



GUIDELINES

**FOR ANTIRETROVIRAL
DRUG THERAPY IN**

KENYA

Enquiries regarding these Clinical Guidelines should be addressed to:

Director
National AIDS and STI Control Programme (NAS COP)
Ministry of Health
P.O. Box 19361
Nairobi, Kenya
Telephone: +254 20 2729502/2729549
Email: headnascop@iconnect.co.ke

NOTES ON DRUG DOSES

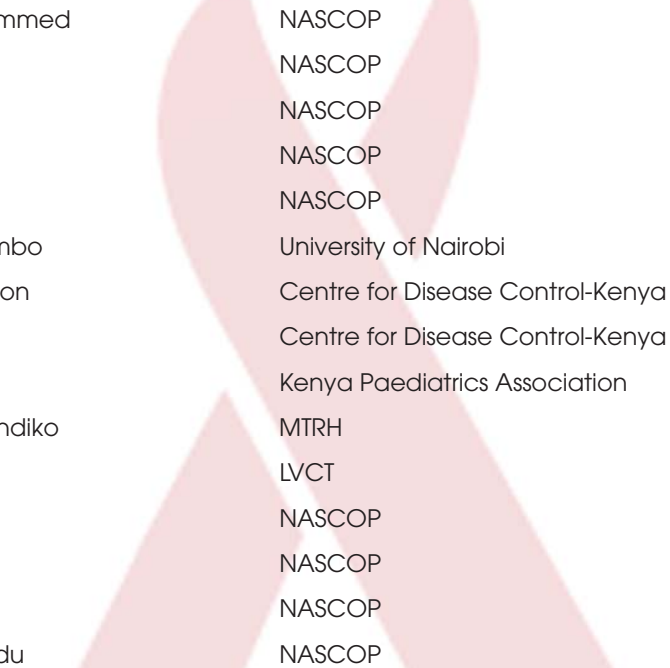
Every effort has been made to ensure that the drug dosages and treatment schedules are correct and in accordance with current accepted medical practice. However, no responsibility can be taken for errors or omissions. When using an unfamiliar drug, clinicians are urged to confirm dosages before prescribing or administering the drug.

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Editors



Dr Ibrahim Mohammed	NASCOP
Dr Isaiah Tanui	NASCOP
Dr Sylvia Ojoo	NASCOP
Dr Emily Koech	NASCOP
Dr Mary Wangai	NASCOP
Dr. Elizabeth Obimbo	University of Nairobi
Dr. Barbara Marston	Centre for Disease Control-Kenya
Dr. Lucy Nganga	Centre for Disease Control-Kenya
Dr. Joe Mbuthia	Kenya Paediatrics Association
Dr. Winstone Nyandiko	MTRH
Dr. Aziz Abdullah	LVCT
Dr Cecila Muiva	NASCOP
Dr Dorine Kagai	NASCOP
Doris Odera	NASCOP
Beatrice Gathendu	NASCOP



FOREWORD

Since the first case of Acquired Immunodeficiency Syndrome was reported in Kenya in 1984, HIV/AIDS has continued to have a devastating impact on all sectors of the society. The prevalence of HIV infected individuals in Kenya has fallen from 14% in 1998 to 7% in 2003 with an estimated 1.5 million Kenyans living with the virus. It is further estimated that 15% of the infected are in urgent need of antiretroviral treatment.

In the early years of the pandemic, the major interventions were aimed at prevention of new infections through creating awareness as well as advocacy for behaviour change. The majority of those who were already infected could only access palliative care as the cost of antiretroviral drug therapy was prohibitive and beyond the reach of many. Fortunately, the last few years have seen the introduction of services that can ameliorate the suffering of people living with HIV/AIDS (PLHA). The current widespread availability of antiretroviral therapy has changed the fortunes of those infected by this virus.

The goals of antiretroviral treatment are to improve the quality of life of the HIV infected, reduce HIV related morbidity and mortality, and restore or preserve their immune function through maximal suppression of viral replication. For this to happen effectively, the treatment should be administered carefully bearing in mind the efficacy of the regimen as well as the tolerability, affordability and availability of the drugs. However, it cannot be over emphasized that the mainstay of managing the HIV/AIDS epidemic still relies primarily on prevention and advocacy for behaviour change.

This 3rd Edition of the Guidelines has been put together by a team of experts drawn from the Public, Private and Academic health sectors that is well versed in various aspects of HIV/AIDS care. It is intended for use by multi-disciplinary teams of Health Care Workers (HCWs) providing care for HIV/AIDS patients. With the publication of these guidelines, the Ministry of Health hopes to ensure the provision of quality care to the HIV-infected through building the capacity of the providers by equipping them with current and simplified knowledge on the management of HIV infection including the rational use of antiretroviral drugs. Because of the difficulties and uniqueness in diagnosis and treatment of HIV/AIDS in children the inclusion of a comprehensive chapter on antiretroviral use in children should provide valuable information to health care providers to improve delivery of quality care to this special group of people.

Bearing in mind the rapidly changing knowledge base on the management of HIV/AIDS and the emerging evidence on antiretroviral use, it is necessary that these guidelines are updated regularly.

Knowing that the amount of time and energy that has been put to this task has been enormous, I would like to pass my sincere gratitude to all those who have been involved in one way or another to successfully develop these guidelines. This is a useful document that should therefore be made available to all health care providers for whom it is intended and who need it most.



Dr James Nyikal MBS

Director of Medical Services
November, 2005



Contributors

Dr. Adungosi J.	- Family Health International
Dr. Aluoch A.	- Kenya Association of Physicians
Dr. Anzala O.	- University of Nairobi
Prof. Bhatt K.M.	- University of Nairobi
Dr. Chebet K.L.	- NASCOP - Ministry of Health
Dr. De-Cock Kevin	- CDC - Director (Kenya)
Dr. Hardika Shah	- Nairobi Hospital
Dr. Ilako, F	- Kenya Association of Physicians
Dr. Karanja Joseph	- University of Nairobi
Dr. Kayita Janet	- Family Health International
Dr. Kinuthia Doris	- Kenya Paediatrics Association
Prof Kokwaro, Gilbert	- Wellcome Trust
Dr. Koskei K.	- Chief Pharmacist - Ministry of Health
Prof. Lule G.N.	- University of Nairobi
Dr. Lwanga Charles	- Nairobi Hospital
Prof. Mati J.K.G	- KOGS
Prof. D. Mbori Ngacha	- University of Nairobi
Dr. Mohammed I.M.	- NASCOP - Ministry of Health
Dr. Mugo Nelly	- Kenyatta National Hospital
Dr. Muia Ndavi P	- KOGS
Dr. Muita Jane	- UNICEF
Dr. Mulindi Sobbie	- University of Nairobi
Mr. Muriithi Gatumo	- NASCOP
Prof. Musoke Rachel	- University of Nairobi
Dr. Mutungi Alice	- University of Nairobi
Dr. Mwangi Margaret	- Kenyatta University Hospital
Prof. Nduati Ruth	- University of Nairobi
Dr. Njagi Ephantus	- University of Nairobi
Dr. Ochiel Stephen	- KOGS
Prof. Ojwang S.B.O.	- University of Nairobi
Dr. Ombuya Godfrey	- Kenyatta National Hospital
Dr. Omondi Ogutu	- Kenyatta National Hospital
Prof. Otieno L.S.	- University of Nairobi
Dr. Owili D.	- Aga Khan Hospital
Dr. Patel S.T	- MP Shah
Dr. Qureshi Zahinda	- University of Nairobi
Dr. Shah Sital	- Aga Khan Hospital
Dr. Siika Abraham	- MTRH
Dr. Tesfaldet G.	- Aga Khan Hospital
Dr. Wairagu S.E.	- Kenyatta National Hospital
Dr. Were Edwin	- Moi University



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We sincerely thank all the members of the ART Task Force, bilateral partners, NGO's, Universities and the ART team, for sparing their time and effort, including the many meetings the authors and editors held to put the chapters together.

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ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
AFB	Acid Fast Bacilli
ANC	Antenatal Care
APV	Amprenavir
ART	Antiretroviral Therapy
ARV	Antiretroviral Drugs
ATV	Atazanavir
AZT	Zidovudine
ALT	Alanine Transaminase
BD	Twice daily
CBC	Complete Blood Count
CCC	Comprehensive Care Centre
CDC	Centre for Disease Control and Prevention
CNS	Central Nervous System
CTX	Cotrimoxazole
CXR	Chest X-Ray
CYP450	Cytochrome P450
D4T	Stavudine
DDI	Didanosine
DDC	Zalcitabine
DMS	Director of Medical Services
DOT	Directly Observed Therapy
DLV	Delavirdine
DS	Double Strength
EFV	Efavirenz
EIA	Enzyme Immunosorbent Assay (ELISA)
ELISA	Enzyme-Linked Immunosorbent Assay (EIA)
EPTB	Extra Pulmonary Tuberculosis
F-APV	Fosamprenavir
FBC	Full Blood Count
FBO	Faith Base Organization
FDCs	Fixed Dose Combinations
FHI	Family Health International
FTC	Emtricitabine
GOK	Government of Kenya
HAART	Highly Active Antiretroviral Therapy
HBC	Home Based Care
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCW	Health Care Worker
M&E	Monitoring and Evaluation
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
MOH	Ministry of Health
IDU	Injecting Drug User
IDV	Indinavir



IEC	Information, Education and Communication
IU	International Units
IPT	Isoniazid Preventative Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
KEMSA	Kenya Medical Supplies Agency
KOGS	Kenya Obstetrics and Gynaecology Society
KS	Kaposi's Sarcoma
LFT	Liver Function Test
LMIS	Logistics Management Information System
LPV/r	Lopinavir/Ritonavir
LPV	Lopinavir
LRTI	Lower Respiratory Tract Infection
MBS	Moran of the Burning Spear
MCH	Maternal and Child Health
MTCT	Mother-to-Child Transmission
MTRH	Moi Teaching and Referral Hospital
NFV	Nelfinavir
NASCOP	National HIV/AIDS and STD Control Programme
NGO	Non- Governmental Organisation
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
OD	Once daily
PARTO	Provincial ART Officer
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PGL	Persistent Generalized Lymphadenopathy
PI	Protease Inhibitor
PLHA	People Living with HIV/AIDS
PML	Progressive Multifocal Leucoencephalopathy
PMTCT	Prevention of Mother-to-Child Transmission
PPP	Public Private Partnership
PCR	Polymerase Chain Reaction
RTV	Ritonavir
RNA	Ribonucleic acid
SQV	Saquinavir
SS	Single Strength
STI	Sexually Transmitted Infection
SDNVP	Single Dose Nevirapine
T20	Enfuvirtide
TAMS	Thymidine Analogue Mutations
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TLC	Total Lymphocyte Count
TPV	Tipranavir
VDRL	Venereal Disease Research Laboratory
VCT	Voluntary Counselling and Testing
VL	Viral Load
WHO	World Health Organisation





CHAPTER 1

1.1 Programmatic Issues of Antiretroviral Therapy in Kenya

Introduction

In Kenya, HIV/AIDS prevalence of HIV is 1.5 million Kenyan. There is an urgent need of c

The introduction of ART has been shown in clinical studies and in practical settings. It is an ethical challenge to the high cost of ART. The majority of HIV infected people in Kenya cannot access this life saving treatment.

