REPUBLIC OF RWANDA

MINISTRY OF HEALTH

Center for Treatment and Research on AIDS, Malaria, Tuberculosis and other Epidemics (TRAC Plus)

Guidelines for the provision of comprehensive care to persons infected by HIV in Rwanda

Version 2009

TRAC *Plus*

Center for **T**reatment and **R**esearch *on **A**IDS, **M**alaria, **T**uberculosis and **O**ther **E**pidemics*

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.

Dr. Richard SEZIBERA

Minister of Health

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Prof. KRAMER Michael
Director General TRAC *Plus*

LIST OF PERSONS THAT PARTICIPATED IN THE REVISION OF THESE GUIDELINES

These are:

Names	Institution
Dr Agnes Binagwaho	MOH
Dr Aimable Mbituyumuremyi	TRAC Plus
Dr Anita Asiimwe	CNLS
Dr Antoine Rwego	TRAC Plus
Dr Bel- Ami Bugingo	TRAC Plus
Dr David Riedel	UMSOM/IHV
Dr David Lowrance	CDC
Dr Emmanuel Musabeyezu	KFH
Dr Eugénie Kayirangwa	CDC
Dr Fabiennes Shumbusho	FHI
Dr Fernando Gonzales	CDC
Dr François Sobela	WHO
Dr Gilbert Tene	ICAP
Dr Grace Muriisa	UNICEF
Dr Innocent Turate	FHI
Dr Jean-D'Amour Ndahimana	TRAC Plus
Dr Jean-Paul Mfizi	TRAC Plus
Dr Jean-Pierre Nyemazi	TRAC Plus
Dr John Ruyonga	TRAC Plus
Dr José Nyamusore	TRAC Plus
Dr Jules Mugabo Semahore	TRAC Plus
Dr Julius Kamugisha	ICAP
Dr Kizito Kayumba	VOXIVA
Dr Laetitia Gahimbaza	INTRAHEALTH/Capacity
Dr Landry Tsague	ICAP
Dr Léonard Kayonde	TRAC Plus
Dr Marthe Mukaminega	EGPAF
Dr Mary Kabanyana	USAID
Dr Michel Gasana	TRAC Plus
Dr Muhayimpundu Ribakare	TRAC Plus
Dr Mwumvaneza Mutagoma	TRAC Plus

Dr Nadine Umutoniwashema	TRAC Plus
Dr Olivier Manzi	CHUK
Dr Placidie Umugwaneza	TRAC Plus
Dr Sabin Nsanzimana	TRAC Plus
Dr Thierry Nyatanyi	TRAC *Plus*
Dr William Nagaba	CDC
Elevanie Munyana	TRAC *Plus*
Josephine Kayumba	TRAC *Plus*
Mr Adolphe Majyambere	TRAC *Plus*
Mr Simon Pierre Niyonsenga	TRAC *Plus*
Phn Ladislas Bizimana	TRAC *Plus*
Pr Cyprien Baribwira	UMSOM/IHV
Pr Michael Kramer	TRAC *Plus*
Rose Gahire	AHF
Stephanie Joseph de Goes	UMSOM/IHV
Torri Ross	UMSOM/IHV

ACRONYMNS AND ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AEB	Accidental Exposure to Blood
AHF	AIDS Healthcare Foundation
ARV	Antiretroviral
AZT	Zidovudine
CD4	Type of lymphocyte (T4)
CDC	Centers for Disease Control and Prevention
CHUK	Centre Hospitalier Universitaire de Kigali
CMV	Cytomegalovirus
CNLS	Commission Nationale de Lutte contre le Sida (National AIDS Control Commission)
CNS	Central Nervous System
CTM	Cotrimoxazole
D4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DNA	Deoxyribonucleic Acid
DOT	Directly observed therapy
EFV	Efavirenz
EGPAF	Elisabeth Glaser Pediatric AIDS Fund
EPTB	Extra pulmonary Tuberculosis
FHI	Family Health International
FTC	Emtricitabine
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HZV	Herpes Zoster virus
ICAP	International center for AIDS and Treatment Program
IDR	Intra-dermal Reaction
IDV	Indinavir
KFH	King Faycal Hospital
M	Month
MAC	Mycobacterium avium complex
MOH	Ministry of Health
NFV	Nelfinavir
NNRTI	Non nucleoside reverse transcriptase inhibitors

NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
OI	Opportunistic infection
PCR	Polymerase chain reaction
PI	Protease Inhibitor
PLHIV	Persons living with HIV
PMTCT	Prevention of Mother to Child Transmission
RNA	Ribonucleic Acid
RTV	Ritonavir
TB	Tuberculosis
TDF	Tenofovir
TPM-	Sputum Negative Pulmonary Tuberculosis
TPM+	Sputum Positive Pulmonary Tuberculosis
UMSOM / IHV	University of Maryland School of Medicine, Institute of Human Virology
UNAIDS	United Nations Agency for AIDS Control
UNICEF	United Nations International Children's Emergency Fund
USAID	United states Agency for International Development
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

TABLES DES MATIERES

CHAPTER I: THE HOLISTIC MANAGEMENT OF PERSONS LIVING WITH HIV/AIDS.

I.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.

I.2. Principles

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.

✓ 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* :
  - Weekly clinical staff meetings: Exchange sessions involving clinicians, Laboratory technicians, Pharmacists, etc. to resolve urgent and/or emerging problems ;
  - The monitoring and selection committee is an ideal forum for communication, information exchange, development and monitoring of the program.

✓ **Defining the rules that regulate the care team:**

- Trust;
- Respect for confidentiality;
- Non-stigmatization.

✓ **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.

✓ **Why psychosocial care in the holistic management of persons living with HIV/AIDS?**

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.

✓ **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.

✓ Activities of psychosocial care

1. Psychosocial consultation

1.1. 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.

1.1.1. 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.

1.1.2. 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.

1.1.3. 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.

2. 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.

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.

4. Group counseling or support groups

4.1. The importance of group counseling:

- 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.

4.2. Organization of group counseling

Aspects to cover:

- 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).

4.3. The role of the counselor

Guide- Facilitate- Support –Stimulate.

4.3. Rôle du conseiller

Guider- Faciliter- Supporter –Stimuler.

5. The Pharmacy and distribution of drugs

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.

6. 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?

7. 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.

8. 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.

8.1. 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.

8.2. 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. PROTOCOL ON PROPHYLAXISIS FOR 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.

II.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 cryptosporidiae, 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.

II.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	- Acute retroviral syndrome. - Candidal vaginitis.	- Persistent generalized lymphadenopathy - Guillain-Barré syndrome. - Myopathy. - Aseptic meningitis.
200-500/mm^3	- Pneumococcal and other bacterial pneumonia. - Pulmonary tuberculosis. - Herpes zoster. - Oropharyngeal candidiasis (thrush) - Cryptosporidiosis. - Oral hairy leukoplakia	- 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	- *Pneumocystis jirovecii* pneumonia - Chronic disseminated Herpes simplex - Toxoplasmosis - Cryptococcosis - Disseminated histoplasmosis & coccidioidomycosis - Chronic cryptosporidiosis - Microsporidiosis - Miliary and other forms of extrapulmonary TB - Progressive multifocal leukoencephalopathy (PML) - Candidal esophagitis	- Wasting. - Peripheral neuropathy. - HIV associated dementia. - CNS lymphomas. - Cardiomyopathy - Vacuolar myelopathy - Progressive polyradiculopathy - Non-Hodgkin's lymphoma
<50/mm^3	- Disseminated CMV - Disseminated *Mycobacterium avium* 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).

✓ Chemo prophylaxis

- 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 prophylaxisin 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.

*N.B: These drugs are not currently available in Rwanda

Table 2 shows the indications for primary and secondary prevention.

Table 2:
Criteria for starting, stopping and restarting prophylaxis for opportunistic infections in HIV-infected adult patients in resource limited countries.

Criteria for	Initiating primary prophylaxis	Stopping primary prophylaxis	Restarting primary prophylaxis	Initiating secondary prophylaxis	Stopping secondary prophylaxis	Restarting secondary prophylaxis
PCP	Every HIV positive person					
Toxoplasmosis	IgG + for Toxoplasma & CD4<100	CD4>200 for 6 consecutive months	CD4<200	History of toxoplasmosis	CD4>200 for >6 months, Rx completed, asymptomatic	CD4<200
TB	No consensus	After 9 months of INH	No consensus	No consensus	No consensus	No consensus
MAC	CD4 <50 after excluding MAC	CD4 >100 for 3 months	CD4 <50	Disseminated MAC	CD4>100 for over 6 months, 12 months Rx completed and asymptomatic	CD4 <100
Cryptococcosis	WHO stage 4 or CD4<100	CD4>100 after 6 months of ARV	CD4<100	Confirmed Cryptococcosis	CD4>100 for over 6 months, 12 months Rx completed and asymptomatic	CD4<100
Herpes simplex	Not applicable	Not applicable	Not applicable	Recurrent severe illness	Not applicable	
Candidiasis	Not applicable	Not applicable	Not applicable	Recurrent severe oral candidiasis	Not applicable	
CMV retinitis	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	

II.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 who live in close contact with carriers of hepatitis B, health personnel and commercial sex workers.

✓ 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.

CHAPTER III. 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.

III.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.

III.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.

III.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.

✓ CD4 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.

✓ The 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.

- 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.

Measures aimed at creating conditions favorable for good adherence are detailed in chapter VI.

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.

III.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 IV. ANTIRETROVIRAL TREATMENT: FIRST LINE REGIMENS

IV.1. Initial assessment and clinical and biological follow up of a patient on a first line ARV regimen

Every patient put on treatment must have strict clinical and biological follow up as part of the personal contract that he enters into with the health care providers when he accepts to start antiretroviral treatment.

✓ Examinations required during the initial assessment of all patients:

A complete clinical examination, screening questionnaire to exclude active TB, and laboratory evaluation: CD4, FBC, Alanine amino transferase (ALAT), and creatinine.

