Ministry of Health

National Antiretroviral Treatment Guidelines for Adults, Adolescents, and Children

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Errors and omissions expected.

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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Acronyms and abbreviations:

3TC	-	Lamivudine
ABC	-	Abacavir
ACP	-	AIDS Control Program
AFB		Acid-Fast Bacilli
AIDS	-	Acquired Immuno-Deficiency Syndrome
ANC	-	Antenatal Clinic
APV	-	Amprenavir
ART	-	Antiretroviral Therapy
ARVs	-	Antiretroviral drugs
ATV	-	Atazanavir
CDC	-	Center for Disease Control
CMV	-	Cytomegalovirus
CNS	-	Central Nervous System
CTX	-	Cotrimoxazole (trimethoprim-sulfamethoxazole)
d4T	-	Stavudine
ddC	-	Zalcitabine
ddI	-	Didanosine
DLV	-	Delavirdine
DNA	-	Deoxyribonucleic acid
DOT	-	Directly Observed Therapy
DRESS	-	Drug Rash, Eosonophilia, and Systemic Syndromes
EFV	-	Efavirenz
ELISA	-	Enzyme-Linked Immunosorbent Assay
FDC	-	Fixed Dose Combination
FTC	-	Emtricitabine
HAART	-	Highly Active Antiretroviral Therapy
HB	-	Heamoglobin
HBV	-	Hepatitis B Virus
HCT	-	HIV Counseling and Testing
HCV	-	Hepatitis C Virus
HSV	-	Herpes Simplex Virus
IND	-	Indanavir
IMCI	-	Integrated Management of Childhood Illness
IRIS	-	Immune Reconstruction Inflammatory Syndrome
JCRC	-	Joint Clinical Research Centre
LPV/r	-	Lopinavir-ritonavir
MoH	-	Ministry of Health
MTCT	-	Mother-To-Child Transmission (of HIV)
MU-JHU	-	Makerere University – Johns Hopkins University
NFV	-	Nelfinavir
NNRTIs	-	Non-Nucleoside Reverse Transcriptase Inhibitors
NsRTIs	-	Nucleoside Reverse Transcriptase Inhibitors
NtRTI	-	Nucleotide Reverse Transcriptase Inhibitor

NVP	-	Nevirapine
OI	-	Opportunistic Infection
PCR	-	Polymerase Chain Reaction
PCR-DNA	-	Polymerase Chain Reaction-Deoxyribonucleic acid
PCP	-	Pneumocystis *carinii* pneumonia now P. *jiroveci* pneumonia
PGL	-	persistent generalized lymphadenopathy
PEPFAR	-	US President's Emergency Plan for AIDS Relief
PIs	-	Protease Inhibitors
PLWHA	-	People living with HIV/AIDS
PMTCT	-	Preventing Mother to Child Transmission
/r	-	low-dose ritonavir
RLS	-	Resource Limitted Setting
RNA	-	Ribonucleic Acid
RTC	-	Routine Testing and Counseling
RTV	-	Ritonavir {as PI pharmacoenhancer}
SQV	-	Saquinavir
STD	-	Sexually Transmitted Diseases
TB	-	Tuberculosis
TDF	-	Tenofovir (Disoproxil Fumarate)
TEN	-	Toxic Epidermal Necrolysis
UN	-	United Nations
UVRI	-	Uganda Virus Research Institute
VCT	-	Voluntary Counseling and Testing
VL	-	Viral Load
WBC	-	White Blood Cells
WHO	-	World Health Organization
ZDV	-	Zidovudine

Foreword

Over the past five years, the Ministry of Health (MOH) in collaboration with the World Health Organisation (WHO), World Bank Multi-country AIDS Program (MAP), Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the United States President's Emergency Plan for AIDS Relief (PEPFAR) and other partners have supported implementation of HIV-treatment programs in Uganda. The increasing availability of cheaper generic drug formulations has permitted expanded HIV-treatment programs in Uganda. Since the government of Uganda launched the universal access to free antiretroviral drugs in 2004, 409 public and private facilities have been accredited to provide antiretroviral therapy (ART) by the end of December 2008, and, of the 357,000 people estimated to need treatment, about 168,000 are already accessing ART countrywide. However, the burden of HIV care is enormous and continues to increase rapidly. An estimated 1.1 million individuals are infected with HIV and this number may increase significantly over the next several years if the current annual rate of 135,000 new infections is not reversed. Major challenges in the delivery of care and treatment include limited infrastructure, human resources and supplies.

The government of Uganda, through the Uganda AIDS commission, developed a National Strategic Plan (NSP) for the period 2007-2012. The objectives of care and treatment in the NSP include increasing access to ART and non-ART care; scaling up HIV counseling and testing to facilitate universal access to treatment by 2012, and integrating HIV prevention into all care and treatment services. As ART is scaled up, there is a growing need for better coordination, improved infrastructure, adherence support, quality improvement, and ARV drug resistance monitoring as more individuals take ARVs for prolonged periods. Sustainability and continuous availability of ARVs for those on treatment remain major concerns.

Uganda continues to recommend a public health approach to ART and is committed to decentralize further the expansion and integration of HIV/AIDS prevention and treatment activities with primary health care services to lower health centers where the majority of PLWHAs lives. The national ARV Treatment and Care Guidelines for adults, adolescents and children have been revised to maintain a standard delivery of ART and to provide HIV program managers and health care providers, an up-to-date practical guide on the use of ART. These guidelines have been developed by the ART Clinical Care Subcommittee of the Ministry of Health National ART Committee, with technical and financial assistance from the World Health Organization and PEPFAR. It is hoped that health care providers will find these guidelines useful in their day-to-day management of people living with HIV/AIDS and that the guidelines will contribute to the provision of quality HIV care in Uganda.

Dr. Sam Zaramba
DIRECTOR GENERAL HEALTH SERVICES

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. Now, twenty seven years later, HIV is the commonest cause of death among the young adults aged 20-45 years. Although the overall HIV prevalence has been reduced from over 18% of the early nineties to below 7%, it is estimated that over one million people (including about 100,000 children under 15 years) are currently infected and, probably a million have already died from HIV. Over the last 25 years, the MOH in collaboration with local and international partners established a care program for HIV infected people. In the past four years, the program integrated antiretroviral therapy (ART) into the comprehensive response to HIV prevention, care and support. Currently, 176,000 out of the 357,000 patients estimated to be in need of ART are already accessing it. This has been possible through initiatives such as the World Health Organization (WHO), the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and the United States President's Emergency Plan for AIDS Relief (PEPFAR).

ART delivery is feasible in a resource-limited setting (RLS) for both adults and children and its effectiveness in Uganda patients is similar to that elsewhere. However, challenges that may limit effectiveness of ART in Uganda include: 1) late initiation of treatment in advanced HIV with resultant increased early mortality 2) prevalent concurrent infections like TB, 3) ensuring uninterrupted ARV drug supply 4) loss to follow-up with treatment interruptions, 5) monitoring ART efficacy and safety, and 6) limited health infrastructure with inadequate human resources. The experience gained during the ART program rollout coupled with new scientific evidence have necessitated a revision of the guidelines. The public health approach to delivery of comprehensive HIV care remains the basis for the Uganda ART guidelines. This focuses on maximizing survival at the population level through standardized sequencing of the available ARVs, delivered to individuals by means of simplified approaches and supported by clinical and basic laboratory monitoring.

It has become necessary to revise the 2003 Edition guidelines in order to incorporate the new knowledge and experiences that have accumulated to date. The new guidelines have also taken into account the 2006 Revision of the WHO global ART recommendations. However, the basic concepts of the 2003 edition have been retained: a standardized formulary for first and second-line ART, with the use of two NRTIs and an NNRTI as the first-line approach; maintenance of the Protease Inhibitor (PI) class as the mainstay of second-line regimens; and simplified patient management with standardized laboratory monitoring to indicate when to Start, when to Substitute for toxicity, when to Switch for failure or Stop therapy (the “four Ss” of simplified clinical decision-making). Consideration has been given to the long-term toxicities of stavudine, widely used in Uganda in first-line treatment for reasons of cost and availability. Tenofovir-containing regimens have been included as alternative first line therapy because of the low toxicity profile and the once-daily administration with potential for improved adherence. The

revised guidelines provide detail on the use of ART in women, integration of HIV prevention into care services and family-based care approaches.

The revised National ARV Treatment and Care Guidelines for Adults, Adolescents and Children contribute to the National Strategic Plan (NSP) and are targeted to reach all health providers who take care of HIV infected patients either directly or indirectly through counseling and referral.

1.1 Objectives of the National ART Guidelines

- To provide a standardized and simplified guide to use of antiretroviral drugs in a comprehensive HIV/AIDS service delivery setting
- To maintain a standard delivery of ART with evidence-based, safe and rational use of antiretroviral drugs
- To serve as a training tool and reference material for health service providers, program managers, and people living with HIV.

2.0 Diagnosing HIV infection and disease

When considering initiating antiretroviral therapy (ART):

- No one, except infants under 18 months with presumptive diagnosis of HIV/AIDS and where there is no access to PCR facilities, should be considered for ART without a confirmed diagnosis of underlying HIV infection. The diagnosis of HIV must be clearly documented by the health provider. In case of infants started on ART on suspicion, they should have their HIV status confirmed as soon as they are 12-18 months when an HIV antibody test can be offered or as soon as the PCR facilities become available.
- Individuals who do not know their serostatus but have signs and symptoms suggestive of underlying HIV infection should receive HIV counseling and testing as part of the integrated services of the health facility.

2.1 HIV counseling and testing (HCT)

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 HCT and follow-up care for people living with HIV/AIDS [PLWHA] including those receiving antiretroviral therapy.

2.1.1 Approaches to HIV counseling and testing

Voluntary counseling and testing (VCT) is an approach where counseling and testing is initiated by a client or patient who wishes to know their HIV status. Unfortunately a number of HIV infected individuals frequently go through health units without proper diagnosis and linkage to care because they have not volunteered to test. As a result of this omission, the diagnosis of HIV infection and subsequently that of AIDS is made very late. In the VCT model, detailed risk assessment and risk reduction counseling are provided. This requires specialized training, skills and is resource (time, personnel and space) intensive. VCT remains a very important model of HCT. However, because of these and other limitations associated with the VCT model, health care provider-initiated approaches have been adopted for HIV testing in health units (Ref Uganda HCT policies).

2.1.2 Health care provider-initiated HIV testing approaches

Health care provider-initiated approaches include routine HIV testing and counseling (RTC), and diagnostic testing. In RTC and diagnostic HIV testing, health care providers initiate the HIV counseling and testing process as is the case for all other investigations. In RTC, HIV testing is offered to all patients or clients presenting to a health facility, irrespective of the presenting complaint. RTC is frequently referred to as the “opt out” approach because all patients are offered HIV testing but have the right to decline the test. In the diagnostic approach on the other hand, HIV testing is offered to patients on clinical suspicion of HIV infection. In both RTC and diagnostic testing brief pre- and post-test information is provided to ensure informed consent, risk reduction, partner notification and testing, and linkage to HIV/AIDS care for infected individuals. With

health care provider-initiated approaches, information and disclosure of results are done in privacy by trained health workers. This provides an opportunity for immediate linkage to care for HIV infected individuals: screening and treatment for opportunistic infections or even preparation for ART can be initiated at the time of diagnosis. It also offers spouses opportunity to test together or shortly after the other.

Whenever possible all patients especially those attending high prevalence clinics for example medical (adult and pediatric) patients, TB, STD clinics, ANC etc should be routinely offered HIV testing as part and parcel of any other care provided. This is particularly important in the case of pediatric patients since these are often the index PLWHA in the family. If this is not possible, HIV testing should at a minimum be offered to all patients with signs and symptoms of HIV infection. Once a woman with young children is noted to be HIV infected, all her children should be offered an HIV test since many slow progressors are commonly seen in pediatric HIV clinics.

Whenever possible, family members of HIV infected individuals should also be offered HIV testing so that they too can receive care and treatment if infected. Additionally, counseling and testing of family members of HIV patients improves the support for adherence to ART and other care interventions.

The benefits of testing and counseling for the HIV in individuals include:

- Improved health through education, appropriate referral to specialized HIV clinics and nutritional advice, particularly infant feeding.
- 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.
- Motivation for accessing PMTCT

2.1.3 HIV counseling for ART in adults and adolescents

There are many patients who know their HIV serostatus through HCT but have yet to consider using ART. When a decision is reached that they should start ART, additional counseling is required to address the following issues and any other that may be considered important:

- That ARV drugs do not provide a cure. The HIV virus may be suppressed but is not eradicated from the body. The individuals on ARVs may be infectious and transmit HIV and therefore HIV prevention is still a necessity (through abstinence, faithfulness or consistent condom use).
- However, for the majority of people who use ARV drugs properly, they are associated with much improved quality of life, reduced HIV transmission risk, and longer survival
- The ARV drugs should be taken daily for life as there is no evidence to date that structured treatment interruption has any benefit. However, under special circumstances e.g. life-threatening toxicity, the medical doctor may stop the patients ART and reinstated when the offending condition has improved.

- The ARV drugs, like any other medication, are associated with side effects. These may include anemia, neuropathy, liver damage, and physical bodily changes.
- The best results are obtained with complete adherence to the treatment regimen
- Some patients may fail to respond to treatment and may require several changes of their drugs with or without success.
- Older children and adolescents need to be prepared to be independent of their caregivers early for ART adherence. This therefore calls for timely disclosure of HIV status to them. Disclosure empowers them to participate more actively in their own care.

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.

2.1.4 Counseling for ART in children

Counseling for both testing and starting ART in children is very important because mortality is highest in those aged under two years. Every health worker should acquire the necessary skills to offer routine counseling and HIV testing to pediatric patients under their care. Counseling for ART in children should consider, among others, the following issues:

- Whenever possible ART should be discussed with the biological parents. The discussions should include long-term support for the treatment.
- Role of other siblings and other family members.
- The role of the parent/guardian for the child's adherence to ART
- The role of other responsible adults for example teachers and school nurses if the child is away from home.
- Children will require ART for a much longer period than the HIV infected adults.
- Over time, children will have to appreciate why they are on prolonged treatment even when they are feeling well. This may be sooner than later if they start the treatment at the age judged to be mature enough to comprehend the information given to them.
- The National guidelines on HIV counseling and testing permit a health worker to counsel and test a child 12 years and above on his/her own. Disclosure has to be planned for and introduced in a sequential manner during follow-up

2.1.5 Counseling for ART in older children:

Many times ARV drugs are introduced to the child who does not appreciate the gravity of the diagnosis. Either because they are diagnosed and put on treatment while still too young or because their HIV infection is diagnosed when the infection is advanced to AIDS and requires immediate ART. However, as the child grows older or improves on treatment he/she requires to get more information regarding the HIV diagnosis and ART. This should be provided in a simple language, based on the child's age and understanding. The counselor should follow the same objectives as with adults and adolescents. The aim should be to make the child responsible for his/her own health with regard to adherence to ART.

The following issues must be considered while counseling:

- Parents/carers should be sensitized to the need and importance of disclosing to the child the HIV problem.
- Health workers must judge readiness of the child to receive the counseling for ART.
- Timing of the disclosure of the HIV sero-status to both newly diagnosed and those graduating into adolescence. Start the process of disclosure from the age of 7 years.
- Children who have been on ART since early childhood and are becoming older need to learn more about their health and their HIV status.
- There may be older children newly diagnosed and requiring ART immediately.
- Parental emotional support to the growing child will be required till the child is deemed mature enough to master her/his own ART where this applies.
- As children grow into adolescence they may require parental (if available) or guardians help to sustain their drug adherence
- Children will require a constant reminder of the need to take their drugs. Special attention will need to be given to those who are away from the biological parents or guardians e.g. in schools, other relatives or foster homes

In a few specialized facilities, child clubs have been formed where HIV infected children meet regularly. These clubs have been given a platform for peer counseling and appropriate support to discuss and find solutions related to ART adherence.

