National Antiretroviral Treatment and Care Guidelines for Adults and Children

Ministry of Health
Edited by:

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*Moses R Kamya, M.Med,*

1st Edition - August 2003

Errors and omissions excepted.
Every effort has been made to ensure that drug dosages and treatment schedules are correct and in accordance with current medical practice. However, medical knowledge is constantly and rapidly changing, particularly in relation to HIV/AIDS. Thus, when using an unfamiliar drug, clinicians are urged to confirm that information (especially with regards to drug usage) complies with the latest standards of practice.

Hence these guidelines will need regular updating based on new knowledge, experiences and practices. We would welcome feedback and comments from the users and experts addressed to:

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<td>Lamivudine</td>
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<td>ABC</td>
<td>Abacavir</td>
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<td>ACP</td>
<td>AIDS Control Program</td>
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<td>AIDS</td>
<td>Acquired Immuno-Deficiency Syndrome</td>
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<td>APV</td>
<td>Amprenavir</td>
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<td>ART</td>
<td>Antiretroviral Therapy</td>
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<td>ARVs</td>
<td>Antiretroviral drugs</td>
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<td>Atazanavir</td>
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<td>CMV</td>
<td>Cytomegalovirus</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>d4T</td>
<td>Stavudine</td>
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<td>ddC</td>
<td>Zalcitabine</td>
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<td>ddI</td>
<td>Didanosine</td>
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<tr>
<td>DLV</td>
<td>Delavirdine</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DOT</td>
<td>Directly Observed Therapy</td>
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<tr>
<td>DRESS</td>
<td>Drug Rash, Eosonophilia, and Systemic Syndromes</td>
</tr>
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<td>EFZ</td>
<td>Efavirenz</td>
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<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
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<tr>
<td>FTC</td>
<td>Emtricitabine</td>
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<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
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<tr>
<td>HB</td>
<td>Hemoglobin</td>
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<td>HBV</td>
<td>Hepatitis B Virus</td>
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<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
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<td>HSV</td>
<td>Herpes Simplex Virus</td>
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<td>IDV</td>
<td>Indinavir</td>
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<tr>
<td>JCRC</td>
<td>Joint Clinical Research Centre</td>
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<tr>
<td>LPV/r</td>
<td>Lopinavir-ritonavir</td>
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<tr>
<td>MoH</td>
<td>Ministry of Health</td>
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<tr>
<td>MU-JHU</td>
<td>Makerere University – Johns Hopkins University</td>
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<tr>
<td>NFV</td>
<td>Nelfinavir</td>
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<tr>
<td>NNRTIs</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitors</td>
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<tr>
<td>NsRTIs</td>
<td>Nucleoside Reverse Transcriptase Inhibitors</td>
</tr>
<tr>
<td>NtRTI</td>
<td>Nucleotide Reverse Transcriptase Inhibitor</td>
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<tr>
<td>NVP</td>
<td>Nevirapine</td>
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<tr>
<td>OI</td>
<td>Opportunistic Infection</td>
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<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<td>PCR-DNA</td>
<td>Polymerase Chain Reaction-Deoxyribonucleic acid</td>
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<tr>
<td>PCP</td>
<td>Pneumocystis carinii pneumonia</td>
</tr>
<tr>
<td>PI</td>
<td>Protease Inhibitors</td>
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<tr>
<td>PLWHA</td>
<td>People living with HIV/AIDS</td>
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<td>PMTCT</td>
<td>Preventing Mother to Child Transmission</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
</tr>
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<td>RTV</td>
<td>Ritonavir {as PI pharmacoenhancer}</td>
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<tr>
<td>SQV</td>
<td>Saquinavir</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TDF</td>
<td>Tenofovir (Disoproxil Fumarate)</td>
</tr>
<tr>
<td>TEN</td>
<td>Toxic Epidermal Necrolysis</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<td>UVRI</td>
<td>Uganda Virus Research Institute</td>
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<tr>
<td>VCT</td>
<td>Voluntary Counseling and Testing</td>
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<td>VL</td>
<td>Viral Load</td>
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<tr>
<td>WBC</td>
<td>White Blood Cells</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>ZDV, AZT</td>
<td>Zidovudine</td>
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Despite the declining trends in HIV infection in Uganda, HIV/AIDS remains a major cause of death among adults and children in Uganda. The number of people living with HIV/AIDS has continued to rise. The current focus for Uganda in the fight against HIV/AIDS is to balance prevention strategies with treatment efforts for people living with HIV/AIDS. Presently, there is hope for people living with HIV/AIDS (PLWHAs) following the discovery of Antiretroviral drugs (ARVs).

Although ARVs do not cure HIV infection, evidence from clinical trials from various countries has shown that they reduce HIV/AIDS related mortality and morbidity. They reduce the incidence of opportunistic infections and other AIDS related illnesses by delaying HIV disease progression. As a result they improve the quality of life and as well increase the life expectancy of PLWHAs.

The case management of Antiretroviral Therapy (ART) is complicated and requires a high level of adherence of patients to the regimen in order for it to be effective. The virus easily becomes resistant to ARV drugs if treatment is not followed consistently. It is therefore essential to build capacity of health workers to provide ART services in a safe and effective manner.

The National ARV Treatment and Care Guidelines for Adults and children have been developed to standardize the delivery of ART and will be a practical guide to health workers providing ART to their patients. These guidelines have been developed by the Clinical Care Subcommittee of the Ministry of Health National Task Force for ART, with technical and financial assistance from the World Health Organization. It is hoped that health care providers will find these guidelines useful in their day-to-day management of people living with HIV/AIDS.

Prof. F.G. Omaswa  
DIRECTOR GENERAL HEALTH SERVICES
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1.0 Introduction

In 1982 Dr. Anthony Lwegaba, then working as a Medical Officer in Kalisizo Health Center, Rakai District, described the first cases of HIV disease in Uganda. It did not take long after that to appreciate that HIV infection was widespread in the country. It is now estimated that over one million people (of which about 100,000 are children under the age of 15) are currently infected and probably over a million have already died from HIV disease.

During the last 20 years the MOH in collaboration with WHO, UNAIDS and other local and international partners has established a comprehensive care program for HIV infected people. This program until recently has not significantly addressed the use of antiretroviral drugs (ARVs) because of their high cost even though the drugs have been found to be effective in improving the quality and quantity of life. Fortunately the cost of these drugs is coming down and there is a positive international response and desire to make them more accessible in resource-limited countries like Uganda. Indeed there is more funding coming in and targeting provision of ART from several global initiatives. Increased access to ARV drugs is now becoming a reality to the majority of our patients and the MoH faces the challenge of preparing health workers, patients and their families to be ready to use the drugs properly. As a first step to prepare for increased access to ARV drugs, the MoH developed a five-year National Strategic Framework for Expansion of HIV/AIDS Care and Support (2001/2-2006/7) in the country.

The development of the National ARV Treatment and Care Guidelines for Adults, adolescents and Children is one contribution to meet this challenge. The guidelines are meant for all health workers who take care of HIV infected patients even though they may not be immediately administering ARVs. The guidelines should help health workers to advise and refer patients appropriately.

2.0 Diagnosing HIV infection and disease

When considering initiating antiretroviral therapy (ART) using antiretroviral drugs:

- No one should be considered for ART without a confirmed diagnosis of underlying HIV infection.
• For those who do not know their serostatus but have signs and symptoms suggestive of underlying HIV infection, they should receive voluntary counseling followed by HIV testing as part of the integrated services or be referred to a voluntary counseling and testing (VCT) center.

2.1 Voluntary counseling and testing (VCT)

HIV counseling is the confidential dialogue between a person and a care provider aimed at enabling the person to cope with stress and make personal decisions related to HIV/AIDS. Counseling is an important component of voluntary confidential counseling and testing [VCT] and follow-up care for people living with HIV/AIDS [PLWHA] including those receiving antiretroviral therapy.  

The benefits of testing and counseling for the individual include:

• Improved health through education and nutritional advice
• Early access to care (including use of ARVs) and prevention of HIV-related illness
• Emotional support and better ability to cope with HIV-related anxiety
• Awareness of safer options for reproduction and infant feeding
• Motivation to initiate or maintain safer sexual behaviors.

2.1.1 VCT for ART in adults and adolescents

There are many patients who know their HIV serostatus through VCT and other testing services but have yet to consider using ART. However, when a decision is reached that they should now start ART, additional counseling is required to address the following issues:

• That ARV drugs don’t offer a cure. The HIV may be suppressed but is not eradicated from the body
• However, for the majority of people who use them, they are associated with much improved quality of life and long survival
• The ARV drugs should be taken for life and daily until there is evidence-based guidance from the ongoing research on structured treatment interruption (STI)

• The drugs, like any other medication, are associated with side effects
• Better results are obtained with better adherence to the treatment regime
• Some patients may fail to respond to treatment and may require several changes of their drugs with or without success.

These issues should be thoroughly discussed by the counselor and any health worker who is directly involved with the patient. Also they should be repeated during follow-up whenever an opportunity arises.

2.1.2 VCT for ART in children
Child counseling particularly that is related to HIV infection is a skill that is not readily available in Uganda. Yet the mortality related to HIV is highest in those aged below two years where introduction of ART becomes important. Counseling for ART in children should consider the following issues:

• Whenever possible ART should be discussed with the natural parents. The discussions should include long-term financial support for the treatment.
• Timing of the disclosure of the HIV positive serostatus to the child.
• Counseling of the child on ART in relation to HIV/AIDS.
• ART and schooling
• Role of other siblings in the family
• The role of the parent/guardian for the child’s adherence to ART

Sometimes ARV drugs are introduced to the child when the gravity of the diagnosis is not well appreciated. However, as the child grows more and more information regarding the HIV diagnosis and ART should be provided in a simple language. Where a child counselor is available, the opportunity should be exploited to achieve the same counseling objectives as with adults and adolescents.

2.1.3 VCT for ART in non-vertical transmission minors
It is not uncommon that minors below the age of consent (<18 years) who are sexually active acquire HIV infection and present for care. This is different from those minors who acquired their HIV infection through vertical transmission. The
common dilemma is when and how the parents or guardians should be informed. This is worse when the minor doesn’t want this to happen but would like to benefit from ART and is willing to have an HIV test.