Clinical and biological follow up of patients on treatment: it is important to closely follow the patients during the first month in order to maximize adherence and to detect any side effects due to ARVs in a timely manner. Thereafter, there should be a systematic clinical follow up every 3 months and a CD4 check every 6 months if CD4 are > 500 cells/ml or every 3 months if CD4 are < 500 cells/ml.

IV.2. The different classes of ARVs

There are three main classes of ARVs in use 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.

IV.3. Other categories of ARVs

Research into new drugs targeting other stages in viral replication is ongoing. Several drugs are currently in existence but are still undergoing therapeutic trials; or are still limited to certain regions. These are:

- Co-receptor antagonists that block fusion and entry of HIV into CD4 cells.
- Integrase inhibitors that block integration of the viral DNA into the host genome.

IV.4. The choice of ARVs: cost and efficacy

At the national level, the choice of ARV is decided by TRAC *Plus*, based on extensive research, review of treatment guidelines agreed upon by experts, and consideration/discussion with other stakeholders during Technical Working Group meetings. 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 CNLS and coordinated by TRAC *Plus* through the Ministry of Health in accordance with the national treatment plan, have allowed equal access to ARV treatment to all of the eligible Rwandan population.

IV.5. Principles for selection of regimens

The principle of a combination of several ARVs is based on the necessity to obtain a potent blockage of viral replication. It is therefore necessary to:

- Either block replication at several levels: the case with the combination of NRTIs with a PI;
- Or block the same level but through different but complementary mechanisms: the case with the combination of NRTIs with an NNRTI.

It is of prime importance to completely block viral replication because any residual multiplication in the presence of the drug in the blood/body will result in selection of resistant subtypes that will compromise the treatment regimen. The association of three different drugs is called Triple therapy.

IV.6. Main associations

- 2 NRTI + 1 NNRTI (1st line regimen)
  or
- 2 NRTI + 1 PI (2nd line regimen)

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.

IV.7. When and how to initiate treatment in an adult patient?

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 artificially block viral multiplication.

✓ The eligibility criteria

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.

✓ Criteria for clinical and immunological eligibility.

Confirmed HIV seropositivity and one of the following two criteria:

- Any patient with WHO clinical stage 4, regardless of CD4 count.
- Any patient with WHO clinical stage 1, 2 or 3, whose CD4 count is < 350/mm^3.

✓ Mandatory Social criteria

- Having disclosed one's HIV serostatus to a family member or someone close.
- Acceptance to be visited at home 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.
- Have a fixed residence within Rwanda (at least six months within the catchment area of the health facility).
- Commit oneself 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.

IV.8. The recommended first line regimen

Adult: The first line regimen recommended by TRAC *Plus* is:

✓ 1st line regimens

1. TDF (Tenofovir) + 3TC /FTC (Lamivudine or Emtricitabine) + NVP (Nevirapine)
2. TDF (Tenofovir) + 3TC / FTC (Lamivudine or Emtricitabine) + EFV (Efavirenz)
3. ABC (Abacavir) + 3TC (Lamivudine) + NVP (Nevirapine)
4. ABC (Abacavir) + 3TC (Lamivudine) + EFV (Efavirenz)

NB: - Give EFV in case of allergy to NVP or to patients on anti-TB treatment.

- Give ABC in cases where TDF is contraindicated (renal insufficiency with CrCl < 50).
- Give ABC (instead of TDF) when initiating ART in a pregnant woman.

Given the large number of names that exists for each drug (branded or generic), it is necessary to emphasize the international generic nomenclature (e.g. use the name Lamivudine (3TC) and not Avolam or Epivir).

✓ **Table 1: Specific dosage of 1st line drugs**

type of drug	Dosage
Lamivudine (3TC)	150 mg twice a day or 300mg 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
Emtricitabine (FTC)	200 mg once a day

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

Detailed 1st line regimen, including substitution options

✓ **Treatment regimen: TDF + 3TC or FTC + NVP**

*Initial phase 15 days 1x/ day (as single dose)	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: TDF + 3TC or FTC + EFV**

Evening (1) TDF 300mg + 3TC(2)300mg /FTC 200mg + 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: 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

✓ **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.

IV. 9. Special cases

✓ HIV-TB co-infection

The incidence of TB in Rwanda has increased during the last ten years due to TB-HIV co-infection. In 2008, 95.8% of all TB patients (all forms combined) were tested for HIV and 34.1% of them tested HIV positive.

HIV testing among TB patients in Rwanda in 2008

Total	Tested	HIV+	On CTX	On ARV
7841	7510	2560	2219	1148
%	95.8%	34.1%	86.7%	44.8%

Infection with HIV results in the progressive destruction of the immunological defense systems and leads to the development of opportunistic infections, one of which is TB.

People infected with HIV are 10-50 times more likely to develop active TB than non-infected people. Indeed, in the absence of antiretroviral treatment 50% of co-infected persons develop active TB disease during their lifetime while the corresponding figure is only 5-10% in people who are not infected with HIV.

Similarly, just as HIV infection accelerates the progression of TB infection to active TB, TB accelerates the progression of HIV by increasing the viral load and reducing the CD4 count.

TB is the leading cause of morbidity and mortality in adults infected with HIV in Africa. The systematic detection and early treatment of TB among persons living with HIV is critical for reducing morbidity and mortality in Africa.

✓ 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 the TB and HIV clinics.

✓ Screening for co-infection

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.

✓ **Using a questionnaire to search for tuberculosis in every new HIV patient and during follow up clinical visits.**

- 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	• 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 tool 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 diagnostic algorithm of the National Tuberculosis and Leprosy control program (PNILT).

IV.10. Provision of care to HIV-infected patients infected by tuberculosis

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

- The treatment regimens 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

The clinical and biological criteria of eligibility are confirmed HIV positive serology and 1 or 2 of the following criteria:

1. Symptomatic patient, stage 4, regardless of the CD4 count ;
2. Symptomatic patient stages 1, 2, 3, with some major signs (TB, esophageal candidiasis, herpes zoster) + CD4 < 500 cells/mm^3.

NB: According to the WHO and CDC classification of the adult HIV patient:

- Extra-pulmonary TB = stage 3
- Pulmonary TB in the preceding year = stage 3

Most HIV-infected TB patients are eligible for ARVs and should be referred to an accredited ARV treatment site.

The treatment priority in co-infected patients is to treat TB first. The right time to start ARV triple therapy depends on the clinical status of the patient and the CD4 count, as indicated in the table below.

ARV treatment can be deferred in certain case of extra-pulmonary TB (TB lymphadenitis, non-complicated pleural infection).

TRAITMENT OF TB in HIV/AIDS PATIENTS	
SITUATION	RECOMMENDATION
PTB and CD4 < 500 / mm3 or EPTB	✦ Start anti-TB treatment. ✦ Start administration of one of the following ARV regimens 2-8 weeks after the start of anti-TB treatment: TDF+ 3TC/FTC+EFV ABC+3TC+EFV ✦ For pregnant women during the first trimester of pregnancy, give: AZT /D4T+3TC+ABC ✦ For pregnant women beginning with the second trimester give: ABC/AZT+3TC+EFV
PTB and CD4 > 500/mm²	✦ Anti-TB treatment. ✦ Do CD4 test after 2 months of anti-TB treatment. If CD4>500 continue with anti-TB treatment only; if CD4<500 start ARV treatment.

D4T= Stavudine ; AZT : Zidovudine ; 3TC : Lamivudine ; EFV : Efavirenz ; ABC : Abacavir

TDF : Tenofovir ; FTC : Emtricitabine

✓ IV.11. Prevention of HIV transmission

- Inform all TB patients about the preventive measures for HIV:
  - Abstinence;
  - Faithfulness;
  - Use of condoms (have a stock of condoms for all TB patients);
  - Treatment of sexually transmitted infections (STIs);
  - Utilization of disposable (non-reusable) syringes for each and every injection.
- Refer all HIV-TB co-infected pregnant women with CD4 > 500 cell/ml to PMTCT for prophylaxis to prevent transmission of HIV to their infants.
- When ARV treatment is indicated, the recommendation is that for people infected simultaneously by both diseases (TB and HIV), they should first start anti-TB treatment and then initiate ARVs 2-8 weeks later.

- If the person needs simultaneous treatment for TB and HIV, the 2 first line regimens are as follows:
  - TDF + 3TC/FTC + EFV
  - ABC + 3TC + EFV
- For pregnant women in the first trimester only, give: AZT + 3TC + ABC or D4T + 3TC + ABC (A regimen containing EFV is possible beginning with the second trimester).
- If EFV is administered simultaneously with rifampin, the usual dosage does not change; it remains 600 mg.
- If a patient on treatment with a regimen containing NVP develops TB, NVP is stopped and is replaced with EFV during the period when the patient is on anti-TB treatment. How is this done?

  The patient will take:
  TDF + 3TC/FTC + EFV 600mg
  ABC + 3TC + EFV 600mg
- NVP is hence stopped and the patient can safely start anti-TB treatment.
- Using PIs with anti-TB treatment is not recommended, and expert opinion should be sought if a patient requires second-line ARVs with anti-TB treatment. These patients should be handled on a case-by-case basis with expert advice.

✓ **Treatment regimen 1: TDF + 3TC/FTC + EFV**

Evening: TDF 300mg + 3TC 300mg/FTC 200mg + EFV 600mg

✓ **Treatment regimen 2:**

Evening ABC 600mg + 3TC 300mg + EFV 600mg

✓ **Special case of the pregnant women:**

Pregnancy is not a contraindication for initiation of ARVs.

Note: For HIV seropositive patients who do not meet the eligibility criteria, recommendations are as follows:

- If CD4 are above 500/mm³, consult (clinical follow up) every 3 months and check CD4 every 6 months.
- If they are below 500/mm³, check the CD4 every 3 months.

