 2.2 and 2.6 million) children < 15 years are infected with HIV worldwide and that of every 2.5 million new HIV infections registered world wide during 2007, 420,000 (between 350,000 and 240,000) occurred in children. 330,000 children died of this disease in 2006.

10.1. Modes of transmission and evolution in children

✦ Mode of transmission

The main mode of acquisition of HIV in children is through vertical transmission (mother to child).

This mode of transmission accounts for over 95% of case of HIV among children. It occurs in utero, during labor and during maternal breastfeeding.

Other modes of transmission include:

- ✦ Blood transfusion.
- ✦ Use of non sterilized or poorly sterilized injection materials.
- ✦ Surgical procedures using non sterilized or poorly sterilized materials (circumcision...).
- ✦ Sexual abuse.
- ✦ Certain surgical procedures and rituals (extraction of false teeth, dissection of the uvula, excisions, tattooing, scarification, piercing, etc.).

10.2. Natural clinical evolution of the infection in children

The natural evolution of HIV in a child infected through the maternal fetal route follows three main forms in terms of evolution:

- ✦ A severe form (30 to 50% of cases in Africa) with the risk of death of 50% within the first 2 years of life (without treatment); especially found in child who are infected in utero.
- ✦ A moderate symptomatic form without opportunistic infections.
- ✦ A slowly progressive form (rare).

Given the high mortality among young children, it is essential to have an early diagnosis so that antiretroviral treatment can be started before 18 months and significantly reduce the morbidity and mortality due to HIV.

10.3. Laboratory diagnosis of HIV in children

The following signs are suggestive of the need to verify if the child does have HIV:

Automatically: malnourished children (obligatory, according to ministerial instruction), children on anti-TB treatment, repeated hospital admissions, children born of HIV-infected mothers.

Signs suggestive of HIV infection in a child:

Oral candidiasis, poor growth (either weight or height), mental retardation, dermatitis or repeated ENT infections, parotitis, frequent infections.

In reality, of the HIV non-infected children born of HIV-infected women:

- 75% of the children will have lost maternal antibodies between 9 and 12 months.
- 90% of the children have lost the maternal antibodies by 15 months.
- 10% of newborns are still HIV seropositive between 15 and 18 months.
- 100% of all the children will have lost maternal antibodies by 18 months.

The definitive confirmation of HIV infection in a children less than 18 months old is done using PCR (DNA PCR diagnosis or RNA PCR = viral load). (see PMTCT section)

✚ In the absence of PCR but CD4 testing is accessible:

- A child is declared HIV-infected until proved otherwise if at least two of the following criteria are met (WHO-August 2006):
 - Sepsis (signs of shock in the presence of severe infection).
 - Severe pneumonia that requires oxygenation.
 - Chronic oral candidiasis after the age of one month or signs of WHO stage 4 (AIDS) - more often severe persistent and unexplainable malnutrition.
- Major signs :
 - CD4 < 20% or CD4 < 1200/mm³ between 0 and 11 months and < 750/mm³ between 12 and 17 months).

Any child who is diagnosed HIV+ without a PCR test should get an HIV serology test at 9 and/or 18 months or (3 months after stopping breastfeeding).

Marasmus makes the clinical diagnosis of HIV difficult because these children are also immunosuppressed and present the same signs (e.g. oral candidiasis, repeated infections).

The question for these children is: is the severe malnutrition due to a nutritional deficiency, TB, HIV or another chronic disease? If the HIV serology is positive, do a PCR.

To answer this question, proceed by exclusion:

- ✦ Admit the child in a nutrition rehabilitation center and start treating malnutrition.
- ✦ Actively look for TB (see annex , screening questionnaire approved by RBC/IHDPC)
 - On history taking: cough >3 weeks or a fever that does not respond to broad spectrum antibiotics.
 - Look for a history of TB in the family, particularly in the parents, siblings and neighbors.
 - Ideally carry out a chest Xray examination of every child and every mother and look for AFBs using gastric lavage (2 times using 3 washouts).
 - Check for intradermal reaction.
 - Unexplained malnutrition (Disseminated TB).

- If there is improvement after nutritional rehabilitation and there are no signs to suggest TB, HIV infection is probable but disseminated TB is also possible (the child is particularly exposed to the 2 diseases).
- **Important remarks:** It is important to observe the response to anti-TB treatment before starting antiretroviral treatment without PCR results in a child aged less than 18 months. The only sign of extrapulmonary TB can be malnutrition without any pulmonary signs; cachectic children (with severe wasting) often no longer present any fever and cough very little; the intradermal reaction is negative (anergy due to deficient cellular immunity that is also linked to malnutrition).

Exclusion of the diagnosis of HIV in a child born of an HIV-infected mother

- Child > 18 months: Negative HIV serology in the absence of maternal breastfeeding (the test is done at least 3 months after weaning).
- Child < 18 months: The HIV serology of an uninfected child born of an HIV-infected mother may become negative beginning at 9 months but can stay positive up to 18 months.

Verify that the child has not been exposed (breastfeeding) during the 3 months preceding the serology test. Two negative PCR tests (of which one is done 1 month after weaning).

Providing care to the child born of an HIV-infected mother:

A close clinical and biological follow up must be instituted for every child that is born of an HIV-infected mother in order to be able to diagnose and treat the child that may need treatment before the age of 18 months.

Clinical follow up (to be undertaken in a PMTCT clinic if possible)

- Every child born of an HIV-infected mother must have a complete examination (weight, height, neurological development, candidiasis, skin problems, lymph nodes, liver, spleen, etc.) every month up to six months of age and then once every 3 months until HIV infection is completely excluded (either by negative HIV serology 3 months after weaning or a negative PCR one month after weaning). This information is recorded in the exposed infant dossier (the pink patient's file).
- If the child presents with signs of growth or neurological retardation, or one of the signs mentioned above, he should be referred to the doctor.
- If HIV infection is confirmed, his quarterly follow up will continue in an ARV treatment clinic using the pediatric HIV patient file (yellow dossier).

Biological follow-up of a child born of an HIV-infected mother

- First PCR at 6 weeks: (= date of first vaccination and start of cotrimoxazole prophylaxis)
NB: PCR at 6 weeks is systematic for each and every exposed infant. If the PCR is positive, refer the child for ARVs. A confirmatory PCR will be done systematically.
- Second PCR: it is done in the following circumstances:
 - Confirmation of the first PCR if it was positive (will be made immediately)
 - Confirmation of positive serology before 18 months (9 and 18 months)
 - If clinical signs suggestive of HIV infection after a first negative PCR.

If HIV infection is confirmed by PCR, the child is transferred to a pediatric HIV care and treatment clinic for ARVs and appropriate follow up in accordance with his age and the national protocol.

Prophylaxis against *Pneumocystis jiroveci* (originally called *carinii*) (PCP) and other infections (diarrhea, malaria, toxoplasmosis, bacterial infections):

Pulmonary infections due to *Pneumocystis* carry a high mortality rate in HIV-infected children, especially during the first year of life, but the risk remains high up to the age of 24 months and at times even in the presence of good immunity.

Initiation criteria :

- Any child born of an HIV-infected mother.
- Beginning at 6 weeks of age or above.

IN CONCLUSION: Each child or baby born of an HIV-infected mother in whom the diagnosis of HIV is not yet formally excluded (by negative HIV serology or negative PCR) must take TMP-SMX (Trimethoprim + Sulfamethoxazole) = Cotrimoxazole = Bactrim® = Eusaprim® at a dosage of 25/ 5 mg/kg 1X/day.