In the year 2000, the cost of ART was USD 70 per year. To meet the goal of the Government of Kenya to provide ART to 95,000 patients by 2005, the Government has increased the number of patients on ART from 54,000 in 2002 to 95,000 in 2005. The Government has also increased the number of ARVs and the number of health facilities providing ART. The Government has also increased the capacity of health facilities to provide ART. The Government has also increased the capacity of health facilities to provide ART.

The government has established a National AIDS and STI Control Agency (NACA) to coordinate and monitor the fight against HIV/AIDS. NACA has also established a National ART Programme to provide ART to HIV infected people. NACA has also established a National ART Programme to provide ART to HIV infected people.

The provision of ART services has been through GOK, faith based, and NGO facilities as well as in the private sector. ART services were originally set up in 15 pilot sites in late 2003. The lessons learnt from these sites are constantly informing program up scaling. The expansion plan is aimed at continually building capacity at regional centres, many of which are now acting as referral and training centres. Initially, priority was given to setting up HIV care services in areas with a high disease burden. Having achieved this goal, the Ministry of Health (MOH) through the National



of society. The Government has an estimated that 15% are in

designated ART sites. The Government has also established a National ART Programme to provide ART to HIV infected people. The Government has also established a National ART Programme to provide ART to HIV infected people.

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to strengthen the fight against HIV/AIDS. The Government has also established a National ART Programme to provide ART to HIV infected people. The Government has also established a National ART Programme to provide ART to HIV infected people.



AIDS and STI Control Program (NAS COP) is in the process of scaling up these services to all the 74 districts.

Access to ART is a critical element of the Ministry's policy which is guided by the following principles:-

- The ultimate goal is universal access to ART to those in need
- The core value of the policy is equity in access to ART services
- Public-private partnerships are to be used to expand access in a phased approach

1.2 IMPLEMENTATION PROCESS

The ART Program Strategy and Operational plan has been developed. It has 7 key objectives that address the following areas: -

1. Management Coordination and Policy Development
2. Human Resources
3. Service Delivery
4. Pharmaceuticals and Related Commodities
5. Infrastructure Development
6. Strategic Information
7. Communication Strategy

1.2.1 Management Coordination and Policy Development

Central Management

The National ART Task Force was born following a meeting held in September 2001 to address the way forward for ART in Kenya. The mandate of the task force is to bring together experts in private, public and faith based health institutions as well as teaching hospitals to deliberate, oversee and harmonize ART implementation. The task force guides the Ministry of Health on various issues related to ART. It meets on a regular basis. The task force has 6 sub-committees that meet and deliberate at length on issues that are then brought back to the main task force for final decision-making or ratification.

The sub-committees are as follows: -

- a) ART Training sub-committee
- b) ART Communication sub-committee
- c) ART Drug sub-committee
- d) Opportunistic Infections Sub-committee
- e) Laboratory sub committee
- f) ART Systems Sub-committee
- g) Operational Research Subcommittee

Provincial Level coordination

Decentralization of key ART activities to the provinces has been essential to the scale up of ART in Kenya. Provincial ART officers (PARTOs) were appointed to spearhead these activities at the provincial or regional levels. The PARTO, in collaboration with other partners involved with HIV-related activities, is responsible for harmonizing the implementation of ART at the provincial level, coordinating monitoring and evaluation activities and holding meetings with stakeholders,



organizing regional training and continuous medical education. Provincial Task Forces under the leadership of the Provincial Medical Officers should consist of implementers and stakeholders working within the province. In the future a district level ART point person will be appointed to support the PARTO and to coordinate ART related activities within the district.

Facility level HIV committees

It is recommended that the facility organize an HIV committee to oversee the facility's HIV-related activities. The HIV committees will nominate a clinician to be responsible for the ART program. A representative from local people living with HIV already in the ART program within the facility is recommended. The HIV committee should ensure integration and/or links between HIV-related activities (e.g. TB, PMCT, paediatric ART).

1.2.1.1 Decentralization

With the increase in demand for HIV care services, the need to decongest provincial and district hospitals and move care closer to the patient have fast become an imperative. To facilitate this, the ART program is in the process of decentralizing services through;

- Decentralization of coordination to the district level by capacity building.
- Developing a referral network of services so that each region will have facilities able to provide services from provincial level hospital up to the health centre/dispensary level. For this to happen facilities will need to recognise their individual capacities (supported by the accreditation process –see below) and develop regional networks to support patient care, laboratory testing as well as commodity distribution and management.
- Devolution of patient care to include developing of nursing cadre to be able to provide clinical care services and training non-professional staff to provide patient support services.

1.2.2 Human Resources

Scaling up ART services has necessitated training of in-service health care and support workers on various aspects of the program including counselling, HIV clinical care and rational ARV drug use, commodity logistics, laboratory diagnostics and monitoring testing among others. The Ministry of Health through NASCOP has developed appropriate curricula and tools to facilitate effective training. Looking into the future it is essential that HIV care be incorporated in all pre-service curricula and programs. Furthermore, as patients remain on ART for long periods of time complications do arise; this, together with the fact that the management of HIV is very dynamic, requires that health care workers providing care be regularly updated and supported to ensure that standards of care constantly improve.

1.2.3 Service delivery and model of care

Comprehensive Care Centres

The model of HIV clinical service delivery through the public sector is based on the phased expansion of Comprehensive Care Centres (CCCs) at national, provincial and district levels



and in Military hospitals. The Government supports the establishment of CCCs in faith based facilities (FBOs) and works with other service providers, including private-for-profit, employer based and non-governmental organizations NGOs to increase access.

Initial emphasis was placed on facilities at national and provincial levels and on selected high volume hospitals. Facilities were progressively selected on the basis of geographical coverage, HIV prevalence, and their state of preparedness to provide ART. All CCCs should provide care and support services in accordance with approved Ministry of Health clinical and service delivery guidelines.

The CCC should

1. Be an **open access** centre for patients and clients with HIV/AIDS.
2. Provide quick and accurate **diagnostic services** to patients with HIV/AIDS and related illnesses.
3. Provide medical services for **treating opportunistic infections** (OIs) in PLHA
4. Provide a **specialist HIV/AIDS clinic** (offering ARV drugs)
5. Provide **nutritional** counselling and support
6. Provide **counselling services and ARV drug adherence support** to PLHA
7. Provide **laboratory testing and monitoring** for PLHA on ARV drugs
8. Co-ordinate **Home-Based Care (HBC) services** as part of the continuum of care for patients with HIV/AIDS attending both in and out patient services
9. Liaise with other services in the community providing **non-medical care** and support for PLHA
10. Provide **comprehensive services for HIV infected children** in an appropriate setting.

Each CCC should ideally be staffed by a care and support team that matches current and anticipated patient load.

The team should work together to offer an integrated service. The basic team usually consisting of staff working both in the CCC and in the main hospital should include the following cadres:

- Medical officer/clinical officer
- Nurse
- Nutritionist
- Laboratory technologist/technician
- Counsellor
- Records information clerk
- pharmacist/pharmaceutical technologist

Entry points and wider comprehensive care links

The CCC has multiple entry points which act as gateways to ART services. These include all testing and counselling services including diagnostic testing (in and out patients including paediatric and medical wards, MCH/ANC, TB services)

Voluntary Counselling and Testing (VCT), Prevention of Mother to Child Transmission (PMTCT) units, STI services and community/Home Based Care (HBC) programs.

Accreditation of facilities for ART service delivery

Accreditation criteria have been developed for public and private facilities providing HIV clinical care and ART. The criteria cover the areas of personnel; equipment; physical facilities; laboratory



facilities; psycho-social support systems; drug dispensing and storage facilities; services provided including linkages with in and with out the facility; data management. The Ministry of Health will be responsible for updating and maintaining the accreditation criteria. It will also develop the methods for assessing and setting standards. MOH will therefore provide, train and support the accreditation teams, design accreditation methods and tools and review accreditation reports

1.2.4 Pharmaceuticals and Related Commodities

The supply chain management system for ARVs includes the following components:

- patients requiring ART
- medical sites (facilities) offering ART
- local or national level warehouses
- ART program managers and policy-makers at central level
- ARV manufacturers.

The management of ARV drugs, whether in the public or private sector, and at all levels of the healthcare system (local, provincial, etc) follows a cycle that comprises the following:

- Selection of the ARV drugs required by the ART program
- Procurement of the drugs (which includes the steps of forecasting and quantification)
- Inventory management, distribution and storage of the drugs
- Use of the drugs (prescribing, dispensing, etc)

This cycle is supported by management functions such as ART program organization, financing of drug procurement, trained staff, information management, monitoring & evaluation; and it operates within a policy and legal framework.