✓ **Table 3: Clinical and biological follow up of patients on treatment.**

Date	Clinical	Laboratory
Pre-ARV	+	CD4, FBC, Creatinine (GPT and C-Xray if there is a clinical indication)
D 15	+ adherence	None
M 1	+ adherence	None
M 2	+ adherence	None
M 3	+ adherence	FBC if on AZT; Creatinine if on TDF; GPT if indicated clinically
M 4	+ adherence	None
M 5	+ adherence	None
M 6	+ adherence	CD4, (FBC, Creatinine if on TDF, GPT if clinically indicated)
After six months		
	Monthly for 1 year + adherence	◆ CD4: every 6 months ◆ Do viral load every 12 months ◆ FBC, Creatinine if on TDF, GPT if clinically indicated

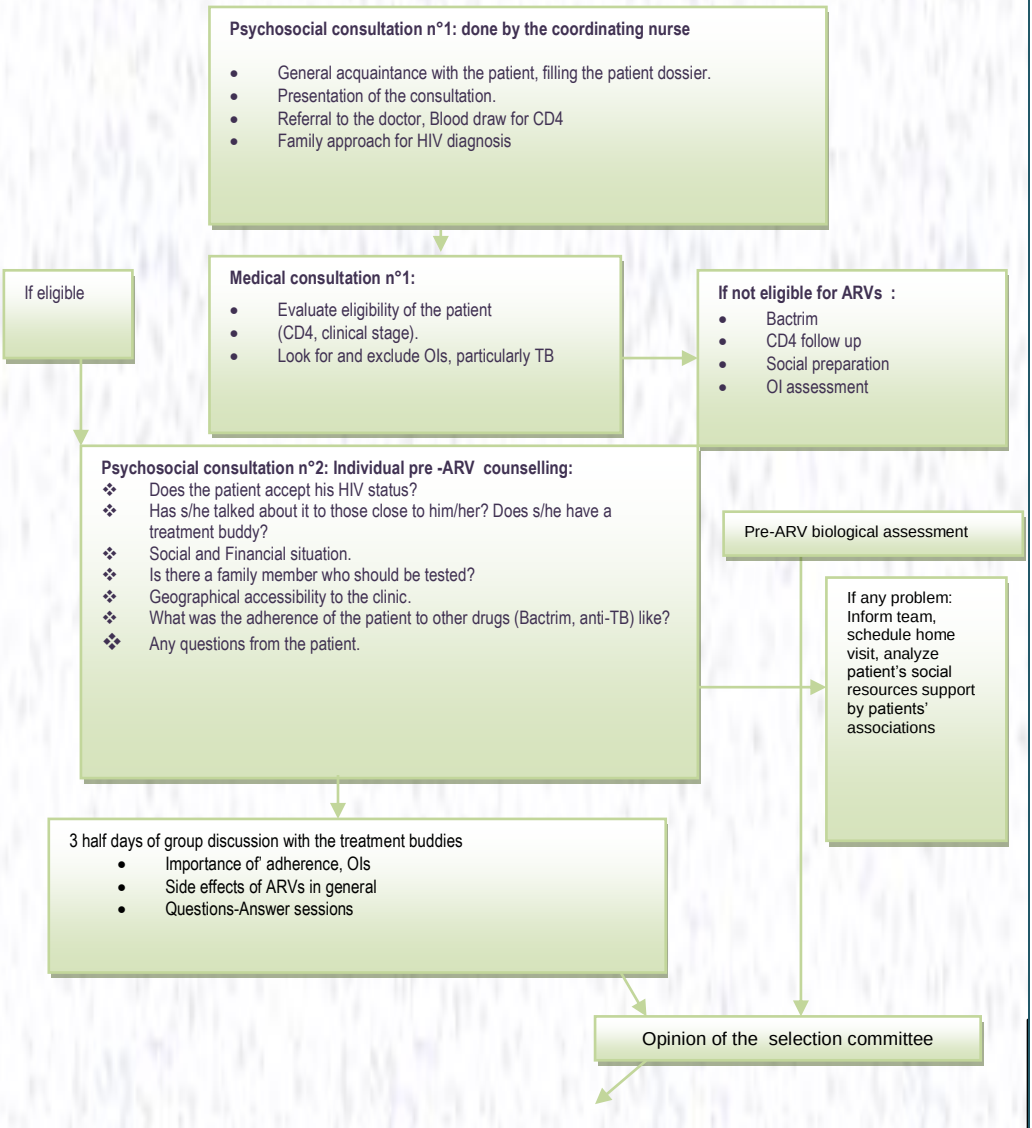
- After a year of treatment in the absence of any problems, a visit every 6 months to the doctor is sufficient while a visit to the nurse counselor should be maintained at least every 3 months. This visit to the counselor will be combined: basic medical follow up, adherence assessment, and follow-up counseling.
- Viral load is recommended once every 12 months or in case of suspected clinical or immunological failure. (see definition below in Chapter 5).

IV.12. Algorithm for the initiation and follow up of antiretroviral treatment.

Before going into the details of this algorithm, it is important to clarify the roles of each member of the team so that we can explain how the latter works.

If at any stage during this process the patient is admitted to hospital, s/he must continue to be followed closely during this period of admission. However, the occurrence of certain OIs (TB, diarrhea or vomiting, any acute episode in general) may delay the initiation of ARV treatment.

If treatment has to be initiated or the patient is already on treatment, then the following model should be followed. During hospitalization/admission, each day the counselor should verify tolerability and adherence by asking how many tablets are remaining and verifying if this corresponds with the correct number of doses taken. This questioning should not be taken as a police interrogation. Counseling with the treatment buddy should also take place in the hospital.


Psychosocial consultation n°1: done by the coordinating nurse
General acquaintance with the patient, filling the patient dossier.
Presentation of the consultation.
Referral to the doctor, Blood draw for CD4
Family approach for HIV diagnosis
Medical consultation n°1:
Evaluate eligibility of the patient
(CD4, clinical stage).
Look for and exclude OIs, particularly TB
If eligible
If not eligible for ARVs :
Bactrim
CD4 follow up
Social preparation
OI assessment
Psychosocial consultation n°2: Individual pre -ARV counselling:
Does the patient accept his HIV status?
Has s/he talked about it to those close to him/her? Does s/he have a treatment buddy?
Social and Financial situation.
Is there a family member who should be tested?
Geographical accessibility to the clinic.
What was the adherence of the patient to other drugs (Bactrim, anti-TB) like?
Any questions from the patient.
Pre-ARV biological assessment
If any problem: Inform team, schedule home visit, analyze patient's social resources support by patients' associations
3 half days of group discussion with the treatment buddies
Importance of' adherence, OIs
Side effects of ARVs in general
Questions-Answer sessions
Opinion of the selection committee

Medical consultation N°2: Day 0, initiation of treatment

- ❖ Verify the absence of OIs.
- ❖ Verify if the pre-ARV biological and psychosocial assessment is complete. What was the opinion or suggestions of the selection committee?
- ❖ Choice of ARV regimen, weigh the patient. Is the patient on bactrim?

- ❖ Consultation by doctor or nurse N° 4 : Month 1
- ❖ Does the patient have any complaints? Weight of the patient?
- ❖ Adherence: how many tablets did you forget last week?
- ❖ Tolerability: go through the main side effects.
- ❖ Biological follow up: interpret the results from the blood examination done the previous day, Plan the next exams and visit, Patient's questions?

Distribution of ARVs in the pharmacy N° 3 : month 1

- Evaluation of adherence.
- Check if the patient has a good understanding of the issues around ARV medications.
- Evaluate tolerabilitv.

Distribution of ARVs in the pharmacy N 4 : 6 weeks

- Evaluation of adherence.
- Check if the patient has a good understanding of the issues around ARV medication..
- Evaluate tolerability

If the patient is on NVP: at M 1 do consultation with doctor or nurse N° 3 :

- ❖ Does the patient have any complaints?
- ❖ Weigh the patient
- ❖ Adherence: How many tablets did you forget during the last week?
- ❖ Tolerability: go through the main side effects.
- ❖ Biological follow up: interpret the results from the blood examination done the previous day, Plan the next examinations and visit,
- ❖ Any questions from the patient?

Distribution of ARVs in the pharmacy N°5 : 10 weeks

- ❖ Evaluation of adherence.
- ❖ Check if the patient has a good understanding of the issues around ARV medication.
- ❖ Evaluate tolerability.

Medical consultation N° 5 : Month 3

- ❖ Does the patient have complaints?
- ❖ Adherence: How many tablets did you forget during the last week?
- ❖ Tolerability: go through the main side effects.
- ❖ Biological follow up: interpret the results from the blood examination done the previous day, Plan the next examinations and visit,
- ❖ Patient's questions? Couple this to follow up counselling.

Distribution of drugs in the pharmacy will continue every month following the same model.

Medical consultation N° 6 : Month 6

This is a very important occasion; it is the time for the first assessment

- Does the patient have complaints?
- Clinical evaluation: OI? Weight measurement? General status? TB screening?
- Adherence: How many tablets did you forget during the last week?
- Tolerability: go through the main side effects.
- Bio logical follow up : Interpret CD4 results
- Any questions from the patient?

CHAPTER V. WHEN AND HOW TO CHANGE THE TREATMENT REGIMEN?

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 4 main situations:

- Toxicity: a severe side effect;
- Treatment failure;
- Pregnancy;
- Drug interactions.

In this chapter, we discuss changing treatment due to toxicity and treatment failure; TB drug interactions have been discussed in the preceding chapter and the situation with pregnancy will be discussed later on. In the case of toxicity, only one drug must be substituted.

In the case of treatment failure, the entire regimen must be changed.

This chapter is divided into 3 parts:

- A. Changing ARV treatment because of toxicity: presentation of different ARV drugs and management of their side effects;
- B. Biological criteria for stopping treatment;
- C. Changing ARV treatment because of treatment failure: definition and management of treatment failure.

V.1. Changing ARV treatment because of toxicity: presentation of the different drugs and management of their 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 PLWHA.

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.

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

Regimen	Toxicity	Alternative drugs
TDF+3TC/FTC + NVP/EFV	✦ 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	✦ Change TDF -> AZT ✦ Change NVP -> EFV (except during 1st trimester of pregnancy) ✦ Change NVP -> LPV/r ✦ Change EFV -> NVP
ABC+3TC +NVP/EFV	✦ 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	✦ Change ABC -> AZT ✦ Change ABC -> AZT ✦ Change NVP -> EFV (except during 1st trimester of pregnancy) ✦ Change EFV -> NVP

V.2. 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, TDF 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.