2.1.6 Counseling for ART in non-vertical transmission minors

It is not uncommon that minors below the age of consent (12 – 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 or other risks at a very early age. The common dilemma is when and how the parents or guardians should be informed and/or involved. This is worse when the minor doesn't want this to happen but would like to benefit from ART after a positive 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 and/or other responsible adults.
- Additional counseling time should be given to the minor to allow for deep understanding of the implications of ART

2.2 Laboratory diagnosis and assessment of HIV infection in adults and adolescents

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.

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 HIV disease. The test can be used also to monitor the effectiveness of ART. Undetectable viral RNA-PCR does not exclude HIV infection. The test uses different cut off points e.g. <50 or <400 viral copies. Generally, viral load should be undetectable in the blood after 6 months of effective ART regimen.

In infants an early diagnosis of HIV infection can be made as early as 4-6 weeks of age using HIV-DNA PCR which used to detect recent infections.

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 repairing of the immune system.

2.2.3 Clinical evaluation for HIV in adults and adolescents

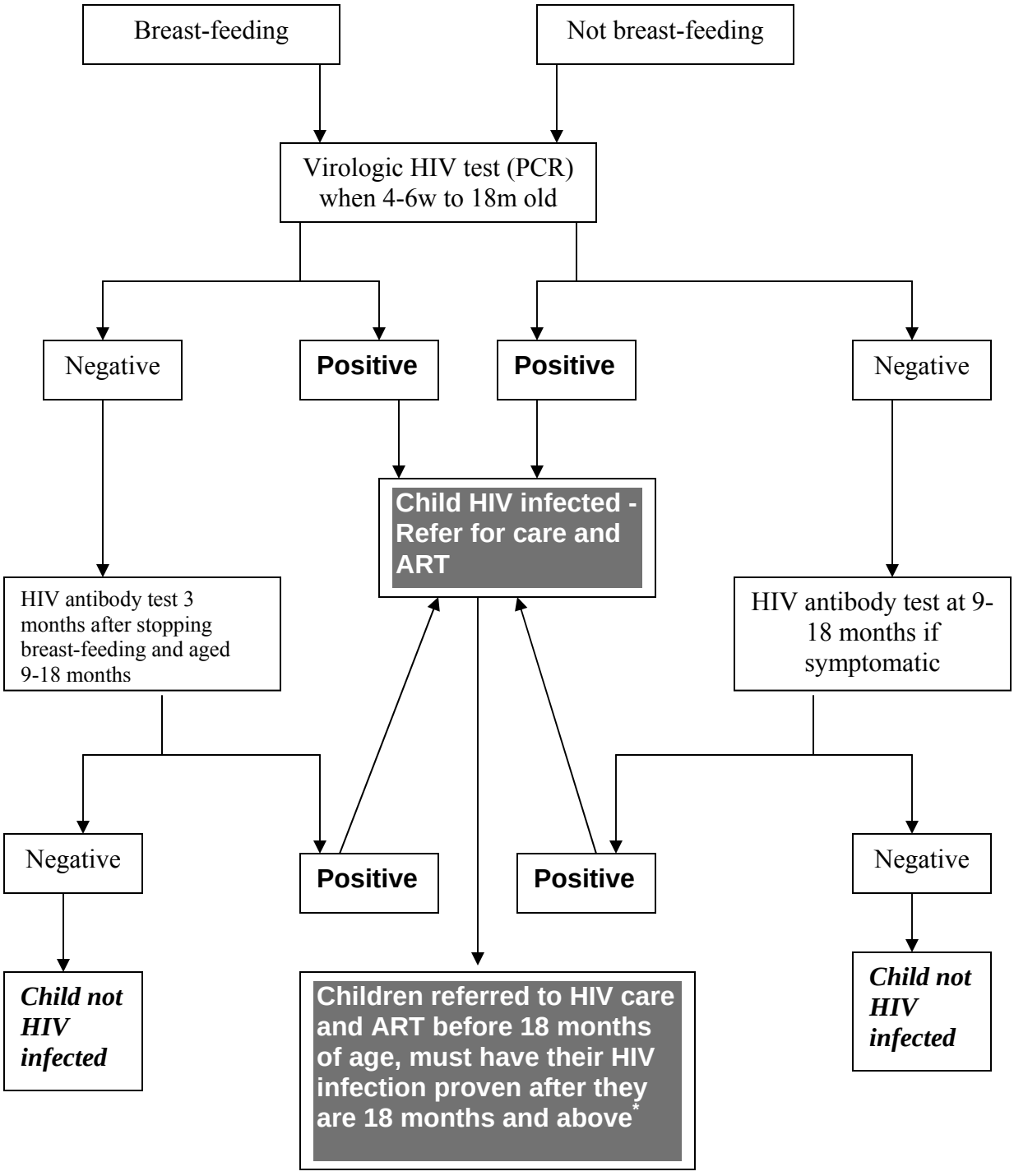
The diagnosis of HIV disease can be made on careful clinical evaluation along with the presenting signs and symptoms of the patient. This is a very common practice particularly where facilities for HIV serology are not readily available. However, an HIV test is required before starting ART. The WHO clinical staging system is useful in clinically deciding the seriousness and severity of the disease and when to start ARVs **(see 6.0)** even when CD4 cell count results are available. Details of the staging system are given in **Appendix 1 & 2.**

2.3 Diagnosing HIV infection in infants and children

2.3.1 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. As maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months in children born to HIV infected mothers, the interpretation of positive HIV antibody test results is difficult in children below this age. A negative HIV antibody test at the age 9-12 months in a non-breast feeding infant or one who ceased breastfeeding 12 or more weeks previously proves non-infection but will require to be confirmed at age 18 months. **Figure 1** gives an algorithm to follow in children aged 18 months or below. Should children continue to breast feed beyond 18 months, the risk of HIV infection still persists even when their antibody test at 18 months is negative.

Figure 1. Diagnosing HIV infection in exposed children aged less than 18 months to facilitate ART and HIV care



Infants who initiate HAART before 6 months of age may test HIV negative on a rapid test at the age of 18 months. Do not stop HAART treatment but consult a senior clinician to help you make a decision.

2.3.2 Laboratory diagnosis of HIV infection in children using virologic tests:

In order to diagnose HIV infection definitively in children aged below 18 months, assays that detect the virus or its components (i.e. virological tests) are required. HIV infection can definitively be diagnosed in most infected infants by four to six weeks of age by using PCR viral diagnostic assays. HIV DNA Virological test is used in testing children below 18 months.

The identification and follow-up of infants born to HIV-infected women are a necessary first step in infant diagnosis. The Uganda National program in charge of PMTCT and ART has put in place diagnostic protocols to ensure systematic testing of HIV-exposed infants and symptomatic children where HIV is suspected. DNA PCR test facilities are now accessible at District and Health Center 4 units with an active ART program. This makes it possible to make an early diagnosis of HIV infection in children less than 18 months. In addition, dried blood spots (DBS) on filter papers can be obtained from the infants by finger or heel-prick and transported to regional referral laboratories for PCR. Children under 18 months of age who are known or suspected to have been exposed to HIV should be closely monitored and should benefit from early interventions including ART and Cotrimoxazole (CTX) prophylaxis. See MoH policy on PMTCT and Early Infant Diagnosis of HIV (EID)

2.3.3 Clinical evaluation in infants and children

A presumptive diagnosis of HIV disease can be made in children under 18 months of age based on clinical evaluation of their HIV exposure history **(see Table 1)**, and their presenting signs and symptoms which would then prompt the clinician to refer the child for laboratory confirmation. HIV disease should be suspected in a child who gets recurrent or persistent bacterial infections or oral thrush or fails to thrive despite adequate nutritional support

Table: 1 Provider initiated diagnostic HIV testing in infants

Population category	Recommendation
HIV exposure unknown – but well infant	• Detailed mother's medical history during and before pregnancy • Get or do mother's HIV serology • Do or refer for PCR test if suspicious
HIV-exposed infant	• PCR at 4-6 weeks **or** at first contact
Any signs/symptoms suggestive of HIV (See Appendix 2)	• PCR test • If positive start ART

3.0 General HIV care

These guidelines are specifically addressing antiretroviral therapy. However, ART should always be seen as one component of general HIV care. The other components, like Home based care, PMTCT, have been described in details in the appropriate guidelines that are published by the AIDS Control Program of the Ministry of Health. Health workers are strongly advised to use them hand in hand with these ART guidelines.

3.1 Comprehensive care for HIV patients

Although ARVs are becoming increasingly available, providers should not forget that patients need comprehensive HIV care services. One way to achieve this is through the "Family Based Care" concept. Family based care involves targeting of the entire family as opposed to individuals, as the focus for HIV care and treatment services. All services including HIV testing, prevention, care and treatment for those who are infected are offered to the entire family including children that may be left out. This approach addresses the complex issues of disclosure and partner testing, condom use and uptake of reproductive health including PMTCT services. It also increases support for the HIV infected individuals, improves treatment adherence, and reduces sharing of drugs as all HIV infected individuals in the household are able to access care and treatment.

A non-ART basic HIV Preventive Care package has been defined in Uganda and should be given to all HIV infected patients irrespective of whether they are taking ART or not. In **Table 2,** we have listed some basic interventions for HIV-infected adults, adolescents and children focusing primarily on those that have been associated with the prevention of illness, mortality and HIV transmission. These can improve the health of patients and households with minimal cost and infrastructure.

- For the individual patient;
  - General basic hygiene practices such as washing your hands with soap and water before eating food or after the use of a toilet; Cotrimoxazole (trimethoprim-sulfamethoxazole, CTX) prophylaxis; isoniazid prophylaxis; Micronutrients;
  - Counseling on reduction in HIV transmission risk either sexually (through abstinence, faithfulness and condom use) or through PMTCT services.
- For the entire household or family;
  - Use of Insecticide-treated mosquito bed nets (ITNs) for malaria prevention; Safe drinking water, and HIV testing and counseling to family members

As part of comprehensive HIV care, it is now routinely recommended that those who test HIV positive with or without signs and symptoms should take daily CTX prophylaxis (160 mg trimethoprim/800 mg sulfamethoxazole for adults and equivalent dose per kg for children) irrespective of their CD4 cell count. This should also includes those patients who initiate ART with CD4+ count of <250. This treatment has been associated with reduction in mortality, and reductions in malaria, diarrhea, and hospitalization. It is also the mainstay of prevention of *Pneumocystis jiroveci* pneumonia (PCP). There is evidence of effectiveness even in areas with high bacterial resistance to CTX.

Cotrimoxazole prophylaxis might benefit even those persons with higher CD4+ counts (>250), and potentially reduce the rate of decline in CD4+ count and stabilize viral load.

3.2 Cotrimoxazole (CTX) prophylaxis for infants and children.

CTX prophylaxis is recommended for all HIV-exposed infants starting at 4–6 weeks of age (or at first encounter with the health care system) and continued until HIV infection can be excluded. **(See 2.3)** For HIV-exposed children of any age that are still breastfeeding, CTX prophylaxis should be continued until HIV infection can be excluded at least twelve weeks after complete cessation of breastfeeding. Providers should focus on CTX prophylaxis in the first six months of life, when the risk of PCP is greatest. CTX prophylaxis may be offered to children living with HIV in all clinical stages, including asymptomatic children irrespective of their CD4 level.

Table 2: Potential basic care and prevention interventions for persons with HIV/AIDS

Intervention	Impact		Comments
	Individual with HIV	Household	
Cotrimoxazole prophylaxis	• Reduction in mortality, malaria, diarrhea, clinic visits, hospitalizations • Possibly stabilizes viral load and slows CD4 cell count decline	• Reduction in diarrhea, malaria, and mortality in children	• Reduction in morbidity for wide range of CD4 cell counts • Low rate of adverse events
Safe drinking water	• Reduction in diarrhea	• Reduction in diarrhoea and mortality	• Efficacy data available among people with HIV on home-based disinfection with chlorine
Isoniazid prophylaxis	• Reduction in incidence of TB • Possible reduction in mortality	• Theoretical benefit of reduced TB transmission	• Questionnaire and through physical exam may be adequate to screen out persons with active TB • Need to treat those diagnosed with active TB
Insecticide-treated bed nets (ITN)	• Reduction in incidence of malaria	• Reductions in malaria and mortality among children	• Long-lasting insecticide-treated bed nets available that eliminate need for retreatment
Micronutrients and vitamin A	• Reduction in morbidity, mortality, and disease progression in adults and children • Possible beneficial effect on CD4 cell count and HIV viral load • Vitamin A improves growth among HIV+ children	• Micronutrient supplementation for pregnant or lactating women improves infant outcomes and may reduce rate of mother-to-child transmission of HIV	• Pregnant women may benefit more from vitamin B complex, vitamin C, and vitamin E rather than Vitamin A alone
Family HIV counseling and testing	• Psychological benefits of HIV-status disclosure • Reduction in HIV transmission	• Opportunity for HIV diagnosis in the family and early access to care and prevention efforts	• High uptake with home-based counseling and testing
Family Planning and Condoms	• Protection against STD and HIV super infection • Prevention of unwanted/unplanned pregnancies	• Protection of the partner and reduction of risk of MTCT	• Family Planning options should be presented to both men and women.

4.0 Antiretroviral therapy (ART)

4.1 Goals of ART

The goals of treatment with antiretroviral drugs are to inhibit viral replication while minimizing toxicities and side effects associated with the drugs. The inhibition of virus replication permits restoration of the immune system. Viral eradication from the host genome is not achievable, thus a cure for HIV is not yet possible. By using highly active antiretroviral therapy (HAART), it is possible to promote growth in children and prolong the survival of all HIV infected patients, reduce their morbidity and improve their quality of life. In summary the goals of ART are:

- 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
- Improvement in quality of life
- Reduction in HIV related morbidity and mortality
- Promotion of growth and neurological development in children

HAART may be defined as therapy which is potent enough to suppress HIV viraemia to undetectable levels (<50 copies/mL), as measured by the most sensitive assay available, and which is durable in its virologic effect. HAART conventionally includes three or more drugs from at least two classes. On the other hand, known sub optimal regimens, e.g. monotherpy, double nucleoside, or certain triple nucleoside combinations are not HAART and are contraindicated in HIV disease.