ARV drugs require a good supply chain management system because they are costly, generally have a short shelf life, require life-long use so they should be continuously available and they also require strict adherence by the patient so as to minimize development of resistance. The key purpose of the drug supply chain, or logistics management system, is to ensure that there is an uninterrupted reliable supply of ARVs, by ensuring the movement of ARVs from one place to another, so that they reach their destination in the required quantity, in the least possible time and at the least possible cost.

A Logistics Management Information System (LMIS), which may be manual or computerized, collects, reports and uses information for decision-making, for example to help in forecasting the quantity of drugs required to re-supply or expand the program. It also provides a way to track the movement of the ARV drugs. Essential data items collected using the LMIS includes Stock-on-hand, Losses & Adjustments and Consumption data over a specified period of time. Good use of the information collected helps prevent under- or over-stocking, and provides information for monitoring & evaluation and planning for the future of the ART program. In order to ensure effective re-stocking of government-supported ART sites as part of the LMIS, a recording and reporting system has been set up at both the central warehouse (KEMSA) and program (NASCOP) level, and at the ART site level. The records and reports include:

- Stock-keeping records (e.g. bin cards)



- Transaction records which record information about stock movements (e.g. Requisition & Issue vouchers)
- Consumption records which record the quantity of ARV drugs dispensed to patients (e.g. Daily Activity Registers)
- Reports (e.g. Monthly ARV Consumption) that are sent by the ART site on a monthly basis to program level or central warehouse level staff to inform them about the status of the ARV drugs at the site.

Monitoring & evaluation of the drug logistics system is used to assess progress; to identify problem areas and to offer potential solutions in the area of drug supply. Indicators used for this include “The number of times a program has been out-of-stock of an ARV drug for more than 5 days”.

It should be noted that commodities involved in providing Comprehensive HIV care include more than ARVs alone, they also include:

- Preventive therapy drugs, e.g. Cotrimoxazole, Nevirapine for PMTCT
- Drugs for treatment of STIs and Opportunistic Infections (OIs), e.g. Fluconazole
- HIV Test kits and laboratory reagents
- Laboratory reagents and supplies for ART baseline and follow-up tests, diagnosing OIs, monitoring Viral load and CD4, and the side effects of ARVs, etc.

A good supply chain should cater for all commodities needed for a HIV care program.

1.2.5 Infrastructure Development

Setting up treatment services has not always required that new buildings be erected. Existing space has been successfully adapted quite well by many public facilities to suit the requirements of new HIV care centres. However, in many public facilities there is often not enough room for an expanding service. Consequently the government, with the support of its partners will provide new buildings in a select number of facilities particularly hard hit with a lack of space.

Inadequate laboratory equipment and systems have been and continue to be a major hindrance to effective ART. The government, with the support of its partners, aims to improve the infrastructure and to avail appropriate equipment to all provincial and district hospitals in the short term.

1.2.6 Strategic Information and Communication Strategy

The main aim of the Communications Strategy is patient and public information, education on and preparation for the widespread accessibility and availability of ART. Information, Education and Communication (IEC) activities are a critical component of the ART policy.

The strategy covers the following aspects:

- 1) Patient education in order to manage expectations, while publicizing the services and the comprehensive care concept
- 2) Reinforcement of the importance of counselling and testing as an important first step
- 3) Promotion of the wellness concept and focus on positive ways that PLHAs can improve their health and extend their lives.



- 4) Promotion of the concept that AIDS can be a manageable disease, but that ARV drugs are not a cure and reinforce the need to continue to prevent transmission when taking ARV drugs
- 5) Promotion of treatment literacy for patients and the wider community, including information supporting adherence to ARV drugs and the importance of continuous treatment
- 6) Communication to health workers and others closely associated with health services about the ART program implementation and patient support

The communications campaign aims to increase the effectiveness and impact of the program, increase ownership and maximize participation encouraging community involvement as well as emphasizing the need for continuing prevention.

1.3 MONITORING AND EVALUATION

1.3.1 Introduction

The purpose of Monitoring and Evaluation in provision of the ART Program is to measure utilization and effectiveness of the program in relation to resource allocation. By keeping track of specific areas of ART program performance, operational problems can be identified and corrective measures put in place on time. The Ministry of Health is responsible for monitoring of the ART program, including ART provision in both the public and private sectors. To this end the Ministry of Health is developing systems that will enable the timely collection of accurate data to inform the program. Together with other stakeholders and partners the Ministry has developed key ART indicators which will generate information that should be reported from all sites. NASCOP is responsible for collecting data from all sites providing ART services. Currently NASCOP has standardized priority indicators selected upon agreement with stakeholders and coordinated by the National AIDS Control Council (NACC) which fit into the National M&E framework. These indicators are contained in the integrated HIV/AIDS M&E reporting tool.

Given that current ART is life long, effective monitoring and documentation of the process is mandatory. For this to be realized an M & E system that captures the key indicators comprehensively, analyses data and reports to the ART program is necessary. For this to happen it is essential that systems used should be institutionalized, data collection systems be sustainable and user friendly; data be submitted to NASCOP at designated intervals through existing systems and a national database be set up and maintained. For effective data collection all facilities providing ART should report service statistics using the standardized tools. NASCOP has the mandate to co-ordinate the review and the development of ART data collection tools, data collection and dissemination plans.

1.3.2 Tools recommended for ART Monitoring

Patient appointment card containing return date, medication including ARVs

1. Patient card/file-containing patient information
2. Daily register-containing a list new and re-attendant records
3. HIV Care Monthly Summary-should capture the national indicators
4. One permanent ART register containing the list of all patients on ARV drugs, date



- started, type of ARVs the patient is on and the CCC NO.
5. One permanent HIV Clinic/CCC enrolment register containing HIV Clinic/CCC numbers of each enrolled client date enrolled and status
 6. One permanent ART register containing the list of all patients on ARV drugs, date started, type of ARVs the patient has been on.

Conclusion

In conclusion, the implementation of ARV drug therapy in Kenya should adopt a pragmatic public health approach to ART provision based on the application of national guidelines, while promoting standardization and quality control. The sustained provision of ART requires the development of systems to sustain delivery of quality HIV care. This should be regarded as a priority both in the public and non governmental health care sector.

In the public sector effective delivery of the ART Program is dependent on strengthening the national health care system. To that effect, major investments are being made to strengthen facilities, develop and train human resources, integrate management systems, secure drug and supply chains, and develop strong strategic information management.

However the cornerstone of the overall strategic approach to rapidly scale up ART is collaboration and partnership between the public, private-for-profit, NGO and faith-based sectors. It is therefore pertinent that the ART task Force remains vibrant to guide the country on both technical and non technical issues.



CHAPTER 2

Initiating Antiretroviral Therapy

2.1 Introduction

Human Immunodeficiency Virus (HIV) belongs to the genus Lentivirus of the family Retroviridae and has been divided into two types:

- HIV type 1 (HIV-1)
 - Responsible for the global pandemic
 - Has several subtypes; in Kenya the commonest are subtypes A and D, however a person can be infected with different subtypes, or with recombinant viruses with features of more than one subtype.
- HIV type 2 (HIV-2)
 - Largely restricted to West Africa, with limited spread to other countries
 - Compared with HIV-1, HIV-2 is less transmissible (5- to 8- fold less efficient than HIV-1 in early-stage disease and rarely the cause of vertical transmission), is associated with a lower viral load, and is associated with a slower rate of both CD4 cell decline and clinical progression.

HIV infection can be transmitted by contact with contaminated blood or bodily fluids through:

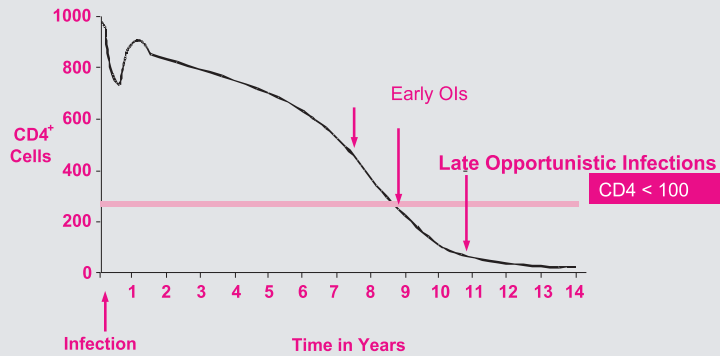
- Sexual contact (unprotected)
- Inoculation with infected blood or blood products
- Sharing or use of contaminated needles
- Vertical transmission from mother to child

Natural History of HIV Infection

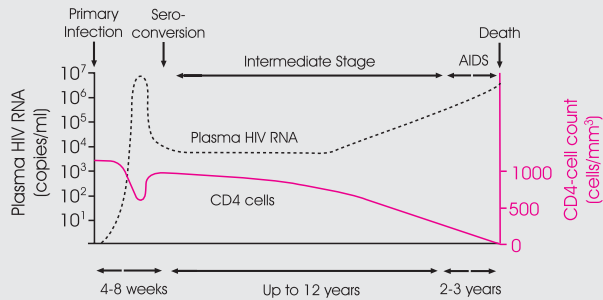
Infection with HIV results in a progressive destruction of the CD4+ T lymphocytes. The destruction of T – cells is mainly due to active viral replication. Viral load determines the rate of CD4 T – cell decline and consequently determines the rate of immunodeficiency and subsequent development of HIV-related opportunistic infections, as illustrated below.