V. 3. 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 (Na – (Cl+CO2)>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 ddI + 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).

V.4. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Névirapine (NVP)

Side effects:

The most common side effect due to NVP is skin rash, found in 20% of patients (particular 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.

✓ Table 2. 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.

- 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)

✓ Table 3: 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)

Side effects:

- 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.

- 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.

- 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.

- 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.

V.5. 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 importance 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/mm3
Platelets	< 49 999/mm3
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	> 3 x higher than normal values
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.

V.6. Changing ARV treatment because of treatment failure: definition and management of treatment failure

✓ **Introduction**

Successful ARV therapy results in clinical and immunological improvement due to interruption 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/mm^3 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.

✓ 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**:

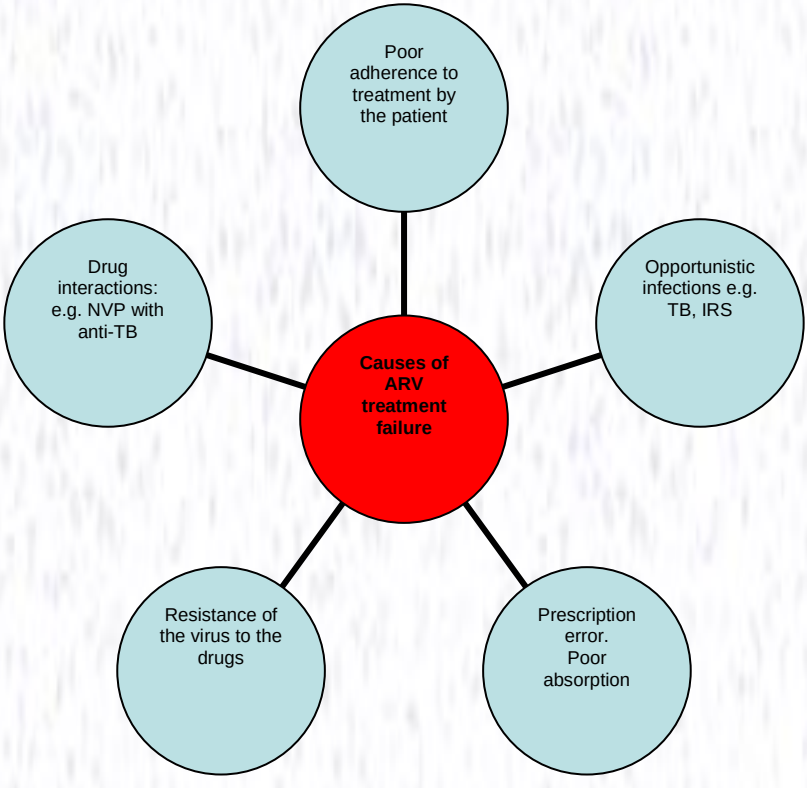
  - A return of CD4 counts to the pre-treatment baseline or below (in the absence of any concomitant infection that is liable to cause a transient reduction in CD4).

  - 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.

✓ Causes of treatment failure :



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

- Given the cost of second 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 CD4s (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.
- Rue 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/ mm3 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-exiting 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.

Date	Clinical	Laboratory
Assessment before 2nd line	+	GPT, creatinine, FBC.
M 1	+ adherence	None
M 2	+ adherence	None
M 3	+ adherence	Creatinine
M 4	+ adherence	None
M 5	+ adherence	None
M 6	+ adherence	CD4, FBC, creatinine, GPT, glycemia, VL
After the sixth month		
	Monthly for 1 year + adherence	• CD4: every 6 months. • Viral load 6 month after start of 2nd line and then once every 12 months. • FBC, creatinine, GPT, glycemia at 12 months. • After 12 months of 2nd line treatment, FBC, creatinine, GPT, glycemia will be done on clinical indications.

First line Regimens	2nd 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)

✓ **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.

V.7. 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.

V.8. 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.

V.9. 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
Ketoconazole Fluconazole	Keto ↘63%; No effect; Flucon ok		LPV ↘13%; Keto ↗ x 3	Dosage does not change	IDV ↗68%; Reduce dose to 600 mg 3 X a ady
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/rit	Nelfinavir	Indinavir
Oral contraceptives	Estradiol ↘20%; Use alternative methods	Estradiol ↗37%; Use alternative methods	Estradiol ↘ 42%; Use alternative methods	Estradiol ↘47%; Use alternative methods alternative	Estradiol ↘ 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 ↘ Warfarin and monitor!			
Theophylline			Theophylline ↘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.

CHAPTER VI. 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.

VI.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.

VI.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.

VI.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 VII. PROVISION OF CARE TO THE PREGNANT WOMAN

According to the data of UNAIDS 2007, 15.4 million of the 33.2 million persons living with HIV in the world, are women. Given the particular vulnerability of women to HIV/AIDS in developing countries by virtue of their status in the couple, difficulties with their access to education and their weak socio-economic status, it is important to pay particular attention to the provision of care to women, especially those who are pregnant.

VII.1. 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.

VII.2. 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.

VII.3. 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.

For people in the reproductive age group and for children that are future parents:

The information to be communicated:

- The risk of HIV transmission in the absence of interventions, the limits and efficacy of the PMTCT program in Rwanda based on the current data;

- The consequence of transmission of HIV to the child (including death, opportunistic infections, stigma, life long exposure to ARVs, life in the future among others for the child; and the socio-economic impact for the society.

VII.4. ARVs for pregnant women who meet the criteria for initiation of ARV treatment

With the growth of the PMTCT program, it is becoming more and more common that HIV seropositivity is discovered during pregnancy. In this case the team that is charged with counseling and proposing the test should always prepare the woman for the possibility of initiating ARV treatment.

Similarly, the team should also discuss with the woman the HIV serostatus of her partner and encourage her to talk with him about this issue if they had never talked about it before.

The first thing to do when a pregnant women is found to be HIV-infected is to do a full clinical assessment and check her CD4 count to see if it is necessary to start her on antiretroviral treatment.

The eligibility criteria for ARVs are no different for the pregnant woman:
- Stage 4 regardless of the CD4 count.
- Any patient with less than 350 CD4/mm^3, regardless of the clinical stage (1, 2, 3).

Those who are not eligible for ARV treatment should be sent to the PMTCT unit.

If treatment is necessary, the woman should be treated with dual consideration:

- To choose an ARV combination that is efficacious on viral replication.
- To remember the presence of the pregnancy.

✓ **When to start treatment:**

For the women eligible for ARVs, treatment should be initiated immediately while avoiding EFV during the first trimester. For women who are not eligible, treatment will be started after 28 weeks of amenorrhea.

Full ARV treatment has dual justification:

- To enable the woman to restore her immunity.
- Protect the child from maternal transmission of HIV: it has been well established that it is the severely immunosuppressed women with a CD4 count CD4 $\leq$ 200/mm3 who are most likely to transmit HIV to their children in utero, intrapartum, and post-partum. This rate can be as high as 25% of all mothers to child transmissions (without considering the risk of maternal breastfeeding).

✓ Which ARVs to prescribe:

The prescription of ARVs should respect the same norms as those for any other adult.

However:

- Aim to prescribe ARVs whose efficacy in PMTCT is well known: AZT, 3TC, and NVP.
- Avoid ARVs that are known to be potentially teratogenic or toxic in pregnant women. For example: EFV (during the first trimester).
- The best choice is therefore to prescribe the combination of AZT + 3TC + NVP. In the case of intolerance to NVP, we should use a PI: LPV/r or Nelfinavir or EFV if the woman is in the second trimester onwards. TDF is not currently recommended to be initiated during pregnancy.
- Clinical and biological monitoring must include tests of tolerance (blood count among others) and efficacy of the treatment just like for any other adult patient, and that of the pregnancy just like for any other pregnant woman.

VII.5. Provision of care to the woman who becomes pregnant while already on triple therapy

This possibility is going to become more and more common as access to antiretroviral drugs increases. Once a woman on antiretroviral treatment becomes pregnant, there is need for dual assessment:

- Ensure the efficacy of the current treatment: that means do a full clinical assessment and CD4 count. It is recommended to do viral load if available. This is essential because the risk of mother to child transmission is particularly high when the CD4 count is low and the viral load is high. If the current treatment is poor in controlling the immunity status of the patient, then it should be changed in conformity with the general guidelines.
- Verify that the current treatment does not contain any drugs that are contraindicated during pregnancy. If present, such a drug should be stopped immediately. If it is EFV, it should be replaced by NVP if the woman is still within the first trimester.

VII.6. Family Planning

The availability of family planning services in the health facility offering PMTCT services is invaluable.

The health care provider should:

- During the immediate post partum period, remind the woman of the importance of family planning.
- Provide appropriate information and help each patient to be well informed before deciding to conceive again or not.
- Support the HIV-infected woman and her partner to use a modern method of contraception of their choice.
- Explain that the use of another method of contraception does not preclude the utilization of condoms and does not protect against HIV transmission.
- If contraception is requested, ensure that the woman and preferably the couple has all the necessary information and counseling that is needed to ensure safe contraception.

CHAPTER VIII: POST EXPOSURE PROPHYLAXIS

VIII.1. 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%.

VIII.2. 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.

✓ 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.

✓ 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		Massive
VIH+ CD4 bas ou pathologie opportuniste	Recommandée	Recommandée	Recommandée
VIH + Asymptomatique	Recommandée	Recommandée	Se discute
Statut VIH inconnu, mais facteur de risque pour le VIH (≥ 1 argument *)	Recommandée	A Recommander	Se discute
Statut VIH inconnu ou source inconnue sans argument (*)	Recommandée	Se discute	Se discute

(*) Arguments en faveur d'une infection à VIH chez le patient source : Une symptomatologie clinique ou biologique compatible avec une primo-infection ou un déficit immunitaire sévère ; des facteurs de risque connus ; la prévalence de l'infection dans l'établissement. Celui qui en bénéficie est la victime VIH - .