Tools to achieve the goals of therapy

- Maximization of adherence to ART. This may require getting a treatment buddy who will support the patient to adhere to his treatment.
- Disclosure of HIV serostatus reinforces patient adherence to ART.
- Rational sequencing of drugs so as to preserve future treatment options
- Use ARV drug resistance testing when appropriate and available
- Use of viral load estimates for monitoring if available

4.2 Principles of ART

Antiretroviral therapy is part of comprehensive HIV care. The guiding principles 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 including no food restrictions.
- Affordability and availability of drugs and drug combinations
- Ongoing support of the patient to maintain adherence

4.3 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 relatively 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;

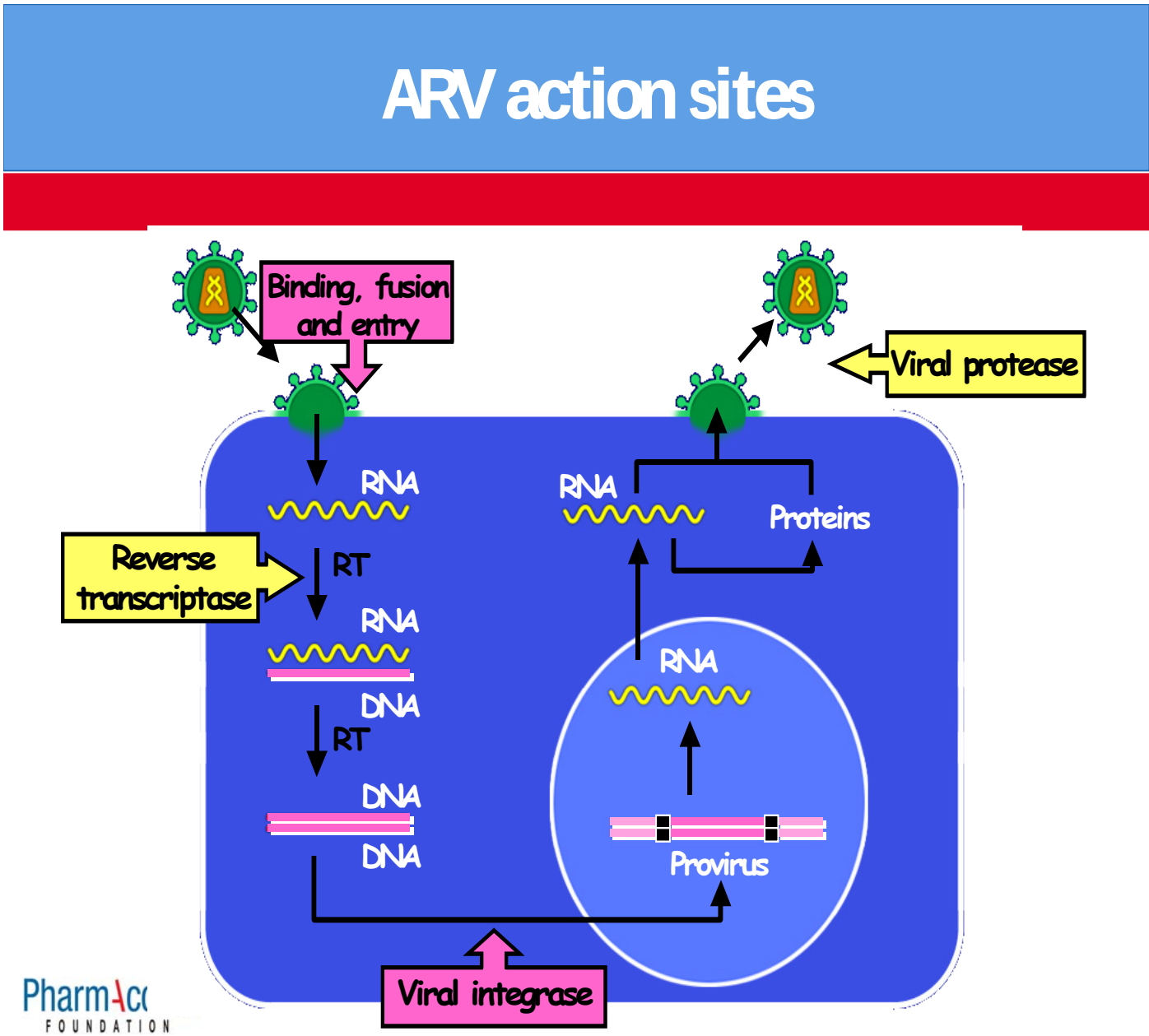
- Drug interactions and drug resistance may decrease the potency of these drugs
- Patients on ART may develop adverse drug reactions
- The HIV drugs are still relatively expensive even though their prices have significantly reduced
- Patients have to take at least 95% of their pills in order to respond 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.
- Children are dependent on adults for adherence to ART

5.0 Available agents for ART

At present antiretroviral drugs come in six classes, each of which attacks a different site (NNRTIs, NsRTIs, NtRTIs all work at the same site) or stage of the HIV life cycle thereby interfering with its reproduction **(see Figure 2):**

- Entry inhibitors also called HIV fusion inhibitors (e.g., enfuvirtide or T-20) prevent the HIV virus particle from infecting the CD4 cell.
- CCR5 antagonists (e.g., Maraviroc) block the CCR5 core receptor molecules that HIV uses to infect new target T cells. Some forms of HIV use a different core receptor and thus some patients may not benefit from maraviroc.
- 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 inhibitors (NtRTIs) e.g. Tenofovir
- 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.
- Integrase inhibitors (e.g., Raltegravir) interfere with the ability of the HIV DNA to insert itself into the host DNA and thereby copy itself.
- 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.

Figure 2: The Life Cycle of Human Immunodeficiency Virus Type 1 (HIV-1) and Major Antiviral Targets.



There are currently over 30 approved antiretroviral agents for the treatment of HIV-1 infection by Food and Drug Administration (FDA), a US Drug Regulatory Agency. All these drugs are also included on the list of WHO pre-qualified HIV medicinal products. These agents encompass all the possible target sites shown in figure 2. **See table 3.**

Table 3: Drugs Used in the Treatment of HIV Infection/ Available Antiretroviral Agents

	Generic name	Brand/Trade name (s)
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
Single Drug Medicines (SDMs)	Abacavir (ABC)	Ziagen
	Didanosine (ddI)	Videx
	Emtricitabine (FTC)	Emtriva
	Lamivudine (3TC)	Epivir, Lamivir, Lamivox, avolam, Virolam
	Stavudine (d4T)	Zerit, Stavir, Stag, Atavex, Avostav, Virostav
	Tenofovir disopropyl fumarate (TDF)	Viread
	Zalcitabine (ddC)	Hivid
	Zidovudine (AZT) (ZDV)	Retrovir, Zidovir, Zido-H, Zidovex
Fixed Dose Combinations (FDCs)	Abacavir + Lamivudine (ABC/3TC)	Epzicom
	Abacavir + Zidovudine + Lamivudine (ABC/AZT/3TC)	Trizivir
	Stavudine + Lamivudine (d4T/3TC)	Zidolam, Stavex L, Virolis,
	Tenofovir + Emtricitabine (TDF/FTC)	Truvada
	Zidovudine + Lamivudine (AZT/3TC)	Combivir, Duovir
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Single Drug Medicines	Delavirdine (DLV)	Rescriptor
	Efavirenz (EFV)	Sustiva, Stocrin, Efavir, Estiva, Viranz
	Nevirapine (NVP)	Viramune, Nevipan, Nevimune, Nevirex
	Etravirine (ETV)	Intelence (TMC 125)
Protease Inhibitors (PIs)		
Single Drug Medicines	Amprenavir (APV)	Agenerase
	Atazanavir sulfate (ATV)	Reyataz
	Darunavir (DRV)	Prezista
	Fosamprenavir calcium (FOS-APV)	Lexiva
	Indinavir (IDV)	Crixivan
	Nelfinavir mesylate (NFV)	Viracept
	Ritonavir (RTV)	Norvir
	Saquinavir mesylate (SQV)	Invirase
	Tipranavir (TPV)	Aptivus
FDC	Lopinavir/Ritonavir (LPV/r)	Kaletra, Aluvia
Fusion Inhibitors		
SDM	Enfuvirtide (T-20)	Fuzeon
Integrase inhibitors		
SDM	Raltegravir	Isentress
CCR5 antagonist		
	Maraviroc	Selzentry
Multi-class Combination Products		
Fixed Dose Combinations (FDCs)	Stavudine + Lamivudine + Nevirapine (d4T/3TC/NVP)	Triomune, Virolans, Nevilast, Stavex LN
	Zidovudine + Lamivudine + Nevirapine (AZT/3TC/NVP)	Combipack, Duovir-N
	Tenofovir DF + Emtricitabine + Efavirenz (TDF/FTC/EFV)	Atripla

6.0 When and how to start ART

6.1 Institutional requirements for starting ART

All health institutions that 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.

6.2 ART initiation 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), and CD4 cell count. A baseline CD4 cell count not only guides the decision on when to initiate ART, it is also essential if CD4 counts are to be used to monitor ART. Viral load testing is very costly at the moment so it should not be part of screening algorithms for initiating ART in Uganda unless it is available at the facility where it can be used as an optional test to provide a baseline viral load. It is recommended that ART should be started **only** in those who are symptomatic and/or have evidence of significant immune system damage.

The previous level for starting anti-HIV treatment was a CD4 cell count of ≤200. Recent research results have compared people who start anti-HIV treatment with a CD4 count above 350 and people who start ART with a CD4 cell count of 250 or below. This analysis showed that people who started treatment with a lower CD4 cell count were more likely to die, develop an AIDS-defining illness, or develop another serious illness. At the same time, there are many patients with a CD4 cell count between 250 and 350 who have remained well and symptom free for long time. We now recommend that anyone with a CD4 cell count of 250 and below should receive ART whether symptomatic or not. Those with a count of 250-350 should start on ART as provided below.

It is recommended to initiate Antiretroviral Therapy in Adults and Adolescents with documented HIV infection and;

- CD4 cell count of 250 cells/mm^3 and below
- CD4 cell count above 250 but below 350 cells/mm^3 in those:
  - Who are co-infected with tuberculosis (TB), or WHO Stage III disease
  - Women who are pregnant
- WHO Stage IV disease irrespective of CD4 cell count
- WHO stage I or II with CD4 cell counts ≤250/mm^3.

Tables 4a and 4b outline the criteria for initiating antiretroviral therapy.

Table 4a. WHO clinical staging and immunological criteria for initiating ART

Clinical Stage (see revised WHO clinical staging, Appendix 1)	CD4 cell count	Comments
I	CD4 guided	Treat if ≤250
II	CD4 guided	Treat if ≤250
III	Consider CD4	Treat if pregnant or symptomatic & ≤350
IV	Treat	Treat

Table 4b. CD4 cell count criteria for initiation of ART

CD4+ count (cells/uL)	Actions
<250	Treat irrespective of clinical stage
250-350	Consider treatment in patients who are symptomatic (WHO Stage III), have TB or are pregnant
>350	Do not initiate treatment

The decision to initiate ART requires knowledge of the patient's CD4 cell count. Fortunately in Uganda CD4 testing has becoming more readily available and accessible, particularly at all the sites that are participating in the various ART national programs, including Health Center 4s. So anyone who is put on ART **must have at least a baseline CD4 cell count.**

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 in those eligible but do not want to use the free ARV program
- Possible religious barriers (some who will be told to throw away their ART and 'be healed by faith' etc.)
- 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; willingness to disclose to family members; ability to travel to the clinic on a regular basis)

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. **Table 5** summarizes a baseline checklist for patients starting ART.

Antiretroviral therapy should not be started when patients:

- Are anemic (Hb below 8g/dl). These patients should be transfused with blood before starting ART. If transfusion is not available, use TDF instead of ZDV in the treatment regimen.
- Have symptomatic liver (e.g., severe jaundice) or kidney disease. They should be sent to a referral ART unit where additional investigations like Hepatitis B surface antigen will be done before an appropriate ART program is initiated.
- Are on chemotherapy for non-HIV related cancers with drugs that are likely to have an additive toxic effect with ARVs

6.2.1 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 and along the WHO staging scheme (including TB), 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 12.**

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, and what other options are available at the treatment site
- A review of possible drug interactions (such as with oral contraceptives)
- The concept of partnership between patient and caregiver
- The life-long commitment to treatment that is being made, the follow up schedule, what laboratory tests are necessary and why
- The critical need to maintain safe sexual practices to prevent HIV transmission and re-infection with HIV
- The importance of drug adherence to a successful outcome and the need to report any perceived side effects of the medications
- The importance of disclosure of status to spouse and other family members for adherence support

- The importance of food hygiene and nutrition
- What to do to avoid pregnancy if unwanted, and what to do if pregnancy is suspected or confirmed

Table 5: Baseline Clinical Evaluation Checklist for Patients Starting ART

Assessment	
1	History: • Level of understanding of HIV/AIDS; the length of time since the diagnosis of HIV infection; • Demographics and lifestyle: whether employed & nature of work • History of previous ART, prior use of nevirapine during pregnancy; • Pregnancy risks: Contraception options and choices, current or planned pregnancy, access to contraceptive services. • Sexual risks and disclosure: Willingness to practice safer sex, disclosure of HIV serostatus, use of condoms, HIV counseling and testing of sex partners and children. • Symptoms of chronic pain and depression • History of opportunistic infections & other significant illnesses e.g. TB & STIs, hospitalizations and surgeries; • Current medications (including anti TB drugs, traditional therapies etc.)
2	Physical Exam: • Weight • Height in infants/children • Nutritional status • Functional capacity and level of disability • Examination of vital signs, skin, eyes, oropharynx (presence of thrush), lymph nodes, lungs, heart, abdomen, genital tract (STIs), extremities, nervous system
3	Baseline Laboratory tests to assess immunosupression and disease aggressiveness • Confirming HIV serostatus • CD4 testing, • Viral load if available and affordable • Full blood count particularly for patients starting on a ZDV-containing regimen • Pregnancy test for women of child bearing potential starting on EFV-containing regimen
4	Baseline investigations to assess general health and diagnose any pre-existing HIV complications. • A sputum smear for AFB for patients who have coughed for more than 2-3 weeks and a chest X-ray for patients who have unproductive cough or whose AFB smears are negative • Urine analysis for proteinuria, etc, particularly for patients starting on TDF containing regimen • Syphilis screening • Serum chemistries (liver and renal function tests), if available ➢ If ALT is elevated, do Hepatitis B surface antigen test, if available or refer • Symptom directed lab tests to diagnose pre-existing illnesses.
5	Staging of disease using WHO clinical criteria **(See Appendixes 1 and 2)**
6	Counselling and assessment of patients' readiness to start therapy including assessment for specific education/information/counselling support needs

6.3 ART initiation 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. 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 6).** 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) but the situation is rapidly improving. 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 6 summarizes the guidelines on when to start Antiretroviral Therapy in infants and older children. Of children who contract HIV infection from their mothers, the majority become symptomatic in the first 1 to 2 years of life. Treatment in these children should be started as early as possible in order to reduce the associated high HIV morbidity and mortality.

Table 6: Recommendations for Initiating Antiretroviral Therapy in Children

Age	CD4%	CD4 Absolute	Recommendation
Infants <12 months	N/A*	N/A*	Treat if PCR positive
12 – 35 months	<20	<750	Treat
36 – 59 months	<20	<350	Treat
5 years and over	<15	<250	Treat as adult

N/A = Not Applicable. Infants less than 12 months should be started on ART irrespective of their CD4 cell count status.

7.0 Recommended regimens of ART

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

We recommend that the first-line regimen for adults and adolescents contain two NRTIs plus one NNRTI. The recommended combinations are;

Table 7: Recommended First Line Regimens Combinations

ZDV/3TC or	***Plus***	**NVP or**
TDF/3TC or		
TDF/FTC or		**EFZ.**
D4T/3TC		

Combinations containing a PI are more expensive and should be preserved for 2nd line treatment.

7.1.1 Rationale for Choice of Initial ART Regimens:

Currently the Initial Treatment Regimens that are widely used in resource limited settings (RLS) and recommended for Uganda are: non-nucleoside reverse transcriptase inhibitor (NNRTI): Efavirenz (EFV) or Nevirapine (NVP) plus a nucleoside reverse transcriptase inhibitor (NRTI) backbone: Stavudine (d4T) + Lamivudine (3TC) or Zidovudine (ZDV) + 3TC. These first line regimens prolong life, have a low pill burden, and have the lowest cost at the present time.