In view of the complicated nature of ART and the need for family support to maintain good adherence, it is recommended that:

- Every effort should be made by the counselor to convince the minor about the need to involve the parents/guardians
- Additional counseling time should be given to the minor to allow for deep understanding of the implications of ART
- If all persuasion fails, then it should be made clear to the minor that ART will not be initiated without approval of the parents/guardians

2.2 Laboratory diagnosis and assessment of HIV infection

HIV infection is usually diagnosed by testing for antibodies against HIV-1 and HIV-2 using an enzyme-linked immunosorbent assay (ELISA) test or a simple/rapid test and confirmed using a supplementary test. Supplementary tests should be another ELISA or simple/rapid test based on a different antigen preparation or a different test principle.

Where signs and symptoms consistent with advanced HIV disease are present, a confirmatory test is not necessary where resources are limited.

2.2.1 Tests to detect the virus itself

Viral load estimations can be done in only a few limited centers and it is a very expensive laboratory test. However, the test helps to determine the degree of viral replication as well as the aggressiveness of the disease. The higher the viral load, the more aggressive the disease. The test can be used also to monitor the effectiveness of ART.

2.2.2 Measuring immune suppression

The degree of immunosuppression can be established by determining the CD4 cell count. The level then can be used to decide when to start ART. Similarly it can also
be used to monitor the effect of the treatment on the immune system.

In the absence of facilities to carry out CD4 cell count, a total lymphocyte count can be used. A total lymphocyte count of $1200/\text{mm}^3$ is approximately equivalent to a CD4 cell count of about $200/\text{mm}^3$.

2.3 **Clinical evaluation**

The diagnosis of HIV disease can be made on careful clinical evaluation along with the presenting signs and symptoms of the patient. This is a very common practice particularly where facilities for HIV serology are not readily available. However, an HIV test is required before starting ART. The WHO clinical staging system is useful in clinically deciding the seriousness and severity of the disease and when to start ARVs (see 5.0) in the absence of facilities to do CD4 cell count. Details of the staging system are given in Appendix 1.

In cases where CD4 counts cannot be assessed, in the presence of HIV-related symptoms a total lymphocyte count of $1200/\text{mm}^3$ or below may be used as an indication for initiating antiretroviral treatment. While the total lymphocyte count only approximates to a CD4 count, in combination with the WHO clinical staging system it is a useful marker of prognosis and survival.

2.4 **Diagnosing HIV infection in infants and children**

2.4.1 **Laboratory diagnosis of HIV infection in children using antibody tests**

The vast majority (about 90%) of children with HIV acquire the infection through mother-to-child transmission. However all will have HIV antibodies transferred from their infected mothers up to the age of 18 months. Antibody tests are only useful after this age when the children have lost most of their mothers’ antibodies and are depending on their own.

2.4.2 **Laboratory diagnosis of HIV infection in children using virologic tests**

HIV PCR and p24 antigen tests can be used to diagnose HIV infection during infancy. HIV infection can definitively be diagnosed in most infected infants by age three
months and virtually in all by the age of six months using PCR viral diagnostic assays.

2.4.3 Clinical evaluation in infants and children
A diagnosis of HIV disease can also be made in children based on clinical evaluation of their presenting signs and symptoms in the absence of laboratory facilities. When the mother of the child is available, her positive HIV test will strengthen the clinical diagnosis in the child. There is also a WHO clinical staging system that can be used to initiate ART and monitor the progression of HIV disease in children similar to that in adults. The details of this staging system are given in Appendix 2.

3.0 Antiretroviral therapy (ART)

3.1 Goals of ART
The goal of treatment with antiretroviral drugs is to prolong the survival of HIV infected patients, reduce their morbidity and improve their quality of life, using the following means:

- The suppression of HIV replication, as reflected in plasma HIV concentration, to as low as possible and for as long as possible
- The preservation or enhancement of the immune function (CD4 restoration), thereby preventing or delaying the clinical progression of HIV disease

The only regimens potent enough to drastically reduce viral replication, prevent the emergence of resistance and ultimately treatment failure for a significant amount of time has involved combinations of at least 3 antiretroviral drugs. Such regimens have been associated with immunologic restoration, slower HIV disease progression, durable therapeutic responses, improvements in the quality of life, and prevention of emergence of drug resistance. Highly active antiretroviral therapy (HAART) is an antiretroviral drug combination regimen of at least three drugs or more that can reasonably be expected to reduce the HIV viral load to undetectable levels (<50 copies/mL) in the treatment of patients with no prior use of ARV drugs.

Tools to achieve the goals of therapy
- Maximization of adherence to ART
• Rational sequencing of drugs so as to preserve future treatment options
• Use resistance testing when appropriate and available

3.2 Principles of ART
Antiretroviral therapy is part of comprehensive HIV care. The guiding principals of good ART include:

• Not to start ART too soon (when CD4 cell count is close to normal) or too late (when the immune system is irreversibly damaged)
• Efficacy of the chosen drug regimens
• Freedom from serious adverse effects
• Ease of administration
• Affordability and availability of drugs and drug combinations
• Ongoing support of the patient to maintain adherence

3.3 Limitations of ART
Antiretroviral drugs are not a cure for HIV. However, when properly used by both patients and health care providers they are associated with excellent quality of life. They are expensive, require an adequate infrastructure and knowledgeable health care workers. Training of health care personnel in the use of ARVs is critical to safe and effective use of these drugs. Even when all these are in place, ART has its own limitations in several ways:

• Drug interactions and drug resistance may decrease the potency of these drugs
• Patients on ART may develop adverse drug reactions
• The HIV drugs are still expensive even though their prices have significantly come down
• Patients have to take at least 95% of their pills in order to respond well (adherence is key to successful therapy)
• The medications have to be taken for life. At present eradication of HIV in the body is not possible
• Some patients may not respond (benefit) to treatment and continue to progress with their HIV disease in spite of doing everything right.

4.0 Available agents for ART
At present antiretroviral drugs come in six classes, each of which attacks a different site or stage of the HIV life cycle thereby interfering with its reproduction (see Figure 1):

- **Non-nucleoside reverse transcriptase inhibitors** (NNRTIs) stop HIV production by binding directly onto the reverse transcriptase enzyme thus preventing the conversion of RNA to DNA.
- **Nucleoside reverse transcriptase inhibitors** (NsRTIs) incorporate themselves into the DNA of the virus, thereby stopping the building process. The resulting DNA is incomplete and cannot create new virus.
- **Nucleotide Reverse Transcriptase Inhibitor** (NtRTI) act at the same stage of the viral life cycle as the NsRTIs. The NtRTI, Tenofovir, is the latest addition to the approved antiretroviral armamentarium. Operationally, it can be viewed as expanding the NsRTI options.
- **Protease inhibitors** (PIs) work at the last stage of the virus reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell. Boosted Protease inhibitors are combinations of low-dose Ritonavir (RTV) with a PI for pharmacoenhancement.
- **Entry inhibitors also called HIV fusion inhibitors** (e.g., enfuvirtide or T-20) prevent the HIV virus particle from infecting the CD4 cell.
- **Integrase inhibitors** interfere with the ability of the HIV DNA to insert itself into the host DNA and thereby copy itself.

**NB:** Entry and integrase inhibitors are currently under development.
Figure 1: The Life Cycle of Human Immunodeficiency Virus Type 1 (HIV-1) and Major Antiviral Targets.

There are currently (July 2003) 19 approved antiretroviral agents for the treatment of HIV-1 infection by Food and Drug Administration (FDA), a US Drug Regulatory Agency. These agents encompass seven nucleoside reverse transcriptase inhibitors (NsRTIs), one nucleotide reverse transcriptase inhibitor (NtRTI), three non-nucleoside reverse transcriptase inhibitors (NNRTIs) and eight protease inhibitors (PIs). See table 1.
Table 1. Available Antiretroviral Agents

<table>
<thead>
<tr>
<th>Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)</th>
<th>Nucleotide Reverse Transcriptase Inhibitor (NtRTI)</th>
<th>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</th>
<th>Fusion Inhibitors</th>
<th>Protease Inhibitors (PIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (ZDV, AZT)</td>
<td>Tenofovir (Disoproxil Fumarate {TDF})</td>
<td>Nevirapine (NVP)</td>
<td>Enfuvitrade (T-20)</td>
<td>Saquinavir (SQV)</td>
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<tr>
<td>Didanosine (ddI)</td>
<td></td>
<td>Efavirenz (EFZ)</td>
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<td>Ritonavir (RTV)</td>
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<tr>
<td>Zalcitabine (ddC)</td>
<td></td>
<td>Delavirdine (DLV)</td>
<td></td>
<td>{as pharmacoenhancer}</td>
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<tr>
<td>Stavudine (d4T)</td>
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<td>Indinavir (IDV)</td>
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<td>Lamivudine (3TC)</td>
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<td>Nelfinavir (NFV)</td>
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<td>Abacavir (ABC)</td>
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<td>Atazanavir (AZV)</td>
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<td>Tipranavir</td>
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5.0 When to start ART

5.1 Institutional requirements for starting ART

All health institutions that will administer ART should be prepared to offer quality and dedicated services. This is because ART is life long and complicated. In our setting, the Ministry of Health has provided policy guidelines on the minimal infrastructure and staffing requirement for any health facility to administer ART. However, in the process of scaling up ART across the country, even health providers in institutions that may not be offering ART should know enough about it in order to sustain an effective referral network as described in the implementation guidelines.

5.2 In adults and adolescents

Initiating ART should be based on the level of HIV immune suppression as assessed by WHO HIV stage (presence or absence of certain HIV related symptoms), or CD4 cell count. If available, the risk of progression and aggressiveness of HIV disease as indicated by the viral load in plasma may be used in addition to WHO stage and CD4 cell count in deciding when to start ART. It is recommended that ART should be started only in those who are symptomatic and have evidence of significant immune system damage. If treatment is started too early, essential resources could be wasted and the risks of unnecessary toxic effects and drug resistance are increased. Similarly
treatment started too late may not be associated with good results because the immune system may take longer to recover.

In Uganda it is recommended to initiate Antiretroviral Therapy in Adults and Adolescents with documented HIV infection and:

- WHO Stage IV disease irrespective of CD4 cell count
- Advanced WHO Stage III disease including persistent or recurrent oral thrush and invasive bacterial infections irrespective of CD4 cell count or total lymphocyte count.
- When CD4 testing is available, ART can be started for patients in WHO stage I, II or III with CD4 cell counts $\leq 200/mm^3$.

If a patient fulfils the above criteria, certain patient-specific factors should also be considered before starting ARVs. These factors include:

- Interest and motivation in taking therapy
- Presence of co-morbidities especially tuberculosis. Patients must have a screening history, physical exam and if necessary, laboratory tests, to rule out active infection. The treatment of co-existing infection takes priority over starting ART.
- Psychosocial barriers
- Financial barriers
- Potential for adherence (willingness to participate in ARV educational sessions and peer support ARV groups, and to complete a personal adherence plan with a counselor;)

Before starting ART the patient should make the final decision regarding acceptance of treatment. This should be made after discussing with the health care providers all issues about the therapy and how they relate to the patient’s own situation.