Dosage of Cotrimoxazole for prophylaxis in children (WHO 2006)

Age	Trimethoprim/ Sulfamethoxazole (TMP/SMX)	TMP/SMX Syrup (200mg/40mg)	TMP/SMX Tablets (400mg/80mg)	TMP/SMX tablets (800mg/160mg)
6 weeks to 6 months	100mg/20mg	2, 5ml	¼ Tablet	-
6 months to 5 years	200mg/40mg	5ml	½ Tablet	¼ Tablet
6 years to 14 years	400mg/80mg	10ml	1 Tablet	½ Tablet
14 years	800mg/160mg	-	2 Tablets	1 Tablet

The HIV-infected child :

Regardless of the age, the clinical stage or CD4 percentage, every HIV-infected child must be put on Cotrimoxazole prophylaxis for life.

Tuberculosis prophylaxis

INH prophylaxis at a dosage of INH 10 mg/kg/day for 6 months is recommended by the National TB program for all children < 5 years in contact with a person suffering from active pulmonary TB.

What to do before you consider starting ARVs to all children infected with HIV?

- Prophylaxis with SMX/TMP.
- Active screening of warning signs of tuberculosis and possibly do a chest X-ray (included in basic assessment) before prescribing ARVs. TB can easily go undetected in young children and the child is easily infected (close contact with his surroundings).
- Nutritional supplement.
- Vitamin A: 50,000 IU between 0 and 6 months, 100,000 IU between 6 and 12 months and 200,000 IU, every 6 months after one year.
- Ensure that the child has completed the vaccination schedule. Encourage supplementary immunization: pneumococcal meningitis, salmonella typhi.
- Systematically consider the anthelmintics for any malnourished child (mebendazole 100 mg 2 X / J during 3 days) one a year.

10.4. When and how to start treatment in a child?

- Every child infected by HIV less than 5 years is eligible to ART regardless of CD4 count and clinical stage
- For children of 5 years and above, use the same criteria as in adults for initiating ART (stage 3 and 4 regardless of CD4, stages 1, 2 if CD4<500).

Recommended first line ARV regimen:

Children that were **not** exposed to single dose NVP in PMTCT

First line regimen	Second line regimen after failure
ABC + 3TC + EFV	AZT + 3TC + Kaletra
ABC + 3TC+ NVP	AZT + 3TC + Kaletra
Alternative first line regimens	Alternative 2 nd line regimen after failure
AZT + 3TC + EFV	ABC + 3TC + Kaletra
AZT + 3TC + NVP	ABC + 3TC + Kaletra

Children below 18 months **who were exposed** to single dose NVP in PMTCT

First line regimen	Second line regimen after failure
ABC + 3TC + Kaletra	AZT + 3TC + Kaletra
Alternative 1st line regimen	Alternative 2 nd line regimen after failure
AZT + 3TC + Kaletra	ABC + 3TC + Kaletra

If there is intolerance to Kaletra, it should be replaced by NFV (Nelfinavir).

N.B: It is recommended that children weighing 12 kg and above should receive tablets if possible and avoid syrups (cost and difficulties in treatment adherence)

Initial assessment and clinical and biological follow up of a child on 1st line ARV treatment:

Same as for adult follow up (PART B CHAPTER 3) while at the same time carrying out growth monitoring.

Date	Clinique	Labo
Pré-ARV	+	CD4, FBC, Systematic chest X-ray if possible
D 15	+ adherence	
M 1	+ adherence	FBC if AZT, GPT if NVP
M 2	+ adherence	Nothing
M 3	+ adherence	FBC if AZT, GPT if NVP

M 4	+ adherence	Nothing
M 5	+ adherence	Nothing
M 6	+ adherence	CD4, FBC, GPT
After six months		
Every six months	+ adherence	CD4 : Every 6 months, other exams will be done according to clinical presentation VL: Every 12 Months

A growth curve must be plotted in the child's patient's dossier. We use the new international curves of the WHO that show weight and height and head circumference. For children > 5 years, we use the CDC curves (unpublished WHO curves beyond 5 years).

Psychomotor development is also another important aspect that needs to be monitored.

Main stages in the psychomotor development of a child between 1 month and 1 year.

1 month	2 months	3 months	4-5 months	6 months	8-9 months	1 year
*Fixation du visage *Poursuite oculaire d'un visage *Sourire fugace	*Sourire réponse *Tient la tête quelques instants *Poursuite oculaire des objets, intérêt visuel	*Tient bien la tête en position assise *Redressement tête en tronc en décubitus ventral	*Préhension volontaire *Tête dans l'axe au tiré-assis *Redressement sur les membres inférieurs	*Tient assis avec appui	*Tient assis sans appui *Tient debout tenu *Début de marche à 4 pattes ou sur le siège ("Shuffle") *Pince pouce-index *Disyllabisme	*Marche seul (N =12 -18 mois) *Prend et lâche les objets sur demande *Dit quelques mots

When and how to change the treatment regimen?

Toxicity

- ✚ Changing treatment in the case of toxicity:
 - If anemia (Hb < 9 g/dl): ABC + 3TC + 1 NNRTI.
 - If hepatotoxicity or severe skin allergy: (see PART B CHAPTER 4).

Treatment failure:

Definitions:

Clinical failure	<ul style="list-style-type: none">- Absence of clinical improvement (growth or psychomotor retardation) after 6 months of ARV treatment.- Appearance of a new OI or malignancy that shows clinical progression of the disease. Recurrence of an OI suffered earlier by the patient. Progression towards a pathological condition that falls within WHO stage 3 or 4.- The recurrence of TB may not represent a progression of HIV disease because it may be a re-infection.- If the patient is asymptomatic, treatment failure can only be defined by either CD4 or viral load.
Immunological failure	<ul style="list-style-type: none">- A fall in the CD4 count to the pre-ART treatment baseline level or even below in the absence of any concomitant illness that could be the cause of a transient fall in CD4 cells.- A fall of more than 50% in the CD4 rate below the peak ever reached after initiating ARV treatment, in the absence of any concomitant illness that could be the cause of a transient fall in CD4 cells.
Virologic failure	<p>Viral load detectable after 6 months of ARV treatment in a patient with good adherence.</p> <p>Recommended 2nd line regimen: See table above.</p>

✚ Therapeutic failure

Adherence in children

The success of antiretroviral treatment in children, just like in adults, depends first and foremost on good adherence.

The success of good adherence depends on the good implementation of the treatment with patient and/or the tutor/guardian of the 3 key principles of adherence:

- ✚ The Knowledge: having all of the necessary knowledge and perfect understanding of this knowledge so as to want to take the treatment.
- ✚ The Will: having the will without any reservations to take the drugs.
- ✚ The Ability: Having the possibility to achieve what is desired.

Aspects of adherence in the young child.

Below a certain age that varies from one child to another, adherence of the child depends completely on the tutor or guardian. This may be one or both the biological parents but in the case of death or abandoned children, this may be a third person: close relative, guardian, foster family or institution.

It is this intermediary who should be convinced of the necessity for good adherence. To do this it is important to work with him/her the three key principles of adherence described above:

- **The knowledge:** This involves ensuring that the guardian receives clear answers to all the questions s/he may ask regarding the treatment.
- **The Will:** In this particular case, this will be addressed at two levels:
 - **That of the guardian:** S/he should strictly apply to the child the rules of treatment. This pre-supposes that s/he will have accepted all the difficulties and constraints.
 - **That of the child:** His will is usually summarized in his acceptance of the treatment which brings into play the form of the drug that needs to be adapted (liquid form), the taste (the child often accepts or refuses the drug based on the taste) and the number of doses and number of units per dose (many doses and units per dose are usually poorly accepted by children).
- **The ability:** Together with the tutor, it is important for one to envisage all the material conditions that are necessary for the success of the treatment.