The current treatment regimens permit rapid scale-up. However, they are also associated with drug toxicities that may be irreversible or lethal. Patients at highest risk of these toxicities are those with advanced disease who are often given the highest priority in ART programs in RLS.

The choice of preferred regimens is based on:

- Efficacy,
- Durability,
- Tolerability (potential toxicities),
- Usage in women and taking into consideration high incidence of unplanned pregnancies (high fertility rates)
- Ease of use (availability of fixed dose combination)
- Cost of drugs
- Cost of laboratory monitoring requirements
- Frequent occurrence of co-infections (TB, hepatitis and Kaposi sarcoma)
- Prevalence of anemia among patients starting ART
- Availability of regimen and continuity of supply to meet demand
- Potential for maintenance of future treatment options (sequencing of ARVs)

7.1.2 NRTIs

Stavudine (d4T) is one of the most effective and cheap NRTI that has made it possible for a wider access to ART in resource limited settings like Uganda. Unfortunately it is associated with progressive disabling peripheral neuropathy especially among patients with advanced HIV disease and those taking concomitant anti-TB drugs. The primary pathology of stavudine related complications are due to mitochondrial toxicity with early apoptosis that may manifest as stigmatizing facial lipoatrophy, limb fat loss, enlargement of breast and abdominal fat, and lactic acidosis (rare but potentially fatal). Since stavudine (d4T) is widely used in first-line regimens, patients on this drug should be monitored closely for these complications and should be switched to ZDV or TDF in a timely fashion to minimize effects of cumulative toxicity. D4T toxicity is uncommon in children below five years, however, its toxic effects have been observed among adolescents. As a result of these problems, D4T is being phased out in Uganda particularly among adults and children aged five years and above.

Zidovudine (ZDV) is associated with anemia (3-5%), which may lead to blood transfusions and rarely to death. Among patients with anemia and advanced disease, the strategy should be to consider using TDF instead.

Tenofovir (TDF) -containing regimens may be considered for alternative first line therapy for the following reasons:

- It has a relatively low toxicity profile
- Can be used in pregnancy, and concurrently with TB medication
- Once-daily administration: Currently TDF is co-formulated with FTC. A single combination pill of EFV, TDF and FTC has been developed. This combination allows for the possibility of a 1-pill/day regimen, with the obvious potential for improved adherence.
- If TDF is used in the first-line regimen this approach reserves the thymidine analogue (ZDV) and PIs for 2nd line therapy.
- It is associated with renal toxicity in a small percentage. (Up to 3% is small but not insignificant. The good news is that it is reversible once it is detected and the drug stopped). A baseline urea/creatinine levels and monitoring of urine for proteinuria on 6 monthly basis is necessary.

7.1.3 NNRTIs

The use of an NNRTI as the third drug is preferable to the use of a PI, since an NNRTI-containing first line regimen:

- Is less expensive
- Preserves the option to use a PI at a later date
- Appears to be safe during pregnancy (NVP, not EFV)
- Allows treatment of TB co-infected patients who are on rifampicin (EFV, not NVP)

Using the fixed-dose combination (currently the least expensive regimen) of d4T, 3TC, and NVP poses a complication with regard to starting and stopping treatment. The recommended NVP dosing regimen starts with a lower lead-in dose of 200 mg once a day

for 2 weeks, followed by 200 mg twice a day thereafter. This schedule is less frequently associated with a rash. Starting a fixed-dose regimen of combination NNRTI-NRTI treatment without the "lead in" dose of NVP may therefore be associated with increased toxicity. In addition, NVP has a much longer half-life than the other drugs in the combination. When such a fixed combination is stopped, it is recommended that the other two NRTI drugs are continued for at least five days to avoid the development of NVP resistance.

There is concern that the use of NVP monotherapy in the PMTCT programs may promote resistance to the drug should these mothers initiate ART. Recent studies indicate that this is unlikely if the mothers initiate ART at least six months after the PMTCT program.

Either NVP *or* EFV should be chosen as the primary NNRTI but both should be available for mutual substitution for toxicity and for issues related to drug choice in pregnancy and TB. **See 7.5.1 and 2.**

7.1.4 Protease Inhibitor (PI)-based Regimens

PI-based regimens are an accepted standard of care for initial regimens. However, their high cost relative to NNRTI-based regimens makes their use too costly in RLS seeking to achieve rapid scale-up of therapy. It is recommended that PIs be reserved for second-line therapy. PIs as initial therapy with a standard dual NRTI backbone are an option for the treatment of pregnant women with CD4 counts of 250−350 cells/mm3, or for individuals for whom NNRTI drugs are severely toxic and triple NRTI therapy is not available or deemed inappropriate.

7.1.5 Triple NRTI Regimens

A triple NRTI regimen should be considered as an alternative for first-line ART in situations where NNRTI options provide additional complications and to preserve the PI class for second-line treatment e.g.:

- In pregnant women with CD4 counts of 250−350 cells/mm3);
- Patients co-infection with viral hepatitis or tuberculosis;
- Patients with severe adverse reactions to NVP or EFV

Recommended triple NRTI combinations are:

- zidovudine + lamivudine + abacavir
- zidovudine + lamivudine + tenofovir.

A 3-NRTI combination containing TDF+ABC+3TC or TDF+ddI+3TC should not be used as triple NRTI regimen at any time because of very high virological failure rates. In addition, studies have shown that patients with high initial VL do not do well with triple nuke regimens. Thus this combination may not be well suited in our setting where most patients have high VL. So it is strongly recommended that the use of triple Nukes should be in specialized centers.

Table 8: Recommended First and Second Line Regimens in Adults and Adolescents

1st Line Regimens	2nd Line Regimens	Comments
Preferred * ZDV/3TC + NVP or EFV	ABC/ddI + LPV/r **or** TDF+3TC* or FTC+ LPV/r	-Relatively inexpensive regimen. -ZDV less toxic than d4T. -ZDV causes anemia -If patient is anemic start with TDF
Alternative 1 TDF+3TC or FTC **plus** NVP or EFV	ZDV+ddI + LPV/r ABC/ddI + LPV/r ZDV+3TC* + LPV/r	-Use of TDF, FTC and EFV has low toxicity, once daily administration, and effective against hepatitis. -When affordable, this combination is the preferred first-line. -Patients who have peripheral neuropathy and anemia may be considered for this first line regimen.
Alternative 2 d4T/3TC + NVP or EFV	ABC/ddI + LPV/r **or** TDF+3TC or FTC + LPV/r	-Generic co-formulated d4T/3TC + NVP is cheap. -d4T, however, is associated with many toxicities -Only d4T 30mg is recommended irrespective of weight.

Adapted and modified from World Health Organization. Antiretroviral Therapy for HIV infection in adults and adolescents: Recommendations for a Public Health Approach (2006 revision)

**3TC can be considered to be maintained in 2nd line regimens to reduce the viral fitness*

The recommendation is to procure and stock a higher proportion of the preferred NRTI and NNRTI and a smaller amount of the alternative drug or regimen that will be used in case of toxicity and/or contraindication of the first choice. For example, TDF can be a substitute for ZDV in patients with severe ZDV-induced anaemia, and EFV can be a substitute for NVP in cases of NVP-associated hepatotoxicity.

First line regimens are recommended at national level to cover the majority of patients. Some patients may be considered for different combinations for various reasons. For example:

- TDF preferred in case of anaemia

- ZDV or TDF preferred in case of background neuropathy
- NVP preferred in women of childbearing for whom effective contraception cannot be assured
- NVP should be avoided among patients requiring simultaneous ARV treatment and TB therapy containing Rifampicin
- PIs may be considered for first line therapy in patients with Kaposi's sarcoma.
- NVP should be avoided in women with a pre-nevirapine CD4+ T cell counts >250 cells/mm^3 because of the increased risk of symptomatic hepatotoxicity and Steven Johnson syndrome
- EFV should be avoided in persons with a history of severe psychiatric illness.
- PIs may be considered for first line therapy in patients with Kaposi's sarcoma

7.1.6 Other remarks:

- The use of Abacavir (ABC) is currently limited by cost
- Certain dual NRTI backbone combinations should not be used within three-drug therapy. These are: d4T + ZDV (proven antagonism), d4T + ddI (overlapping toxicities) and 3TC + FTC (interchangeable, but should not be used together).
- TDF+ddI or TDF+ABC are not durable ART options
- LPV/r is reserved for 2nd line treatment
- ATV/r and LPV/r are the two preferred PIs. The two are similar with respect to tolerability and potency. ATV/r has the advantage of being dosed once daily.

Recommended dosages and other drugs for adults and adolescents are listed in Appendix **5**. Relevant drug toxicities and major drug interactions for the recommended agents and other drugs are listed in Appendices **3** and **4**.

7.2 Recommended second line of ART regimens in adults and adolescents

It is recommended that the entire regimen be changed if treatment failure occurs. The choice for 2nd line regimens depends on the first line choice. (**See Table 8**). The PI class is reserved for second-line treatments, preferably supported by two new NRTIs. There are insufficient data on the differences between ritonavir-boosted PIs (ATV/r, LPV/r, FPV/r, IDV/r, or SQV/r) to allow the recommendation of one agent over another.

For economic reasons and for the simplicity of administration since it is available as a FDC, only LPV/r is being recommended as the PI for second line regimen for treatment failure. In addition, the recent approval of a heat-stable tablet formulation eliminates the need for refrigeration. LPV combined with low dose RTV (LPV/r) is potent and well tolerated. On the negative side, the drug is incompatible with rifampicin.

In addition to LPV/r, there are other protease inhibitors that may become available on the market (such as ATV/r, DRV/r) that can be used as alternatives to LPV/r. None of the PIs is currently recommended for use with rifampicin.

The basic principle is ideally to support the chosen boosted PI with a dual NRTI backbone composed of two unused NRTIs. Among the previously unused NRTIs, ddI is a key drug for the construction of second-line regimens. ZDV and d4T, despite different toxicity profiles share a high rate of cross-resistance and the use of one of these drugs in the 1st line regimen generally precludes the use of the other in 2nd line combinations.

The second-line regimens that offer more activity include ddI/ABC as dual NRTI components or TDF/FTC. We recommend continuing 3TC in the setting of treatment failure because it may confer a viral replicative defect and/or residual antiviral activity.

Before changing to 2nd line, baseline LFTs should be done for monitoring hyperlipidemia. In addition the patient should be further counseled to point out the following:

- The patient needs to know why they failed,
- That it may not have been their fault,
- To re-emphasize that the drugs can still work,
- To talk them through the new regimen especially as PIs have high gastro-intestinal side effects
- To emphasize the need to monitor for lipidemia and development of diabetes mellitus.

7.2.1 What to do after 2nd Line Treatment Failure

Salvage regimens are not readily available on the public free ART program so no salvage therapy regimens have been recommended. Decisions to continue a failing 2nd line regimen should be made on a case by case basis and in consultation with experts in ART. Because a failing ARV regimen that contains nucleoside analogues and a protease inhibitor may still have a beneficial effect on the immune status of the patient, there is reason to continue with it if no other treatment option is available. This is particularly true if there is evidence of good clinical response. Stopping may be considered if a patient fails to tolerate available 2nd line regimen or has fulminant life threatening and incurable OIs. It is important to carefully evaluate the benefits, adverse effects and cost of continuing ART. Laboratory monitoring needs, pill burden, toxicity/drug interactions and drug costs generally increase progressively when patient moves from 1st line to salvage regimens.

However, when the patient can afford the costs of salvage therapy, there are options of new drugs on the market that are being used for the highly treatment-experienced patient. These agents include PIs like darunavir, NNRTIs like etravirine, Integrase inhibitors like raltegravir and chemokine receptor (CCR5) blockers like maraviroc. Prior to the use of these agents, viral loads, resistance tests and profile tests for the receptor blockers are required. Although very costly, these procedures form the standard of care in resource rich settings which may be affordable to a selected few patients in our setting. In this case, the patient should be referred to a specialized ART clinic where the doctors are familiar with salvage therapy.

7.3 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, EFV cannot be used in children under the age of 3 years or weighing less than 13 kg due to lack of appropriate dosing information. **See table 9**.

Table 9: Recommended First and Second Line Antiretroviral Regimens for Children and Infants

1st Line Regimens	2nd Line Regimens	Comments
Preferred * d4T/3TC + NVP or EFV	ABC/ddI + LPV/r or ARV/r **or** TDF[1]+3TC or FTC + LPV/r **or** ZDV/3TC + ATV/r	-d4T is safe and still preferred in children below 5 years -Generic fixed dose formulation is preferred as d4T/3TC + NVP and is cheap. -Change d4T to ZDV when children are aged ≥5 years
Alternative** ZDV/3TC + NVP or EFV	ABC/ddI + LPV/r or ATV/r **or** TDF[1]+3TC or FTC+ LPV/r	-Relatively inexpensive regimen and available as generic fixed dose combination of ZDV/3TC/NVP. -ZDV less toxic than d4T. -ZDV may cause anemia -If child is anemic start with d4T and switch to ZDV as soon as the anemia recovers
Alternative*** D4T/3TC + LPV/r	ABC + ddI + NVP or EFV	For previously exposed infants during PMTCT programs

[1] Please note that TDF is contraindicated in children aged <3yrs.
* For children initiating HAART when aged less than 5 years
** For children initiating or being switched from d4T containing regimens at the age of 5 years and above
*** For infants up to 12 months initiating HAART with previous exposure to NVP or EFV

7.3.1 Pediatric Fixed Combinations

Several manufacturers have developed pediatric versions of Fixed Dose Combination tablets (FDCs) which can be dosed more accurately in children than split adult FDCs and which are easier to prescribe and administer than individual single drug formulations. The tablets are scored, crushable and dispersible in water and may be dosed in children up to 24.9 kg including infants as small as 3kg. The currently available pediatric FDCs contain d4T or ZDV, 3TC and NVP and have a higher proportion of NVP which makes them better suited for dosing in children who metabolize nevirapine more rapidly than adults. The recent availability of d4T-based pediatric FDCs may facilitate an easier way to prescribe and administer pediatric ARVs than individual single drug formulations. FDCs may lead to better adherence and therefore better outcomes with pediatric ART.

Children already on treatment with pediatric single drug formulations or adult split FDCs may benefit from switching to pediatric FDC tablets, especially in settings where adherence is a concern. Children who are receiving a regimen of d4T, 3TC and NVP can be switched over to pediatric FDCs easily, using the recommendations for maintenance doses. A switch to pediatric d4T/3TC/NVP FDCs may be considered for children who are on treatment with ZDV/3TC/NVP if there is evidence of toxicity. Before switching to FDCs treatment failure must be ruled out (no evidence of disease progression or falling CD4 percentages or counts). Regimens being well tolerated and clinically effective should not be switched simply because FDCs are available.

See appendix 6 for the list of registered formulations as well as dosing for these formulations. Different manufacturers' formulations have different concentrations of the three components and are therefore not interchangeable and must be dosed according to their respective dosing schedules.

7.4 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 ABC/ddI) plus a PI (LPV/r), but for infants whose original first line regimen contained a protease inhibitor (LPV/r), an NNRTI should be added to the nucleoside backbone chosen. **See Table 9.** Use of PIs other than LPV/r is more problematic in children due to lack of suitable pediatric drug formulations for IDV, SQV and ATV. ATV/r is not currently available as a pediatric formulation but when indicated can be given as separate entities.