Anti retroviral therapy should not be started when patients:

- Are anemic (HB below 8g/dl). These patients should be transfused before starting ART. If transfusion is not available, use D4T instead of ZDV in the treatment regimen.
• Have symptomatic liver (e.g., severe jaundice) or kidney disease
• Are on chemotherapy for non-HIV related cancers with drugs that are likely to have an additive toxic effect with ARVs

5.2.1 Baseline clinical assessment
Before any patient is started on ART they should undergo baseline clinical assessment to include:
• A medical history
• Physical examination
• Laboratory investigations
• Counselling

The baseline medical history should include essential demographic characteristics; the past medical history including major illnesses (particularly tuberculosis), hospitalisations and surgeries; the length of time since the diagnosis of HIV infection, current medications and symptoms. In the case of women, current or planned pregnancy and the access to contraceptive services should be reviewed.

The baseline physical examination should include vital signs, weight, and detailing of any abnormalities of the skin, oropharynx, lymph nodes, lungs, heart, abdomen, extremities, nervous system, eyes (including fundi if possible), and genital tract. Baseline investigations should include those outlined in table 2 and 9.

The preparation of the patient for ART should start with baseline counselling. The issues discussed should include:
• A review of the expected benefits and potential side effects of the regimen chosen,
• A review of possible drug interactions (such as with oral contraceptives),
• The concept of partnership between patient and caregiver,
• The probable life-long commitment to treatment that is being made,
• The critical need to maintain safe sexual practices to prevent HIV transmission and re-infection.
- The importance of drug adherence to a successful outcome and the need to report any perceived side effects of the medications.

Table 2: Clinical Evaluation Checklist for Patients Starting ART

<table>
<thead>
<tr>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Level of understanding about HIV/AIDS;</td>
</tr>
<tr>
<td>Whether coping</td>
</tr>
<tr>
<td>What specific education/information/counselling support is needed</td>
</tr>
<tr>
<td><strong>2</strong> Sexual risks:</td>
</tr>
<tr>
<td>Willingness to practice safer sex</td>
</tr>
<tr>
<td>Disclosure of HIV serostatus</td>
</tr>
<tr>
<td>Use of condoms</td>
</tr>
<tr>
<td><strong>3</strong> Household socio-economic circumstances</td>
</tr>
<tr>
<td>Family health</td>
</tr>
<tr>
<td>What support is available</td>
</tr>
<tr>
<td><strong>4</strong> History of opportunistic infections &amp; other significant illnesses e.g. TB</td>
</tr>
<tr>
<td><strong>5</strong> Current weight (trend) &amp; presence of symptoms</td>
</tr>
<tr>
<td><strong>6</strong> Current clinical stage (WHO classification)</td>
</tr>
<tr>
<td><strong>7</strong> Lifestyle:</td>
</tr>
<tr>
<td>Whether employed &amp; nature of work</td>
</tr>
<tr>
<td>Nutritional status</td>
</tr>
<tr>
<td><strong>8</strong> Screen for presence of:</td>
</tr>
<tr>
<td>STI’s</td>
</tr>
<tr>
<td>Occult TB</td>
</tr>
<tr>
<td>Chronic pain</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Mental illness</td>
</tr>
<tr>
<td><strong>9</strong> Pregnancy risks:</td>
</tr>
<tr>
<td>Contraception options and choices</td>
</tr>
<tr>
<td><strong>10</strong> Functional capacity and level of disability</td>
</tr>
<tr>
<td>What assistance is available or required</td>
</tr>
<tr>
<td><strong>11</strong> History of previous ART</td>
</tr>
<tr>
<td>Adherence and tolerability issues</td>
</tr>
</tbody>
</table>

5.3 In children and infants

Although the pathogenesis of HIV and the underlying principles of ART are similar in adults and children, there are specific physiologic, clinical, practical and social issues to consider when treating HIV-infected children with ART. Experience and expertise in counseling children is growing in Uganda but is still limited. Data on the efficacy of ARVs in adults can generally be extrapolated to children, but issues of pharmacokinetics, formulations and ease of administration require special consideration. (See appendix 5) The differences in the natural history of HIV infection and the predictive value of surrogate markers between adults and children
impact on decisions about starting and switching ART. Suitable formulations for children are not available for some ARVs (particularly the protease inhibitors). Further, as young children metabolize drugs differently from adults, caution should be taken when deciding on dosages for various age groups. Since children are growing and hence weights keep changing, ARV doses need to be adjusted from time to time. When in doubt the attending clinician should consult or refer the child.

Table 3 summarizes the guidelines on when to start Antiretroviral Therapy in infants and older children. Of children who contract HIV infection from their mothers, the majorities become symptomatic in the first 2 years of life. Treatment in these children should be started as early as possible since morbidity and mortality is highest in young children. HIV disease should be thought of in a child who gets recurrent or persistent bacterial infections or oral thrush or fails to thrive despite adequate nutritional support.

| Table 3: Recommendations for Initiating Antiretroviral Therapy in Children |
|-----------------------------|---------------------------------|---------------------------------|
| Age                        | Diagnosing HIV infection       | Recommendation for ART         |
| <18 months                 | 1. Clinical assessment         | 1. WHO Pediatric Stage III (AIDS) |
|                            | 2. Positive HIV test or       | irrespective of CD4 cell percentage |
|                            | history in mother              | 2. Advanced Pediatric Stage II disease |
|                            | Optional                        | 3. WHO Pediatric Stage I disease |
|                            | 3. PCR-DNA if available        | (asymptomatic) or Stage II disease |
|                            | 4. p24 Ag if available         | with CD4 cell percentage <20% |
| >18 months                 | 1. Clinical assessment         | 1. WHO Pediatric Stage III (AIDS) |
|                            | 2. Positive HIV test           | irrespective of CD4 cell percentage |
|                            |                                 | 2. Advanced Pediatric Stage II disease |
|                            |                                 | with no CD4 count |
|                            |                                 | 3. WHO Pediatric Stage I disease |
|                            |                                 | (asymptomatic) or Stage II disease |
|                            |                                 | with CD4 cell percentage <15% |

NB: For children started on ART at <18 months on the basis of 1 & 2 they should have an HIV test when they attain the age of 18 months

6.0 Recommended regimens of ART

6.1 Recommended starting (first line) regimens in adults and adolescents

In initiating ART a 3drug combination should be used. This combination may contain 2 NRTIs plus 1 NNRTI or a PI. Combinations containing a PI are more powerful but more expensive. Two first line regimens have been recommended that are quite powerful and reasonably priced. (See table 4 below) This ART initiation
recommendation is for patients who have never been exposed to ARVs or those who had been on treatment but stopped all drugs at once for more than 3 months.

**Table 4: Recommended First Line Antiretroviral Regimens in Adults and Adolescents in Uganda**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pregnancy &amp; TB Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV/3TC + NVP or EFZ</td>
<td>Give NVP in pregnant women or women for whom effective contraception cannot be assured</td>
</tr>
<tr>
<td>OR</td>
<td>Give EFV for patients requiring simultaneous ARV treatment and TB therapy containing Rifampicin</td>
</tr>
<tr>
<td>d4T/3TC + NVP or EFZ</td>
<td></td>
</tr>
</tbody>
</table>

Fixed combinations containing the above drugs also are recommended, as they may be cheaper, user friendly and facilitate better adherence because of low pill burden. Such combinations include ZDV/3TC and d4T/3TC/NVP. Some of these fixed combinations are available as generics and may be cheaper than branded names. Please note that these first line regimens are recommended at national level to cover the majority of patients in Uganda. Some patients may be considered for different combinations for various reasons as may be decided by the attending doctor.

The use of one of the NNRTIs as the third drug makes the recommended first line regime:

- Less expensive
- Provides option to use a PI at a later date
- Preserves safety during pregnancy except EFZ
- Allows to treat TB co-infected patients who are on Rifampicin with Efavirenz containing regimens

Recommended dosages and other drugs for adults and adolescents are listed in Appendix 4. Relevant drug toxicities and major drug interactions for the recommended agents and other drugs are listed in Appendices 6.
6.2 Recommended second line of ART regimens in adults and adolescents

It is recommended that patients experiencing treatment failure switch from a first line to a completely different second line combination regimen. Two options for second line regimens have also been recommended. (See Table 5).

<table>
<thead>
<tr>
<th>First Line Regimens</th>
<th>Second Line Regimens for Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV/3TC + NVP or EFZ</td>
<td>D4T/ddI + LPV/r</td>
</tr>
<tr>
<td>d4T/3TC + NVP or EFZ</td>
<td>ZDV/ddI + LPV/r</td>
</tr>
</tbody>
</table>

For economic reasons and for the simplicity of administration, only LPV/r is being recommended as the PI for second line regiment for treatment failure. LPV/r combined with low dose RTV is potent and well tolerated. On the negative side, experience in pregnancy is limited, and the drug is incompatible with Rifampicin.

However, there are other protease inhibitors that are available on the market that can be used as alternatives to LPV/r. These include:

- Nelfinavir (NFV) can be used as an alternative for the PI component of second line therapy if a boosted PI is not available or clinically contraindicated. NFV doesn’t need refrigeration and is safe in pregnancy. The pill burden is 10 tablets/day (1250 mg 12-hourly), diarrhea is a common side effect and it cannot be combined with Rifampicin.

- Indinavir (IDV) when combined with low dose Ritonavir (RTV) for pharmacoenhancement it no longer needs to be taken on an empty stomach, can be taken twice a day and is incompatible with Rifampicin. The pill burden is 6-8 tablets/day (800 mg 8hourly or 12-hourly if combined with ritonavir 100 mg) and the patient needs to take plenty of fluids to avoid renal stones. Also there is a need to refrigerate RTV for longer-term stability.

- Saquinavir (SQV) combined with low dose RTV can be administered once or twice a day and is compatible with Rifampicin. Its disadvantage is the need for refrigeration of current RTV formulation for stability beyond 30 days.
6.3 Recommended first line ART regimens for infants and children

Most of the ARVs available for adults can also be used for children though not all of them have suitable formulations. Dosages are based on either body surface area or weight. The first line regimens recommended in Uganda for children are the same as for adults and adolescents. However, EFZ cannot be used in children under the age of 3 years or weighing less than 13kg due to lack of appropriate dosing information. See table 6.