✓ 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

VIII.3. 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.

✓ 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.

✓ 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 IX. PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV (PMTCT)

IX.1. Introduction

PMTCT is one of the domains in which ARVs have shown great efficacy. Following the clinical trials that evaluated the impact of AZT against a placebo in preventing mother to child transmission of HIV, it was found that AZT reduced the risk of mother to infant transmission of HIV by two-thirds.

IX.2. The steps of PMTCT

The PMTCT program has 5 main objectives:

- Primary prevention of HIV infection: ensure that the woman does not become HIV infected.
- Prevention of unwanted pregnancies: this is family planning.
- Prevention of intra-uterine transmission of HIV.
- Prevention of intra-partum transmission of HIV (during labor).
- Prevention of post-partum transmission of HIV (through breast milk).

The first two objectives are not discussed in this chapter as they fall under the domain of counseling.

IX.3. The different stages and rates of mother to child transmission (in the absence of treatment)

Mother to child transmission can occur at any moment but mainly occurs during labor. There is a risk of transmission of 30-50% which occurs as follows:

- Before delivery: intra-uterine (5 to 10%).
- During labor: (10 to 20%).
- After delivery/labor (breastfeeding): this risk is as high as 15 to 20%, depending on the duration of breastfeeding.

IX.4. Factors that facilitate mother to child transmission of HIV

In general, the more immunosuppressed the mother is, the higher the risk of mother to child transmission of HIV, especially in-utero after the second trimester.

Three factors favor transmission of HIV from the mother to the child:

1. The clinical status of the mother.
2. The labor conditions.
3. Maternal breastfeeding.

✓ Clinical status of the mother

The risk of transmission is highest when:

- Viral load is high.
- The clinical stage is poor (WHO stage 3 or 4).
- Presence of associated systemic infections: (TB, hepatitis B or C, Malaria) or localized ones (genital infections).
- Low CD4 cell counts, with a very high risk when CD4 are less than 350 CD4 / mm^3.

✓ Labor

Factors that increase the risk of transmission during labor are:

- Failure to respect measures for clean delivery;
- Prolonged labor, beyond 12 hours;
- Premature rupture of membranes for over 4 hours;
- Home delivery;
- Abnormal delivery;
- Presence of hemorrhagic fluid or meconium.

✓ Breastfeeding

As we will explain in more details below, mixed feeding is the form of nutrition that most favors mother to child transmission through breast milk.

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IX.5. Different interventions to reduce Mother to Child transmission of HIV

This chapter explains the strategies used in reducing mother to child transmission of HIV, with a particular emphasis on the trials and interventions that have proven efficacy. This prevention revolves around four main axes:

- Primary prevention of transmission of HIV infection: do whatever it takes to ensure that future parents are not infected by HIV.
- Prevention of unwanted pregnancy in HIV-infected women.
- Prevention of transmission through the use of pharmaceutical (ARV) and obstetrical interventions :
    - In utero.
    - In the peri-partum period.
    - In the post partum period.
- The provision of care to the infected woman, her child and her family.

NB: Triple therapy may be recommended depending on the status of the mother.

✓ Primary prevention of HIV/AIDS

Primary prevention involves setting up an information, education and communication program, screening and treatment of any associated sexually transmitted infections, promotion of condom use (male or female condoms), and finally counseling on HIV to promote HIV testing.

This strategy has the aim of preventing HIV infection among parents by strengthening or improving their knowledge in the domain of HIV/AIDS, adoption of safer behaviors, utilization of condoms and the possibility of knowing their HIV status.

✓ Prevention of unwanted pregnancies in women infected with HIV.

HIV infection presents a real dilemma given the desire to have children in most women especially those in Africa where procreation has an important social and cultural value. For an HIV-infected woman who does not want to have more children, one should strengthen family planning services to ensure effective prevention of pregnancy. It is in this context that we always talk of double protection, a strategy that allows the prevention of STIs as well as unwanted pregnancies.

Hence, choice of the method of contraception should take into consideration the risks of both unwanted pregnancy and STI/HIV. On the other hand, in case of pregnancy desire, the woman should be advised on the safest/least risky situation for her and her child.

In this case it will involve a complete clinical evaluation of the mother and CD4 examination. It is after putting together all this information that it is possible to determine the risk for the child and the best preventive strategy to be adopted.

In certain cases, a poor clinical status associated with a low CD4 count (<350/mm^3) may require to temporarily discourage pregnancy until such a time when the risk is lower for the child by restoring the mother's immunity through the use of ARV treatment.

✓ Prevention of transmission through the use of pharmaceutical (ARV) and obstetrical interventions

Prevention of intra-uterine transmission

Prevention at this stage is important because when children are infected at this stage, the resulting illness is usually very serious. Prevention at this stage involves ART (Triple Therapy) for the mother who meets the eligibility criteria for ARV treatment.

In reality, all HIV-infected women, whether pregnant or not, should be put on triple antiretroviral treatment in accordance with the medical indications. For the pregnant woman, treatment should be started from the beginning of the second trimester (at the end of embryogenesis when the risk of teratogenicity is very high). If this date has already passed, then start treatment as soon as possible.

The treatment must not include the combination of DDI + D4T which is very hepatotoxic in pregnant women and carries a risk of severe lactic acidosis (each of these two drugs can be used separately, but not the two combined together).

EFV (Stocrin), whose teratogenic effect has been demonstrated in cynomolgus monkeys can be used beginning with the second trimester but should be avoided during the first trimester.

The regimen should also contain drugs whose effect on the reduction of mother to child transmission is well proven such as AZT, 3TC, NVP.

Hence, a good first line treatment regimen for the pregnant women can be constituted as follows:

AZT + 3TC + NVP.

For the other details, refer to the chapter in the National PMTCT Guidelines.

IX.6. Peripartum transmission: Measures to promote "clean delivery" during labor

During labor, avoid any interventions that may increase the risk of blood exchange between the mother and the infant, or result in lesions of the skin or mucosa. The risk is high once membranes are ruptured, when there is placental separation, and as the baby crosses the genital tract with all the maternal secretions.

Clean delivery, therefore consists of six measures:

- Avoid invasive procedures if possible: artificial rupture of membranes, episiotomy, forceps delivery.
- Limit the practice of artificial rupture of membranes to the following cases: poor or failed progress in labor, fetal distress, cervical dilatation of 7 cm or above.
- Avoid unnecessary vaginal examinations especially after rupture of membranes.
- Clean the genital tract, the skin and the mucous membranes of the new born with chlorhexidine 0.25%.
- Do not drain the umbilical cord towards the baby.
- Avoid any lesions of the baby's skin or mucous membranes.

Elective caesarean section at 38 weeks has been proposed but the risk of morbidity and mortality due to the operation itself should weigh against the benefit of its indication in developing countries.

IX.7. Prevention of transmission during the post partum period

One of the principal causes of the observed difference between MCT in Africa and Europe is maternal breastfeeding, which is responsible for 14% of MCT, and can be as high as 30% in cases of latent maternal infection during breastfeeding. Given this reality, it is obvious that replacement feeding would eliminate MCT during the post natal period. However, the socio-cultural and economic conditions (acceptability, feasibility, cost, duration) of the families may make it impossible to choose this option.

Another possible alternative is exclusive breastfeeding for a short period. But it should always be remembered that artificial feeding is the ideal choice only when undertaken under safe conditions.

Advice to the HIV-infected mother regarding the best choice for feeding her child will depend on her financial means and her capacity to implement the mode of feeding chosen.

The health worker should explain to the mother the advantages and disadvantages of breastfeeding compared to those of replacement feeding in order to enable her to make an informed choice of the feeding method for her child. The health care worker should therefore, support and accompany the mother in choosing and implementing the feeding method for her child, always remembering that mixed feeding increases the risk of MCT.

If the mother chooses breastfeeding, she must respect the following conditions:

- Maternal breastfeeding must be exclusive, that is, do not give any other foods or drinks; not even water.
- Exclusive breastfeeding does not prohibit the administration of oral drugs to the child.
- Exclusive breastfeeding must be short, not exceeding 6 months.
- The counselor must explain to the mother how to position the baby properly during breastfeeding to avoid tugging on the nipples that may result in cracks or abscesses. These present an increased risk of transmission of the virus.
- Weaning must be early (6 months at the latest) with a safe transition. The transition involves getting the baby used to receiving breast milk by spoon or cup in preparation for abrupt weaning. Early weaning is not recommended unless both the mother and the baby are comfortable with feeding using the cup.
- In order to avoid breast engorgement, an injection of Estradiol 5mg is recommended for the mother who either does not want to breastfeed or wants to wean her child.

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.

IX.8. Provision of care to the Infected woman, her child and family

It should be emphasized at all stages of PMTCT (at each of its 4 steps), that interventions must not be limited to the mother-infant couple but to the entire family: the spouse or spouses and all the siblings. This particularly concerns the propositions for testing and the provision of comprehensive care to the entire family.

It is important to highlight the fact that the active participation of the spouse greatly facilitates the different stages of provision of care to the pregnant woman; whether at the level of her treatment if she needs treatment or in the choice of the mode of feeding.

The provision of care to the child, whether infected with HIV or not will be addressed in the chapter on care for the child.

✓ Aspects of the national PMTCT protocol

Historical background of the PMTCT program in Rwanda

The national program for the prevention of Mother to Child transmission (PMTCT) of HIV in Rwanda started in 1999 with a pilot phase at Kicukiro Health Centre. An evaluation of that phase, conducted after one year of implementation, guided the national expansion of PMTCT. By the end of December 2008, 341 health facilities were providing PMTCT services.

The national PMTCT protocol has undergone modifications and based on findings from different studies has evolved and a more efficacious protocol with less risk of causing resistance has been adopted.

✓ **The protocol that is currently recommended in Rwanda**

Drug interventions

- Gestational age of less than 34 weeks.

- CD4 check as soon as possible and clinical staging.
- The patient comes with the CD4 result.
- The patient is eligible for ART triple therapy if she is in WHO stage 4 or if she has < 350 CD4/mm^3 regardless of the clinical stage.