7.5 ART Recommendations for special groups

7.5.1. Women of childbearing potential or who are pregnant

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 first trimester, prior to recognition of pregnancy and during the primary period of fetal organ development. Efavirenz (EFV) should therefore be avoided unless effective contraception can be assured. NVP is the NNRTI of choice for women as most HIV-infected women are of child bearing potential.

For pregnant women, ART should be initiated with WHO clinical stage 3 or 4 disease or those with CD4 below 350 irrespective of clinical stage. It is recommended that they use ZDV + 3TC and (NVP or ABC if available) as these have been widely used in pregnancy with a wealth of pharmacokinetic data available. Alternative NRTI drugs to be used in pregnancy include d4T and ddI. However, the dual NRTI combination of d4T/ddI should not be used during pregnancy due to the potential increased risk of lactic acidosis.

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.

For pregnant women with higher CD4 counts, NVP should be used with caution. Severe NVP induced hepatotoxicity is more common in ART naïve women with higher CD4 i.e.> 250cells/mm^3 and tends to occur within the first six to twelve weeks of therapy. Suggested treatment options for such women with CD4 between 250 and 350 include;

- Starting with EFV if pregnancy is after 1st trimester
- Starting a triple based NRTI regimen e.g. ZDV + 3TC +ABC or ZDV + 3TC +TDF
- Treating with NVP and monitoring closely for at least 12 weeks if EFV is not available
  - Education of the patient on symptoms of concern like rash, fever, and abdominal pain,
  - More frequent visits in the first weeks of therapy (e.g. every two weeks),
  - Evaluation of baseline liver enzymes and close monitoring thereafter. If the liver enzymes (AST and/or ALT) increase to more than 5 times the upper limit of normal without an alternative explanation, then NVP should be permanently discontinued.
  - Discontinue NVP immediately if any symptoms of hepatotoxicity develop.
- Substituting EFV or NVP with a PI
- Delaying therapy until CD4 counts fall below 250/mm3 as a last resort

Each of these approaches has advantages and disadvantages - **see table 10** for approaches to initial therapy in women with CD4 counts in the range of 250 and 350

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 EFV) and the PIs (NFV and all low dose RTV boosted PIs)] can lower blood concentrations of oral contraceptives so 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.

The use of condoms is recommended for all women regardless of hormonal contraceptive use and pregnancy status as they protect against other sexually transmitted diseases as well as HIV super infection. Additional or alternative contraceptive approaches (in addition to consistent use of condoms) should be used in order to avoid pregnancy in women receiving PIs and NNRTI drugs.

For HIV-infected women receiving ART who become pregnant, continue the current ARV regimen unless it contains EFV. If it does, substitution with NVP or a PI or ABC should be considered if in the 1st trimester. Continue the same ARV regimen during the intrapartum period and after delivery.

For HIV-infected pregnant women without indications for ARV treatment, or those who are breast-feeding, they should be referred to the PMTCT program.

Table 10: Clinical situations and recommendations for the use of antiretroviral drugs in pregnant women and women of child-bearing potential

Clinical Situation	Recommendation
A: HIV-infected women with indications for initiating ARV treatment with potential to become pregnant	First-line regimens: ZDV + 3TC + NVP or TDF + 3TC + NVP Efavirenz (EFV) should be avoided unless effective contraception can be assured. Exclude pregnancy before starting treatment with EFV. Counsel on sexual activity, reproductive plans, and use of effective contraception
B: HIV-infected women receiving ART who become pregnant	**Women** • Continue the current ARV regimen unless it contains EFV. If it does, substitution with NVP or a PI or ABC should be considered if in the 1st trimester. • Continue the same ARV regimen during the intrapartum period and after delivery. **Infants** • 1-week ZDV or single-dose NVP or 1-week ZDV + single dose NVP.
C1: HIV-infected pregnant women with indications for ARV treatment CD4<350 cells/mm^3	**Women** • Follow the treatment guidelines as for non-pregnant adults except that EFV should not be given in the 1st trimester. • First line regimens: ZDV + 3TC + NVP or TDF + 3TC + NVP • Consider delaying therapy until after the 1st trimester if not severely ill **Infants** • 1-week ZDV or single-dose NVP or 1-week ZDV + single-dose NVP.
C2: HIV-infected pregnant women with indications for ARV treatment **BUT** CD4>250<350 ceels/mm^3	**Women** ZDV + 3TC + NVP or TDF + 3TC + NVP and monitor closely for hepatotoxicity over 12 weeks • Starting with a triple based NRTI regimen e.g. ZDV + 3TC +ABC or ZDV + 3TC +TDF **Infants** • 1-week ZDV or single-dose NVP or 1-week ZDV + single dose NVP.
D: HIV-infected pregnant women without indications for ARV treatment	Refer for PMTCT program **Women** • ZDV starting at 28-32 weeks. Continue ZDV at the same dose in labour. In addition, women should receive single-dose NVP at the onset of labour and one week of ZDV/3TC **Infants** • Single-dose NVP and 1-week ZDV
	Alternative regimen: ZDV + *3TC* **Women** • ZDV + 3TC starting at 33 weeks or as soon as possible thereafter. One dose nevirapine in labour. Continue in labour and for 1 week postpartum. **Infants** • Single-dose NVP and 1-week ZDV

Clinical Situation	Recommendation
	Alternative regimen: NVP only **Women** • Single-dose NVP – for women presenting for the first time in labour **Infants** • Single-dose NVP
E: HIV-infected pregnant women with indications for starting ARV treatment but treatment is not yet available	Follow the recommendations under D, but preferably use the most efficacious regimen that is available and feasible.
F: HIV-infected pregnant women with active tuberculosis	If ARV treatment is initiated, consider: (ZDV or d4T) + 3TC + TDF or ABC. If treatment is initiated in the 3rd trimester (ZDV or d4T) + 3TC + EFV can be considered. If ARV treatment is not initiated, follow the recommendations under D.
G1: Women of unknown HIV status at the time of labour	If there is time, offer HIV testing and counseling and if positive, initiate intrapartum ARV prophylaxis. **Women** • Single-dose NVP. If in advanced labour do not give the dose but follow the recommendations under H and refer postpartum to ART program **Infants** • Single-dose NVP **Women in early stage** • ZDV + 3TC in labour and 1-week ZDV + 3TC postpartum and refer to ART program **Infants** • 1-week ZDV+3TC If there is insufficient time for HIV testing and counseling during labour, then follow recommendations under H and refer mother to ART program.
G2: Women in labour known to be HIV-infected who have not received any ARV drugs	If there is time, initiate intrapartum ARV prophylaxis **Women:** • Single-dose NVP. If in advanced labour do not give the dose but follow the recommendations under H and refer postpartum to ART program **Infant:** • Single-dose NVP **Women:** • ZDV + 3TC in labour and 1-week ZDV + 3TC postpartum and refer to ART program **Infant:** • 1-week ZDV+3TC
H: Infants born to HIV-infected women who have not received any ARV drugs	**Infants** • Single-dose NVP as soon as possible after birth and 1-week ZDV If the regimen is started more than 2 days after birth, it is unlikely to be effective. In any case refer infant to ART program

7.5.2 People co-infected with tuberculosis and HIV infections

Co-management of TB and HIV is complicated by drug interactions between rifampicin and both the NNRTI and PI classes, IRIS, pill burden, overlapping toxicities, and adherence issues. Active TB may be present when ART needs to be initiated or develop during treatment. For patients with active TB in whom HIV infection is diagnosed and ART is required the first priority is to initiate standard anti-TB treatment.

NNRTI levels are reduced in the presence of rifampicin. There is however no benefit in increasing the dose of EFV from 600 to 800mg in patients weighing less than 60kg. EFV should not be used in women of childbearing potential without adequate contraception or in women in the first trimester of pregnancy. NVP is an alternative option but carries the risk of hepatotoxicity, in women with higher CD4 counts above 250 cells/mm^3. Therefore NVP containing regimens should only be considered as a last option in such women and regular laboratory monitoring of liver enzymes is advised.

Triple NRTI regimens are considered an alternative regimen in patients undergoing TB treatment. ZDV+3TC+ABC and ZDV+3TC+TDF can be used safely with rifampicin. Both regimens can be used safely in patients with higher CD4 cell counts where the risk of toxicity for NVP is increased, and in HBV/HIV co infection. Pregnant women can take ZDV+3TC+ABC safely.

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 <250/mm^3, 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. So they should initiate ART when they have stabilized on their TB treatment, which is usually within 2-6 weeks.

For those with CD4 250-350/mm^3 they should start ART after the intensive TB treatment phase, which usually lasts for 2 months. In patients with CD4 counts above 350cells/mm^3, patient is reassessed for ART eligibility after TB treatment.

In cases where a person needs TB and HIV treatment concurrently, first line treatment options include ZDV/3TC or TDF/3TC plus EFV, ZDV+3TC+ABC and ZDV+3TC+TDF. For HIV and TB co infected pregnant women, **see table 10.**

For persons co-infected with HIV and HBV, use ZDV+3TC+TDF **(See table 11).**

In the exceptional circumstances where CD4 cell counts cannot be obtained, ART should be initiated two to eight weeks after the start of TB therapy when the patient has stabilized on TB treatment.

Table 11: Antiretroviral Therapy for Individuals with Tuberculosis Co-Infection

Situation	Recommendations
Pulmonary TB and CD4 count <250/mm^3 or extra pulmonary TB or WHO stage IV	**Start TB therapy and when tolerated (usually within 2 to 6 weeks) ADD one of these regimens:** • ZDV/3TC/EFV or TDF/3TC/EFV – not to be used in first trimester of pregnancy or in women of childbearing potential without assured contraception • ZDV+3TC+TDF - can be used in persons co-infected with HIV/HBV. No interaction with rifampicin. • ZDV/3TC/NVP, TDF/3TC/NVP - *used only if in rifampicin-free continuous phase*
Pulmonary TB and CD4 250-350/mm^3	**Start TB therapy for 2 months THEN start one of these regimens:** • ZDV/3TC/EFV or NVP • TDF/3TC/EFV or NVP • ZDV+3TC+ABC or ZDV+3TC+TDF – can be used in women who are pregnant and those with high CD4 >250
Pulmonary TB and CD4 >350/mm^3	Defer ART. Treat TB first. Monitor clinically and also do CD4 counts. Re-evaluate patient at eight weeks and the end of TB treatment

7.5.2.1 ART and TB related Immune Reconstruction Inflammatory Syndrome (IRIS)

(See Chapter 11)

7.5.2.2 TB in patients on ART

In patients that develop active TB within six months of initiating first line ART, one has to consider modification of treatment and the possibility of ART failure. Although ART decreases the incidence of TB by at least 80%, the risk of developing TB is still higher than in the HIV negative population. Previously undiagnosed TB may present within the first six months as part of IRIS. If TB occurs during the first six months following the initiation of ART, this should not be considered as a treatment failure and the ART regimen has to be adjusted for co-administration of a rifampicin containing TB regimen.

If TB develops more than six months after the initiation of ART, the decision as to whether the TB diagnosis represents ART failure depends on the CD4 count and viral load if available or whether the TB is pulmonary or extra pulmonary, or whether there are other non-TB clinical stage 3 or stage 4 events. The development of TB after six months of ART initiation without other clinical and immunological evidence of disease progression should not be regarded as representing ART failure. However, extra pulmonary TB should be considered as indicating treatment failure.

7.5.2.3 Second line ART for patients with TB

There are significant drug interactions with PIs and rifampicin. Unboosted PIs cannot be used with rifampicin containing regimens because PI levels are sub-therapeutic therefore boosted PIs (Lopinavir 400mg/ritonavir400mg twice daily or SQV 400 mg/RTV 400mg can be considered but with close laboratory monitoring for hepatotoxicity (RTV 400 mg is quite hepatotoxic). Rifabutin if available, maybe used in place of rifampicin but is contraindicated in patients with WBC counts below 1000/mm3. We should avoid use of any of the current PIs with rifampicin.

7.5.3 People co infected with Hepatitis and HIV

Hepatitis B infection is endemic in many resource-limited settings including Uganda where the seroprevalence ranges between 3-10%. The presence of HIV infection in patients with HBV is associated with higher rates of progression to advanced liver disease like cirrhosis. These patients are at an increased risk of hepatotoxicity during HIV treatment.

Antiviral agents with activity against both HBV and HIV e.g. 3TC, FTC and TDF are recommended as first line agents in patients co-infected with HBV. In situations where both HIV and HBV require treatment, the ART regimens must contain 3TC and/or TDF. It is preferable to use TDF and 3TC together as both drugs have anti-HIV and anti-HBV activity and the use of TDF or 3TC as the only anti-HBV drug can result in more rapid development of resistance. EFV is the preferred NNRTI option as the use of Nevirapine is not recommended for those with marked elevations of ALT (grade 4 or higher). When

these individuals fail 1st line, they should in as much as possible continue with 3TC or FTC+TDF in their second line regimen unless they have access to another anti-HBV drug.

Rapid increases in Hepatitis-B viremia may occur while on ART as part of IRS and present with symptoms of acute hepatitis (fatigue, abdominal pain and jaundice). These reactions tend to occur in the first few months of ART and may be difficult to distinguish from ART induced hepatotoxicity. Drugs active against HBV should be continued during a suspected flare and if the patient is on 3TC monotherapy, TDF should be added. If it is not possible to distinguish a serious HBV flare from ART toxicity, all ARV drugs should be withheld until the clinical condition improves. HBV flares may also occur when anti-HBV active drugs are stopped and it is therefore recommended that in patients with chronic HBV, 3TC should be continued as part of second line ART following initial ART failure even if it has been used in first line.

For HCV infection, the optimal treatment is pegylated interferon alpha and ribavirin (RBV) but it is very expensive and not readily available. The initiation of ART in HIV/HCV co-infected patients should follow the same principles and recommendations as for the initiation of ART in HIV-monoinfected patients. However, the patients should be followed up more closely because of the major risk of drug-related hepatotoxicity. Specific interactions of some ARVs and anti-HCV drugs include

- Ribavirin and DDI – pancreatitis/lactic acidosis (do not give concomitantly)
- Ribavirin and ZDV – anemia (monitor closely)
- Interferon and EFV – severe depression (monitor closely)

Concurrent treatment of both HIV and HCV may be complicated by pill burden, drug toxicities and drug interactions. In patients with high CD4 cell counts (>250) it may be preferable to treat HCV before HIV, while in those who need ART it may be preferable to initiate ART and delay HCV therapy in order to obtain better anti-HCV response rates after immune recovery. EFV is the NNRTI of choice in patients with HIV/HCV confection or a triple NRTI regimen maybe used. NVP should be used with care and requires close monitoring. Patients with abnormal liver enzymes at baseline before ART initiation should be screened for HBV or HCV by serology wherever possible or be referred to where this can be done. EFV should be introduced after withdrawal of NVP following hepatotoxicity.

8.0 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 6 months and thereafter every three months. Monthly visits should be combined with those of drug dispensing, as they provide useful opportunities to reinforce adherence. However, after 6 months, the drug dispensing visits may not correspond with those for clinical follow-up. In this case the patient should be encouraged to report any problem to the ART clinician when they come for their drugs and not to wait for the scheduled clinical visit. At all clinic visits, HIV 'prevention with positives' messages should be reinforced. These should include partner HIV testing, condom use for the sexually active, encouragement regarding faithfulness and abstinence, and prevention of mother to child transmission of HIV (PMTCT), including promotion of family planning.