<table>
<thead>
<tr>
<th>Table 6: Recommended First Line Antiretroviral Regimens for Children and Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen</strong></td>
</tr>
<tr>
<td>ZDV/3TC + NVP or EFZ OR d4T/3TC + NVP or EFZ</td>
</tr>
</tbody>
</table>

6.4 Recommended second line ART regimens for infants and children

Second line therapy for children in the event of first-line regimen failure would include a change in nucleoside backbone (e.g., from ZDV/3TC to d4T/ddI) plus a PI (NFV or LPV/r). See Table 7. Use of PIs other than LPV/r and NFV is more problematic in children due to lack of suitable pediatric drug formulations for IDV and SQV.

<table>
<thead>
<tr>
<th>Table 7: Recommended Second Line Regimens in Children and Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line Regimens</strong></td>
</tr>
<tr>
<td>ZDV/3TC + NVP or EFZ d4T/3TC + NVP or EFZ</td>
</tr>
</tbody>
</table>

6.5 Recommendations for special groups

6.5.1 Women of childbearing potential or who are pregnant

For pregnant women it is recommended that they use ZDV, 3TC and NVP as these have been widely used in pregnancy with a wealth of pharmacokinetic data available. EFZ is contraindicated due to its potential teratogenic effect on the fetus in the first trimester.
The choice of ART in women with the potential to become pregnant must include consideration of the possibility that the ARV drugs may be received during the early first trimester, prior to recognition of pregnancy and during the primary period of fetal organ development. Women who are receiving ART should have available to them effective and appropriate contraceptive methods to prevent pregnancy if they wish to do so. For those who would like to become pregnant, they should be encouraged to consult their doctors so that appropriate adjustment in the regimens is made if necessary. It is important to note that some ARVs [the NNRTIs (NVP and EFZ) and the PIs (NFV and all low dose RTV boosted PIs)] can lower blood concentrations of oral contraceptives and additional or alternative contraception needs to be used to avoid pregnancy in women receiving these drugs. There are insufficient data on drug interactions with injectable hormones (e.g., Depo-Provera®) to make recommendations regarding the need for additional contraception, but theoretically since hormone levels are much higher with injectable preparations compared to oral contraceptives, interactions with ARVs may be less significant.

For pregnant women, it may be desirable to initiate ART after the first trimester, except in those who are severely ill, where the benefit of early therapy outweighs any potential fetal risks. Additionally, the dual NsRTI combination of d4T/ddI should only be used during pregnancy when no other alternatives exist, due to the potential increased risk of lactic acidosis in pregnant women.

6.5.2 People co-infected with tuberculosis and HIV infections

It is recommended that people co-infected with TB/HIV complete their TB therapy prior to beginning ARV treatment unless they have severe HIV disease (CD4 <50/mm³, or WHO stage IV disease or the presence of disseminated TB). For these patients the risk of dying of HIV disease even when on proper and effective TB treatment is high. For those with CD4 50-200/mm³ they should start ART after the intensive TB treatment phase, which usually lasts for 2 months. In cases where a person needs TB and HIV treatment concurrently, first line treatment options include ZDV/3TC or d4T/3TC plus EFZ. For pregnant women in their first trimester, use SQV/r if available. Except for SQV/r, PIs are not recommended during TB treatment with Rifampicin due to their interactions with the latter drug. (See table 8)
Table 8: Antiretroviral Therapy for Individuals with Tuberculosis Co-Infection

<table>
<thead>
<tr>
<th>Situation</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB and CD4 count &lt;50/mm³ or extrapulmonary TB or WHO stage IV</td>
<td>Start TB therapy PLUS one of these regimens:</td>
</tr>
<tr>
<td></td>
<td>• ZDV/3TC/EFZ</td>
</tr>
<tr>
<td></td>
<td>• d4T/3TC/EFZ</td>
</tr>
<tr>
<td>Pulmonary TB and CD4 50-200/mm³ or total lymphocyte count &lt;1200/mm³</td>
<td>Start TB therapy for 2 months THEN start one of these</td>
</tr>
<tr>
<td></td>
<td>regimens:</td>
</tr>
<tr>
<td></td>
<td>• ZDV/3TC/EFZ</td>
</tr>
<tr>
<td></td>
<td>• d4T/3TC/EFZ</td>
</tr>
<tr>
<td>Pulmonary TB and CD4 &gt;200/mm³ or total lymphocyte count &gt;1200/mm³</td>
<td>Treat TB first. Monitor clinically or do CD4 counts</td>
</tr>
<tr>
<td></td>
<td>if available. Start ART when indicated.</td>
</tr>
</tbody>
</table>

7.0 Follow-up and monitoring patients on ART

Patients on ART need close monitoring to assess their adherence to the prescribed regimen, tolerance and side effects of the medications and efficacy of the treatment. Once someone starts on ART a schedule for follow-up and monitoring should be drawn up. It usually includes a first visit two weeks or earlier after initiation (which may be useful to also evaluate and reinforce adherence to ART), then monthly for 3-6 months and thereafter a minimum of every three/six months. Monthly visits, which can be combined with drug dispensing, are encouraged, as they provide useful opportunities to reinforce adherence.

7.1 Clinical guidelines for monitoring ART

Regular patient evaluation and monitoring of ART is important to assess effectiveness of this intervention and to insure safety.

7.1.1 Clinical monitoring

7.1.1.1 Clinical assessment

Clinical assessment should include thorough history on all events that may have taken place since the patient started on ART. These may include any illnesses or new infections, hospitalisations and any other medications including traditional herbs and remedies. In the case of women the health worker should enquire for any missed periods to detect early pregnancy. This is then followed with physical examination to include vital signs, weight, and detailing of any abnormalities that may be related to
drug toxicity or development of new opportunistic infections. Also at each visit the patient should have access to a counsellor to evaluate and reassert adherence issues.

7.1.1.2 Clinical monitoring for toxicities and effectiveness of antiretroviral drugs/regimens

As noted, patients should be informed about the symptoms of ARV drug toxicities and what to do when they do develop. They should be advised to seek medical care or stop therapy if they develop severe skin eruptions and/or jaundice. See Appendix 6.

Whether CD4 cell monitoring is available or not, clinical evaluation of the effectiveness of ART is important and helpful. The evaluation should be done at every opportunity when a patient meets with the health worker, be it at a health facility or in the community. The basic parameters examined should include:

- The patient’s perception of how he/she is doing on treatment;
- Changes in body weight over the course of therapy;
- Changes in the frequency and/or severity of HIV-associated symptoms (e.g., fevers, diarrhoea);
- Physical findings (e.g. oropharyngeal or vulvovaginal candidiasis);
- Signs and symptoms of immune reconstitution syndromes or HIV-related disease progression.

7.2 Laboratory guidelines for monitoring ART

7.2.1 Basic laboratory tests for monitoring toxicity and treatment response of antiretroviral therapy

Certain laboratory investigations are recommended as the absolute minimum to manage patients on ART. These should either be available on site or by transportation of specimens to a local reference laboratory (in which case results should rapidly be returned to the requesting clinician). Such tests are needed to identify potential toxic reactions e.g. anemia due to ZDV, and then to trigger changes in drug regimes according to recommended protocols; or as adjuncts to monitoring the
effectiveness of ART. Increases in total lymphocyte counts are reasonable, though imprecise reflections of immune response to ART. Tables 2 and 9 summarize the recommended investigations for ART monitoring.

Other tests may be indicated based on the suspicion of a drug toxicity or clinical disease progression. Sometimes it may even be better to refer the patient to a better-equipped facility for more advanced evaluation.
Table 9: Recommended Investigations for ART

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Level available</th>
<th>Objective</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute minimum tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV antibody test</td>
<td>All levels</td>
<td>Diagnose HIV and initiate ART</td>
<td>Once before ART</td>
</tr>
<tr>
<td>Haemoglobin or hematocrit</td>
<td>All levels</td>
<td>Monitor degree of anaemia – if severe transfuse before ART or use d4T instead of ZDV</td>
<td>Every 6-12 months &amp; when indicated</td>
</tr>
<tr>
<td><strong>Basic recommended tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WBC + differential</td>
<td>All levels</td>
<td>Monitoring neutropenic side effects</td>
<td>6 monthly</td>
</tr>
<tr>
<td>LFTs: alanine or aspartate aminotransferases</td>
<td>District hospitals</td>
<td>Monitor hepatitis co-infection and hepatotoxicity</td>
<td>6-12 monthly</td>
</tr>
<tr>
<td>Serum creatinine and/or blood urea</td>
<td>District hospitals</td>
<td>Monitor renal function</td>
<td>6 monthly</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>District hospitals</td>
<td>Monitor hyperglycaemia in patients on Protease Inhibitors Change therapy to appropriate regimen</td>
<td>When indicated</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>District hospitals</td>
<td></td>
<td>When indicated</td>
</tr>
<tr>
<td><strong>Desirable tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>District hospitals</td>
<td>Monitor hepatitis co-infection and hepatotoxicity</td>
<td>When indicated</td>
</tr>
<tr>
<td>Serum lipids</td>
<td>Referral hospitals</td>
<td>Monitoring hyperlipidaemia for those on Protease Inhibitors</td>
<td>When indicated</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>Referral hospitals</td>
<td>Monitoring immune response to therapy</td>
<td>6 monthly</td>
</tr>
<tr>
<td><strong>Optional tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load</td>
<td>Research Centres</td>
<td>Monitoring viral response to therapy</td>
<td>6-12 monthly</td>
</tr>
</tbody>
</table>
7.2.2  CD4 lymphocyte counts

CD4 lymphocyte counts are one of the most useful and reliable ways of assessing whether a patient on ART is responding to therapy. In those who respond rises of $>100$ CD4 cells/mm$^3$ are to be expected in the first 6-12 months in the ARV naïve, adherent patient with drug susceptible virus. Higher elevations can be seen and the response often continues in subsequent years in individuals with maximum virological suppression. Immunologic failure on therapy can also be assessed. In adults, a useful definition is a return to the pre-therapy baseline or a fall of $>30\%$ from the peak CD4 cell count.

The current technology for measuring CD4 counts is too costly to perform and requires flow cytometry set up which is only limited to a few research centres in Uganda. However cheaper ways of performing CD4 cell counts are being developed. Such a system, Dynabeads assay technology that uses anti-CD4 monoclonal antibody-coated magnetic beads, is already under use in Arua Regional Referral Hospital.