His availability in relationship to the time when the child is supposed to get his drugs (which must respect and sleeping/wake up pattern of the child), how **he** relates to the child (a child will only accept certain things from particular persons), the possibility to, if necessary, respect confidentiality (the other family members may not have to know that the child is affected).

The older child

It involves getting the child to be independent as soon as possible. This is usually done in two stages beginning from the stage above:

- A period during which the tutor will seek to progressively make the child responsible for his treatment.
- A period during which the child will take his treatment by himself under the surveillance of the tutor.

The capacity of the child to become self-sufficient in following treatment varies from one child to another. In some children, the beginning of this self-sufficiency can begin as early as 5 years while in others one has to wait much later to attempt the approach.

At this stage, the three key principles for ensuring good adherence must be addressed:

- **The knowledge:** Little by little the child will begin asking the reasons for the treatment. One should be able to discern this search for information which the child will never express through direct questions.
- **The will:** The child should completely accept the reality of his treatment. Remember that a child forgets very easily when he is doing other things. For taking his drugs, it will be essential to create reminders by associating the ingestion of drugs to some obligatory activities of his day to day life (e.g. brushing teeth or taking breakfast). The child must always be monitored even when he starts taking his treatment by himself.
- **The ability:** Issues regarding treatment in the young child are the same; new problems will arise as the child begins schooling particularly the re-adaptation of his drug schedule to his new mode of life. Drugs should never be taken at school. In most cases, the school is not aware of the child's illness.

Teamwork as the backbone for good adherence

Adherence is a key aspect of the comprehensive care and requires the participation of all health care workers. Each intervener must not act in an isolated manner but in synergy and complementally with the other.

Health care providers should adapt their interventions to fit the domain of children:

- **The doctor:** Should have adequate knowledge in pediatric care and if possible practical experience in providing care to children.
- This is also applicable to all other health care providers: nurses, nursing assistants, etc.
- An adapted psychological support is usually necessary and one or more people should have been trained in this.
- The in-charge of the Pharmacy should ensure that pediatric formulations are always available and participate in counseling (of the child and tutor) when distributing the drugs.
- Social workers should pay special attention to the families and ensure that they have the minimum necessary for them to provide adequate care to the children: what to use to come for clinic visits, how to pay the costs of care if necessary, etc.
- Community linkages are also essential because quite often, the families where these children live are already made vulnerable by the disease and are consequently in a precarious situation. The existence of linkage persons or treatment buddies is indispensable.

- All health care providers in their different domains must have job aids adapted to children.
- In conclusion: good adherence is the outcome of teamwork where each member acts in a complementary manner with the aim of creating, for the child and guardian, the best physical, psychological and material conditions for the success of the treatment.
- Tools (Tales, images, cartoons) explaining the disease that are adapted to age and are being using in many countries were conceived by Saint Pierre University teaching Hospital in 1999; they have been adapted and are available in Rwanda.

Evaluation of the immune status of the child:

The indications for treatment are based on findings from the clinical examination (with assessment in accordance with the WHO criteria), and on the degree of immune deficiency based on the CD4 cell percentage. Before the age of 6 years, the blood cells of the child undergo a lot of physiological variations to change from a predominantly lymphocyte white blood cell structure that is present at birth, to a white blood cell structure dominated by polymorphonuclear blood cells, a transformation that is completed towards the age of 6 years.

In a child that has no HIV, CD4 cells always account for over 25% of the total lymphocytes. If the later are physiologically as high as 6,000 at birth, the CD4 cells are 1,500 which represents 25% of all lymphocytes.. As the total number of lymphocytes decreases, the CD4 cells also decrease but their proportion always remains ~25%. It is not until 6 years that the adult situation is reached and the total lymphocytes stabilize at ~2,000, and the normal CD4 count becomes ~500 (25%) see annex XIV.

Calculation of CD4 percentage: Formula

$CD4\% = CD4 \text{ counts in cells/ml} \times 100 / \text{total Lymphocytes}$

Example:

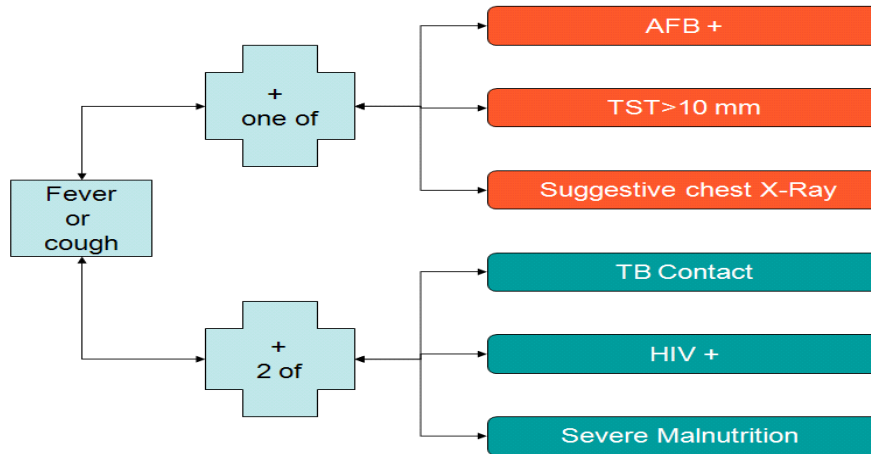
A child of 12 months with total CD4 count of 1,000, white blood cells of 12,000 and lymphocytes of 55%.

Total Lymphocytes = $12,000 \times 0.55 = 6,600$ and $CD4\% = 1,000 \times 100 / 6,600 = 15 \%$.

The score system for the diagnosis of tuberculosis in children (TB unit)

A score has been developed by the national TB control program in collaboration with the Rwandan society of pediatricians.

Anti-TB treatment is started in the presence of chronic fever or cough with one of the following signs: (positive direct examination or IDR > 10mm or suggestive chest x-ray); or with 2 of the following signs (contact with known case of TB, HIV infection, severe malnutrition).