8.1 Clinical guidelines for monitoring ART in adults and adolescents

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

8.1.1 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 menstrual periods to detect early pregnancy. This is then followed by physical examination including vital signs, weight, and 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 and HIV prevention issues. The clinical assessment should include evaluations of other potential individual risks, such as sexual transmission of HIV and pregnancy.

8.1.2 Clinical monitoring for toxicities

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 whenever they develop any skin rash or stop therapy if they develop severe skin eruptions and/or jaundice.

For the skin rash, the health worker should decide if the rash is dry or wet. A dry skin rash is without any blistering. In this case the patient should be monitored closely while he/she continues with the drugs. A wet skin rash is where there are blisters. All medications should be stopped, patient admitted and closely monitored in case he/she requires additional treatment such as steroids. If in doubt a more experienced clinician should be consulted for advice. **See Appendix 3 & 4**

8.1.3 Clinical assessment of ART effectiveness

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;
- Improvement in appetite
- 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 IRIS or HIV-related disease progression

8.2 Laboratory guidelines for monitoring ART

8.2.1 Basic laboratory tests for monitoring toxicity & 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. **Table 12** summarizes 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 12: Recommended Investigations for ART

Investigation		Level available	Objective	Frequency
Absolute minimum tests	HIV antibody test	All levels	Diagnose HIV and initiate ART	Once before ART
	Haemoglobin or hematocrit Urine analysis for those put on TDF	All levels	Monitor degree of anaemia – if severe transfuse before ART or use TDF instead of ZDV	When indicated or if on ZDV, at 4, 8 & 12 weeks and thereafter when indicated
Basic recommended tests	Total WBC + differential	All levels	Monitoring neutropenic side effects	6-12 monthly & when indicated
	CD4 cell count	All ART participating units	Monitoring immune response to therapy	6 monthly or when suspect failure
	LFTs: alanine or aspartate aminotransferases	District hospitals	Monitor hepatitis co-infection and hepatotoxicity	When indicated. For women who start ART with CD4 250-350, that include NVP 4, 8, 12 wks
	Serum creatinine and/or blood urea	District hospitals	Monitor renal function	When indicated. For pts on TDF, before start and every 6 months
	Serum glucose	District hospitals	Monitor hyperglycaemia in patients on Protease Inhibitors	When indicated
	Pregnancy test	All levels	Change therapy to appropriate regimen when pregnant Assess pregnancy status among adolescent girls since they may not reveal that they are sexually active	When indicated
Desirable tests	Bilirubin	District hospitals	Monitor hepatitis co-infection and hepatotoxicity	When indicated
	Serum lipids	Referral hospitals	Monitoring hyperlipideamia for those on Protease Inhibitors	When indicated
	Serum lactate	Referral Hospitals	Diagnosing lactic acidosis when on NRTI e.g. d4T or ddI	When symptoms suggest lactic acidosis
Optional tests	Viral load	Referral Hospitals & Research Centres	Monitoring viral response to therapy & diagnosing HIV in children <18 months	Every 12 months or when suspect failure

8.2.2 CD4 lymphocyte counts

In addition to regular clinical evaluation, the 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 by suppressing their VL, 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 of immunological failure is a return to the pre-therapy baseline or a fall of >50% from the peak CD4 cell count. It is essential not to base a significant clinical treatment decision on a single CD4 result, rather use serial measurements to see the trend.

8.2.3 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 referral hospitals and research centres. 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 quantification in plasma or serum will become available in Uganda soon in order to improve the effectiveness of ARV programmes and the care of individual patients.

8.3 Monitoring of ART in infants and children

Monitoring ART in children is similar to that in adults. In addition, it should include regular assessment of weight, height, head circumference, developmental milestones and neurological symptoms. In children growth and development are important clinical monitoring indicators.

Children below five years should have their weight, height and head circumference taken and recorded on their growth charts. After five years do the weight and height only. The growth charts provide a useful guide when monitoring the child's progress on ART. Therefore the parents/guardians should be encouraged to carry them to the clinics for each visit.

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 8 years, CD4 percentages are better than absolute counts. Absolute CD4 cell counts normally fall as a child grows but the percentage remains consistent. (See also section 9.3)

8.4 Follow-up at ART implementing centers

In the past few years, 450 health units have been accredited by the MoH to be able to participate in the national ART program. These units include hospitals, (both public, NGOs and private), health centers 4 and 3. The staff working at these units have received ART related training and new ones are being trained. Bigger units like regional and teaching hospitals and research centers like Joint Clinical Research Center (JCRC) are routinely providing support to the smaller units. All these units play a major role in ART follow-up which 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 clinician.
  - Weight; this should be recorded at every visit. Any unexplained loss should prompt careful re-evaluation of the patient.
  - Haematology (Hb and FBC) and biochemistry investigations should be done whenever there are symptoms of intercurrent infections and when there are symptoms suggestive of severe toxicity to ARV drugs. For patients on ZDV, a haemoglobin should be done more frequently, at 4, 8 and 12 weeks after initiation of ART in order to detect anemia early.
  - CD4 cell count should be done once every 6 months or earlier if patient is not clinically responding to ART
  - Changes in ART, OI prophylaxis and other concomitant medications based on clinical and laboratory assessment. Record any drugs given for prophylaxis (e.g. cotrimoxazole, fluconazole)
  - 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, 3-day recall, or nurse administered questionnaires: even the very young are able to give a clue to their adherence (always chat with them about the subject), reports from the treatment supporter or relatives
  - Discuss the role/action of the treatment supporter
  - Healthy living including abstaining from alcohol intake
- Identifying patients that need more sophisticated investigations and refer them to better equipped facilities
- Assess sexual transmission risk of the individual and provide 'positive prevention' counseling that includes safer sex practices, partner testing, disclosure of HIV status, PMTCT and reproductive health
- Screen for TB at every visit

8.5 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 service providers in order to deal with possible complications without much delay.

Where such organizations do have outreach care services, they could also include monitoring ART adherence, HIV testing for sexual partners of index clients and their household members. They should also reinforce HIV prevention messages, address stigma and social support for people living with HIV infection. This requires the ART implementing centers working hand in hand with these organizations.

To ease collaboration between ART implementing centers and the community organizations or networks, standard operating procedures (SOPs) or memoranda of understanding should be put in place to guide and inform the collaborations. Also the MOH Community Based care guidelines should be consulted for additional guidance on community follow-up.

8.6 ART data management and reporting

As more health units in Uganda provide ART services, there is need to collect relevant data that will help the health units to monitor their patients. This information will also assist the Ministry and stakeholders to monitor the performance of the ART programme and the emergence of early warning indicators of HIV drug resistant strains. The patient monitoring system comprises of a minimum set of data elements that are collected and reported using standardized forms. The various forms comprise of:

- The Facility held HIV care/ART card that maintains a record of the client's basic information and their follow up chronic AIDS care/ART
- Patient held ART card is a short summary record of the client and follow-up appointments
- The Pre-ART register lists all clients who are enrolled in chronic HIV/AIDS care including ART at the facility.
- The ART register maintains a longitudinal record of the follow up care of clients who are enrolled into ART
- The quarterly cross sectional reporting form is completed at the end of every quarter to keep track of all clients on ART and chronic HIV/AIDS care.
- The cohort analysis form is used for summarizing treatment outcomes

The data should be collected by all those units providing ART services and chronic AIDs care and should include the following information:

- At all levels of the health care system (National, District and Health Facility) for programme monitoring.
  - Information that is collected and reported on a quarterly basis includes:
    - ✓ Number of individuals receiving chronic AIDS care during the quarter
    - ✓ Cumulative number of individuals ever enrolled in chronic AIDS care by the end of the quarter
    - ✓ Number of individuals in chronic AIDs care who received cotrimoxazole prophylaxis at their last visit in the quarter.
    - ✓ Number of individuals enrolled in chronic AIDS care during the last quarter
    - ✓ Number of pregnant females enrolled in chronic AIDS care in the last quarter

- ✓ Percentage of infants born of HIV-infected women started on cotrimxazole prophylaxis within 2 months of birth
- ✓ Number of individuals receiving HIV care/ART who were screened for TB at their last visit in the quarter
- ✓ Number of individuals receiving HIV care/ART who started TB treatment during the quarter
- ✓ Number of individuals who are eligible for ART but have not yet started treatment during the quarter.
- ✓ Percentage/Number of adults with advanced and all children with HIV infection receiving ART during the quarter
  - ♦ Percentage of adults and children receiving first-line regimen
  - ♦ Percentage of adults and children receiving second line regimen
  - ♦ Percentage of adults and children receiving other regimens
- ✓ Cumulative number of individuals ever started on ART by the end of the quarter
- ✓ Number of ART naïve individuals who started ART during the quarter
- ✓ Percentage of individuals still alive and known to be treatment 6, 12 months and annually after initiation of therapy

➢ Information collected annually for monitoring HIV drug resistance Early Warning Indicators
- ✓ Percentage of individuals starting ART who are prescribed an appropriate standard first-line regimen (target should be100%)
- ✓ Percentage of individuals who are still prescribed a standard first-line regimen 12 months from initiation of treatment (target should be >70%)
- ✓ Percentage of individuals who attended all clinic appointments on time during the first year of ART (target should be >80%)
- ✓ Percentage of individuals lost to follow up during the first 12 months on ART (target should be <20%)
- ✓ Percentage of months in the year where there were no drug stock outs at the health facility (target should be 0)

➢ Information collected annually during special surveys and ART data quality assessments
- ✓ Number of health workers in the health facility trained in ART service delivery in accordance with national standards
- ✓ Percentage and number of health facilities offering ART that have access to laboratory services for monitoring ART
  - ♦ Percentage and number of health facilities that have access to CD4 cell count services.

- At the health facility level for patient monitoring

➢ Information collected routinely for patient and programme monitoring at the health facility
- ✓ Percentage of individuals receiving HIV care/ART whose immediate family members have been tested for HIV
- ✓ Percentage of individuals referred by the health facility for HIV care at another facility

- ✓ Distribution of care entry points of patients enrolled in chronic AIDS care at the facility
- ✓ Percentage of patients who demonstrate ≥95% adherence to their ARV medication
- ✓ Reasons for poor adherence
- ✓ Percentage of pregnant females linked with PMTCT interventions
- ✓ Percentage of new mothers whose infants are linked to care
- ✓ Reasons for ART treatment interruptions
- ✓ Distribution of reasons for substituting, switching or stopping ART
- ✓ Number, nature and frequency of side effects, opportunistic infections and other problems

The data collected should be forwarded to heads of health sub-districts, the district directors of health services and to the MoH headquarters at the AIDS Control Program (ACP) at the end of each quarter. It is anticipated that once the normal reporting mechanism of passing through established institutions at health sub-district and district to Ministry of Health has been established and functional, the reporting loop from health facilities to MOH will be phased out. At the health sub-district and district levels information should be used to inform the drugs, reagents and other logistics procurement processes, estimate staff requirements, 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 and also allow for proper budgeting for the National ART Program.

9.0. When to change therapy in adults and adolescents

9.1 Introduction

The indication for changing a patient's ART regimen must be clearly identified. It is of paramount importance that the provider especially distinguishes between switching because of treatment failure and switching because of other indications (toxicities, pregnancy, weight changes in case of children and development of TB). Where treatment failure is suspected, in the absence of resistance testing, the ART regimen needs to be reconsidered as a whole. In contrast, changing an ART regimen due to other indications like toxicity usually involves replacing one of the implicated drugs in the regimen by a suitable alternative.

9.2 Indications for changing regimens

The reasons for altering an initial antiretroviral regimen include:

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

9.2.1 Changing for treatment failure

The decision on when to switch from first-line to second-line therapy is critical. If the decision is made too early, potential further survival benefit from any remaining first-line effectiveness is lost; if it is made too late, the effectiveness of second-line therapy may be compromised. Treatment failure can be defined as clinical, immunological or virological failure. When treatment failure is defined on the basis of clinical and/or CD4 criteria the diagnosis may be made later than when viral load is being monitored.

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 and adherence has been assessed and optimized. Clinical failure should be differentiated from IRIS, which is usually seen within the first six months after the institution of therapy, and is related to pre-existing conditions. Although management of IRIS can be difficult, changing the antiretroviral regimen in this circumstance is not indicated

Immunological failure is measured by the level of CD4 cells. The CD4 cell count remains the strongest predictor of HIV-related complications, even after the initiation of therapy. For a patient who has been on ART for **at least six months or a year,** immunologic failure can be defined as;

- A fall in CD4 counts of more than 50% on two or more occasions from the on-treatment peak value or
- A return to, or below, the pre-therapy baseline or
- Persistent CD4 levels below 100 cells/mm3.

Patients starting with low CD4 counts may demonstrate slow recovery, but persistent levels below 100 cells/mm^3 represent significant risk for HIV disease progression. Caveats to be noted are that intercurrent infections can result in transient CD4 count decreases, and that, with relatively infrequent monitoring (e.g. every six months), the true peak of the CD4 cell count may be missed. As a general principle, intercurrent infections should be managed and time allowed for recovery before the CD4 cell count is done to guide on the need to switch ART.

Virologic failure is considered to have occurred if there is detectable virus after 12 weeks of therapy. As measuring viral load is not readily available in RLS, it is not recommended for the routine monitoring of treatment in the present guidelines. Where viral load testing is available, virologic failure is defined as a plasma HIV-1 RNA level above 1,000 copies/ml in a person who has been on a regimen for more than six months and in whom drug adherence is determined to be sufficient. An undetectable viral load mandates that ART should not, in general, be switched irrespective of the CD4 cell count or the clinical stage. **Table 13** summarizes the definitions of treatment failure.

Table 13: Clinical, CD4 cell count and virological definitions of treatment failure for patients on a first-line antiretroviral regimen

Clinical failure	New or recurrent WHO stage 3 or 4 condition after the first six to twelve months of ART
CD4 cell (Immunological) failure	• Fall of CD4 count to pre-therapy baseline (or below); or • 50% fall from the on-treatment peak value (if known); or • Persistent CD4 levels below 100 cells/$mm^{3,}$
Virological failure	Plasma viral load above1 000 copies/ml

9.2.1.1 Causes of treatment failure

Treatment may fail because of:

- Prolonged use of ARVs even with excellent adherence in some cases
- 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
- Recurrent drug stockouts which then contribute to poor adherence
- Other unknown reasons

Factors that increase the risk of treatment failure

- Prior antiretroviral treatment that may not have been disclosed to the health worker
- Very sick patients with very low CD4 cell counts or high viral load at the time of initiating therapy
- Poor clinic attendance record
  - Increased distance from treatment center
- Side effects or disease processes like intractable vomiting and diarrhea

9.2.1.2 How to Change therapy in treatment failure

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. In practice, treatment failure should be considered only after ascertaining that poor response is not due to very low levels of adherence. That is, poor response remains even after improving adherence.

Clinicians are encouraged to make decisions to change therapy on a case-by-case basis and should seek the opinion of colleagues experienced in the management of HIV. This is important because a small number of patients may have poor immunologic response despite good virologic suppression (the disconnect syndromes) and IRS (see section on IRIS) may be confused with clinical failure. Clinical status, the CD4 cell count, and the plasma HIV-1 RNA level (if available) can be used in an integrated fashion to determine whether HIV disease is progressing on therapy and whether a change from first-line to second-line therapy should be made. Some ART clinics have established switch meetings of experts to review cases and utilize all available information before a switch to second-line therapy is made. It is strongly recommended that also all other ART clinics form the "Switch Therapy Committees" composed of doctors, Clinical officers, counselors and Pharmacists/Pharmacy technicians that regularly discuses issues on switching therapy before it occurs. The team approach should also be able to identify the factors that may have contributed to failure of the initial regimen and address them before the change is made to avoid premature failure of the second-line regimen.