7.2.3  Plasma HIV-RNA levels (Viral Load)

When available, plasma HIV-1 RNA is a useful indicator of the activity of an ARV regimen in individual patients. However, due to its high cost and technical demands, such facility is only available in a few research centres in Uganda such as JCRC, UVRI and MU-JHU core laboratory at Mulago National Referral Hospital. The lack of availability of viral load monitoring implies that treatment failure will need to be assessed immunologically and clinically, rather than virologically. One of the implications of this is that diagnosing treatment failure may be delayed until clinical features do develop. As with CD4 cell count, it is hoped that inexpensive and implementable methods for viral quantitation in plasma or serum become available in Uganda soon in order to improve the effectiveness of ARV programmes and the care of individual patients.

7.3  Monitoring of ART in infants and children

Monitoring ART in children is similar to that in adults and it should include regular assessment of weight, height, developmental milestones and neurological symptoms. In children growth and development are important clinical monitoring indicators. These are assessed using growth charts. These charts provide a useful guide when
monitoring the child’s growth. Where available laboratory indices of CD4 lymphocyte counts and HIV viral load levels could also be used in assessing response to therapy. For children below the age of 6-8 years, CD4 percentages are better than absolute counts. Absolute CD4 cell counts normally fall as a child grows but the percentage remains consistent.

In the event of treatment failure or drug toxicity there may be a need to change or modify therapy. If therapy is to be changed then one should use drugs that were not used in the first regimen. Follow the guidelines as for adults. Note that in the presence of neurodevelopmental deterioration the new regimen should contain at least one drug that is known to penetrate the blood brain barrier, i.e., zidovudine, stavudine or nevirapine.

7.4 Follow-up at hospital level
As ART becomes more available, many hospitals will be starting patients on ARVs and also undertake their follow-up. The role of hospitals in follow-up should include:

- Monitoring patients response to ART
  - Symptom checklist to detect intercurrent illness, HIV disease progression or adverse events to ART. The severity and likely relationship of events to ART, should be documented by the attending doctor.
  - Weight. This should be recorded at every visit. Any unexplained loss should prompt careful re-evaluation of the patient.
  - Haematology and biochemistry investigations should be done at least once every 6-12 months and when there are symptoms suggestive of severe toxicity to ARV drugs. The results should then guide on the subsequent clinical management actions (including switching drugs for toxicity, e.g. suspected hepatitis, renal disease, pancreatitis).
  - CD4 cell count if facilities are available should be done once every 6-12 months or earlier if patient is not responding to ART
  - Changes in ART, OI prophylaxis and other concomitant medications based on clinical and laboratory assessment
  - For females of child bearing age, ask about pregnancy (missed periods)
• Provide continuous counseling to ensure adherence to ART
  ➢ Assessment of adherence by pill counts and nurse administered questionnaire
  ➢ Discuss the role/action of the treatment supporter
• Undertake more complicated investigations and where indicated refer patients to better equipped facilities
• To provide consultative backup to other ARV providing services

7.5 Follow-up at lower level facilities
Patients who are started on ART need not always be followed up at those hospitals where therapy was initiated. They could be followed up at some of the lower health facilities such as Health Centers (HC) 4, 3 and 2. Most HC-4 establishments have a medical officer while others have at least a clinical officer. The role of these health facilities in the ART follow-up should include:

• Monitoring patients response to ART
  ➢ Symptom checklist to detect intercurrent illness, HIV disease progression or adverse events to ART.
  ➢ Weight. This should be recorded and compared with previous entry. Any unexplained loss should prompt careful re-evaluation of the patient and referral to hospital if necessary.
  ➢ Haematology (Hb and FBC) investigations should be done at least once every 6-12 months and when there are symptoms suggestive of severe toxicity to ARV drugs. Abnormal results should prompt referral to the hospital.
  ➢ For females of child bearing age, ask about pregnancy (missed periods)
• Provide continuous counseling to ensure adherence to ART
  ➢ Assessment of adherence by pill counts and nurse administered questionnaire
  ➢ Discuss the role/action of the treatment supporter
• Establish and/or strengthen link with community support activities and referral networks
7.6 Follow-up in a private clinic setting
Some patients may prefer to be followed up in private clinics even when they have obtained their ART from a public setting. This is acceptable as long as:

- The private clinic has the expertise and knowledge to manage ART
- The link exists for consultations with other experienced ART providers
- The clinic follows MoH ARV guidelines and standard of care
- The clinic has been accredited by MoH

7.7 Follow-up at community level
Community based organizations are important in providing continuous support to patients on ART. This demystifies ART and ensures better adherence to treatment. However, there should be an effective referral network between these organizations and other ART services in order to deal with possible complications without much delay. Where such organizations do have outreach care services, they could also include monitoring ART. This requires the ART providers working hand in hand with organizations.

7.8 ART data collection and management
As more health units in Uganda join the ART program, there is need to collect relevant data that will guide the monitoring and evaluation process. The data should be collected by all those involved in the implementation of the scaling up of ARV use in the country. Data on the following information should be collected:

- Number of patients accessing ART from the facility including their age, sex, etc.
- Total number of patients screened for ART and those who qualify
- Number who attend follow-up clinics and how many default including common reasons for defaulting
- Descriptive information on adherence
- Nature and frequency of side and toxic effects
- Number of patients who develop treatment failures and their reasons
- Information on drug procurement and distribution system include stock turnover, cost recovery and patient purchase power
- Information on laboratory services including number and nature of tests done at health facilities and those referred to other centers, etc. Information that can be found by review of the HIV-ART patient record cards.

The data collected should be forwarded to both the district directors of health services and to the MOH headquarters at the AIDS Control Program (ACP). At the district level information should be used to identify bottlenecks in the ART program and find solutions. At ACP the data should be used to improve policies and guidelines on the program at national level.

### 8.0. When to change therapy

#### 8.1 Reasons for changing regimens

The reasons for altering an initial antiretroviral regimen include:

- Inconvenient regimens such as dosing/number of pills that may compromise adherence
- Treatment failure
- Drug adverse effects
- Occurrence of active tuberculosis and/or pregnancy
- Economic constraints for those buying their own drugs

The decision to change any regimen should be based on careful evaluation of the patient including clinical history and physical examination and relevant basic laboratory investigations. Where facilities are available, changes in CD4 cell counts when compared with the baseline may also influence the decision to change therapy. An assessment of adherence to medications should also be made and remaining treatment options considered. The possibility of an initial viral resistance, drug interaction and dietary issues will also need to be considered.

#### 8.2 In adults and adolescents

##### 8.2.1 Inconvenient regimens

Many patients are poor at taking tablets particularly for a long time. With frequent dosing the problem gets worse. Some find it difficult to take pills at places of work where they may not want to be seen doing so. All these may affect adherence to
treatment and may lead to failure. Such problems should be identified early in therapy through regular and proper adherence profile evaluations that will guide appropriate changes.

8.2.2 Changing for treatment failure

Treatment failure can be defined as clinical, immunologic and/or virologic failure. Clinical failure is defined as clinical disease progression with development of an opportunistic infection or malignancy when the drugs have been given for at least six months to induce a protective immune system restoration. This needs to be differentiated from an immune reconstitution syndrome, which can be seen within the first eight weeks after the institution of therapy, if a subclinical infection is present at the time. Although management of immune reconstitution syndromes can be difficult, changing the antiretroviral regimen in this circumstance is not indicated.

Immunologic failure can be defined as a fall in CD4 counts more than 30% on two or more occasions from the peak value or a return to, or below, the pre-therapy baseline. There is no accepted definition of immunologic failure that can be used if CD4 counts are not available. Virologic failure has no uniformly accepted definition but continued detectable viremia is indicative of incomplete viral suppression. As measuring viral load is not an option in the majority of our centers, and is not recommended for the routine monitoring of treatment in the present guidelines. The reader is referred to other existing guidelines for further reading on the use of viral load monitoring of ARV treatment.

8.2.2.1 Assessment of treatment failure

This can be:

- **Clinical**: Clinical deterioration in somebody who had shown improvement. This may be due to development of a new WHO stage 4 diagnosis or the occurrence of recurrent bacterial or fungal infection.

- **Immunologic**: Persistently declining CD4 cell counts on two or more occasions
• **Virologic:** Failure to suppress the viral load to undetectable levels within six months or repeated detection of the virus where suppression had been achieved.

Some patients may clinically continue to benefit from therapy even when the laboratory results suggest failure. Where options of what to do next are limited it is advisable to continue with therapy but under closer monitoring or refer the patient to a more advanced center.

### 8.2.2.2 Causes of treatment failure

Treatment may fail because of:

- Unsatisfactory patient adherence to treatment e.g. missing too many doses etc.
- Viral resistance to one or more drugs. The resistance may have been present at the beginning of therapy or due to cross-resistance with other ARV drugs.
- Use of less potent antiretroviral regimens.
- Impaired drug absorption.
- Altered drug pharmacology
  - Interactions with other drugs
  - Food-drug interactions
  - Interactions with other diseases e.g. tuberculosis
- Other unknown reasons

Factors that increase the risk of treatment failure:

- Prior antiretroviral treatment.
- Very sick patients with very low CD4 cell counts or high viral load at the time of initiating therapy.
- Poor clinic attendance record.
- Side effects or disease processes like intractable vomiting and diarrhea.

### 8.2.3 Changing for toxicity

In the setting of a good therapeutic response, the development of a clearly definable toxicity permits single drug substitutions without compromising the overall regimen. For example, d4T can be substituted for ZDV for ZDV-related symptoms or anemia.
and NVP can be substituted for EFZ when EFZ related central nervous system symptoms are unremitting. For other toxicities, for which a specific agent cannot be identified as causal, and/or low-grade but intolerable side effects which frequently compromise adherence, a complete regimen switch to the second line drugs is recommended. If an interruption in therapy is indicated to permit resolution of toxicity, the entire regimen should be temporarily interrupted in order to prevent the emergence of drug resistance.

8.3 In infants and older children
The principles for changing therapy in children are similar to those described for adults. For the very young children the administration of prescribed dosing/number of pills depends entirely on the parents or guardians. So it is important that they appreciate the regimen and that they will follow the related instructions diligently to ensure adherence. In children, important clinical signs of antiretroviral drug failure include:

- Lack of growth in response to treatment
- Falling off the growth curve in a child who had shown an initial growth response to therapy
- Loss of neurodevelopmental milestones
- Development of encephalopathy
- Recurrence of infections, such as recurrent oral candidiasis refractory to treatment.