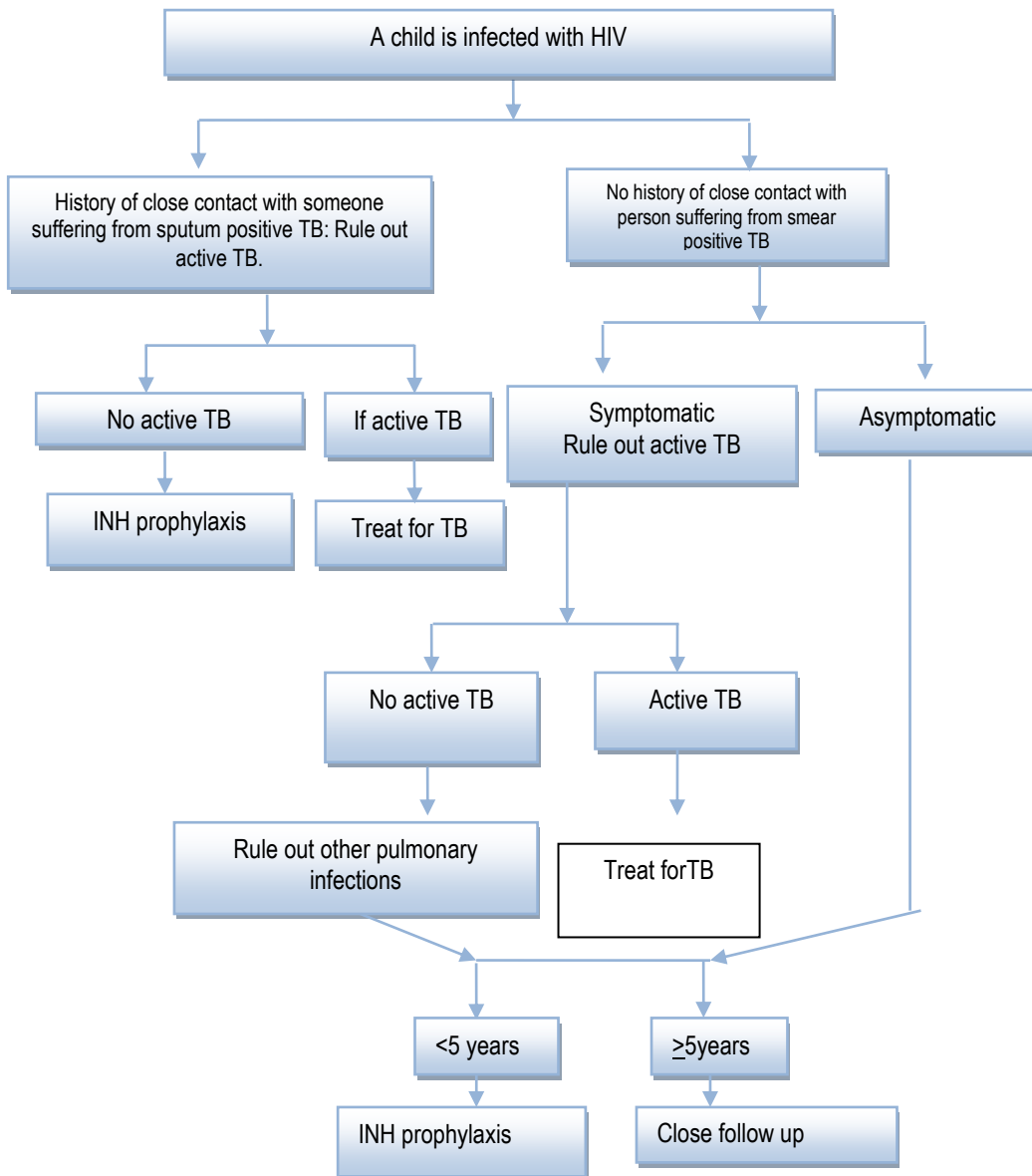
Characteristic	0	1	2	3	4	T
Duration of the disease (weeks)	< 2	2 to 4		>4		
Nutrition (% weight for age)	> 80%	60-80%	60%			
History of TB in the family	None	Reported by family		Positive sputum or clear proof		
Malnutrition				No improvement after 4 weeks		
Tuberculin test				Positive		
Unexplained fever and night sweats			No response to antimalarials or antibiotics			
				Lymphadenopathy >1cm		
				Abdominal mass Ascites		
				CSF abnormalities		
				Swelling of joints or bones G		
					Angular deformation of the vertebral column	
Total Score						

ANNEX

Annex 1: Calendar for the follow up of HIV exposed infants

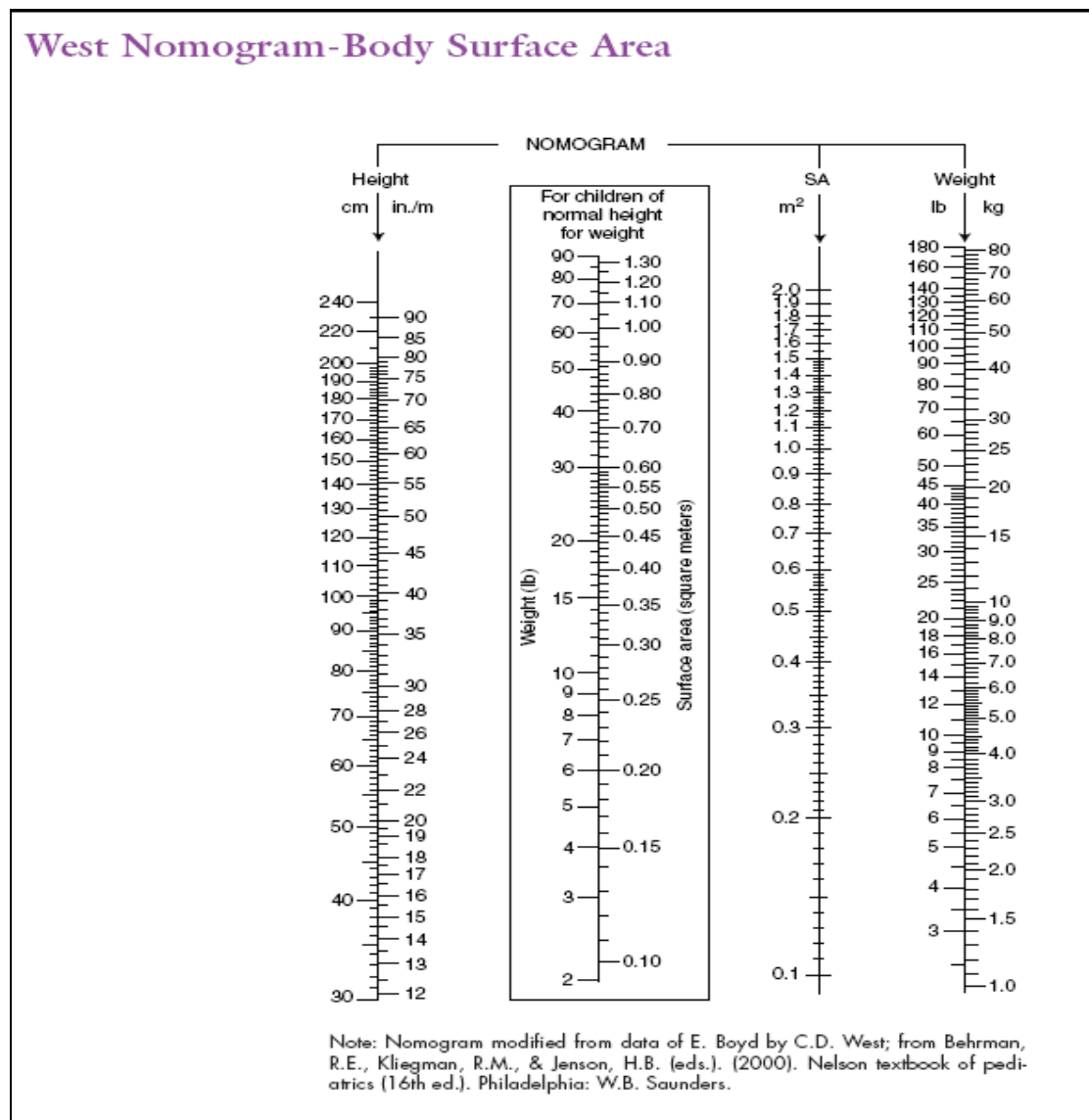
Age in weeks/moment	At birth	6 Wks	10 Wks	14 Wks	5 Mos	6 Mos	9 Mos	12 Mos	15 Mos	18 Mos	
History	X	X	X	X	X	X	X	X	X	X	
Feeding and growth assessment	X	X	X	X	X	X	X	X	X	X	
Assessment of psychomotor development	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	
Determination of HIV status		PCR/DNA	Repeat PCR/DNA if the child is symptomatic Or do HIV screening using rapid tests 6 weeks after weaning from breast milk.							HIV testing with rapid tests	
Cotrimoxazole prophylaxis		X	← Continue until HIV infection is excluded and the child is no longer at risk of HIV infection →								
Assessment of the risk of tuberculosis	← At every visit →										
Vaccination	X	X	X	X			X				
Nutritional counseling and support	X	X	X	X	X	X	X	X	X	X	
Adherence counseling	X	X	X	X	X	X	X	X	X	X	
NB: This is the minimum and children should be reviewed more frequently if necessary.											