Natural History of Untreated HIV-1 Infection



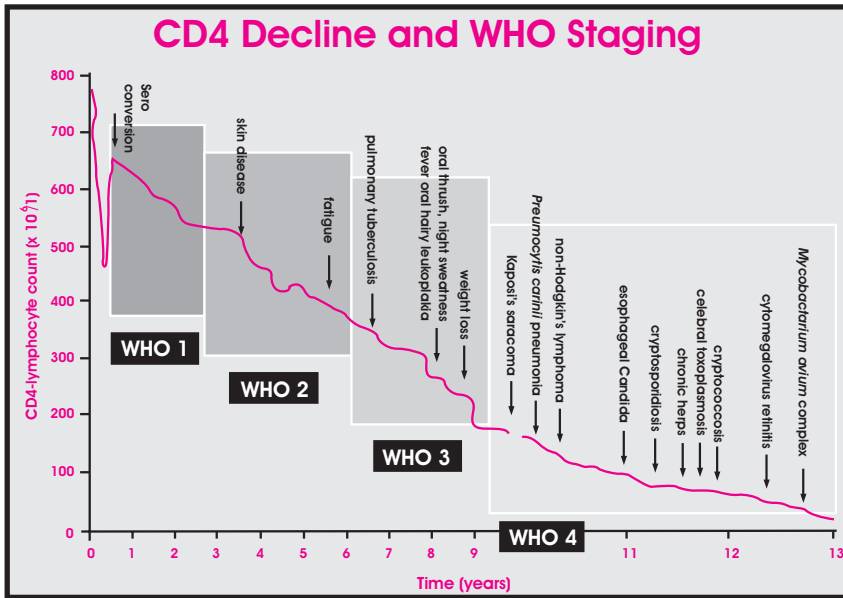
Changes in Plasma HIV RNA Correlate with HIV Disease Progression



Adapted from Piatak M Jr et al Science 1993;259:1749-1753 and Weiss RA Science 1993;260:1273-1279.



Clinical Progression of HIV Infection



From the above illustrations, it is quite clear that both viral load and CD4 count correlate well with the prognosis of HIV disease. The CD4 count also correlates well with the clinical picture, thus the use of this parameter as an indicator of time to initiate treatment.

2.2 Basic Evaluation for ART

2.2.1 Pre-treatment Evaluation

All patients seeking HIV care in comprehensive care centres, or other health care settings should have a complete medical history taken, a thorough physical examination and as complete and appropriate a laboratory evaluation as possible carried out. The purpose of this comprehensive clinical assessment is to:

- Confirm the presence of HIV infection if not previously or reliably done
- Stage HIV disease
- Detect the presence of any existing illnesses particularly the common and serious opportunistic infections.
 - **Screening for TB should be carried out in all patients.** This should largely be based on the history and examination; a routine CXR is not required in all patients.
 - Most HIV infection is a sexually transmitted; thus all HIV positive adult patients should be assessed for symptoms of STIs and syndromic management provided where indicated.
- Review concomitant medications, including traditional therapies, alcohol, cigarette use and non-prescribed drug use
- HIV positive patients being assessed for treatment should be started on cotrimoxazole preventive therapy unless contraindicated (see section 2.3.2)



- HIV positive patients should be offered multivitamin supplementation particularly where nutritional requirements may not be adequately met. This is because multivitamins may act as potent antioxidants and reduce HIV replication, slowing disease progression.

Evaluation of the patient should include weight, nutritional and social assessment, as well as assessment of other factors that may impact on adherence.

2.2.2 Clinical Staging

The WHO Clinical Staging is designed to be used where HIV infection is confirmed with an antibody or a virological test. It is useful for determining prognosis, monitoring patients' clinical progress and prioritizing the use of preventive interventions. Apart from this, it is particularly useful for providing guidance as to when to start or review ARV drug therapy as well as help assess clinical response to therapy in the absence of appropriate laboratory tests. For the revised WHO Clinical Staging in Adults and Adolescents see Appendix Table 13.

2.2.3 Laboratory Assessment

As of early 2005, there are still many public facilities providing care for HIV positive individuals which do not have access to basic laboratory tests ideally suited for pre-treatment and on-treatment assessment of patients on ART. These tests are undoubtedly useful. However, lack of access to them should as much as possible not be a barrier to access to ART. Thus, in settings where some haematological or biochemical tests are not available or accessible, clinical information should guide decisions of patient management where possible, taking into account intended drug regimens.

- Basic tests

The following are the baseline laboratory tests that should be performed whenever possible:

- Full blood count with differential
- Serum transaminases (preferably serum alanine aminotransferase (ALT/SGPT))
- Serum creatinine
- Serum glucose
- Pregnancy test
- CD4 cell count
- Sputum for AFB where a sample is available

CD4 count serves as the most important biological (laboratory) indicator of the degree of immunosuppression in patients with HIV infection and the most important prognostic indicator for patients starting ART. The CD4 count is particularly useful in asymptomatic HIV positive patients, some of whom may be severely immunocompromized and qualify for treatment. It should therefore be carried out where it is available. As discussed below, symptomatic HIV positive patients should nonetheless be started on ART in the absence of a baseline CD4 measurement.

- Desirable tests:

These cover the range of laboratory parameters which may be affected variously by ARV drugs. They include tests that help assess for other conditions that may affect treatment as well as those that may occur more commonly in HIV positive patients or whose prognosis is made worse by HIV infection.



- Bilirubin
 - Amylase
 - Serum lipids
 - Screening for cervical cancer
 - Hepatitis B (and C) serology
 - VDRL
- Optional tests:
 - Viral load.

The viral load in conjunction with the CD4 count is a useful prognostic indicator. It is however not essential for treatment initiation; **the patient's clinical status and the CD4 count are given paramount consideration when assessing the need to institute ART.**


- Other tests should be carried out according to clinical need

Once therapy has begun, clinical and laboratory assessments should be carried out regularly to monitor for toxicity as well as for assessment of treatment efficacy. (See Chapter 4)

2.3 Antiretroviral Therapy

2.3.1 Goals of Antiretroviral therapy

From the point of view of patients the primary goal of therapy is improvement of quality of life consequent to the reduction in morbidity, a result of treatment induced immune recovery. The goals of therapy can therefore be summarized as follows:

- 
1. Improvement of the patient's quality of life
 2. Reduction of HIV related morbidity and mortality
 3. Restoration and/or preservation of immunologic function
 4. Maximal and durable suppression of the viral replication

Tools to achieve the goals of therapy include:

1. Patient education to ensure long term adherence to treatment associated with treatment success. This should cover
 - a. why lifelong continuous treatment is necessary and the expected benefits of treatment
 - b. adherence and its relation to treatment outcome, drug resistance
 - c. potential side effects of treatment and what to do in the event of side effects
 - d. necessity for regular follow up
 - e. need to avoid recreational and non prescribed drugs including herbal medication whose interactions with ARV drugs are undefined or undesirable
2. Provider education and experience. Providers should be able to
 - a. assess and prepare patients to ensure long term adherence to treatment



- b. use drugs rationally allowing for future treatment options
- c. ensure regular and adequate monitoring of patients
- d. manage complications of treatment and be able to change or discontinue treatment appropriately

2.3.2 Principles of Antiretroviral Therapy.

- ART is one part of comprehensive HIV care, which includes counselling, psychosocial and nutritional support, prevention and treatment of OIs, reproductive health care (including contraception where needed, pre-pregnancy counselling, PMCT, STI prevention and treatment and screening for cervical cancer) in addition to HIV drug treatment.

- **Cotrimoxazole Prophylaxis**

It is recommended that opportunistic infections are addressed first before starting antiretroviral therapy. Active OIs should be treated and patients stabilized prior to initiation of ART. Prevention of OIs is also important; it is current national policy that **all HIV positive patients be given cotrimoxazole prophylaxis unless contraindicated**. This recommendation is in line with revised WHO guidelines on the use of cotrimoxazole prophylaxis in HIV positive patients in Africa, and is supported by currently available evidence. Where administration of cotrimoxazole to all HIV patients would overwhelm clinical services, cotrimoxazole administration can be prioritised for those with symptomatic infection and/or CD4 < 350 cells/mm³. To help facilitate access to this basic service, consideration should be given to provision of cotrimoxazole therapy in alternative settings (e.g. community programs or out-patient clinics).

There is no clear evidence to support a decision and timing on when to discontinue cotrimoxazole prophylaxis in patients on ART in resource limited settings. In view of the broad benefit derived from this simple intervention even in patients with relatively good immune status, and the complexity of having entry and exit criteria based on CD4 levels in this setting, **it is recommended that all patients on ART continue taking cotrimoxazole unless contraindicated**. Cotrimoxazole is an effective prophylactic agent against the following infections in HIV positive patients:

- Toxoplasmosis
 - PCP
 - Common bacterial infections, including bacterial pneumonia, sepsis
 - Diarrhoea including that caused by *Isospora belli*
 - Malaria
- Starting antiretroviral therapy is not an emergency; patient preparation prior to ART should never be overlooked. In any case the benefits of ART take several weeks to become apparent
 - Maximum achievable adherence is essential for successful ART.

2.3.3 When to start antiretroviral drug therapy.

The optimum time to start antiretroviral therapy in HIV-infected individuals remains unresolved; however there is clear evidence to support initiating treatment in patients with severe



immunosuppression and/or symptoms indicative of immune system damage.

Ideally, treatment should be started before irreversible impairment of the immune system has occurred. Since the development of immunosuppression subsequent to HIV infection is a continuum, the exact point of equipoise beyond which the immune system becomes irretrievably damaged has yet to be defined. The decision as to when to start treatment is further complicated by the limitations of currently available ARV drugs. The risks and benefits of early or delayed treatment initiation can be summarized as shown below.

Early Treatment	
Benefits	Risks
Control of viral replication easier to achieve and maintain	Greater cumulative drug-related adverse effects
Delay or prevention of immune system compromise	Earlier development of drug resistance, if viral suppression is suboptimal
Lower risk of resistance with complete viral suppression	Limitation of future antiretroviral treatment options.
Possible decreased risk of HIV transmission	

Delayed Treatment	
Benefits	Risks
Avoidance of treatment- related negative effects on quality of life and drug-related toxicities	Possible risk of irreversible immune system damage
Preservation of future treatment options	The increased possibility of progression to AIDS
Delay in development of drug resistance associated with treatment failure	The increased risk of HIV transmission to others during a longer untreated period
More time for the patient to understand treatment demands	
More time for the development of more potent, less toxic, and better-studied combinations of antiretroviral drugs	



Use of the WHO criteria for treatment initiation *in resource poor settings*, based predominantly on assessment of symptoms, results in greater overall benefits than using any CD4 cell thresholds; this supports using WHO methods as a way of prioritizing those who need treatment at this time of treatment scale-up. As the local ART program matures it is likely that there will be a move towards harmonization of treatment initiation guidelines with other international guidelines.