It is also recommended that all ART implementing sites consult the AIDS Treatment Information Center (ATIC) based at the Infectious Diseases Institute, at Mulago Hospital, for support before any decisions are made to change medications. ATIC also has been designated by the MoH to provide country wide support and guidance on management of

ART related toxic and side effects. They can be contacted at any time of the day or night on a Toll Free Number 031-2-307 245.

9.2.2 Changing for toxicity

About one-half of patients experience some form of toxicity to ART during follow-up. Toxicity requiring a change in therapy occurs in 5-20% of patients by 18 months.

Guiding principles in the management of ARV drug toxicity are:

1. Determine the seriousness of the toxicity
2. Evaluate concurrent medications and establish whether the toxicity is attributable to an ARV drug or drugs or to a non-ARV medication taken at the same time
3. Consider other disease processes (e.g. viral hepatitis in an individual on ARV drugs who develops jaundice) because not all problems that arise during treatment are caused by ARV drugs
4. Manage the adverse event according to severity

As a general principle, mild toxicities do not require discontinuation of therapy or drug substitution, and symptomatic treatment may be given. Moderate or severe toxicities may require substitution with a drug in the same ARV class but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilized and the toxicity is resolved.

The general principle is that single-drug substitution because of toxicity should involve drugs belonging to the same ARV class. If toxicity is related to an identifiable drug in a regimen the offending drug can be replaced with one that does not have the same side effects e.g.

- Substitution of ZDV or TDF for d4T in cases of neuropathy
- TDF or d4T for ZDV where anemia occurs
- NVP for EFV for CNS toxicity or in pregnancy

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.

Regardless of their severity, adverse events may affect adherence to therapy. A proactive approach to managing toxicity is recommended. Discussing the potential side effects of the ART regimen with the patient before the initiation of therapy and during the early stages of treatment, as well as support during minor and moderate adverse events can increase the likelihood of adherence to therapy. The patient should be familiar with signs and symptoms of toxicities that are serious and require immediate contact with the health care team. This is particularly important for toxicities that can be life threatening, including NVP-associated Stevens-Johnson syndrome, hepatitis, lactic acidosis or abacavir-associated hypersensitivity reaction.

9.2.2.1 Indications for changing therapy for toxicity

Table 14 gives out examples of specific drug toxicities and suggested substitutions.

Table 14: Drug specific indications for changing regimens

ARV drug	Common associated toxicity	Suggested substitute
ABC	Hypersensitivity reaction	ZDV or TDF or d4T
ZDV	Severe anaemia or neutropenia Severe gastrointestinal intolerance	TDF or d4T or ABC
	Lactic acidosis	TDF or ABC
D4T	Lactic acidosis Lipoatrophy/metabolic syndrome	TDF or ABC
	Peripheral neuropathy	ZDV or TDF or ABC
TDF	Renal toxicity (renal tubular dysfunction)	ZDV or ABC or d4T
EFV	Persistent and severe central nervous system toxicity (hallucinations or psychosis)	NVP or TDF or ABC (or any PI)
	Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	NVP or ABC (or any PI)
NVP	Hepatitis	EFV or TDF or ABC (or any PI)
	Hypersensitivity reaction with wet skin rash	TDF or ABC (or any PI)
	Severe or life-threatening rash (Stevens-Johnson syndrome)	

9.2.3 Occurrence of active tuberculosis and/or pregnancy

It is important to note that there is need to change the ART regimen once pregnancy or tuberculosis occurs during ART in order to minimize the risk of teratogenicity, drug interactions and toxicity. See section on ART in special groups.

9.2.4 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.

9.2.5 Economic constraints

The MOH policy is to provide free ARVs to all patients attending accredited ART centers including those in the private sector. However, there are patients who may opt to pay for their own antiretroviral drugs. When they run out of resources, a clinician may need to switch to a more affordable formulation to avoid interruption of therapy should they refuse to join the public ART program.

9.3 Indication for changing regimens in infants and older children

The principles for changing therapy in children are similar to those described for adults. 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

Like in adults, 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 50% 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.

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., ZDV, d4T, or NVP.

10.0 Challenges of ART

When patients adhere to ART they benefit from a 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 status. Some of these challenges will be discussed below.

10.1 Immune Reconstitution Inflammatory Syndrome (IRIS)

Soon after initiating HAART some patients may experience symptoms and signs of inflammation. Patients may present with painful and swollen lymph nodes, chest symptoms, and unexplained fevers among others. These observations usually are due to a phenomenon termed the Immune Reconstitution Inflammatory Syndrome or 'IRIS'. Other names for IRIS include Immune Restoration Disease (IRD) and paradoxical reactions. IRIS occurs when the immune response against a particular antigen increases after the start of ART, leading to an inflammatory reaction. Initiation of ART can also unmask previously undiagnosed infections by improving the inflammatory response due to the repair of the immune system.

Common IRIS related diseases in Uganda include *Tuberculosis* (TB), *Cryptococcal meningitis,* CMV retinitis, genital ulcers from Herpes Simplex, and Kaposi's sarcoma.

IRIS events may occur in up to 40% of patients treated for TB who start ART and up to 5% in those with cryptococcal disease. The risk is higher in those with advanced HIV disease with low CD4 counts. IRIS events often occur between 2-8 weeks of ART initiation and less commonly after many months of ART. The diagnosis of IRIS should be considered by ART providers when a patient who has recently started ART (last 3 months) develops new symptoms when they should be getting better. This is particularly the case in patients with a known co-infection such as TB or cryptococcal meningitis who seemed to be responding well and adhering to treatment but then deteriorate within weeks after starting ART.

10.1.1 Examples of specific IRIS events

Tuberculosis: TB IRIS presents with worsening clinical symptoms after initial improvement and may occur in up to 40% of persons with TB who initiate ART. Patients with pulmonary TB may develop worse chest symptoms, new infiltrates on chest film, and enlarged lymph nodes that may become tender or form abscesses. TB meningitis and/or tuberculomas may present with confusion, fits and/or new focal neurological features. Abdominal TB may present with intestinal obstruction or even bowel perforation. TB IRIS is more common if ART is started early in the course of TB treatment and in patients with low CD4 counts. Most cases resolve without any intervention and ART can be safely continued. However, serious reactions like tracheal compression from massive lymphadenopathy or respiratory difficulty may require use of corticosteroids.

Cryptococcal meningitis: IRIS events against cryptococcal meningitis may cause dangerous clinical deterioration with increased intracranial pressure and therefore increasing headache and/or vomiting, confusion and fits and visual disturbance.

10.1.2 Principles of Management of IRIS

The management of IRIS should be based upon the following questions:

1. *Is the responsible antigen being treated appropriately (e.g. TB, cryptococcal meningitis)?*
    - If the TB or Cryptococcal infection is being adequately treated then it will not be necessary to alter this treatment.
    - If the treatment has not been adequate or the adherence of the patient to the prescribed treatment has been poor, then treatment failure must be considered. In this case, appropriate specimens should be sent for culture and re-treatment of the infection initiated.
    - If the infection was unknown/undiagnosed/untreated and has only been 'unmasked' by ART, then appropriate therapy should be initiated immediately.
2. *Should the ART be continued or stopped?*
    - Once the diagnosis of IRIS has been made, patients should continue with their ART. Stopping should only be considered if there is a strong suspicion of drug toxicity.
3. *What other treatment can be used to treat IRIS patients?*
    - IRIS reactions are typically self-limiting, although may require the use of a brief course of corticosteroids to reduce inflammation for central nervous system or severe respiratory symptoms.

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, development of drug resistance and subsequent immunologic and clinical failure. Factors that contribute to good adherence include;

- Use of simplified, well-tolerated regimens involving as fewer pills as possible administered no more than two times per day.
- Patient counseling and education both before ART and during treatment. 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 or a close relative or friend 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.
- Directly observed therapy (DOT) may be introduced with caregivers' or family members' assistance or treatment supporter. This maybe more useful for an initial 'training' period for patients but may not be sustainable for very long periods.
- Personal adherence plans that are integrated into patient routine activities. The plans should be regularly reviewed to incorporate changes in life style and

job/work requirements. They should be shared with the ART health unit who should make appropriate adjustments, e.g. scheduled treatment visits.
- Health systems that ensure availability of drugs, supplies and human resources at all times (see **10.5**).

Ongoing attention to, and reinforcement of, adherence throughout the entire course of ART is an essential part of any successful treatment program. Once treatment has begun, continued monitoring of adherence is essential. These monitoring tools include:

- Pill counts, but is subject to error and manipulation.
- Validated patient questionnaires that are easy to administer in the outpatient setting.
- Three day recall during clinic visits
- Spot checks at home

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 or without 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. There is need for the health workers to be prepared to deal with these children and adolescents. 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
- Becoming independent of the carers who hitherto have been responsible for the adolescent's health
- Love and sexual life and need for family planning, including use of condoms

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. In any ART team, there should be at least one counselor interested and trained in dealing with these complicated issues.

10.4 ART in children

Children, who have to start ART particularly when they 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 budgets upwards for drugs to meet requirements for those buying their drugs
- 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 and minimizing stigma.

Another important group is that of children who have been previously healthy, become severely sick or had repeated ill-health but get diagnosed late (slow progressors).

- They may be initiated on ART without their consent. On "recovering" from their acute illness they may not be ready to continue with the medication
- It becomes difficult to time when to disclose their HIV sero-status
- Their parents/guardians may suffer depression brought on by the child's HIV illness and this might lead to their failure to provide appropriate support for the sick child
- For children that are diagnosed late and in advanced states of HIV disease, there are likely to suffer from IRIS or even fail to recover from their illness

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

11.1 Primary prophylaxis

Primary prophylaxis with various agents is used to prevent the development of opportunistic infections when a patient becomes severely immunosuppressed with a CD4 cell count of <250. This is one way of improving the quality and quantity of life in patients with HIV disease. The commonest agent used in primary prophylaxis is co-trimoxazole (CTX) which has been proven to prevent a wide range of bacterial infections as well as PCP, toxoplasmosis and malaria. CTX is now routinely given (1 double strength or 2 single strength tablets daily) to all patients (both adults and children) who test HIV positive even when their CD4 cell count is still high. This means that even patients started on ART, should continue with their CTX until their immune system has been adequately repaired as evidenced by a high CD4 of 350-500 for over six months.

Other primary prophylaxis agents used include fluconazole for the prevention of cryptococcal infection given as 100-200 mg daily with meals

11.2 Secondary prophylaxis

Secondary prophylaxis is used in those patients who have been treated for an opportunistic infection like cryptococcal disease. In this case prophylactic treatment is given to prevent the recurrence of the opportunistic infection. Some patients are initiated on ART following a diagnosis of an opportunistic infection like cryptococcal meningitis. They should also continue with their cryptococcal meningitis treatment (fluconazole 200 mg daily) as well as with their ART.

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 or non-medical exposure e.g. rape and defilement, 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). However, the transmission rate may be higher if a large inoculum is received and if there has been concomitant tissue destruction.

The types of exposures to HIV infected materials that should be considered for post-exposure prophylaxis (PEP) include:

- 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
- Non medical exposure e.g. road traffic accidents and rape or defilement

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. They should implement universal precautions for the prevention of exposure to potentially infectious material. The program should include:

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

All personnel should be 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. The general public and the police must be sensitized to handle non-medical HIV exposure with centers that provide PEP and assist victims access the services without unnecessary delays.

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:

- Wash the wound/exposed area thoroughly with soap and water
- For the eye or mouth, if contaminated, rinse with plenty of water
- Report the injury to a senior staff member, supervisor, or the PEP designated officer of the unit
- Take ARVs recommended for PEP immediately: these should be started within 2 hours if possible and at the latest within 72 hours of the exposure.
- 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 HCT 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. However, PEP could still be used if the source is considered high risk, when there is a possibility of a highly infectious window period.
- If the exposed health worker is HIV-positive, no further PEP is necessary, but the health worker should be referred for further counseling and long-term HIV management.
- If the health worker is HIV negative, and the source patient is HIV positive then continue with the ARV drugs for a period of four weeks; repeat health worker's HIV test at 6 weeks, 3 months 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 exposure
- 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:
- ZDV (300 mg twice daily) + 3TC (150 mg twice daily)
- ZDV (300 mg twice daily) + FTC (200 mg daily)
- TDF (300 mg once daily) + 3TC (300 mg once daily)
- TDF (300 mg once daily) + FTC (200 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/r (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 or up to 4 weeks.

In spite of the above recommendations, experience has shown that:
- Despite the risk, those put on 3 drugs have a higher rate of failure to complete the recommended period of treatment of 4 weeks
- Regimens containing EFZ are poorly tolerated and are associated with a higher rate of failure to complete therapy
- Two drug regimen is as successful as three drugs even with those in the high risk category

As a result of these observations, we are recommending **a two-drug regimen** irrespective of the type or risk exposure.

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. For more information please contact MOH or see PEP National Guidelines.

APPENDIX 1: WHO Staging for HIV Infection and Disease in Adults & adolescents

Clinical Stage I:

1. Asymptomatic
2. Persistent generalised lymphadenopathy

Performance Scale 1: Asymptomatic, normal activity

Clinical Stage II:

1. Moderate weight loss (less than 10% of presumed or measured 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, tonsillitis, otitis media and pharyngitis

And/or Performance Scale 2: Symptomatic but normal activity

Clinical Stage III:

1. Severe weight loss (more than 10% of presumed or measured 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 (current)
7. Severe bacterial infections such as pneumonias, pyomyositis, empyema, bacteremia or meningitis
8. Acute necrotizing ulcerstive stomatitis, gingivitis or periodontitis
9. Unexplained anemia (<8gm/dl), neutropenia ($<0.5\times 10^9$ per litre), or chronic thrombocytopenia ($<50\times 10^9$ per litre)

And/or Performance Scale 3: Bed-ridden 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 pneumonia* (PCP)
3. Recurrent severe bacterial pneumonia
4. *Toxoplasmosis of the brain*
5. Cryptosporidiosis with diarrhoea for more than 1 month
6. Chronic isosporiasis
7. Extrapulmonary cryptococcosis including meningitis
8. Cytomegalovirus infection (retinitis or infection of other organs)
9. Herpes simplex virus (HSV) infection, mucocutaneous for more than 1 month, or visceral at any site
10. Progressive multifocal leukoencephalopathy (PML)
11. Any disseminated endemic mycosis such as histoplasmosis, coccidioidomycosis
12. Candidiasis of the oesophagus, trachea, bronchi or lungs
13. Atypical mycobacteriosis, disseminated
14. Recurrent non-typhoid salmonella septicaemia
15. Extrapulmonary tuberculosis
16. Lymphoma
17. Invasive cancer of the cervix
18. Kaposi's sarcoma
19. 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
20. Atypical disseminated leishmaniasis
21. Symptomatic HIV-associated nephropathy or symptomatic HIV associated cardiomyopathy

And/or Performance Scale 4: Bed-ridden for more than 50% of the day during the last month

APPENDIX 2: WHO Clinical Staging of HIV for infants &children with HIV infection

Clinical Stage I:

1. Asymptomatic
2. Persistent generalised lymphadenopathy

Clinical Stage II:

1. Unexplained persistent hepatosplenomegaly
2. Papular pruritic eruptions
3. Extensive wart virus infection
4. Extensive molluscum contagiosum
5. Recurrent oral ulcerations
6. Unexplained persistent parotid enlargement
7. Lineal gingival erythema
8. Herpes zoster
9. Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
10. Fungal nail infections