Annex 2: Algorithm for initiating INH prophylaxis



Annex 3: Body Surface Area

Normogram



Annex 4: Calculation of body surface area (BSA)

1st method

$$\text{Body surface area: } BSA = \sqrt{\frac{\text{Hgt}(\text{cm}) \times \text{Wgt}(\text{kg})}{3600}} \text{ m}^2$$

Example: A child of 3 years who weighs 12 kg, and whose height is 80 cm:

Height = 80cm

Weight = 12kg

Body surface area = 80 X 12 = 960

960 / 3600 = 0.267

The square root of $0.267 = 0.53\text{m}^2$

2nd method:

Body surface area: $\frac{4W + 7}{W + 90}$ (W: weight of the child)

3rd method:

The body surface area for newborns and children can be determined by using the Nomogram method.

Example:

A child of 3 years who weighs 12 kg and has a height of 80 cm:

Height = 80cm

Weight = 12kg

Draw a straight line beginning from height in the left column towards weight in the right column.

The point of intersection of this line with the column SA is the body surface area in square meters.

$$SA = 0.52\text{m}^2$$

Annex 5: Calculation of estimated creatinine clearance using the cockcroft & gault formula

In men:

$$Cl\ Cr\ (ml/min) = 140 - [(Age\ (years) / Plasma\ Creatinine\ (\mu mol/l) \times weight\ (Kg) \times 1,25]$$

In women:

$$Cl\ Cr\ (ml/min) = 140 - [(Age\ (years) / Plasma\ Creatinine\ (\mu mol/l) \times weight\ (Kg) \times 1,08]$$

If we use mg/dl of creatinine for the woman:

$$DFG[ml/min] = 0,85 \cdot \frac{(140 - age[ans]) \cdot poids[kg]}{72 \cdot \text{s\u00e9rumcr\u00e9atinine}[mg/dl]}$$

For the man:

$$DFG[\text{ml} / \text{min}] = \frac{(140 - \text{age}[\text{ans}]) \cdot \text{poids}[\text{kg}]}{72 \cdot \text{sérumcréatinine}[\text{mg} / \text{dl}]}$$

N.B: Cl Cr (ml/min) < 80ml/min measures renal insufficiency with high sensitivity and the ability to reproduce it over time in a given patient makes it possible to monitor a known moderate renal insufficiency.

Annex 6: Summary of drugs used in Rwanda, their abbreviations and commercial names

Name of drug	Abbreviation	Commercial name
Nucleoside Reverse Transcriptase inhibitors (NRTIs)		
Zidovudine	AZT	Retrovir®
Lamivudine	3TC	Epivir®
Stavudine	D4T	Zerit®
Emtricitabine	FTC	Emtriva®
Didanosine	DDI	Videx®
Abacavir	ABC	Ziagen®
Nucleotide Reverse Transcriptase inhibitors (NRTIs)		
Tenofovir	TDF	Viread®
Non Nucleoside Reverse Transcriptase inhibitors (NNRTIs)		
Nevirapine	NVP	Viramune®
Efavirenz	EFV	Stocrin®
Protease Inhibitors (PI)		
Lopinavir /Ritonavir	LPV/r	Kaletra®
Nelfinavir	NFV	Viracept®
Indinavir	IDV	Crixivan®
Ritonavir	RTV	Norvir
Combinations		
	D4T+3TC+NVP	Triviro/Triomune®
	AZT+3TC	Duovir®, Combivir®
	AZT+3TC	Avocomb®
	D4T + 3TC	Coviro ®

Annex 7: Other ARVs available outside Rwanda

Name of drug	Abbreviation	Commercial name
Nucleoside Reverse Transcriptase Inhibitors		
Zalcitabine	DDC	Hivid®
Non-nucleoside Reverse Transcriptase Nucleoside inhibitors		
Delavirdine	DLV	Rescriptor®
Etravirine	ETR	Intelence®
Protease Inhibitors		
Amprenavir	APV	Agenerase®
Atazanavir	ATV	Reyataz®
Fosamprenavir	APV	Lexiva®
Saquinavir	SQV	Fortase, Invirase®
Darunavir	DRV	Prezista®
Tipranavir	TPV	Aptivus®
Entry Blockers		
Enfuvirtide	T 20	Fuzeon®
Maraviroc	MVC	Selzentry®
Integrase Inhibitors		
Raltegravir	RAL	Isentress®

Annex 8: Zidovudine

✚ Category :

A Nucleoside Reverse Transcriptase Inhibitor (NRTI) antiretroviral agent

✚ Important Information:

Present as a combination drug with Lamivudine (3TC) = Duovir.

✚ Side effects :

- Zidovudine is generally well tolerated. The commonest side effects (in 5% of patients) are: moderate headache, nausea, vomiting, weight loss and muscle pains; these often disappear in a couple of weeks.
- Bone marrow toxicity (Myelotoxicity) is also possible. The appearance of fatigue, pallor, dyspnea or fatigue after the initiation of AZT should elicit an active investigation to look for anemia. Anemia can appear within the first 4-6 weeks following the initiation of treatment while neutropenia normally appears 3-6 months after treatment initiation. The appearance of these signs depends on the duration of treatment, the bone marrow reserve and the stage of the disease. Since patients are often malnourished and often present with advanced disease; it is possible that these side effects occur earlier than stated above.
- Macrocytosis is common and is not an indication for changing treatment. It is a sign of good adherence.
- Like with other nucleoside analogues, cases of lactic acidosis and hepatic steatosis have been reported, although these are more frequent with Stavudine (D4T). Lactic acidosis is rare but must be considered in all patients who present with fatigue, abdominal pain, nausea, and vomiting and/or unexplained breathlessness.
- Hepatotoxicity, less frequent.
- Myopathies, rare.
- Discoloration of the fingernails may occur but is not an indication for changing treatment.

✚ Alternatives in case of side effects :

Replace AZT with D4T except in case of lactic acidosis in which case treatment must be stopped. Replace AZT with TDF if renal function is normal.

✚ Contra-indications:

- ✚ Severe anemia (Hb < 7.0 g/dl).
- ✚ Severe neutropenia (neutrophils < 750/mm³).
- ✚ Severe renal insufficiency (creatinine > 3 times the normal values).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- ✚ Known history of intolerance.
- ✚ Zidovudine must never be prescribed simultaneously with Stavudine (d4T), because they are antagonists.

✚ Adult dosage:

- ✚ One 300 mg capsule twice a day.
- ✚ In case the combination form of Zidovudine/Lamivudine, is used, the dose is one 300/150 capsule, twice a day

✚ Information for the patient:

- ✚ Can be taken with or without food.
- ✚ Can be used during pregnancy
- ✚ The patient must seek immediate medical attention if s/he develops the following symptoms: dyspnea, abdominal pain, fatigue, nausea, vomiting.

Annex 9: Lamivudine

✚ Category :

A Nucleoside Reverse Transcriptase Inhibitor (NRTI) antiretroviral agent

Important information

- ✚ Well tolerated, with minimum toxicity.
- ✚ Can be used during pregnancy.