While the decision to start therapy should be based on medical criteria, other factors that may impact on the patient's capacity to adhere to treatment, such as social circumstances and support systems, should always be considered. Counselling is important to ensure patient understanding, acceptance and readiness to start and continue long-term treatment.

Specific recommendations on when to start ART

The following are the current recommendations for initiating ART in adults and adolescents with documented HIV infection:

If CD4 testing is not available:
<ul style="list-style-type: none"> • All patients with WHO Stages III and IV disease • Patients with WHO Stage II with TLC < 1200/mm³
If CD4 testing is available:
<p>WHO stage I or II HIV disease if CD4 count < 200/mm³</p> <p>WHO stage III disease if CD4 < 350.</p> <p>WHO stage IV disease, irrespective of the CD4 cell count</p>
<p>Asymptomatic patients with CD4 < 350 should be observed and CD4 count monitored regularly. In such patients ART should be initiated before CD4 count falls below 200 cells / mm³ e.g. when CD4 count is between 200 and 250 cells/mm³</p>

While the total lymphocyte count (TLC) correlates poorly with the CD4 cell count in asymptomatic persons, it is a useful marker of prognosis and survival in symptomatic patients and it can therefore be used in case CD4 assessment is not possible.

2.3.4 What to start with: ARV drugs for treatment -naïve patients

ARV drugs currently available do not cure HIV but suppress viral replication, thus preventing further disease progression and immune system damage. For adequate treatment potency and efficacy, antiretroviral drug therapy usually involves a combination of a minimum of three antiretroviral drugs from different classes.



Classes of ARV drugs

1) Nucleoside Reverse Transcriptase inhibitors (NRTIs)	
Zidovudine (AZT)	Abacavir (ABC)
Stavudine (d4T)	Emtricitabine (FTC)
Didanosine (ddI)	Zalcitabine (ddC)
Lamivudine (3TC)	
Tenofovir Disoproxil Fumarate (TDF) (nucleotide reverse transcriptase inhibitor)	
2) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Nevirapine (NVP)	
Efavirenz (EFV)	
Delavirdine (DLV)	
3) Protease inhibitors (PI)	
Lopinavir/Ritonavir (LPV/r)	Fosamprenavir (f-APV)
Nelfinavir (NFV)	Tipranavir (TPV)
Ritonavir (RTV)	
Saquinavir (SQV)	
Indinavir (IDV)	
Atazanavir (ATV)	
Amprenavir (APV)	
4) Fusion Inhibitor (Entry Inhibitors)	
Enfuvirtide (T20)	

General recommendations of what to start with

Of the above listed drugs and the possible combinations that can arise from them, current evidence supports the use of 2 basic regimens: a NNRTI-based regimen or a ritonavir boosted (PI/r) based regimen. When choosing the initial treatment regimen the following factors should be considered:

- Co-morbidity or co-existing conditions such as tuberculosis, liver disease, pregnancy or pregnancy potential
- Adherence potential
- Dosing convenience with regard to frequency of dosing and pill burden (consider fixed dose combinations where possible) and food and fluid considerations
- Potential adverse drug effects
- Potential drug interactions with other medications



In general, a minimum combination of three drugs from at least 2 different classes in the following combinations is preferred

(i) 2 NRTIs + NNRTI

(ii) 2 NRTIs + PI/r* (ritonavir boosted PI)

- o On current evidence, single PI based therapy is no longer considered as a preferred regimen due to reduced potency compared to the above. It may however sometimes be necessary to use this in specific patient groups.
- o Triple nucleoside combination therapy is also currently not recommended for first-line treatment; such combinations have been shown to be inferior to the standard 2-class recommended regimens. There are however occasions when this combination may be the only suitable treatment in some patient groups.
- o Mono- or dual- therapy should not be used due to inadequate potency.
- o The combination of ddI and d4T should be avoided, particularly in pregnancy, because of increased risk of fatal lactic acidosis with hepatic steatosis and/or pancreatitis. This combination should be used only when other NRTI drug combinations have failed or have caused unacceptable toxicity or side effects

2.3.5 Standardized National Antiretroviral Drug Regimens

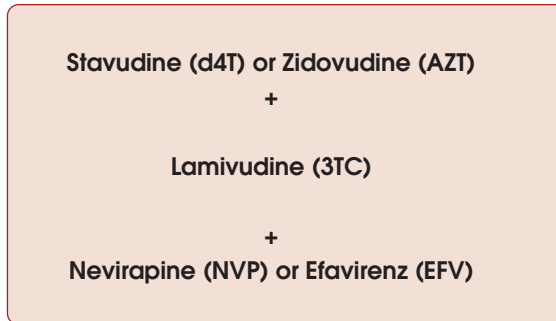
The Ministry of Health has decided on standardized antiretroviral drug regimens recommended for use in Kenya. The process of formulating the regimens took into account the needs of a public health approach to scaling up of ART, which has to take into account availability, benefit to the majority and affordability. In addition, the regimens chosen have been selected with efficacy, tolerability and opportunities for second line treatment in mind. Use of this public health approach has several advantages, including simplifying procurement and drug logistics management; simplifying treatment options for clinicians; allowing simple sequencing of treatment and preservation of certain ARV drugs at a population level. HIV medicine is a rapidly evolving field; consequently rapid changes in the area of treatment and care are likely to occur. For this reason national treatment guidelines are likely to be amended or revised as a result of new evidence or changes in availability of drugs.

Fixed dose combinations (FDCs) are the preferred formulations for the initial combination treatment in the standardized regimen and are recommended where available. FDCs have advantages over single drugs including simplifying procurement and drug logistics management and may be easier to take due to reduced pill burden, allowing for an increased level of adherence to treatment. It is likely that more FDCs will be available in the future. As of September 2005, FDCs were available for the following drugs:

- Stavudine and Lamivudine
- Stavudine, Lamivudine and Nevirapine
- Zidovudine and Lamivudine
- Zidovudine, Lamivudine and Nevirapine
- Tenofovir and Emtricitabine
- Abacavir and Lamivudine
- Abacavir, Lamivudine and Zidovudine



2.3.5.1 First line regimen for adults and adolescents:



The NRTI backbone of stavudine (d4T) and lamivudine (3TC) is cost-effective and efficacious with potency equal to that of other preferred NRTI combinations. However due to toxicity, it may be necessary to change patients from stavudine to other NRTIs for example to either zidovudine (AZT) or tenofovir (TDF). The AZT/3TC combination while more costly than d4T/3TC, is also effective and better tolerated. However since anaemia is a common presentation in HIV-infected patients in our population, either secondary to nutritional deficiencies or as a result of HIV or other diseases, stavudine or other NRTIs that do not cause marrow suppression may be preferable to zidovudine as initial treatment in many individuals in this setting.

The only randomized trial comparing efavirenz (EFV) and nevirapine (NVP) failed to show that NVP was inferior to EFV. However, several observational cohort studies have demonstrated that efavirenz performs better than nevirapine with regard to efficacy. The two drugs can be used interchangeably in situations where one or the other is not well tolerated or can not be used. Nevirapine has the advantage of being able to be used in pregnancy or in women with pregnancy potential. It is also available in FDCs with a cost advantage over efavirenz. **NVP toxicity is more likely to occur if CD4 count at treatment initiation is >250 in female patients and > 400 in male patients.** Efavirenz is preferred in patients with HIV/TB co-infection who are on rifampicin as part of their anti-TB treatment. Rifampicin is an inducer of the liver enzyme systems that metabolise these drugs and reduces serum concentrations of both drugs, NVP to a greater extent than EFV. EFV has however been shown to be effective in the treatment of HIV/TB co-infected patients.



Drug dosages

Generic Name	Form	Dosing recommendation	Food Effect
Stavudine	15, 20, 30 or 40 mg capsules	Body weight • > 60 kg: 40 mg BD • < 60 kg: 30 mg BD	Take without regard to meals
Lamivudine	150 mg or 300 mg tablets	150 mg BD OR 300 mg OD	Take without regard to meals
Zidovudine	100 mg capsules, 300 mg tablets	300 mg BD	Take without regard to meals
Nevirapine	200 mg tablets	*200 mg OD for 14 days; thereafter, 200 mg BID	Take without regard to meals
Efavirenz	50, 100, 200 mg capsules or 600 mg tablets	600 mg daily on an empty stomach, at or before bedtime	Take on an empty stomach: High-fat/ high-caloric meals increase peak plasma concentrations of capsules by 39% and tablets by 79%

*Nevirapine is started at a lower dose of 200mg OD during the first 2 weeks of therapy to reduce the incidence of hepatotoxicity and severe rash; if tolerated the dose is escalated to 200mg BD. Exclude pregnancy prior to initiating Efavirenz.

2.3.5.2 Second-line ARV Drug Regimens for Adults and Adolescents

The main principle of second-line treatment is to use as many new drugs as possible in the new regimen, taking into account likely ARV drug resistance patterns and class cross resistance. Treatment failure of patients on either EFV or NVP results in resistance to both of these drugs, eliminating them as viable future treatment options.

Once a patient has failed a regimen containing 3TC then this drug or emtricitabine (FTC) cannot be used as an *effective part* of a treatment regimen in the future. Patients who have failed a d4T-based regimen develop cross resistance to AZT and vice versa. These 2 NRTIs should therefore not be used sequentially particularly where failure is diagnosed using clinical (or immunological) criteria. If viral load testing is used routinely and treatment failure diagnosed very early at low viral loads before there is development of several d4T or AZT related mutations (Thymidine Analogue Mutations or TAMs), it may be possible to use these drugs in subsequent treatment regimens, especially if subsequent treatment choices are supported by drug resistance testing. Due to cross resistance involving the NRTI class, accumulation of d4T or AZT related mutations (TAMs) results in reduced efficacy of other NRTIs including TDF and ABC further complicating treatment options following first line ART failure.