What to do:

- Refer (accompany) to an ARV treatment center or start triple therapy as soon as possible after the clinical assessment.
  - AZT-3TC-NVP (Duovir-N)
  - If Hb < 7 g/dl : D4T-3TC-NVP

- If the patient does not meet the eligibility criteria, she will receive the ARV combination as follows :
  - The mother will receive AZT 300 mg 2 times per day beginning at 28 weeks of pregnancy or as soon as possible up to the beginning of labor and a single dose of AZT (300mg) + 3TC (150mg) + NVP (200mg) at the beginning of labor.
  - After delivering, the mother will receive AZT 300 mg + 3TC 150 mg (Duovir) 2 times a day for seven days.

- Hemoglobin levels should be monitored closely because AZT is contraindicated if the hemoglobin level is below 7g/dl.

- If the patient's CD4 results are not yet available, the above protocol should be followed but should be reviewed after receiving the CD4.

- Gestational age above or equal to 34 weeks.

Start ARV treatment (Triple therapy: AZT (300mg) + 3TC (150mg) + NVP (200mg)) at the same site, regardless of the clinical stage or the CD4 level:

- AZT-3TC-NVP
- If Hb< 7g/dl: D4T-3TC-NVP

- Regardless of the circumstances, the patient should start ARVs during the same week in order to reduce the viral load as much as possible and hence reduce the risk of transmission as much as possible.
- To achieve this, during the first visit of any pregnant woman after 34 weeks of gestational age, it is recommended that on that day (whether it is at an ARV site or not) the patient should: ,
  - Consult with the doctor (if possible).
  - Be counseled on treatment
  - Have pre-ARV assessment
  - Have CD4 blood draw or be given an appointment.
- Ideally, the following day, the patient will begin ARVs if the second counseling is successful and the pre-ARV assessment favorable, even if the CD4 results are not available. The patient will then follow group counseling and will be referred to the selection committee even if she has already started ARVs.

Important remarks:

Since the risk of hepatitis and skin rash secondary to NVP is greatly increased when CD4 >250/mm^3, we recommend that clinical and biological follow up (liver function tests) be carried out attentively for all concerned patients.

- Analysis of the CD4 results will at times be done after the patient has started ARVs. The doctor will then decide whether to stop triple therapy after the woman delivers or not:
  - The patient who meets the eligibility criteria for the initiation of ARVs in adults will continue with triple therapy after she delivers.
  - The patient who does not meet the eligibility criteria for ARV treatment in adults will stop NVP the day after she delivers and will continue with AZT-3TC (2 times a day) for 7 days and then stop all ARVs.
- The baby will as soon as possible (within 48 hours) receive a single dose of NVP syrup (2mg/kg, or ~ 1 ml) combined with AZT syrup (2x4 mg/kg, or ~ 1 ml morning and evening) per day for a month.

The patient is diagnosed as HIV-infected in the labor room

- She will receive a single dose of AZT (300mg) + 3TC (150mg) + NVP (200mg) at the beginning of labor. After delivering, she will receive: AZT 300mg + 3TC 150 mg 2 x/day for 7 days.
- The child will also receive as early as possible (within 48 hours) a single dose of NVP accompanied by syrup AZT 2x4 mg/kg per day for a month.

The patient is HIV negative but the husband is HIV-infected (discordant couple).

She will also receive a single dose of AZT (300mg) + 3TC (150mg) + NVP (200mg) at the beginning of labor and AZT + 3TC for one week after delivering.

This is important because she can re-infect herself between the time she was tested and the time she delivers.

The child will also receive as early as possible (within 48 hours) a single dose of NVP syrup (2mg/kg) accompanied by AZT syrup 2x4 mg/kg per day for a month.

CHAPTER X. PROVISION OF CARE TO THE CHILD INFECTED WITH HIV

Children are also affected by HIV/AIDS. Data from UNAIDS in December 2007 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 2007.

X.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.).

✓ 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.

X.2. 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).

In summary :

Interpretation of serology results of a child born of an HIV-infected woman		
Age	HIV serology of the child	Interprétation
< 9 months	The HIV serology test is not necessary apart from confirming the mother's serology (exposure). The diagnostic options are PCR and, in the absence of PCR, the CD4 percentages and the presumptive clinical diagnosis using the WHO criteria.	
9-15 months	+ HIV serology	The child may be HIV + or -. The only way to confirm HIV status of the child is to use the PCR. In the absence of PCR, do presumptive clinical diagnosis using the WHO criteria. Redo confirmatory serology at 18 months.
	- HIV serology	In the absence of maternal lactation for at least 3 months, the child is not HIV infected (Doing the virology test is useless).
15-18 months	+ HIV serology	The child is probably HIV+, but should be confirmed by either serology at 18 months or PCR. In the absence of PCR: Use CD4 percentage and presumptive clinical diagnosis using the WHO criteria. Redo serology at 18 months.
	- HIV serology	The child is not HIV-infected (useless to do a PCR virologic test) in the absence of breastfeeding for at least 3 months.
> 18 months	+ HIV serology	The child is HIV-infected (useless to do a PCR virologic test)
	– HIV serology	The child is not HIV-infected (useless to do a PCR virologic test) in the absence of breastfeeding.

In Rwanda, the diagnosis of HIV infection in children aged less than 18 months born from HIV-infected mothers is done as follows:

- When PCR is accessible :

- First PCR: at 6 weeks carried out in a PMTCT site (= date of the first vaccination and the start of Cotrimoxazole prophylaxis, so that the mother may remember this date).

The aim of this PCR is to detect children that are infected in utero or in the peri-partum period. Without ARV treatment, these children usually present with a rapidly fatal disease.

If the PCR is positive, the results are confirmed with another PCR test if possible without delaying the start of ARV treatment if the child is less than 18 months.

However, WHO accepts diagnosis based on a single positive PCR test because at times it is not easy to do 2 PCR tests.

A negative PCR at 6 weeks does not rule out HIV infection in a child who is still breastfeeding.

> Note: If for some reasons, a child has not had a second PCR to confirm the diagnosis, he should be considered HIV-infected until proof to the contrary (confirmatory serology between 9 and 18 months).

- Second PCR: It has the aim of ruling out HIV infection in children who have breastfed. These ones are usually at a lesser risk of death than the child infected earlier on in life.

  For this reason, and given the limited means for carrying out PCR tests, if the child's first PCR at 6 weeks is negative, we do not carry out a second PCR unless:

  - There is poor evolution in the presence of HIV positive serology.
  - The mother wishes to stop breastfeeding at 6 months but this presents risks of malnutrition and bacterial infections.
  - It is therefore necessary to verify that the child is not infected at the time of weaning at 6 months = PCR at 5 months and if PCR is negative then provide counseling and health education to support weaning at 6 months on condition that a nutritional supplement is provided in case of indigence and that the HIV negative status will be confirmed 3 months following the stoppage of breastfeeding. Under no circumstances should weaning be proposed if the mother does not have the necessary means to adequately and properly feed her child.
  - An HIV infected child with a positive PCR should continue breastfeeding.

Before carrying out a PCR test, it is advisable to first check the serology of the child who is shedding maternal antibodies beginning at 6 months; a PCR is done when and only when the serology is positive in a child < 18 months.

- 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/mm^3 between 0 and 11 months and < 750/mm^3 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 6, screening questionnaire approved by TRAC Plus and the TB Unit):

  - 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).*

X.3 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.

X.4. 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.

X.5. 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).

X.6. 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: is done if the first PCR is positive or 1 month before stopping breastfeeding; most often this will be when the child is 5 months old.

  If the child has clinical signs at any time before 18 months, then a second PCR is done.

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 Pneumocytis 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 in adults is still very controversial in Rwanda, but not for the young child. INH prophylaxis at a dosage of INH 5 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.

✓ **Dosage for INH prophylaxis in children by weight category.**

INH prophylaxis: 5 mg/kg (maximum 300 mg) per day single dose for 6 months								
< 5kg	6-10 kg	11-20kg	21-25kg	25–30kg	31-35kg	35-40kg	Kg	>50kg
¼ tab of 100 mg	1/2 100 mg tablet	1100 mg tablet	1 and1/4 100 mg tablet	1 and 1/2 comp de 100mg	1 and ¾ comp de 100 mg	2 100 mg tablets	2 and 1/2 100 mg tablets	3 100 mg tablets

X.7. When and how to start treatment in a child?

For a child aged above 18 months, when HIV serology is positive.

For a child aged below 18 months, do PCR if available; start ARV for each child that has positive PCR. If PCR is not available, start ARVs if there is a strong suspicion of HIV infection (positive HIV serology with signs of AIDS (stage 4); or for an asymptomatic child with 2 or more of the following signs: oral candidiasis, severe pneumonia, severe septicemia), with CD4 < 20%.

✓ **Indications for initiating ARV treatment in children.**

Age	Clinical and immunological criteria.	Treatment decision.
0 to 18 months	Whatever the clinical stage is Whatever the CD4 count/percentage is	Start ARV treatment
18 to 35 months	Clinical stage 3 or 4 Or stage 1, 2 with CD4 < 25% or <1000 /mm3	Start ARV treatment
36 – 59 months	Clinical stage 3 or 4 Or clinical stage 1, 2 with CD4 < 20% or <750 /mm3	Start ARV treatment
60 months	Clinical stage 3 or 4 Or stage 1, 2 with CD4 < 350/ mm3	Start ARV treatment

✓ **Recommended first line ARV regimen:**

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

First line regimen	Second line regimen after failure
ABC + 3TC + NVP	AZT + 3TC + Kaletra
ABC + 3TC+ EFV	AZT + 3TC + Kaletra
Alternative first line regimens	Alternative 2nd line regimen after failure
AZT + 3TC + NVP (if ABC is not available or there is allergy)	ABC + 3TC + Kaletra or 4 ARVs (AZT+ ABC + 3TC + Kaletra)
AZT + 3TC + EFV (if ABC is not available or there is allergy)	ABC + 3TC + Kaletra

2. 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 2nd line regimen after failure
AZT + 3TC + Kaletra	ABC + 3TC + Kaletra or 4 ARVs (AZT+ 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)

If the child also has TB :

- If 8-10 kg: AZT or ABC + 3TC + NVP × 2% or + EFV 300 mg per day, taken as a single daily dose. The dose of NVP should be doubled if there is concomitant administration of Rifampin. The patient's liver function tests should be monitored closely: GPT at 1, 3, and 6 months for children.
- If > 8-10 kg: AZT or ABC + 3TC+ EFV. It should be remembered that the plasma concentration of EFV is reduced by 20% due to the enzymatic stimulation of the cytochrome P450 by rifampin.