✚ Precautions:

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value)
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values)

✚ Adult dosage:

- One 150 mg capsule twice a day or two 150mg capsules once a day.
- ✚ In case the combination form of Zidovudine/Lamivudine, is used, the dose is one 300/150 capsule, twice a day.

✚ Pediatric dosage:

- ✚ See PART C, CHAPTER 3

✚ Information for the patient:

- ✚ Can be taken with or without food. .

Annex 10: Emtricitabine (FTC)

✚ Category :

A Nucleoside Reverse Transcriptase Inhibitor (NRTI) antiretroviral agent

✚ Important information:

- ✚ Can be taken with or without food.
- ✚ Can be taken during pregnancy
- ✚ Like with other nucleoside analogues, cases of lactic acidosis and hepatic steatosis have been reported

✚ Precautions:

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).

✚ Adult dosage:

- ✚ One 200 mg capsule once a day or 10mg/ml for the oral solution.

✚ Information for the patient:

Annex 11: Didanosine (DDI)

✚ Category :

A Nucleoside Reverse Transcriptase Inhibitor (NRTI) antiretroviral agent

✚ Side effects :

- ✚ Didanosine is generally well tolerated. The commonest side effect is nausea.
- ✚ Didanosine can be linked to pancreatitis that may be severe. It must not be prescribed for patients with alcohol abuse and must be stopped if there is a suspicion of pancreatitis (abdominal pain, high plasma amylase) or if there is a history of pancreatitis. Most cases of pancreatitis occur when DDI is taken concurrently with D4T.
- ✚ Didanosine can cause peripheral neuropathies, especially if combined with stavudine (d4T).
- ✚ Like with other nucleoside analogues, cases of lactic acidosis and hepatic steatosis have been reported. , Although these are more frequent with Stavudine (D4T), lactic acidosis is rare but must be considered as a possibility in patients who present with fatigue, abdominal pain, nausea, and vomiting and/or unexplained dyspnea.
- ✚ Can be used during pregnancy although the risk of lactic acidosis and hepatic steatosis is increased during concurrent utilization of Didanosine and Stavudine (D4T). It is recommended to avoid this combination and only use it in case of absolute necessity, in which case supplementary clinical and biological monitoring are necessary.
- ✚ Cautious use during pregnancy.

✚ Alternatives in case of side effects :

Seek specialized expert opinion as this is a second line drug.

✚ Contra-indications:

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- ✚ Known history of previous intolerance.
- ✚ Concurrent utilization of Didanosine and Stavudine (d4T) during pregnancy: do not use.

- ✦ Do not use Didanosine in patients who abuse alcohol or those with previous history of pancreatitis.

- ✦ **Adult dosage:**

- ✦ For patients above 60 Kg of weight, two 200 mg capsules per day as single dose or in two doses a day.

- ✦ For patients weighing less than 60 Kg, one 250-mg capsule, once a day.

- ✦ If Didanosine is combined with TDF, the daily dose of DDI is reduced to 250 mg in patients weighing over 60 kg.

- ✦ **Information for the patient:**

- ✦ To be taken on empty stomach (An hour before or two hours after a meal).

- ✦ It is important to inform the patient the possibility or not of concomitant use of other ARVs.

Annex 12: Stavudine (D4T)

✚ Category :

A Nucleoside Reverse Transcriptase Inhibitor (NRTI) antiretroviral agent

✚ Important information :

Often prescribed in a combination form with Lamivudine (3TC) and Nevirapine (NVP) = Triomune.

✚ Side effects :

- ✚ Stavudine may cause peripheral neuropathies, especially when combined with Didanosine (DDI). This effect is dose dependent. See Annex 5 towards the end of the chapter regarding the management of the side effects.
- ✚ Elevated liver transaminases
- ✚ Pancreatitis (clinical or only biological)
- ✚ Lipodystrophy/lipoatrophy
- ✚ Like for all other nucleoside analogues, cases of lactic acidosis and hepatitis steatosis have been reported.
- ✚ Can be used during pregnancy although the risk of lactic acidosis and hepatic steatosis is increased during concurrent utilization of Didanosine (ddI) and Stavudine (D4T). One should always avoid this combination.
- ✚ Must never be combined with Zidovudine (ZDV) because they are antagonistic.

✚ Alternatives in case of Side effects :

- ✚ In case of neuropathy, replace D4T with TDF; or AZT if there is no other alternative.
- ✚ In case of lactic acidosis: Stop ARV treatment and wait until the patient is stabilized clinically and biologically and then replace D4T with TDF.
- ✚ In case of lipodystrophy: Replace D4T with TDF or ABC.

✚ Contra-indications :

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- ✚ Known history of intolerance.
- ✚ The concurrent use of Stavudine and Didanosine is only allowed in absolute necessity and under strict surveillance.

✚ Adult dosage :

- ✚ One 30 mg capsule twice a day per day (Triviro30).

✚ Pediatric dosage :

See PART C, CHAPTER 3

✚ Information for the patient :

- ✚ Can be taken with or without food.

Annex 13: Abacavir (ABC)

✚ Category :

A Nucleoside Reverse Transcriptase Inhibitor (NRTI) antiretroviral analogue

✚ Important information for the prescriber

- ✚ Abacavir is generally well tolerated. Gastro-intestinal side effects are nausea and diarrhea. Lactic acidosis and hepatic steatosis are believed to be less frequent than with other nucleoside agents.
- ✚ 3 to 5% of Caucasian patients taking Abacavir develop a hypersensitivity reaction that occurs in an average of 10 days after initiating treatment (93% of reactions occur in the first 6 weeks). Symptoms include :

- ✚ Fever;
- ✚ Cough;
- ✚ Cutaneous Erythema;
- ✚ Dyspnea;
- ✚ Headache;
- ✚ Fatigue, malaise;
- ✚ Nausea/vomiting;
- ✚ Diarrhea;
- ✚ Abdominal pain;
- ✚ Joint and muscular pains

Symptoms disappear on stopping treatment but if the patient is exposed again to the drug, a fatal hypersensitivity reaction may occur. Abacavir must never be prescribed for a patient who has ever been suspected of a hypersensitivity reaction to the drug. If Abacavir is stopped for this reason (hypersensitivity) all remaining drugs must be retrieved from the patient to avoid accidental ingestion in the future.

- ✚ Before prescribing Abacavir, all prescribers must be familiar with the presentation, diagnosis and the management of the hypersensitivity reaction.

✚ Contra-indications :

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- ✚ Known history of intolerance. A patient who has had a hypersensitivity reaction to Abacavir (even if it was a mere suspicion of it), must never be re-exposed to Abacavir.

✚ Adult dosage :

One 300 mg capsule twice a day or 600mg once a day.

✚ Information for the patient :

- ✚ ABC can be taken with or without food.
- ✚ Patients taking Abacavir should be told to visit a health facility immediately if they develop symptoms suggestive of hypersensitivity syndrome.

Annex 14: Tenofovir (TDF)

✚ Category :

A Nucleotide Reverse Transcriptase Inhibitor (NRTI) antiretroviral agent

✚ Side effects :

Tenofovir is generally well tolerated.

- ✚ Most common side effects are nausea and diarrhea.
- ✚ Moderate renal insufficiency is a less common occurrence. The acute form is quite rare.
- ✚ Rare cases of lactic acidosis and hepatic steatosis.

✚ Alternatives in case of side effects :

TDF can be changed to AZT or d4T.

Contra-indications:

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- ✚ Severe renal insufficiency (creatinine > 3 times the normal levels).
- ✚ Association with other nephrotoxic substances.
- ✚ Severe hepatotoxicity (Liver function tests > 5 times the normal values)
- ✚ Known history of intolerance.