Clinical Stage III:

1. Unexplained moderate malnutrition not adequately responding to standard therapy
2. Unexplained persistent diarrhoea (14 days or more)
3. Unexplained persistent fever (above 37.5 ºC, intermittent or constant, for longer than one month)
4. Persistent oral candidiasis (after first 6 weeks of life)
5. Oral hairy leukoplakia
6. Acute necrotizing ulcerative gingivitis/periodontitis
7. Lymph node TB
8. Pulmonary TB
9. Severe recurrent bacterial pneumonia
10. Symptomatic lymphoid interstitial pneumonitis
11. Chronic HIV-associated lung disease including bronchiectasis
12. Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5 x 109/L^3) or chronic thrombocytopenia (<50 x 109/ L^3)

Clinical Stage IV:

1. Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
2. Pneumocystis pneumonia (PCP)
3. Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
4. Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site)
5. Extrapulmonary TB
6. Kaposi sarcoma
7. Oesophageal candidiasis (or Candida of trachea, bronchi or lungs)
8. Central nervous system toxoplasmosis (after the neonatal period)
9. HIV encephalopathy
10. Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month
11. Extrapulmonary cryptococcosis (including meningitis)
12. Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
13. Chronic cryptosporidiosis (with diarrhoea)
14. Chronic isosporiasis
15. Disseminated non-tuberculous mycobacteria infection
16. Cerebral or B cell non-Hodgkin lymphoma
17. Progressive multifocal leukoencephalopathy
18. HIV-associated cardiomyopathy or nephropathy

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 especially in women with CD4 greater than 250

Hyperglycemia

- Results from peripheral and hepatic insulin resistance, insulin deficiency, and a reduced capacity of the 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 includes unexplained gastrointestinal symptoms (abdominal pain, nausea, vomiting, anorexia, diarrhea, hepatomegaly, distension), wasting, dyspnoea, ascending weakness, and/or paraesthesias
- Lab shows elevated lactate (>2-5 mmol/ml), elevated anion gap ($Na - [Cl + CO_2] > 16$,
- Treatment may require life support and intravenous bicarbonate

Fat misdistribution

- 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 involves 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

Skin rash

- Rash reactions are most common with NNRTIs, especially Nevirapine 10-20%. Most rash reactions are mild, maculopapular and occur within the 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 wet and associated with fever, desquamation, mucous membrane involvement, blistering, or arthritis

APPENDIX 4: Antiretroviral Drug Toxicity

Antiretroviral Drug	Primary toxicities	Minor toxicities	Monitoring/Management
Zidovudine (ZDV)	Hematological (Anemia, neutropenia, thrombocytopenia), myopathy, GI intolerance	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. Stop if elevated. Restart when resolved or change to ABC
Stavudine (d4T)	Painful neuropathy, lipoatrophy, lactic acidosis, hepatitis, pancreatitis	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
Tenofovir (TDF)	Renal dysfunction		Monitor renal function at baseline, and every 6 months. Avoid use in pregnant women except if other alternatives are not available.
Abacavir (ABC)	Hypersensitivity reaction,	Lactic acidosis	Discontinue therapy and don't restart when resolved
Nevirapine (NVP)	Skin rash, Stevens-Johnson syndrome, hepatoxicity		Low-dose over first 2 weeks minimizes rash occurrence. If mild or moderate continue cautiously or substitute with EFV. If severe stop NVP and permanently if hepatitis +ve
Efavirenz (EFV)	Nightmares, rash, hepatitis	Dizziness,	Rash in 10% but rarely severe <1%; CNS symptoms often resolve 2-4 weeks. Stop if hepatitis is confirmed.
Lopinavir/Rotinavir	Diarrhea, skin rash	Headache, weakness	Diarrhea rarely severe
Nelfinavir (NFV)	Diarrhea, lipid, glucose & liver abnormalities,		Diarrhea occurs 10-30% at start of therapy but often resolves on its own
Indinavir (IDV)	Nephrolithiasis, hepatitis, lipid, glucose abnormalities	Headache, rash, retinoid-like effects, alopecia,	Ensure adequate re-hydration (1.5 L/day). Monitor liver enzymes
Emtricitabine (FTC)	Lactic acidosis with hepatic steatosis	Hyperpigmentation Skin coloration	Do serum lactate if suspicious symptoms exist

APPENDIX 5: Antiretroviral dosage regimens for adults and adolescents

Drug Class	Drug	Dose	Comments
Nucleoside RTIs	Zidovudine (ZDV)	300 mg twice daily	
	Stavudine (d4T)	30 mg twice daily	
	Lamivudine (3TC)	150 mg twice daily or 300mg once daily	Well tolerated No food restrictions Also active against hepatitis B
	Didanosine (ddI)	400 mg once daily	250mg once daily if <60 kg or with TDF
	Abacavir (ABC)	300 mg twice daily	
	Emtricitabine (FTC)	200 mg once daily	
Nucleotide RTI	Tenofovir (TDF)	300 mg once daily	
Non-nucleoside RTIs	Efavirenz (EFV)	600 mg once daily	Should be taken at bedtime
	Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily	This is the 'lead in dosing'
	Delavidrine (DLV)	400 mg three times a day	It has several drug interactions
	Etravirine (ETV)	200 mg twice daily	
Protease Inhibitors	Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily	533 mg/133 mg twice daily if combined with EFV or NVP
	Nelfinavir (NFV)	1250mg twice daily	
	Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily	Dose adjustment when combined with an NNRTI may be required
	Saquinavir/ritonavir (SQV/r)	1000 mg/100 mg twice daily or 1600 mg/100 mg once daily	Dose adjustment when combined with an NNRTI may be required
	Atazanavir (ATV)	400 mg once daily	ART/r 300 mg/100 mg once daily
	Tipranavir (TPV)	500 mg twice daily	
	Duranavir (DRV)	600 mg/100 mg twice daily	
Fusion Inhibitors	Enfuvirtide (T-20)	90 mg (1 ml) twice daily	Injected subcutaneously into the upper arm, thigh or abdomen
Integrase Inhibitors	Raltegravir (ISENTRESS)	400 mg twice daily	
Fixed combinations	D4T/3TC/NVP (Triomune)	30mg/150 mg/200 mg as 1 tablet twice daily	d4T-40mg is being phased out due to toxicity
	ZDV/3TC/ABC (Trizivir)	300 mg/150 mg/300 mg as 1 tablet twice daily	Use tablet with d4T 30 mg
	TDF+FTC+EFV (Atripla)	300mg/ 200mg/600mg as 1 tablet daily	Take at bedtime because of efavirenz
	ZDV/3TC (Combivir)	300 mg/150 mg as 1 tablet twice daily	

APPENDIX 6: Antiretroviral dosage regimens for Children and Infants

Nucleoside reverse transcriptase inhibitors (NRTIs)			
Drug	**Dose**	**Formulations**	**Comments**
Zidovudine (ZDV)	For >6wks – 12yrs 180 -240 mg/m^2 twice daily >12yrs 300mg twice daily Intravenous: 1.5 mg/kg infused over 30 minutes, every 6 hours until oral dosing is possible. For children with suspected nervous system involvement dose of 240mg/m2 per dose given twice daily may be more beneficial.	Syrup: 10 mg/ml Capsules: 100 mg and 250 mg (May be opened and dispersed in water or on to a small amount of food and immediately ingested) Tablet: 300 mg	Do not use stavudine with zidovudine (ZDV) due to an antagonistic effect No food restrictions Use with caution in children with anemia due to potential for bone marrow suppression
Stavudine (d4T)	<30kg 1mg/kg bd >30kg 30mg bd >60kg 40mg bd	Oral solution: 1 mg/ml (requires refrigeration after reconstitution) Capsules: 15 mg, 20 mg, 30 mg, 40 mg (Can be opened and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated)	Well tolerated. Do not use stavudine with zidovudine (ZDV) due to an antagonistic effect
Lamivudine (3TC)	6 wks – 12 yrs; 4mg/kg twice daily >12yrs 150mg twice daily	Syrup; 10mg/ml available Tablet; 150 mg	Well tolerated. No food restrictions Also active against hepatitis B
Didanosine (ddI)	<3 months: 50mg/m2/dose twice daily 3 months to <13 years: 90−120 mg/m2/dose twice daily Maximum dose, ≥13 years or >60 kg: 200 mg/dose twice daily or 400mg once daily	Oral solution from paediatric powder/10 mg/ml (Should be kept refrigerated) Chewable tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg (not be swallowed whole but can be crushed or dispersed in water or clear juice) Enteric-coated beadlets in capsules: 125 mg, 200 mg, 250 mg, 400 mg (designed for once daily dosing preferred but still not widely available)	ddI is degraded rapidly unless given as an enteric formulation or combined with buffering agents or antacids In children this effect may be less marked and ddI may not have to be administered on an empty stomach
Abacavir (ABC)	<6months – 16yrs 8mg/kg twice daily >30kg: 300mg twice daily	Oral solution: 20 mg/ml Tablet: 300 mg	Parents must be warned about potential ABC hypersensitivity reaction ABC should be stopped permanently if hypersensitivity

			reaction occurs No food restrictions
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Drug	**Dose**	**Formulations**	**Comments**
Efavirenz (EFV)	Syrup: 30 mg/ml (Note: syrup has lower bioavailability and ratio of 1.3 syrup to solid formulation is suggested to achieve an equivalent dose) Capsules: 50 mg, 100 mg, 200 mg Tablets: 600 mg	Syrup: 19.5 mg/kg/day Capsule / tablet: 15mg/kg/day Weight greater than 40 kg, 600 mg once daily Wt Kg Dose (mg) 13-15 200 15-20 250 20-25 300 25-32 400 >32 600 capsules, once a day at night	Insufficient data on dosing for children <3 years old Can be given with food but if taken with food, especially high-fat meals, absorption is increased by an average of 50% Best given at bedtime in order to reduce CNS side-effects, especially during first two weeks
Nevirapine (NVP)	160−200 mg/m^2 to maximum dose of 200 mg taken twice daily <8yrs 4mg/kg once daily for 14 days then 7mg/kg twice daily >8yrs 4mg/kg once daily for 14 days then 4mg/kg twice daily	Oral suspension: 10 mg/ml Tablet: 200 mg For MTCT prevention: 2 mg/kg/dose within 72 hours of birth once only. If the maternal dose of nevirapine was given less than 2 hours before delivery, then administer 2 mg/kg/dose to the infant immediately after birth and repeat within 24−72 hours of first dose. If the infant weight is not available, administer 0.6 ml oral suspension.	Parents must be warned about a potential severe, life-threatening rash during the 14-day lead-in period. The once-daily induction dose is used to reduce the frequency of rash. Should be permanently discontinued and not restarted in children who develop severe rash Drug interactions: avoid nevirapine if rifampicin is co administered Can be given without regard to food
Protease inhibitors			
Lopinavir/ritonavir (LPV/r) [co formulation]	>2yrs: 2.9ml/m^2 twice daily with food. Max. 5ml/m^2 twice daily	Oral solution: 80 mg/ml lopinavir plus 20 mg/ml ritonavir Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir (Should not be crushed or opened; must be swallowed whole) Tablets: 100 mg lopinavir + 25 mg ritonavir (Should be taken with food)	Should be taken with food Preferably, oral solution and capsules should be refrigerated; however, can be stored at room temperature up to 25°C for two months; at >25°C drug degrades more rapidly There are many drug-to-drug interactions because RTV inhibits cytochrome P450
Atazanavir/ritonavir ATV/r	310mg/m2 once daily (od) Wt 15kg - < 20kg 8.5 mg/kg ATV and 4mg/kg RTV od Wt > 20kg 7mg/kg and RTV 4mg/kg od Maximum dose 300mg RTV	ATV Oral powder 50mg/1.5g dispersible powder ATV Capsules 100, 150, 200 and 300mg capsules	Should be taken with meals Approved for children over 6 years but has been used in 3mths – 6yr olds Store in cool dry place protect

	and 100mg RTV once daily	Must be taken with 100mg capsule/liquid of ritonavir	from light (15-25^{o}C) No combination pill available (ATV+Rtv) Currently recommend for 2nd line therapy **(Discuss with experts prior to use)**
FIXED-DOSE COMBINATIONS (FDCs)			
Drug	**Dose**	**Formulations**	**Comments**
Stavudine (d4T) plus lamivudine (3TC) plus nevirapine (NVP) (Triomune)	30 mg/150 mg/200 mg as 1 tablet twice daily Maximum dose: one 30-mg d4T-based tablet twice daily **For dosing of children, please see the dosing chart**	Tablet: d4T (30 mg) plus 3TC (150 mg) plus NVP (200 mg); or Tablet: 6mg stavudine/30 mg lamivudine/50 mg nevirapine (Triomune baby) Tablet: 12 mg stavudine/60 mg lamivudine/100 mg nevirapine (Triomune junior)	Contains a fixed dose of NVP, therefore cannot be used for induction as nevirapine dose escalation required (see NVP dosing recommendations)
Zidovudine (ZDV) plus lamivudine (3TC) plus Nevirapine (NVP) (Dvir-N)	300mg/150/200 as 1 tablet twice daily **For children, please see the dosing chart**	Tablet: ZDV (30mg) plus 3TC (150mg) plus NVP (200mg) Tablet: ZDV(60mg) plus 3TC 30mg) plus NVP (50mg) (Baby combivir)	
Zidovudine (ZDV) plus lamivudine (3TC) (Combivir)	Zidovudine - 180-240mg/m2/dose twice daily Lamivudine - 4mg/kg/dose twice daily Maximum dose: 1 tablet/dose twice daily	Oral solution: not available Tablet: ZDV (300 mg) plus 3TC (150 mg) Tablet: ZDV 60mg plus 3TC 30mg (Baby combivir)	
Stavudine (d4T) plus lamivudine (3TC)	Stavudine- 1mg/kg/dose twice daily Lamivudine - 4mg/kg/dose twice daily Maximum dose: 1 tablet/dose twice daily **For children, please see the dosing chart**	Tablets: d4T (30 mg) plus 3TC (150 mg) Tablets: d4T (6mg) plus 3TC (30mg) – (Lamivir-S baby) Tablet: d4T (12mg) plus 3TC (60mg) (Lamivir-S Junior)	
Zidovudine (ZDV) plus lamivudine (3TC) plus abacavir (ABC)	Zidovudine - 180-240mg/m2/dose twice daily Lamivudine - 4mg/kg/dose twice daily Abacavir - 8mg/kg/dose twice daily Maximum dose: 1 tablet/dose twice daily	Oral solution: not available Tablet: ZDV (300 mg) plus 3TC (150 mg) plus ABC (300 mg)	Parents must be warned about potential ABC hypersensitivity reaction ABC should be stopped permanently if hypersensitivity reaction occurs Pharmacokinetic data: Available only for adults and adolescents

APPENDIX 7: Karnofsky (Performance) Score [KS]

Able to carry on normal activity, No special care is needed →	100	Normal; no complaints; no evidence of disease
	090	able to carry on normal activity; minor signs or symptoms of disease
	080	Normal activity with effort; Some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed →	070	Cares for self; unable to carry on Normal activity or to do active work
	060	Requires occasional assistance And frequent medical care
	050	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly →	040	Disabled; requires special care and assistance
	030	Severely disabled; hospitalization is Indicated, though death is not imminent
	020	Very sick; hospitalization is necessary; Active supportive treatment is necessary
	010	Moribund; fatal processes are progressing rapidly
	000	Dead

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