It is preferable to wait until the end of the intensive phase of anti-TB treatment before initiating ARVs. If ARV treatment is urgent (stage 4 or CD4 <15%), ARV treatment should be initiated 15 days after initiating anti-TB treatment (if the latter is well tolerated). If a child who is on or in need of Kaletra is on anti-TB treatment (case of a child exposed to NVP during PMTCT or on second line treatment), refer the child to a reference treatment center or seek expert opinion by telephone.

✓ **ARV treatment in a child undergoing treatment for tuberculosis:**

It is preferable to wait until the end of the intensive phase of anti-TB treatment before initiating ARVs. If ARV treatment is urgent (stage 4 or CD4 <15%), ARV treatment should be initiated 15 days after initiating anti-TB treatment (if the latter is well tolerated)

If the child is already on ARV treatment, continue with ARV and start anti-TB treatment.

If < 10 kg or < 3 years:

1. Child < 1 year and not exposed to NVP in PMTCT and not on treatment with Lopinavir /ritonavir (Kaletra) : ABC or AZT + 3TC + NVP×2 or EFV (300mg single dose per day (capsules or 1/2 tablet) ; currently used by pediatricians for any child aged below 3 years. The dose of NVP should be double because of the concomitant administration of Rifampin. Monitor the patient's liver functions closely (ALAT at 2 weeks, 1, 3 and 6 month). These children should be followed up in a reference center.

2. Child < 1 year and on treatment with Lopinavir /ritonavir (Kaletra): Refer the child to a reference center.

If > 10 kg or > 3 years:

- ABC or AZT or D4T + 3TC + EFV. The dose of EFV is increased by a third due to the concomitant administration of Rifampin (eg: if the normal dose is 300mg => give 400mg).
- If the child is on Lopinavir ritonavir Lpv/r: refer child to a reference center.
- Use TDF if it is an adolescent > 15 years with weight > 37.5kg (adult dose).

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.

- TB patients infected with HIV receive a comprehensive care package that includes :
  - The correct clinical care and treatment;
  - Directly observed anti-TB treatment;
  - The necessary palliative care;
  - Counseling and psychosocial support.

This comprehensive care is organized by level and should actively involve the community and the families.

✓ **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.

	Wk. -2	Wk. 0	Wk. 2	Wk. 4	Wk. 8	Wk 12	>12 wks.
Growth and monitoring and development		X		X	X	X	Every visit
Physical examination		X	X	X	X	X	Every visit
Clinical staging (verify any regression of clinical signs) I		X			X	X	Every visit
Cotrimoxazole prophylaxis	Continue regardless of age or CD4 level						
Prescription of ARV		X	X	X	X	X	Every visit (Ensure the correct doses)
Disclosure of diagnosis	To be discussed on every visit depending on the level of development and maturity of the child. A						
Adherence counseling		X	X	X	X	X	Every visit
Full hemogram				X if on AZT			Every 6 months
ALAT							If indicated
CD4 % and/or count							Every 6 months
TB screening			X	X	X	X	Every visits
Pregnancy test	If clinically indicated (Sexually active adolescent)						

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.

✓ **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.

- Psychomotor development of the new born 0- 24 months :

Age	Gross Motor functions	Fine motor functions	Language	Eye movement, cognitive l behavior
1 month	Raises head when lying on abdomen	Grasps a finger	• Makes gurgling noises • Calms down by familiar voice	Stares at examiner and follow him momentarily with the eyes
3 to 4 months	Holds head steady when seated • When lying on his abdomen, can rise up on his arms with extended legs (4 months).	Begins to grasp objects	Laughs loudly Vocalizes in a sustained manner	• Smiles to the examiner. • Holds out the palm and hand towards a person or object. • Turns head when called
6 to 7 months	• Sits briefs without support • Turns self from lying on back to supine position. • Sits unassisted (8 to 9 month). • Begins to stand with support (9 to 10 month).	• Passes an object from hand to the other l • Puts feet in the mouth	Vocalizes several syllables • Rolls over. • Repeats : mama	Distinguishes familiar faces and is worried by strangers.
1 year	• Stands without support Walks when held by hand. • Walks unsupported (12 to 15 months).	• Release objects. • Gives out an objects when told to	• Says 3 words including at least one other than Papa Mama. • Imitates bye bye (10 months). • Understands simple orders.	• Helps when being dressed up. • Repeats funny dibes.
2 years	• Runs without falling, climbs and descends stairs without support • Kicks a ball on order	• Turns pages of a book. • Scribbles	• Understands well, makes phrases of 2 to 3 words, expresses himself by « I » • Calls self by name	• Helps to organise things.. • Plays with other children

X.8. 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	- 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	- 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	Viral load detectable after 6 months of ARV treatment in a patient with good adherence. Recommended 2nd line regimen: See table above.

- Echec thérapeutique :

X.9. Adherence in children

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

The success of good adherence depend 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.

✓ Special 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 counts in cells/ml X 100/ total Lymphocytes

Example:

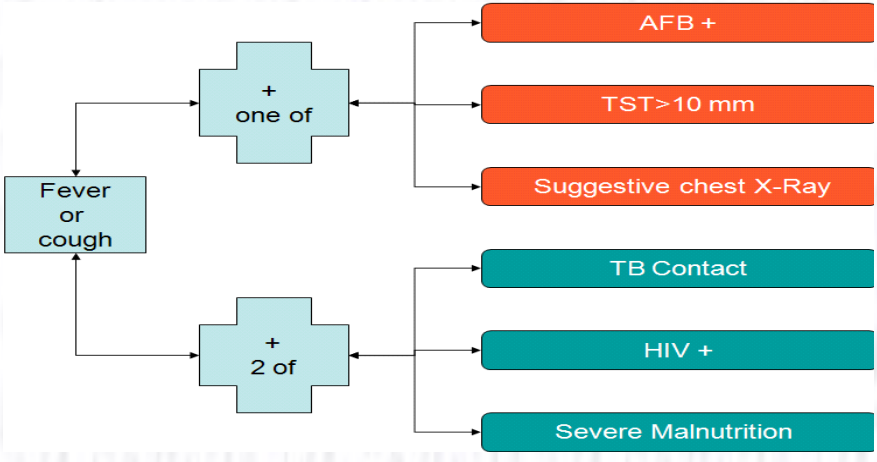
A child of 12 months with total CD4 count of 1,000, white blood cells of 12,000 and lymphocytes of 55%.

Total Lymphocytes = 12,000 X 0.55= 6,600 and CD4% = 1,000 X100/6,600 = 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).



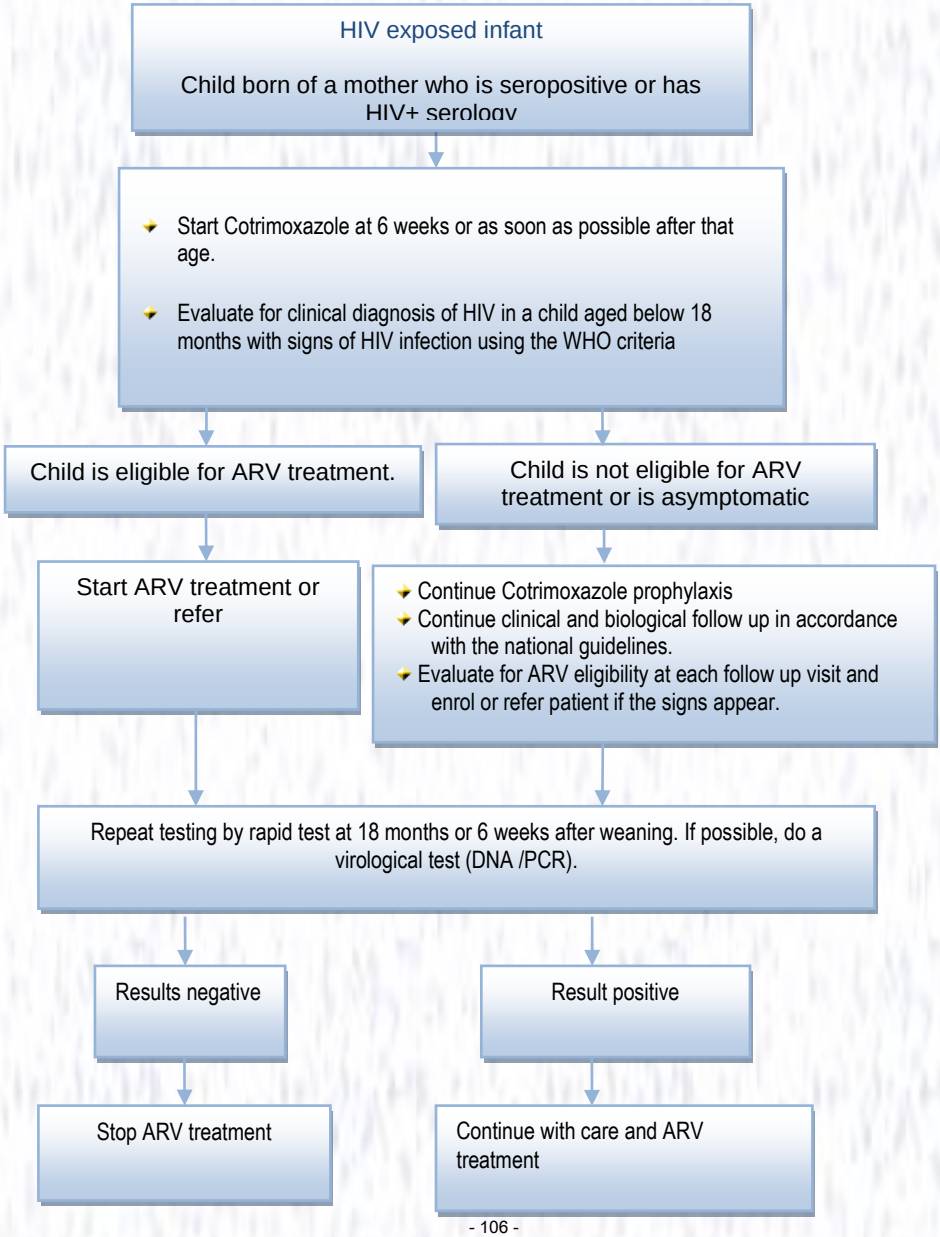
Characteristic	0	1	2	3	4	T
Duration of the disease (weeks)	<2	2 to 4		>4		
Nutrition (% weight for age)	>8 0%	60-80%	60%			
History of TB in the family	None	Reported by family		Positive sputum or clear proof		
Malnutrition				No improvement after 4 weeks		
Tuberculin test				Positive		
Unexplained fever 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