✚ Important notes :

Tenofovir increases the plasma concentration of DDI, therefore reduce the prescribed dose of the latter (DDI): (1×200 mg).

✚ Adult dosage:

One 300 mg tablet, once a day.

✚ Pediatric dosage :

Not recommended for use in patients aged below 18 years.

✚ Information for the patient:

Can be taken with or without meals/food.

Annex 15: Nevirapine (NVP)

✚ Category :

A Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) antiretroviral analogue

✚ Side effects :

The most common side effect associated with NVP is skin rash which occurs in 20% of patients (particularly black women) particularly in the first 8 weeks after initiating treatment. This rash is usually minor or moderate but requires interruption of treatment in 5 to 7% of patients. Potentially fatal skin reactions have been reported.

The risk is diminished by reducing the dose during the first 14 days: the dose is 200 mg per day for the first 14 days followed by 200mg per day. Table 2 describes the different stages of the severity of the skin reactions while the treatment algorithm for managing the dermatological toxicity is found in annex 1. Note that NVP must be stopped if there is a grade 3 reaction.

✚ Adult dosage:

- One 200 mg capsule once a day for the first 14 days and then one 200mg capsule twice a day.

✚ Pediatric dosage:

See PART C, CHAPTER 3

Information for the patient:

- Can be taken with or without food.
- Can be used during pregnancy. It is recommended to monitor liver function tests.
- It is important during counseling to inform the patient that s/he has to seek medical attention immediately if s/he develops a skin rash or pruritis.

If a patient stops NVP for more than 2 weeks (for reasons of adherence for example), and there are no contraindications for reintroduction, treatment should be re-started in a similar way to treatment initiation (i.e. half dose for the first 14 days).

Annex 16: Efavirenz (EFV)

✚ Category :

A Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) antiretroviral analogue

✚ Side effects :

- ✚ Skin rash is a side effect that occurs in 15 to 25% of patients. The rash is usually minor or moderate, but may necessitate interruption of treatment in 2% of cases. Potentially fatal skin reactions have also been reported. The algorithm for managing skin toxicity is found in annex 3.
- ✚ Central nervous side effects occur in at least 50% of patients and may include nightmares, vertigo and insomnia. It is therefore better to take the medication just before going to bed. The side effects usually disappear after the first month and require interruption of treatment in only 2 to 5% of patient.
- ✚ Hepatotoxicity is less frequent and less severe than with NVP, but elevation of hepatic functions to 5 times the normal values has been reported in 2 to 6% of patients. The treatment algorithm for managing liver toxicity is found in Annex 4.
- ✚ Efavirenz is teratogenic and must never be used by pregnant women during the first trimester.

✚ Contra-indications:

- ✚ Possible pregnancy or expected pregnancy.
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- ✚ Severe renal insufficiency (creatinine > 3 times the normal value). Note: According to Bartlett, the dose should not be changed in case of renal insufficiency.
- ✚ Known history of intolerance.

✚ Adult dosage:

One capsule of 600 mg once a day.

✚ Pediatric dosage:

See PART C, CHAPTER 3

✚ Information for the patient:

- ✚ Can be taken with or without food, but should not be taken with fatty meal.

- To be taken at night just before going to bed.
- Patients should be informed that Efavirenz can cause nightmares, vertigo, depression and insomnia and that often those side effects disappear after three to four weeks. The patient should be advised to come back for medical consultation if these symptoms appear and to never stop treatment without medical advice.

✚ Important remarks:

NNRTIs stay in the blood for a long time after stopping the drug. It is therefore advised to continue taking NRTI (D4T, 3TC...) for 5 to 7 days after stopping taking EFV or NVP or any other NNRTI in order to avoid creating a state of monotherapy.

Annex 17: Nelfinavir (NFV)

✚ Category :

Protease Inhibitor antiretroviral agent.

✚ Side effects :

The commonest side effects are gastrointestinal (soft stools and/or diarrhea) that occur in 10 to 30% of patients. Diarrhea is so common that many prescribers systematically provide empirical symptomatic treatment (e.g. Loperamide, Imodium®) whenever Nelfinavir is prescribed, to be used when necessary. Treatment may have to be interrupted in 2% of patients.

Like for all Protease inhibitors, Nelfinavir may be associated with Insulin resistance, diabetes, hyperlipidemia and lipodystrophy.

✚ Alternatives in case side effects :

- Seek specialized expert opinion as this is 2nd line drug. .

✚ Important information :

- Like with all other Protease Inhibitors, Nelfinavir is metabolized by the liver and has multiple interactions with several drugs. Special attention should be paid to the other drugs the patient is taking before it is prescribed.
- Protease inhibitors can reduce the plasma concentrations of oral contraceptives, and alternative or complementary methods of birth control should be used.
- Can be used during pregnancy.

✚ Contra-indications:

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- Known history of intolerance
- Treatment with rifampicin for tuberculosis.

✚ Adult dosage:

Five capsules of 250 mg (1250 mg) twice a day.

✚ Pediatric dosage:

See PART C, CHAPTER 3

✚ Information for the patient:

- ✚ Nelfinavir must be taken with food, preferably with a fatty meal or snack.
- ✚ Patients must be warned that diarrhea is common and must receive instruction on how to manage this side effect.

Annex 18: Lopinavir/ritonavir (LPV/r)

✚ Category :

Protease Inhibitor (PI) antiretroviral agent.

✚ Side effects :

- The most common side effects are gastrointestinal, particularly diarrhea which occurs in 15 to 25% of patients.
- Like with other protease inhibitors, LPV/r is linked to insulin resistance, diabetes, hyperlipidemia and lipodystrophy.

✚ Alternatives in case of side effects :

- Seek specialized expert opinion as this is a 2nd line drug.

✚ Important information :

- Like with all other Protease Inhibitors, Lopinavir/ritonavir is metabolized by the liver and has multiple interactions with other drugs. Special attention should be paid to the other drugs the patient is taking before it is prescribed.
- Protease inhibitors can reduce the plasma concentrations of oral contraceptives, and alternative or complementary methods of birth control should be used.
- Can be used during pregnancy.

✚ Contra-indications :

- Severe renal insufficiency (creatinine > 3 times the normal value).
- Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- Known history of intolerance.
- Treatment using Rifampicin containing drugs: after a special consultation, the dose of Kaletra can be modified (double the dose of Kaletra) or increase the dose of Ritonavir to 200mg (split in 2 doses). T

✚ Adult dosage :

Two capsules (Each containing 200 mg of LPV and 50 mg of RTV) twice a day.

✚ Pediatric dosage:

See PART C, CHAPTER 3

✚ Information for the patient:

- ✚ To be taken with a meal.
- ✚ Tablets containing 200 mg of LPV and 50 mg of RTV can be kept at room temperature.

Annex 19: Indinavir (IDV)

✚ Category :

Protease Inhibitor (PI) antiretroviral agent.

✚ Side effects :

- ✚ Renal stones (nephrolithiasis) have been observed in 10% of patients. Hydration is necessary: take at least 1.5 liters of fluids per day.
- ✚ Gastrointestinal side effects are less common than with other protease inhibitors.
- ✚ Cases of renal toxicity have also been reported.
- ✚ Asymptomatic indirect hyper bilirubinemia has been observed in 10 to 15% of patients, and is not an indication for modification of treatment.

Like with all other protease inhibitors, LPV/r is linked to insulin resistance, diabetes, hyperlipidemia and lipodystrophy.

✚ Alternatives in case of side effects:

- ✚ Seek specialized expert opinion as this is a 2nd line drug.