From this discussion it is clear that with the current (standard regimens in use) ARV drugs available, coupled with patient monitoring reliant on clinical with or without immunological criteria, it may not always be possible to construct a second-line regimen consisting of fully effective new NRTI

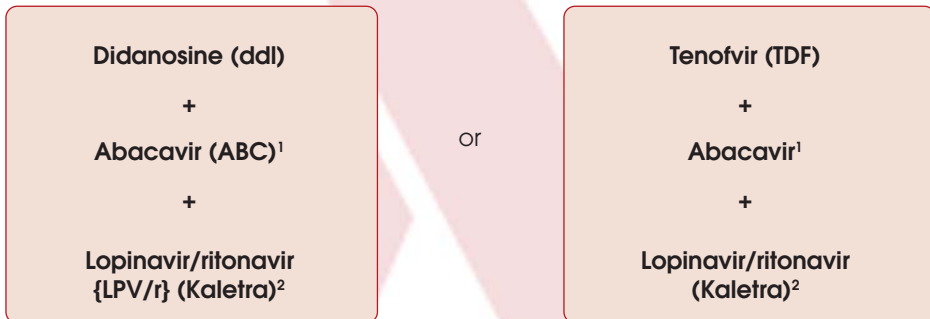


drugs; the potency other drug (s) used in second-line treatment therefore become very crucial.

As with treatment initiation, the decision to change ARV drug regimens should be approached with careful consideration of several factors. These include

- A thorough treatment history; it is important to know of previous drugs used, duration, reasons for discontinuation, hypersensitivity or toxicity
- Adherence history on medication and likely adherence if a new and possibly more complex regimen is introduced
- Clinical and, where possible, immunological and virological indicators. Treatment failure needs to be ascertained as much as is possible.
- Access to new ARV drugs and the time frame. **Patients should not discontinue a failing drug regimen until a new drug regimen is available and ready for use.**
- **When drug regimens are changed because of treatment failure, new drugs should never be introduced one at time**
- The clinician should have some basic understanding of cross resistance between ARV drugs from the same class.

Standardized National Second-line ARV Drug Regimen for Adults and Adolescents



1. Patients requiring second line treatment who develop ABC hypersensitivity can be treated with Kaletra+TDF with or without AZT OR Kaletra+ddl.
2. Nelfinavir can be used instead of LPV/r in cases where refrigeration is not available or ambient temperatures prohibit the safe use of LPV/r. All pharmacies stocking ARV drugs should have a refrigerator. Kaletra can be kept at a maximum temperature of 25° C for up to 2 months and can therefore be dispensed to patients without refrigerators; in these circumstances patients should store the drugs in a cool dry place. (Compare insulin storage in homes without refrigerators)



Drug dosages

Generic name	Form	Dosing recommendation	Food effect
Didanosine	Enteric coated(EC): 125, 200, 250 or 400 mg Buffered tabs: 25, 50, 100, 150, 200 mg	Body weight >60: 400 mg OD (buffered or EC capsules) or 200 mg BD (Buffered tabs) Body weight < 60 kg: 250 mg OD (Buffered tabs or EC capsule) or 125 mg BD (buffered tabs)	Take 1/2-1 hour before or 2 hours after meal. Levels decrease 55%;
Abacavir	300mg tablets	300mg BD	Take without regard to meals. Alcohol increases ABC levels to 41%
Tenofovir disoproxil fumarate (TDF)	300mg tablets	300mg BD	Take without regard to meals.
Lopinavir / Ritonavir	Each capsule contains LPV 133.3 mg + RTV 33.3 mg	(LPV 400 mg + RTV 100 mg) 3 capsules BD	Moderate fat meal increases AUC of capsules by 48%. Take with food
Nelfinavir	250 mg tablets or 625 mg tablets	1250 mg BD or 750 mg TID	Essential to take with fatty meal or snack. Levels increase 2 – 3 fold.

2.3.6 ARV Drug Considerations for Specific Patient Categories

a) Women of childbearing potential, pregnant women, women with previous exposure to single dose NVP (See Chapter 6)

- (i) The indications for initiation of ARV drug therapy in HIV positive pregnant women are as summarized in Table 6.1. The goals of treatment are the same as those for other adults and adolescents. If possible treatment should not be initiated until after the first trimester (period of foetal organogenesis). Selection of an antiretroviral combination should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy.
- (ii) Efavirenz should be avoided in woman of child-bearing potential unless effective and consistent contraception is used for example, IUCD, bilateral tubal ligation or vasectomy in only sexual partner. Teratogenic effects have been reported when EFV is used in early pregnancy.
- (iii) A significant proportion of mothers exposed to single dose NVP for PMCT develop resistance to NVP which may have an adverse impact on NVP-based treatment outcome. Failure of NVP-based regimen seems to be more likely if ART is started within a few months following SDNVP use. For mothers exposed to single-dose Nevirapine for PMCT requiring treatment it is likely that many will receive a NVP-based regimen. Where available **LPV/r-based treatment may be preferred**. However, for reasons of access and availability, women exposed to SDNVP can be started on standard first-line treatment with NVP or EFV. In such cases treatment response



should be monitored closely. (See Ch 6).

- (iv) Contraception: all HIV-infected men and women should be advised to use condoms correctly during **all** sexual encounters. Condoms should be made freely available to patients in care. To further minimize the risk of undesired pregnancy, additional effective contraception should also be offered where appropriate. The possibility of drug interactions should be taken into account when use of hormonal contraceptives is considered.

b) Nevirapine and CD4 levels

Nevirapine has been associated with a 12-fold increased risk of symptomatic severe hepatotoxicity **in women with pre-treatment CD4 T cell counts > 250 cells/mm³** and men with pre-treatment CD4 > 400cells/mm³. Although the manufacturer **recommends that nevirapine should be avoided in women with pre-treatment CD4 count above 250 cells / mm³**, it may not always be possible to adhere to this recommendation. Alternative drugs such as efavirenz should be used if possible. Where alternative drugs are not available or suitable and treatment is required, then **NVP should be used with careful monitoring** of the patient.

c) People with Tuberculosis Disease and HIV Infection.

- (i) The treatment of tuberculosis in patients with HIV infection should follow the same principles for TB treatment in persons without HIV infection
- (ii) Treatment of HIV/TB co-infection is complicated by
- Complex rifampicin drug interactions with NNRTIs and PIs
 - Pill burden and adherence
 - overlapping drug toxicity
 - Risk for and consequences of developing immune reconstitution syndrome.
- (See chapter 8)

For these reasons, where difficulties of treatment of both infections arise or are anticipated, TB treatment should be given priority and cotrimoxazole prophylaxis started. ART can be commenced when feasible. General recommendations of when to start ART in TB/HIV co-infected patients are as shown in the table below:

Recommendations for When to Start ART in HIV/TB Co-Infected Patients

CD4 Count	Treatment Recommendation
CD4 count not available	Start anti-TB treatment Start ART as soon as practicable, preferably in the continuation phase. If EPTB start ART in the intensive phase where feasible
CD4 <100/mm ³	Start anti-TB treatment Start ART as soon as possible
CD4 count 100-350/mm ³	Start anti-TB treatment Start ART after intensive phase of TB treatment
CD4 count >350/mm ³	Treat TB. Defer ART and follow up patient



TB/HIV - What to start with:

The first line ARV drug treatment recommendation for ARV drug-naïve patients with TB and HIV who require ART while still on rifampicin is:

Stavudine or Zidovudine + Lamivudine + Efavirenz (600 mg/day).

Co-infected patients should always be given pyridoxine (50mg OD) particularly in view of the additive risk of peripheral neuropathy associated with using stavudine and isoniazid concomitantly. Patients starting ART in the continuation phase of TB treatment who are not on rifampicin can use the NVP based regimen.

ARV drug-naïve TB/HIV co-infected patients requiring ART while still on rifampicin may not be able to use EFV, for example, if they are women at risk of pregnancy or in early pregnancy or in case of intolerance to EFV; in such cases, **triple nucleoside analogue** treatment may be considered (either Abacavir + Lamivudine + Zidovudine **OR** Tenofovir + Lamivudine + Zidovudine). Such treatment should be given with the advice and supervision of a senior clinician. Triple nucleoside ART should NOT be used in TB/HIV co-infected patients who have previously failed ART.

Treatment of TB in ART-experienced patients who have failed at least one regimen and are on a PI-containing regimen is very challenging; it should always be discussed with a senior clinician.

Ideally, patients with dual infection and on PI-containing regimens should be given Rifabutin instead of rifampicin as part of their TB therapy. This drug is however costly at the moment and may not be accessible to the majority of such patients.

d) Other Opportunistic Conditions

In general opportunistic infections should be attended to as a matter of priority in patients who need ART. ART should be started when the patient is stable and has been prepared to start treatment. However in some cases, the early benefits of potent ART outweigh any increased risk associated with drug issues raised by treating multiple conditions concurrently. In such cases potent ART should be started as soon as possible. These conditions include

- Cases of chronic diarrhoea not responding to standard treatment (cryptosporidiosis, microsporidiosis)
- Kaposi's sarcoma
- Progressive Multifocal Leucoencephalopathy

2.3.7 Alternative Regimens

There are circumstances where patients will be given regimens that are different from the standardized national regimens, for example patients from the private sector. These patients may transfer in to the public sector services for care and often they will have used or be using regimens that are different from those recommended for use in the public sector. There are also patient categories (see above) who may not be able to use the standard recommended first line regimens for various reasons including toxicity, intolerance or co-infections. Apart from this, as access to drugs changes, national guidelines may themselves evolve in the future to include some of these alternative regimens. Examples are given of such regimens and suitable second line changes.