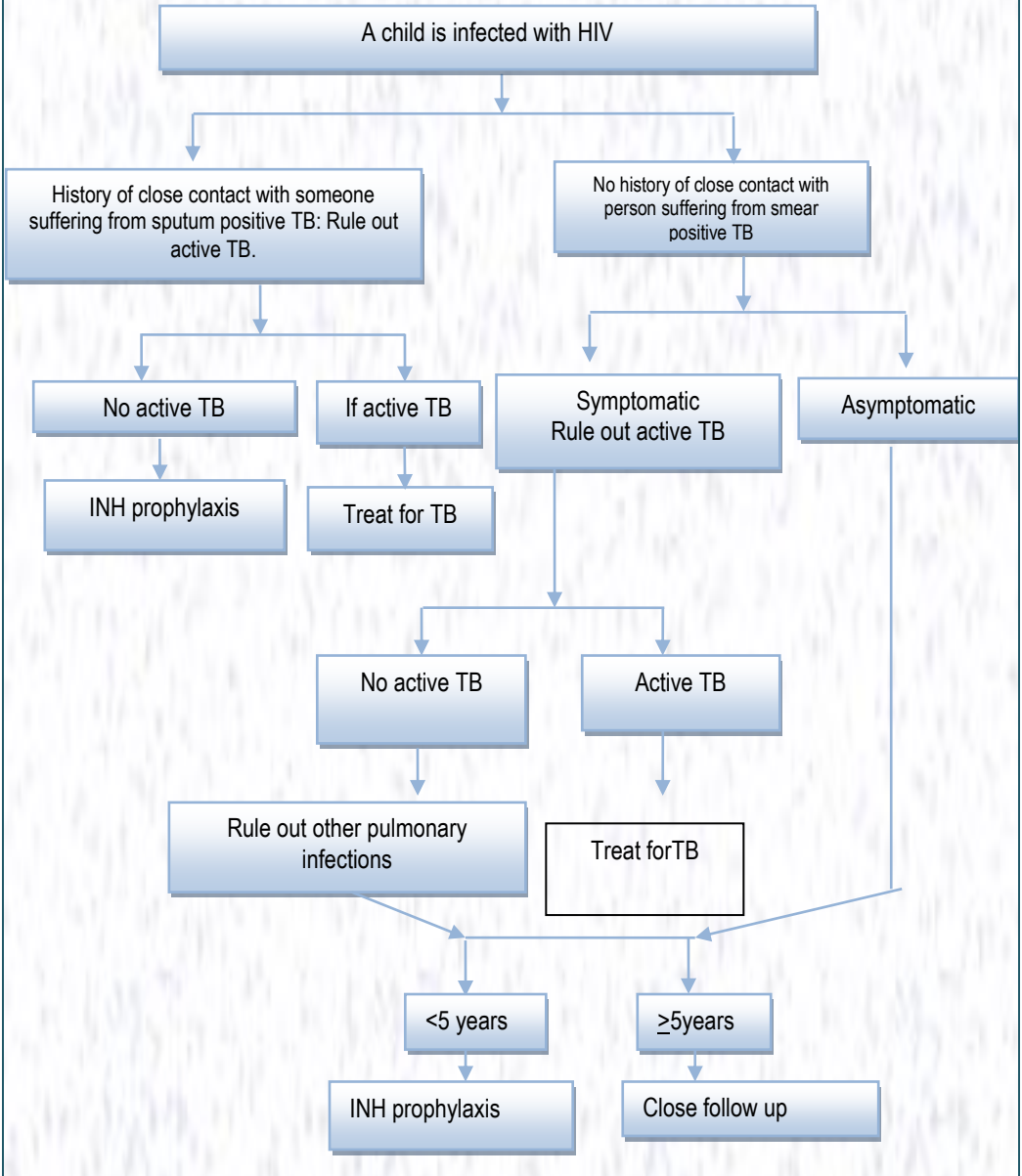
Annex 1: Calendar for the follow up of HIV exposed infants

Age in weeks/months	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: Presumptive Diagnosis of HIV infection in a child aged below 18 months when virological test is not available

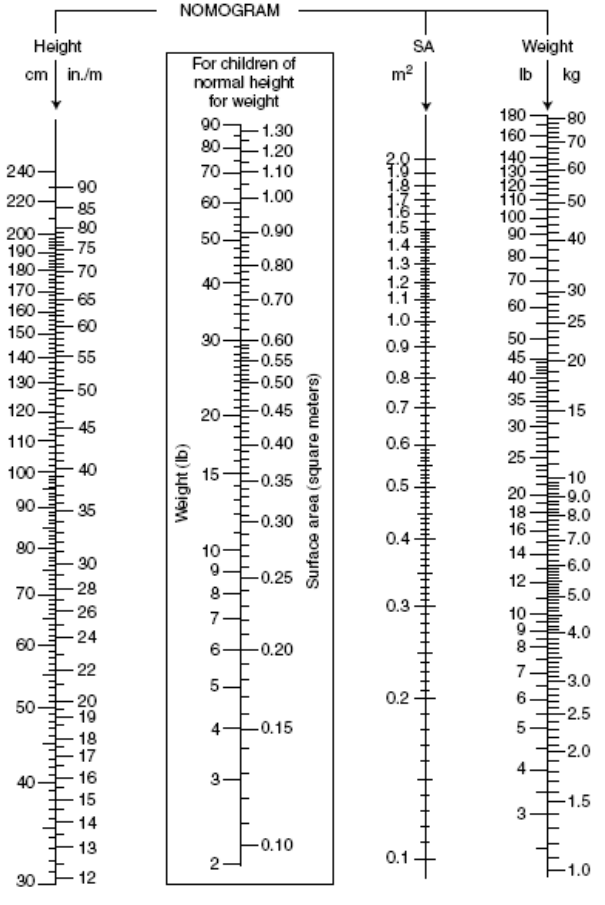


Annex 3: Algorithm for initiating INH prophylaxisis



Annex 4: Body Surface Area Normogram

West Nomogram-Body Surface Area



Note: Nomogram modified from data of E. Boyd by C.D. West; from Behrman, R.E., Kliegman, R.M., & Jenson, H.B. (eds.). (2000). Nelson textbook of pediatrics (16th ed.). Philadelphia: W.B. Saunders.

Annex 5: Calculation of body surface area (BSA)

1st method

Body surface area: $BSA = \sqrt{\frac{Hgt(cm)xWgt(kg)}{3600}}$ m²

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 = 0.53m²

2nd method:

Body surface area: $\frac{4\,W + 7}{W + 90}$ (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= 0.52m²

Annex 6: Calculation of estimated creatinine clearance using the cockcroft & gault formula

In men:
Cl Cr (ml/min) = 140 – [(Age (years) /Plasma Creatinine (µmol/l) x weight (Kg) x 1,25]
In women:
Cl Cr (ml/min) = 140 – [(Age (years) /Plasma Creatinine (µmol/l) x weight (Kg) x 1,08]

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

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

For the man:

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

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 7: 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 8: 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 9: 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/mm^3).
- 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 10: 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 11: 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 12: 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 13: 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 14: 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 15: 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 16: 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.

Table 2. Cutaneous toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Erythema, Pruritis	Disseminated maculopapular eruption or dry desquamation.	Occurrence of vesicles or wet desquamation or ulceration or association with fever or pain.	Occurrence of the following symptoms: involvement of mucous membranes, suspected Stevens Johnson syndrome, erythema multiforme, necrosis, or exfoliative dermatitis.

- Hepatotoxicity is also common, occurring mainly in the first 6 weeks but at times up to 18 weeks after the start of treatment. The risk factors for hepatotoxicity are: female gender, abnormal hepatic enzymes, co-infection with Hepatitis B and/or C and high CD4 counts (>250).
- Although usually minor, hepatotoxicity may be fatal and health care providers must be aware of the need to check the liver function of their patients at the beginning of treatment and as often as it is necessary in case of anomaly or hypochondrial pain. Table 2 describes the different stages in the severity of the hepatic toxicity while the treatment algorithm for managing the toxicity is found in annex 2. NVP must be stopped completely in case of grade 3 toxicity (Liver transaminases > 5 times the normal values; see table 3).

Table 3: Hepatatoxicity:

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

- NVP reduces the plasma concentrations of estrogen hormonal contraceptives. Alternative or complementary contraceptive methods should be used (See PART C, CHAPTER 3 page 93).

Contra-indications:

- Severe renal insufficiency (creatinine > 3 times the normal value). According to Bartlett, the dose should not be changed in case of renal insufficiency.
- Severe hepatic insufficiency (Liver function tests > 5 times the normal values).
- Known history of intolerance
- Contra-indicated in case of concurrent use of Rifampicin for the treatment of Tuberculosis.

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 the 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 17: 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 18: 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 ripampicin 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 19: 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 had 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 20: 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 21: 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 22: 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.