In areas where CD4 cell count facilities are available, the definition of immunologic failure suggesting a need to change therapy includes a return in CD4 cell percentage to or below pre-therapy baseline. Because CD4 cell count (and to a lesser extent CD4 percentage) normally decline with age in children until they reach adult levels at about age 8 years, CD4 cell decline on therapy is difficult to use to assess failure of therapy in younger children. However, for children 8 years of age or older, a confirmed fall (on two or more occasions) of 30% or more in CD4 cell count or percentage from the peak value observed after 6 months or more of ART can be used as a potential indication of treatment failure, as in infected adults.
9.0 When to stop therapy

Once a patient starts on ART he should continue with the treatment without interruption for life. In real life treatment interruption is very common and may present in the following ways:

- Structured treatment interruption (STI)
  - Interruption is guided by immunological status assessment using CD4 cell counts and viral loads where available
- Structured intermittent treatment (SIT)
  - A regular period when a patient is on and off drugs
- Drugs holidays
  - As a result of inconveniency or something else
- Irregular taking of drugs,
  - As a result of poor adherence
- Permanent discontinuation of therapy

The reasons and goals for treatment interruption may differ greatly. When discussing rationale or risks, it should be clear why treatment is being interrupted:

- Due to the wish of the patient
- To improve adherence and patient psyche (“life sentence” removed)
- To reduce long-term toxicities
- For immunological reasons
- As a salvage strategy. To give time for the recovery of the wild type virus.

It should be realized that most treatment interruptions presumably occur without the clinician’s knowledge. For this reason alone, treatment interruptions are an important aspect of antiretroviral therapy, whether one as a clinician approves of them or not. To categorically oppose treatment interruption means to disregard the realities of treatment.

9.1 What happens to viral load and CD4+ T-lymphocyte levels during treatment interruptions?

Almost all patients who stop treatment experience a rebound in viral load within a few weeks, even those who had reached undetectable HIV levels over several years. Viral
The viral load usually rebounds above the level of detection within 10-20 days. The viral load in compartments such as those in the brain parallels changes in the plasma, and this also probably applies to semen and vaginal fluid. Patients must therefore be informed about the higher risk for transmitting HIV.

Treatment interruptions can have serious immunological consequences. CD+ cell counts often fall within a short time to pre-treatment levels. The hard-earned successes of ART therefore fade rapidly. CD+ T cell losses vary greatly between patients but may reach 200 or 300/µl within a few weeks. The higher the CD+ T cells and the faster they rise while on ART, the more the decrease. Age also seems to play a role – the older the patient, the more extensive the immunological deterioration is likely to be. The loss in CD+ T cells during interruptions may not be regained as quickly when therapy is reinstated.

9.2. The risks
These include development of resistance and clinical problems. Viral resistance has to be anticipated whenever there is viral replication in the presence of sub optimal drug levels, and when resistant mutants have a selective advantage over the wild-type virus. However, in case of single drug interruptions, the probability of development of resistance in individual patients may not be particularly high. It is the repeated treatment interruptions that bear a higher risk of resistance, especially for NNRTI- or 3TC containing regimens.

Sharp and high rises of HIV viremia following treatment interruptions may occasionally present as a retroviral syndrome. The symptoms are similar to those of acute HIV infection, with lymphadenopathy, fever and general malaise.

9.3. SIT – A strategy for the future?
There are a number of studies of structured interrupted treatment currently going on. Some of these studies have indicated that ultra-short interruptions, such as seven days on and seven days off treatment, the viral load usually continues to be very low. If this trend is found to be consistent, particularly with longer interruptions, SIT could be utilized to reduce drugs, costs and long-term toxicities.
9.4. Practical tips for treatment interruptions

- Don’t try to convince patients to interrupt therapy – a clear risk/benefit analysis is currently not possible!
- Those who have no problems with ART should not interrupt therapy
- The patient’s wish should be respected. However, information should be provided on clinical (retroviral syndrome), immunological (loss of CD4+ cells) and virological (resistance) consequences.
- Patients must be aware that the risk of infection is increased – even after long and complete viral suppression, viral load returns to initial levels after 4-6 weeks without ART.
- CD4+ cells and viral load should be monitored at least monthly during interruptions if this is affordable.
- Risk of resistance is possibly higher with NNRTIs. Choose robust regimens and stop NNRTIs one to two days earlier if possible
- Avoid interruptions in severely immunocompromised patients. ART should be continued until there is sufficient immune system recovery with CD+ cell count >350/µl.
- Resistance testing during treatment interruptions is pointless. In most patients with multidrug resistance, treatment interruption leads to a gradual shift back to the wild-type virus and loss of resistance as the mutations disappear in about two weeks.

10.0 Challenges of ART

When patients adhere and comply with ART they benefit from very good quality of life almost similar to those who are HIV negative. However, there are many challenges patients and their carers face in order to achieve this perfect status. Some of these challenges will be discussed below.

10.1 Immune reconstitution syndrome

For many opportunistic infections including TB, there can be a transient worsening of the infection 2-3 and sometimes up to 8 weeks after ART initiation; this is referred to as the immune reconstitution syndrome. The risk is high in those with advanced HIV
disease. For patients with TB, this syndrome has been reported to occur in as many as 30% of patients in the developed world. The syndrome is characterized by fevers, lymphadenopathy, worsening pulmonary lesions and expanding central nervous system (CNS) lesions. These reactions are typically self-limiting, although may require the use of a brief course of corticosteroids to reduce inflammation for CNS or severe respiratory symptoms. Initiation of ART can also unmask previously undiagnosed infections by improving the inflammatory response due to the repairing of the immune system. In general, ART should not be interrupted for immune reconstitution syndromes, however, where there is doubt, opinion of a senior HIV physician should be sought.

10.2 Patient adherence

ARV drug adherence is well recognized to be one of the key determinants of success of therapy. Conversely, poor adherence can lead to treatment failure, the evolution of drug resistance and subsequent immunologic and clinical failure. One study demonstrated a strong relationship between virologic response and adherence to therapy. The study found that 78% of the patients who took >95% of the prescribed drug doses had undetectable viral load at 6 months, whereas only 18% of patients who took <70% of the prescribed doses had undetectable viral load at the same time point.

Adherence is promoted by simplified, well-tolerated regimens involving as few pills as possible administered no more than two times per day. It is important to counsel patients carefully in advance of initiating therapy. This is typically a coordinated effort involving physicians, nurses, counselors and other health care providers including a treatment supporter if involved. ART should not be started at the first clinic visit. A period of education and preparation to try to maximize future adherence is important. Once treatment has begun, continued monitoring of adherence is essential. Pill counts are quantitatively useful in monitoring adherence but are subject to error and manipulation. In contrast, validated patient questionnaires have been shown to be one of the more reliable, easy to institute tools to monitor adherence in the outpatient setting.

Directly observed therapy (DOT) may be introduced with caregivers’ or family members’ assistance or treatment supporter. Sites with tuberculosis treatment
programs may particularly wish to consider this although the open-ended nature of ART, as opposed to the limited course of treatment for tuberculosis, raises questions about sustainability of such an approach. Using DOT for an initial ‘training’ period for patients may be more useful. However, ongoing attention to, and reinforcement of, adherence throughout the entire course of ART is an essential part of any successful treatment program.

It is recommended that each patient recruited into a treatment program should complete a personal adherence plan. The adherence plan should include the identification of a treatment supporter (or companion) that will assist the patient to adhere to his/her drugs. The treatment supporter will be charged with checking on the patient at least once a week that the daily markings of the tablets taken by the patient on the treatment record. In order for this strategy to succeed, each treatment supporter should receive sufficient orientation to ARV adherence at least once. This should be preferably before the patient starts on ART and if not feasible at least in the next three months of ART.

10.3 ART in the adolescents

With improved care and understanding of HIV disease many infected children are surviving into adolescence and adulthood. Management of these children during these transitions face similar problems encountered in other chronic diseases like diabetes. Whereas experience in this field is still limited, there is need for the health workers to be prepared to deal with these children and adolescents as ART is scaled up in Uganda. Some of the issues that need to be addressed by counselors, health workers and parents/guardians include:

- Drug dosage and regimen changes as dictated by the growing youth including the onset and duration of puberty. Puberty is a time of somatic growth and hormone-mediated changes, with females acquiring additional body fat and males additional muscle mass.
- Changing lifestyle and self image
- Peer exposure and pressure at school, in the community and within the family
- Educational needs and achievements. For example involvement of the school health system in administration and monitoring ART.
• Handling drug adverse events and its impact on adherence

All health workers dealing with ART in children need to be aware of these problems and be prepared to deal with them as they arise.

10.4 ART in children
Children, who have to start ART particularly when there are very young, face multiple challenges. The challenges are worse when one or both of their parents die before ART is initiated or when they’re already on therapy. Some of these include:

• Lack of or limited appropriate formulations of drugs for specific age groups
• Increasing expenses for drugs as the child grows. The need to adjust upwards budgets for drugs to meet requirements even though the actual prices of medications is falling
• Lack of or diminishing resources and support for the children either because of death of a parent(s) or burnout of a guardian or caring relatives and friends.
• Timing of disclosure of HIV serostatus and related counseling for the chronic medication.
• Fear and related stress from repeated painful procedures by the children and their parents or guardians
• Involvement of other people and carers (e.g. school nurses) in the dispensing of drugs when away from home for long periods or when attending school. The challenge of sustaining confidentiality.

10.5 Sustainable ARV drug supplies and delivery systems
The key to successful ART program is having a continuous supply of drugs for patients among other things. The participating health units in the ART program should ensure that they don’t run out of any item of the recommended ARV drugs. Ordering drugs should be based on the consumption rate and done in plenty of time. Procurement and delivery procedures should be agreed upon with the relevant authorities at the beginning of the program.
Health units participating in the ART program should be aware of the following possible problems:

- Drug requirements will keep increasing every month depending on the number of new patients put on ART
- The ever increasing volume of procured drugs and other ART related supplies will add strain on storage facilities, security, revenue collection system and transport requirements

11.0 ART and primary or secondary prophylaxis

Primary and secondary prophylaxis against various opportunistic infections is one way of improving the quality and quantity of life in patients with HIV disease. However, with ART the immune system can be adequately repaired such that prophylaxis can be withdrawn. Where facilities are available for CD4 cell count, patients who have maintained a count above 200/mm$^3$ for over 6 months their prophylaxis against PCP, toxoplasmosis, cryptococcal and bacterial infections (above 400/mm$^3$ for tuberculosis) can be safely withdrawn.