Alternative First line	Subsequent Second Line
AZT/3TC/EFV or NVP	ddl/ABC ³ / Kaletra ¹ or TDF/ABC ³ /Kaletra ¹ ;
ddl/d4T/EFV or NVP	TDF/3TC/Kaletra ¹ or ABC/3TC/Kaletra ¹
TDF ² /3TC/EFV or NVP	AZT/TDF/Kaletra ¹ or AZT/Kaletra ¹
TDF ² /FTC/NVP or EFV	AZT/TDF/Kaletra ¹ or AZT/Kaletra ¹
ABC/3TC/AZT	NNRTI/Kaletra ¹ /TDF or NNRTI/Kaletra ¹ /ddl
d4T/ddl/ IDV ⁴	TDF/3TC/Kaletra or ABC/3TC/Kaletra
AZT/3TC/IDV ⁴	TDF/ABC/Kaletra or ddl/ABC/Kaletra

1. LPV/r preferred but Nelfinavir can be used in case there is no cold storage for Kaletra or where the ambient temperature is too high. All pharmacies stocking ARV drugs should have a refrigerator. Kaletra can be kept at a maximum room temperature of 25° C for up to 2 months and can therefore be dispensed to patients without refrigerators; in these circumstances patients should store the drugs in a cool place.
2. Ideally patients on a Tenofovir-based regimen, like other patients on ART, should be followed up using routine viral load testing to detect failure early. If failure is detected early TDF may be re-used in a subsequent regimen and the option for using ABC and ddl remain. If, on the other hand, failure is diagnosed late (either immunologically or clinically as is the case in most of our clinics at the moment) resistance to TDF is likely to have developed with cross-resistance involving ABC and ddl. In such cases AZT (or d4T) is the only drug that would still be fully effective.

Tenofovir **should not** be given in combination with ddl due to unpredictable virological and immunological response, unpredictable ddl pharmacokinetics and increased ddl associated toxicity.
3. Patients who develop ABC hypersensitivity on second-line treatment can be treated with Kaletra/TDF with or without AZT **OR** Kaletra/ddl.
4. Patients who fail a PI-based first line regimen should not use a non-boosted PI alone for second line treatment

2.4 Adherence to Antiretroviral Therapy

Adherence to ART is well recognized to be an essential component of individual and programmatic treatment success. Higher levels of adherence are associated with improved virological and clinical outcomes and rates exceeding 95% are desirable in order to maximize the benefits of ART. This means taking the correct dose of drugs at the right times and observing any dietary restrictions. **Adherence is therefore central to the success of ART.**

Forms of Non-adherence include:

- Missing one dose of a given drug



- Missing a dose of all the three drugs
- Missing multiple doses
- Not observing the time intervals
- Not observing the dietary restrictions
- Not taking the correct dose of any drug

Non-adherence can lead to poor clinical, immunological and virological outcomes. The consequences of non adherence include:

- Incomplete viral suppression
- Continued destruction of the immune system and decrease of CD4 cell count
- Progression of disease
- Emergence of resistant viral strains
- Limited future therapeutic options and higher costs for individual treatment which translates to higher program costs.

The proper education of patients before the initiation of and during ART is vital for the success of adherence strategies. Such education should cover basic information about HIV and its manifestations, the benefits and side effects of ARV medications, how the medications should be taken and the importance of not missing any doses.

General measures which can help to increase adherence

- Do not rush into starting ARV drugs – ensure that a patient is ready to start and continue long term treatment.
- Involve the patient in the plan of care
- Provide simple written information – information on HIV in general, ARV drugs and adherence issues
- Use Fixed Dose Combinations (FDCs) if possible
- Ensure a continuous , sustainable supply of drugs
- Warn patients about common side effects and give information on what to do should these arise
- Encourage patients to identify a ‘‘Treatment Buddy’’ – ideally a house member (or members), who can accompany them to clinic appointments and help to support them with adhering to treatment on a day - to - day basis
- Develop capacity of patient support groups to enable them to sustain patient education and adherence
- Ensure the same adherence messages are given by all health care workers – even brief reinforcement of these messages at every clinic visit is recommended.
- Keep an organized appointments diary; without this the providers will be unaware of patients missing appointments, and hence not picking drugs.

After the initiation of therapy, it is essential to maintain support for adherence. This should involve adherence assessments whenever there is a visit to a health centre, reinforcement of adherence principles to the patient by continuous treatment supporters, and the continuous involvement of relatives, friends and/or community support personnel.



Methods for Assessing Adherence

Adherence assessment should be combined with adherence counselling at each visit. The idea is to identify those patients who are having most difficulty with adhering to treatment so that extra assistance can be offered to these individuals. Methods used to assess adherence include self report, pill counts, attendance and pharmacy records and clinical or laboratory markers indicating failure of treatment.

In summary, adherence counselling should be an ongoing process during each clinic visit and should be part of all care programs.





CHAPTER 3

Pharmacotherapeutics of Antiretroviral Drugs

3.1 Characteristics of available Antiretroviral (ARV) Drugs

Currently there are four classes of drugs used in the management of HIV-infected patients.

- 1) **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** include Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Zalcitabine and Zidovudine. Nucleotide Reverse Transcriptase Inhibitors (NtRTI) work in virtually the same way as the NRTIs and currently include Tenofovir disoproxil fumarate (TDF).
- 2) **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** include Efavirenz, and Nevirapine. Delavirdine is not available in Kenya.
- 3) **Protease Inhibitors (PIs)** include Indinavir, Nelfinavir, Ritonavir, Saquinavir, Lopinavir, Atazanavir, Amprenavir, Fosamprenavir and Tipranavir
- 4) **Entry Inhibitors** in use include the Fusion Inhibitor, Enfuvirtide.

Patients initiated on Antiretroviral therapy (ART) should be managed with a maximally suppressive regimen (e.g. 2 NRTIs + NNRTI; 2NRTIs + PI/ritonavir; 2NRTIs + 1 PI). Clinical issues such as drug toxicity, ability to adhere to treatment regimens, drug interactions and laboratory abnormalities should be considered when initiating and in the course treatment. Other factors to consider when selecting the ART regimen are:

- Side-effect profile and laboratory monitoring requirements
- Potential for maintenance of future treatment options
- Anticipated patient adherence
- Co-existent conditions and the use of concomitant medications (e.g. co-infections, metabolic abnormalities)
- Pregnancy or the risk thereof
- Potential for infection with a virus strain with reduced susceptibility to one or more ARV drugs (e.g. due to prior exposure to NVP for PMTCT)
- Availability and cost.

As most patients will be on multiple drug therapy, the clinician should be alert to the potential for multiple drug interactions. Thus, the choice of antiretroviral agent to use should be made with consideration given to potential drug interactions and overlapping toxicities e.g. with those drugs whose metabolism involves the hepatic cytochrome P450 (CYP450) enzyme pathway. Some of the PIs and NNRTIs (i.e. Ritonavir, Indinavir, Nelfinavir, and Delavirdine) inhibit the CYP450 pathway; others (e.g. Nevirapine) induce the CYP450 metabolism. CYP450 inhibitors have the potential to increase blood levels of drugs metabolized by this pathway.

Adding a CYP450 inhibitor can sometimes improve the pharmacokinetic profile of selected agents (e.g. adding Ritonavir to the hard-gel formulation of Saquinavir) as well as contributing an additive antiviral effect. However, these interactions can also result in life-threatening drug toxicities. As a result, health-care providers should inform their patients of the need to discuss any new drugs, including over-the-counter (OTC) agents and alternative medications that they may consider taking, and should give careful attention to the relative risks versus benefits of specific combinations of agents.

The characteristics of the ARV drugs for use in adults as well as the interactions between ARVs and other common drugs are as shown in the **Appendix, Tables 1-10**.





Chapter 4

Monitoring Antiretroviral Treatment and Changing Therapy

4.1 Monitoring treatment

Patients on ART need close monitoring in order to:

- Assess adherence to the prescribed regimen
- Evaluate them for drug intolerance and side effects
- Assess efficacy of treatment

Monitoring of therapy involves both clinical and laboratory parameters

4.1.1 Clinical monitoring for patients starting ART

Regular clinical evaluation is important for

- Assessing response to and efficacy of treatment
- Monitoring toxicity to ART.

While the recommended frequency of visits for clinical monitoring should be as described below, patients should be encouraged to attend the clinic in between appointments if they experience any problems of concern.

- The first planned visit should take place 2 weeks after initiating therapy. This appointment should focus on ensuring that the medicines are being taken and stored correctly. Any side effects should be noted and addressed accordingly. Patients on nevirapine should have the dose of nevirapine adjusted at this point if the drug is well tolerated.
- If the patient is stable subsequent planned clinical visits should be carried out at monthly intervals and the focus should be on assessing the patient's clinical progress and checking for any side effects of the drugs.
- After 6-12 months following initiation of ART, *clinical* appointments may be spaced at 3 month intervals in compliant and clinically stable patients with a good understanding of the treatment. Drugs may still need to be collected monthly to ensure continued adherence support. Monthly appointments for stable patients can be devolved to the pharmacist/pharmacy technician or a nurse trained to be able to effectively triage HIV-infected patients. Patients should be clearly informed that in case of any medical problems in between clinical appointments, they will be seen by a clinician.

Once a large number of patients are followed up this way, clinics should build in flexibility to allow for such patients to be seen as required.

At each clinical visit:

- Plot the patient's weight and note the trend.



- Determine the patient’s physical condition.
 - Ask about and check for symptoms and signs of anticipated adverse reactions (e.g. pallor if on AZT; rash in patients on NVP; features of peripheral neuropathy or lipoatrophy in patients on d4T) and those related to the patients immunological status
 - Ask about symptoms and check for signs suggestive of TB. Screening for TB in patients on ARV is important because of the high prevalence of TB thus the management through
- Address the development of severe side effects. Treatment of severely ill patients, once these have started treatment, should be done in a hospital setting, IRIS. (See
- Check drug levels. Patients are less likely to be able to take their drugs as they may not be able to afford them.
- Provide regular follow-up. Patients are less likely to be able to afford them.
- Assess and manage side effects. Patients are less likely to be able to afford them.
- Conduct regular follow-up. Patients are less likely to be able to afford them.