✚ Important information :

- ✚ Like with all other Protease Inhibitors, IDV is metabolized by the liver and has multiple interactions with several drugs. Special attention should be paid to the other drugs the patient is taking before it is prescribed.
- ✚ Protease inhibitors can reduce the plasma concentrations of oral contraceptives, and alternative or complementary methods of birth control should be used.

✚ Contra-indications:

- ✚ Severe renal insufficiency (creatinine > 3 times the normal value).
- ✚ Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- ✚ Known history of intolerance. .
- ✚ Tuberculosis treatment using rifampicin.
- ✚ Pregnancy.

✚ Adult dosage:

- ✚ Four 200 mg capsules eight hourly of two 400 mg capsules eight hourly.
- ✚ The dose is 800mg 3 times a day on empty stomach
- ✚ When used in combination with Ritonavir: 800 mg IDV + 100 mg RTV, twice a day.
- ✚ In this case, it can be taken with or without food

✚ Pediatric dosage:

- See PART C, CHAPTER 3

✚ Information for the patient:

- To be taken on empty stomach (An hour before or two hours after a meal)
- If used in combination with Ritonavir, it can be taken with or without food.
- It is important to take large amounts of water or other fluids when using IDV, at least 6 big glasses of water a day. Patients must be advised to seek immediate medical attention if ever they develop lumbar pain, abdominal pain or hematuria.

Annex 20: Ritonavir

- A strong P 3A Cytochrome (CYP3A) inhibitor.
- When administered in small doses (100 or 200 mg, 1 to 2 times a day) with other PIs, it significantly increases their plasma concentrations (boosting), thus making it possible to reduce the dose of the PIs.

Annex 21: Technical guidelines on Cotrimoxazole, INH and Fluconazole

Cotrimoxazole (TMP-SMX)

✚ Category :

Antibiotic

✚ Side effects :

- Skin rash most often presents as a pruritic or dermato-toxic maculo-papular eruption but may (rarely) progress into the Stevens Johnson syndrome.
- The most frequent side effects are gastro-intestinal (nausea, diarrhea), fever, cough, elevated transaminases, neutropenia, and especially skin rash and pruritis. They usually occur in the first two weeks following the initiation of treatment.
- When possible, there should be an interval of six weeks between the initiation of Cotrimoxazole and the initiation of Zidovudine.
- Cotrimoxazole can also cause hepatitis or an asymptomatic elevation of liver enzymes (transaminases). Where possible, there should be an interval of eight to twelve weeks between the initiation of Cotrimoxazole and the initiation of NVP.

- Cotrimoxazole is given throughout the pregnancy.
- HIV-infected pregnant women, who should normally receive intermittent preventive treatment with Fansidar, should receive Cotrimoxazole prophylaxis regardless of clinical stage or CD4 count.
- In case of doubt as to which drug may have caused the side effect (e.g. if it is NVP or Nevirapine in the case of skin rash), it is always advised to stop the two, beginning with Cotrimoxazole. And then if it is proven that it is the one responsible, it can be re-introduced in accordance with the following de-sensitization algorithm:

TMP/SMX (40mg TMP + 200 mg SMX/5 ml) syrup:

- 1 ml per day for 3 days, then
- 5 ml per day for 3 day, and then
- 10 ml per day for 3 days, and then
- 20 ml per day for 3 days, and then.
- 1 tablet double dose per day or 1 tablet single dose per day

✚ Contra-indications:

- Allergy to sulfonamides.
- Severe renal insufficiency (creatinine > 3 times the normal value).
- Severe hepatic insufficiency (Liver function tests > 5 times the normal values).

✚ Adult dosage:

- The normal dose for pneumocystis prophylaxis is one tablet of double-strength Cotrimoxazole (960mg) once a day.
- An alternative regimen for pneumocystis prophylaxis is one tablet of double Cotrimoxazole, three times a week.
- For the guidelines on the treatment of pneumocystis and other acute diseases: (See OI guidelines)

✚ Pediatric dosage:

See PART C, CHAPTER 3

✚ Information for the patient:

- Can be taken with food.
- Must be taken with water.

Fluconazole

✚ Category:

Antifungal agent

✚ Important information for the prescriber:

- Well tolerated; side effects are rare but may include nausea, vomiting, headache and a reversible alopecia.
- Inhibits the hepatic enzymes P450; drug interactions are possible.
- Should be used with caution during first trimester pregnancy.

✚ Contra-indications:

- Severe renal insufficiency (creatinine > 3 times the normal value).
- Severe hepatic insufficiency (Liver function tests > 5 times the normal values).

✚ Adult dosage:

- The normal dose for prophylaxis against meningococcal meningitis is two 200mg capsules per day for 8 weeks and then one capsule per day.
- The normal dose for the treatment of esophageal candidiasis is 200 mg once a day for 14 days.

✚ Pediatric dosage :

See PART C CHAPTER 3 H

✚ Information for the patients :

Can be taken with or without food.

Annex 22: Third Line Regimen in Children

Drug	Weight band (> 6 years)	Dosing per kg BD	Dosage (mg) BD	Ritonavir (mg) BD	Comments
Darunavir (Formulation: Tablet: 75 mg; 150 mg;	>= 20 kg-< 30 kg		375	50	Darunavir/rtv should not be used in children below 3 years of age given toxicity was observed in juvenile rats aged 23 to 26 days dosed with darunavir Darunavir/rtv should be used with caution in patients with severe hepatic impairment. No dose adjustment is required in patients with renal impairment. Not to combine with : astemizole,

300 mg and 600 mg)					alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), terfenadine, midazolam, triazolam, cisapride, pimoziide and the ergot alkaloids combination with Rifampicin St John's wort, shall be avoided mothers should be instructed not to breastfeed if they are receiving darunavir.
	>=30 kg- < 40 kg		450	60	RTV 100 mg can be used in this weight band
	>= 40 Kg		600	100	Same dosing as adults

Raltegravir Formulation: Tablet: 400 mg.				With food preferably Levels decreased with rifampicin (others such as phenytoin, phenobarbital, carbamezipine Safety of RAL in pregnant women has not been established. Avoid with Rifampicin , Etravirine and efavirenz both decrease serum concentrations of RAL, however the clinical importance is unknown.
	Age			RAL is not approved for use in children <16 years of age.
	>16 years	-	400 mg	
	>6 years and <u>body weight >25 kg</u>		400 mg	Investigational dose in children >6 years of age (and body weight >25 kg)
	2-6 years	6mg/kg BD		Investigational
Etravirine (ETR)				Etravirine has a high genetic barrier to developing resistance, and remains active against nevirapine- and efavirenz-resistant viruses if limited NNRTI mutations are present. <i>Despite insufficient data to recommend a pediatric dose, etravirine is being used in the salvage therapy setting in pediatrics.</i> Always administer ETR following a

Formulations Tablets: 100 mg and 200 mg				meal. Area under the curve (AUC) of ETR is decreased by about 50% when the drug is taken on an empty stomach. Patients unable to swallow ETR tablets may disperse the tablets in a small amount of water. Instruct patients to stir the dispersion well and consume it immediately. The glass should be rinsed with water several times, and each time the rinse water should be swallowed completely to ensure that the entire dose is consumed. No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency Dose adjustment is not required in patients with renal impairment.
				Etravirine should not be coadministered with the following ARVs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, unboosted protease inhibitors (PIs), nevirapine, or efavirenz.
	<u>> 6</u> <u>years</u>	5.2 mg/kg	(maximum 200 mg) twice daily	Investigational dose currently in Phase II trial