12.0 Post-exposure prophylaxis

In persons who have been accidentally exposed to HIV through needle-stick inoculation or through contamination of mucous membranes by secretions it has been shown in a limited number of studies that immediate administration of antiretrovirals may prevent infection from occurring. In this situation ART needs to be continued for one month. Occupational exposure to potentially infectious material may occur through an injury with a sharp object that has been used on a patient or through the contamination of mucous surfaces with patients’ blood or secretions. It is estimated that the transmission rate of HIV from an infected patient to a health worker through needle stick accidents is about 0.3% (3 in a 1000). Available data, though small, indicate that by administering zidovudine immediately after the accident and continuing the treatment for a month reduces the transmission rate to negligible levels. It has also been suggested that the transmission rate may be higher if a large inoculum is received and if there has been concomitant tissue destruction.
The following types of exposures to HIV infected materials should be considered for post-exposure prophylaxis (PEP):

- Needle-stick injury or injury with a sharp object that has been used on a patient
- Mucosal exposure of the mouth or eye by splashing fluids
- Intact skin exposed to a large volume of blood or potentially infectious secretions
- Broken skin exposed to a small volume of blood or secretions

12.1 Prevention of occupational exposure in health facilities

All health facilities in the private and public sector should adopt a policy for the prevention of occupational accidental exposure to blood borne pathogens. Health facilities should implement universal precautions for the prevention of exposure to potentially infectious material. The program should include:

- Training of all employees in handling and disposal of infectious materials
- Provision of guidelines for prevention and control of infections within their facilities
- Provision of equipment and supplies necessary for prevention and control of infections, such as, educational materials, disposable gloves, disposable syringes and needles and sharp bins
- Monitoring mechanism to ensure implementation

All personnel should be made aware of the risks involved in improper handling of such material and the steps necessary for preventing exposure should be clearly displayed in posters. Messages should promote avoiding re-capping of needles, using “sharps bins” for disposing of sharps, and exercising caution in performing any risky procedures.

Health personnel should also be conscious that though blood and secretions from patients may be infectious, simple contamination of unbroken skin does not comprise a significant risk but contamination of intact mucous surfaces of the mouth and eyes does.
12.2 Procedure to be followed in the event of injury with a sharp object

In the event of an injury with a sharp object such as a needle or scalpel that has been used on a patient or in the event of a mucous surface being contaminated with blood or secretions from a patient the following steps should be followed:

- Express blood from wound if bleeding
- Wash exposed area thoroughly with soap and water or antiseptic solutions such as polyhexdrine if available
- Rinse eye or mouth if contaminated with plenty of water
- Report the injury to a senior member or staff or the supervisor or the PEP designated officer of the unit
- Take antiretroviral drugs recommended for post-exposure prophylaxis immediately – these should be started within 1 hour if possible and at the latest within 72 hours of the exposure (persons presenting after 72 hours of the exposure should also be considered for PEP).
- Ascertain the HIV status of the patient and the injured health worker after providing appropriate counseling – the standard rapid HIV antibody tests that are currently used in the VCT program should be used and the results of the tests obtained as quickly as possible.

Depending on the results of the HIV tests the following actions should be taken:

- If the source patient is HIV negative no further PEP is necessary for the exposed health worker
- If the exposed health worker is HIV positive no further PEP is necessary, but the health worker should be referred for further counseling and management on a long-term basis
- If the health worker is HIV negative and the source patient is HIV positive then continue antiretrovirals for a period of four weeks; repeat health worker’s HIV test at 3 and 6 months after the initial test. Should the health worker seroconvert during this period then provide appropriate care and counseling and refer for expert opinion and long term management.
- If it is not possible to determine the HIV status of the source patient then assume that the source is positive and proceed according to guidelines in the previous bullet.
12.3 **Antiretroviral drugs to be used in post-exposure prophylaxis**

The exposure should be classified as “low risk” or “high risk” for HIV infection as below:

**Low risk:**
- Solid needle, superficial exposure on intact skin
- Small volume (drops of blood) on mucous membrane or non-intact skin exposures
- Source is asymptomatic or VL <1500 c/mL

**High Risk:**
- Large bore needle, deep injury, visible blood on device, needle in patient artery/vein
- Large volume (major blood splash on mucous membrane or non-intact skin exposures
- Source symptomatic, acute seroconversion, high viral load

Immediately after exposure all exposed individuals should take PEP according to the assumed risk. Those of low risk should take 2-drug combination and the high risk, a 3-drug combination. Where the risk cannot be ascertained, a 2-drug combination should be used.

The recommended 2-drug combinations are:
- AZT (300 mg twice daily) + 3TC (150 mg twice daily)
- d4T (40 mg twice daily) + 3TC (150 mg twice daily)
- d4T (40 mg twice daily) + ddI (400 mg once daily)

The recommended 3-drug combinations are:
- Any of the above 2-drug combinations + EFZ or a Protease Inhibitor
- EFZ should be avoided if pregnancy is suspected
- Preferred combination is: +EFZ (600 mg once daily), NFV (1250 mg twice daily), or LPV/RTV (400 mg/100 mg twice daily)
The chosen regimen is continued until the results of HIV tests for patient and injured health worker are known.

12.4 Post-sexual exposure prophylaxis

There is not enough evidence to recommend prophylaxis against infection following casual sexual exposure. However in the event that there has been sexual abuse or rape then it is recommended that the victim be counseled and provided with the drugs recommended for post-occupational exposure prophylaxis. It is important to try and determine the HIV status of the perpetrator. If this is not possible then it may be assumed that the perpetrator is HIV positive and the victim is provided with the treatment as listed in 12.3.

In the event of rape it is important to arrange for counseling and support to be provided to the victim. The victim needs to be provided with information regarding STIs, pregnancy and legal matters.

13.0 Preventing mother to child transmission (PMTCT)

For those mothers who are pregnant but not receiving ART, the MoH has already drawn up guidelines on the prevention of the mother from transmitting HIV to her child. The country is already implementing a PMTCT program at many sites using Nevirapine or Zidovudine as single drug intervention (Table 10).

<table>
<thead>
<tr>
<th>Table 10: Recommended Regimens for PMTCT Intervention.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
</tr>
</tbody>
</table>
| **Mother** | 200 mg stat at the beginning of labor or latest 30 minutes before delivery | • 300 mg twice daily for at least 4 weeks before delivery **then**  
• 300 mg every 3 hrs during labor **then**  
• 300 mg twice daily for 1 week after delivery |
| **Infant** (Within 72 hours of birth) | Syrup 2 mg/kg stat | Syrup 5 mg/kg twice daily for one week |

For more information please contact MoH or see PMTCT National Guidelines.
14.0 General HIV care

14.1 Comprehensive care for HIV patients

In Uganda, treatment options have increased, and ARVs are increasingly becoming available. However, the availability of ARVs is directly linked with a person’s ability to finance their treatments, and proximity to a centre in which the medications can be acquired and appropriate monitoring achieved. The cost of ARVs remains largely prohibitive as these medications are obtained through out-of-pocket financing. However, in recent years, there have been dramatic decreases in drug pricing which has resulted in an increase in the number of persons able to afford these drugs. Inadequate infrastructure, the high cost and complexity of administering ARVs and a small number of well trained personnel continue to be critical barriers in implementing increased access to ARVs in Uganda. As a result, only a small portion of the Ugandan population has access to ARVs currently.

However, all this is bound to change, as there is a concerted global and national effort to avail resources as well as the falling ARV drug prices. ART should now be added to the basic care package for comprehensive care for HIV patients including the 10-point care program for both adult and children:

- Early diagnosis of HIV and related infections
- Aggressive treatment of acute illnesses
- Aggressive treatment and prevention of opportunistic infections
- PCP prophylaxis in HIV exposed and infected children below 1 year
- Psychosocial support
- Nutrition support and multivitamin supplements particularly in children
- Growth and developmental monitoring in children
- Active immunization in children
- Active deworming
- Home based care
- Palliative care
- Antiretroviral therapy whenever available
- Referral system that ensures access to comprehensive HIV care
**APPENDIX 1**

**WHO Staging System for HIV Infection and Disease in Adults**

**Clinical Stage I:**
1. Asymptomatic  
2. Persistent generalised lymphadenopathy

**Performance Scale 1:** Asymptomatic, normal activity

**Clinical Stage II:**
1. Weight loss less than 10% body weight  
2. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular stomatitis)  
3. Herpes zoster within the last 5 years  
4. Recurrent upper respiratory tract infections, e.g., bacterial sinusitis

**And/or Performance Scale 2:** Symptomatic but normal activity

**Clinical Stage III:**
1. Weight loss more than 10% body weight  
2. Unexplained chronic diarrhoea for more than 1 month  
3. Unexplained prolonged fever, intermittent or constant, for more than 1 month  
4. Oral candidiasis  
5. Oral hairy leukoplakia  
6. Pulmonary tuberculosis within the past year  
7. Severe bacterial infections such as pneumonias, pyomyositis

**And/or Performance Scale 3:** Bedridden for less than 50% of the day during the last month

**Clinical Stage IV:**
1. HIV wasting syndrome – weight loss of more than 10%, and either unexplained chronic diarrhoea for more than 1 month, or chronic weakness or unexplained prolonged fever for more than 1 month  
2. *Pneumocystis carinii* pneumonia  
3. *Toxoplasmosis of the brain*  
4. Cryptosporidiosis with diarrhoea for more than 1 month  
5. Extrapulmonary cryptococcosis  
6. Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes  
7. Herpes simplex virus (HSV) infection, mucocutaneous for more than 1 month, or visceral of any duration  
8. Progressive multifocal leukoencephalopathy (PML)  
9. Any disseminated endemic mycosis such as histoplasmosis, coccidioidomycosis  
10. Candidiasis of the oesophagus, trachea, bronchi or lungs  
11. Atypical mycobacteriosis, disseminated  
12. Non-typhoid salmonella septicaemia  
13. Extrapulmonary tuberculosis  
14. Lymphoma  
15. Kaposi’s sarcoma  
16. HIV encephalopathy – disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing slowly over weeks or months, in the absence of concurrent illness or condition other than HIV infection that could account for the findings

**And/or Performance Scale 4:** Bedridden for more than 50% of the day during the last month
APPENDIX 2

Proposed WHO Staging System for HIV Infection and Disease in Children

### Clinical Stage I:
1. Asymptomatic
2. Persistent generalised lymphadenopathy

### Clinical Stage II:
1. Unexplained chronic diarrhea
2. Severe persistent or recurrent candidiasis outside the neonatal period
3. Weight loss or failure to thrive
4. Persistent fever
5. Recurrent severe bacterial infection

### Clinical Stage III:
1. AIDS-defining opportunistic infections, i.e., cryptococcal meningitis, histoplasmosis, toxoplasmosis, non-typhoid salmonellosis, *Pneumocystis carinii* pneumonia, cryptosporidiosis, cytomegalovirus (CMV) disease, disseminated herpes simplex virus (HSV) infection, coccidiodomycosis, candidiasis of the oesophagus, trachea, bronchi or lungs, atypical mycobacteriosis, extrapulmonary tuberculosis
2. Severe failure to thrive
3. Progressive encephalopathy
4. Malignancy
5. Recurrent septicaemia or pneumonia
APPENDIX 3

ART-associated adverse clinical events

Hepatotoxicity
- Usually an otherwise unexplained elevation of ALT that may be asymptomatic or may be associated with symptoms of hepatitis (e.g. Jaundice, anorexia, dark urine).
- May be caused by any ARV drug and may be more frequent or severe in those with chronic hepatitis such as HBV or HCV
- Worst offender is usually Nevirapine.

Hyperglycemia
- Results from peripheral and hepatic insulin resistance, insulin deficiency, and a reduced capacity of liver to extract insulin
- It occurs with all PIs in 3-17% and within the first 60 days.
- When this occurs, hyperglyceamia should be treated and continue with the drug.

Lactic acidosis
- Probably due to mitochondrial toxicity. NRTIs inhibit DNA polymerase gamma, which is responsible for mitochondrial synthesis
- Presentation include unexplained gastrointestinal symptoms (abdominal pain, nausea, vomiting, anorexia, diarrhea, distension), wasting, dyspnea, ascending weakness, and/or paresthesias
- Lab shows elevated lactate (>2-5 mmol/ml), elevated iron gap (Na – [Cl + CO₂] >16, where possible, patients on PIs should have baseline fasting lipid profiles and repeated every 6 months
- Treatment may require life support and intravenous bicarbonate

Fat maldistribution
- Lipodystrophy syndrome includes visceral or central fat accumulation (“buffalo hump”, visceral, abdominal fat collection, breast enlargement, and lipomas) and/or peripheral fat atrophy (thin extremities, facial thinning, buttock thinning)
- Treatment involve exercise programs and cosmetic surgery

Hyperlipideamia
- Changes in blood lipids including cholesterol and triglycerides usually attributed to PIs. The mechanism is unclear, but may be due to PI interference with lipid metabolism. Very high levels may lead to pancreatitis and related cardiovascular disease.
- Preferred intervention is diet and exercise but some patients may need additional medication
- Where possible, patients on PIs should have baseline fasting lipid profiles and repeated every 6 months
first 12 weeks without systemic findings. Severe reactions occur in 1% and include:

- Stevens-Johnson syndrome
- Toxic epidermal necrolysis (TEN)
- Drug rash, eosonophilia, and systemic syndromes (DRESS) with fever and multiple organ involvement

- Discontinue drug if rash is associated with fever, desquamation, mucous membrane involvement, blistering, or arthritis
## APPENDIX 4

### Antiretroviral dosage regimens for adults and adolescents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside RTIs</td>
<td>Zidovudine (ZDV)</td>
<td>300 mg twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stavudine (d4T)</td>
<td>40 mg twice daily</td>
<td>30 mg twice daily if &lt;60 kg</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (3TC)</td>
<td>150 mg twice daily</td>
<td>250 mg once daily if &lt;60 kg</td>
</tr>
<tr>
<td></td>
<td>Didanosine (ddI)</td>
<td>400 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abacavir (ABC)</td>
<td>300 mg twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emtricitabin (FTC)</td>
<td>200 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Nucleotide RTI</td>
<td>Tenofovir (TDF)</td>
<td>300 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside RTIs</td>
<td>Efavirenz (EFZ)</td>
<td>600 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nevirapine (NVP)</td>
<td>200 mg once daily</td>
<td>For 14 days, then 200 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Delavirdine (DLV)</td>
<td>400 mg three times a day</td>
<td>It has several drug interactions</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>400 mg/100 mg twice daily</td>
<td>533 mg/133 mg twice daily if combined with EFZ or NVP</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir (NFV)</td>
<td>1250 mg twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indinavir/ritonavir (IDV/r)</td>
<td>800 mg/100 mg twice daily</td>
<td>Dose adjustment when combined with an NNRTI may be required</td>
</tr>
<tr>
<td></td>
<td>Saquinavir/ritonavir (SQV/r)</td>
<td>1000 mg/100 mg twice daily</td>
<td>Dose adjustment when combined with an NNRTI may be required</td>
</tr>
<tr>
<td></td>
<td>Atazanavir (AZV)</td>
<td>400 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tipranavir</td>
<td>500 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Fusion Inhibitors</td>
<td>Enfuvirtide (T-20)</td>
<td>90 mg (1 ml) twice daily</td>
<td>Injected subcutaneously into the upper arm, thigh or abdomen</td>
</tr>
<tr>
<td>Fixed combinations</td>
<td>D4T/3TC/NVP</td>
<td>40 mg/150 mg/200 mg as 1 tablet twice daily</td>
<td>Use tablet with d4T 30 mg for &lt;60 kg if available</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/ABC</td>
<td>300 mg/150 mg as 1 tablet twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC</td>
<td>300 mg/150 mg as 1 tablet twice daily</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 5

Antiretroviral dosage regimens for Children and Infants

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside RTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (ZDV)</td>
<td>For &gt;6wks – 12yrs</td>
<td>240 mg/m² twice daily</td>
<td>Syrup; 50mg/5ml available</td>
</tr>
<tr>
<td></td>
<td>&gt;12yrs 300mg</td>
<td>twicedaily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;30kg 1mg/kg bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;30kg 30mg bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60kg 40mg bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syrup; 50mg/5ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>&lt;30kg 1mg/kg bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;30kg 30mg bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60kg 40mg bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>6 wks – 12 yrs;</td>
<td>4mg/kg twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;12yrs 150mg</td>
<td>twicedaily</td>
<td></td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>6wks – 8months</td>
<td>100mg/m² twice daily</td>
<td>90mg/m² twice daily if combined with ZDV</td>
</tr>
<tr>
<td></td>
<td>&gt;8months 120mg/m²</td>
<td>twicedaily</td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>&lt;6months – 16yrs</td>
<td>8mg/kg twicedaily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;30kg 300mg</td>
<td>twicedaily</td>
<td></td>
</tr>
<tr>
<td><strong>Non-nucleoside RTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFZ)</td>
<td>Wt Kg</td>
<td>Dose (mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13-15</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-20</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-25</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25-32</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;32 capsules, once a day at night</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>&lt;8yrs 4mg/kg once daily for 14 days then 7mg/kg twice daily</td>
<td>Oral solution</td>
<td>10mg/ml available</td>
</tr>
<tr>
<td></td>
<td>&gt;8yrs 4mg/kg once daily for 14 days then 7mg/kg twice daily</td>
<td>Oral powder</td>
<td>available</td>
</tr>
<tr>
<td></td>
<td>1-12 months 75mg/kg twice daily</td>
<td>Always round up the dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;12 months 55-65mg/kg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20kg 1250 mg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lopinavir/Ritonavir</td>
<td>&gt;2yrs: $2.9\text{ml/m}^2$ twice daily with food. Max. $5\text{ml/m}^2$ twice daily</td>
<td>5ml oral solution ≅ 3 capsules.</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Fixed combinations</strong></td>
<td><strong>D4T/3TC/NVP</strong></td>
<td>40 mg/150 mg/200 mg as 1 tablet twice daily</td>
<td>Tablet broken up as per weight of the child</td>
</tr>
</tbody>
</table>
## APPENDIX 6

### Antiretroviral Drug Toxicity

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>Primary toxicities</th>
<th>Minor toxicities</th>
<th>Monitoring/Management</th>
</tr>
</thead>
</table>
| Zidovudine (ZDV)    | Hematological (Aneamia, granulocytosis, thrombocytopenia, macrocytosis), hepatic, myopathy | Blue to black discoloration of nails, nausea and headache | For severe anemia:  
  - Reduce dose or change to d4T or transfuse  
  For myopathy:  
  - Discontinue if CPK high |
| Lamivudine (3TC)    | Painful peripheral neuropathy, pancreatitis | Skin rash, headache | Do serum amylase.  
  Discontinue if elevated.  
  Restart when resolved or change to ABC |
| Stavudine (d4T)     | Painful peripheral neuropathy, lactic acidosis, pancreatitis, hepatitis | Insomnia, anxiety, panic attacks | Severe peripheral neuropathy, abnormal serum amylase and transaminases, discontinue therapy |
| Didanosine (ddI)    | Pancreatitis, painful peripheral neuropathy | Abdominal cramps, diarrhea | Discontinue if neuropathy severe, raised serum amylase and transaminases |
| Abacavir (ABC)      | Hypersensitivity reaction, | Lactic acidosis | Discontinue therapy and don’t restart when resolved |
| Nevirapine (NVP)    | Skin rash, hepatotoxicity | | Low-dose over first 2 weeks minimizes rash occurrence. If mild or moderate continue cautiously or substitute with EFZ. If severe discontinue NVP and permanently if hepatitis confirmed |
| Efavirenz (EFZ)     | Nightmares, rash, hepatitis | Dizziness, | Rash in 10% but rarely severe <1%; CNS symptoms often resolve 2-4 weeks. Discontinue if hepatitis is confirmed.  
  Diarrhea rarely severe |
| Lopinavir/Rotinavir | Diarrhea, skin rash | Headache, weakness | Diarrhea occurs 10-30% at start of therapy but often resolves on its own |
| Nelfinavir (NFV)    | Diarrhea, lipid, glucose & liver abnormalities, | | |
| Indinavir (IDV)     | Nephrolithiasis, hepatitis, lipid, glucose abnormalities | Headache, rash, retinoid-like effects, alopecia, | Ensure adequate rehydration (1.5 L/day).  
  Monitor liver enzymes |
## APPENDIX 7

### Karnofsky (Performance) Score [KS]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>090</td>
<td>able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>080</td>
<td>Normal activity with effort; Some signs or symptoms of disease</td>
</tr>
<tr>
<td>070</td>
<td>Cares for self; unable to carry on Normal activity or to do active work</td>
</tr>
<tr>
<td>060</td>
<td>Requires occasional assistance And frequent medical care</td>
</tr>
<tr>
<td>050</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>040</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>030</td>
<td>Severely disabled; hospitalization is Indicated, though death is not imminent</td>
</tr>
<tr>
<td>020</td>
<td>Very sick; hospitalization is necessary; Active supportive treatment is necessary</td>
</tr>
<tr>
<td>010</td>
<td>Moribund; fatal processes are progressing rapidly</td>
</tr>
<tr>
<td>000</td>
<td>Dead</td>
</tr>
</tbody>
</table>