4.1.2 Laboratory tests

- Laboratory tests can be used to:
- Monitor drug levels
 - Assessing side effects

Tests for monitoring

All classes of antiretroviral drugs should be used. In order to anticipate and manage side effects, the following laboratory tests are recommended, where available:

- Complete blood count
- ALT/SGPT
- Creatinine
- Pregnancy test for women of child-bearing age
- Fasting lipid profile and glucose, particularly if protease inhibitors are used
- Serum amylase

These tests should be carried out at baseline before treatment initiation and at appropriate intervals thereafter depending on the ARV drug regimen as well as on the patient’s clinical status. Ideally these tests should be available on site particularly in all district level facilities. If a

Laboratory tests. The following laboratory tests below are



facility does not have the capacity to carry out these tests on site, arrangements should be made to transport specimens to a local or regional reference laboratory.

Follow-up schedule for laboratory tests

Many of the ARV related laboratory abnormalities are likely to occur in the early stages of treatment. Furthermore, it is during this phase of treatment when immune recovery is beginning that opportunistic conditions are still likely to be present and the immune reconstitution inflammatory syndrome occur (IRIS. See Ch 8). Thus, depending on ARV drugs used laboratory monitoring is often more intense in the early part of treatment and the diagnosis of drug related laboratory abnormalities may be complicated by the presence of co-morbidity and the use of other drugs with similar toxicities.

However, some of the ARV drug side effects occur late in treatment and may be picked up if routine monitoring is continued beyond the initial phase following treatment initiation. Fortunately, serious side effects are often accompanied by symptoms. In many cases, these can be successfully investigated on the basis of the known drug toxicity as well as the symptomatology, thus the need for clinicians to assess patients thoroughly when they present with symptoms. Various laboratory parameters should be carried out as summarised below.

- ALT after 1-2 months of treatment when NNRTIs are used. If normal, repeat the test at 3 months, 6 months and thereafter 6-monthly interval or earlier if clinically indicated². Nevirapine related hepatotoxicity is more likely to occur in women especially if CD4 count at **treatment initiation with NVP** is >250 cells/mm³.
- CBC after 1-2 months if AZT is used for treatment¹. If normal, repeat at 3 months, 6 months and thereafter 6-monthly intervals. Most AZT related anaemia occurs within the first 3 months of treatment, is more common in women and those with pre-existing anaemia.
- HIV per se can cause renal abnormalities; it is therefore useful to carry out regular renal function tests. Due to reported renal toxicity in some patients on Tenofovir, patients on this drug require monitoring of their renal function. Care should be taken when using nephrotoxic drugs with TDF. Since other NRTIs including 3TC, AZT and d4T require dose adjustment in moderately severe renal impairment, creatinine measurement where available should be carried out in all patients. Where renal function can not be assessed patients should nonetheless be started on standard ART unless the clinical picture indicates otherwise.
- Fasting lipids and glucose annually, if a patient is on protease inhibitors⁴.
- Evaluation for pregnancy should be carried out for women of child-bearing potential and pregnancy tests done when indicated⁵.
- The clinical picture should always be taken into account when monitoring for toxicity and will often prompt tests as appropriate to the patient presentation



Summary table of schedule of laboratory tests

Test	Baseline	MONTHS					
		1	3	6	12	18	24
HIV EIA	X						
CBC	X	X ¹	X ¹	X	X	X	X
LFT(AST/ALT)	X	X ²	X ²	X	X	X	X
Creatinine	X ³			X ³	X		X
Fasting lipids	X ⁴				X ⁴		X ⁴
Pregnancy test	X ⁵						
CD4	X			X	X	X	X
Viral load	X				X		X

X implies test recommended for all patients

1. Schedule when AZT is used
2. Schedule when NVP is used
3. Schedule in patients on TDF and other NRTIs
4. Schedule if PIs used
5. Pregnancy test should be done initially if EFV is to be used; otherwise as required.

Tests for assessing efficacy of treatment

- While clinical monitoring of patients is useful for assessing efficacy of treatment, for effective monitoring of treatment response, CD4 and quantitative HIV RNA PCR (viral load) measurements are essential and should be used where available.

CD 4+ lymphocyte counts

CD4 cells are a type of lymphocyte which plays a central role in the effective functioning of the immune system. HIV targets these cells and uses them for replication, resulting in their death. The CD4 cell count is a laboratory marker of the strength of the immune system. Normal count in adults ranges from 500-1800 cells per cubic millimetre.

Where possible, a CD4 count should be determined at baseline and thereafter at 6 monthly intervals. Where crucial treatment change decisions are being considered, at least two tests on separate occasions should be carried out. CD4 count should not be measured during a concurrent infection; measurement should be delayed until 2-4 weeks after recovery. For consistency, CD4 measurements in a patient should be carried out in the same laboratory and preferably at the same time of day. Laboratories carrying out CD4 measurements should have in place arrangements for adequate internal and external quality control and assurance.

Viral Load

The viral burden in peripheral blood can be determined by using quantitative HIV PCR RNA assays (viral load). During the period of primary infection in adults, plasma HIV RNA copies initially rise to high levels. Within weeks to a few months, coincident with the body's humoral and cell-



mediated immune response, RNA levels decline to a pseudo steady state. Patients with lower HIV copies at this point have slower disease progression and improved survival compared with those with high HIV RNA copies. As HIV disease progresses the viral load gradually rises to ever higher levels. The higher the viral load the faster the disease progression.

Where available, the viral load should be done routinely at baseline and then at 6-monthly intervals. Crucial treatment change decisions should ideally be based on at least two tests done on separate occasions. Generally the viral load should be undetectable 6 months after initiating effective ART, although patients starting treatment with very high viral loads may take longer to achieve full suppression.

Since viral load is not currently widely available, its use may be rationalized. Under these circumstances viral load should be done if possible

- When treatment failure is suspected. Where failure is clear from both clinical and immunological changes it is not necessary to carry out a viral load, unless this is done for monitoring purposes
- Suspected poor adherence: in early treatment if adherence is optimized patients may go on to successfully suppress viral replication on the same regimen.
- CD4 response less than expected or falling without evidence of clinical failure. The average CD4 response following 1 year of effective therapy is in the order of 150 cells/mm³ or more. Some patients may however have a poor CD4 response despite full virological suppression. Once viral suppression is confirmed this should not be considered failure of treatment and should not necessitate a change in treatment.

Resistance testing

In the majority of patients who have never received ARV drugs, the wild type or non-mutant virus predominates. In the course of normal viral replication billions of new viral copies are formed per day. Despite this prolific rate of reproduction, the replication of HIV virus is a very inefficient process. The viral enzymes used during replication make many mistakes while copying the parental viral genome into progeny virus, and these mistakes translate into numerous mutations. Some of these random mutations result in ARV drug resistance. During ARV drug therapy, the disappearance or suppression of wild-type virus creates the environment in which these mutant viruses can become the dominant species. The degree of suppression provided by a treatment regimen is therefore a critical factor in the “emergence” of HIV drug resistance.

Resistance assays may assist clinicians in optimising antiretroviral treatment regimens for their patients. Resistance testing, where available, can be used for persons failing anti-retroviral treatment to aid decision making on subsequent treatment regimens. Drug resistance in a patient failing treatment should be performed while the patient is on the failing drug regimen (or within 4 weeks of stopping the failing regimen). HIV drug resistance should not be performed in patients with a viral load of < 1000 copies of RNA/ml because results obtained may be unreliable.

There are 2 main types of resistance testing:

Genotypic Assays

These detect drug resistance mutations that are present in the relevant viral genes. They may



involve sequencing of the entire reverse transcriptase and protease genes while others go for selected mutations that are known to confer drug resistance.

Phenotypic Assays

These assays measure the ability of viruses to grow in various concentrations of antiretroviral drugs. They are more expensive and time consuming to perform.

Both genotyping and phenotyping assays are limited due to the lack of uniform quality assurance for all available assays, relative high cost and insensitivity for minor viral species.

Currently resistance testing is not available for routine individual patient management in Kenya.

Drug resistance surveillance is however planned as an essential part of monitoring the national ART program.

4.2. Changing Therapy

Indications for changing therapy include

- Drug toxicity and/or intolerance
- Treatment failure
- Drug interactions/co-morbidity
- Planned or unplanned pregnancy (see chapter 6)
- Interruption of drug supply
- Changes in guidelines
- Changes in access to drugs
- Cost of treatment

The decision to change any regimen should be based on careful evaluation of the patient including clinical history, physical examination and relevant laboratory investigations.

4.2.1 Toxicity (See Appendix Table 6)

Adverse drug reactions (ADRs) are gross clinical or biochemical abnormalities that arise from drugs used correctly as recommended. Adverse events are the most common reasons for switching or discontinuing therapy and for medication non-adherence. Drug toxicity or ADRs, may be precipitated or exacerbated by

- Use of concomitant medications with overlapping and additive or synergistic toxicity, e.g. stavudine with didanosine; ARV drugs and anti-TB treatment. Overlapping toxicity profile can also lead to confusion as to which drug is responsible when toxicity develops.
- Co-morbid conditions that may increase risk of developing or exacerbate adverse events. These include dual treatment of TB and HIV, alcoholism, hepatitis B or C co-infection all of which are likely to increase the risk of hepatotoxicity.
- Drug to drug interaction may lead to an increase in dose-related toxicities, e.g. Fluconazole increases NVP levels and may increase NVP related toxicity

Although the majority of patients will tolerate treatment fairly well, adverse events have been reported with virtually all antiretroviral drugs. Most patients who experience ADRs get symptoms



that can be considered “mild” (nausea, fatigue, dizziness); however to many patients these undesired effects may be very distressing especially considering that patients may have been asymptomatic prior to treatment initiation. It is therefore important to inform patients of likely side effects and what they should do when they occur. Patients should be reassured that most mild side effects occur early in treatment and resolve within the first few weeks after treatment initiation. Supportive treatment should be given if necessary. Rarely, it may be necessary to change treatment.

Less commonly ADRs are serious and may even be life threatening. These may be acute, occurring early in treatment (e.g. NVP associated rash or Steven’s Johnson syndrome) or after several months of ART (e.g. lactic acidosis) **(See ARV Clinical Manual)**

ARV Drug Class Adverse Effects

<p>NRTIs</p> <ul style="list-style-type: none"> ■ Peripheral neuropathy ■ Pancreatitis ■ Lipodystrophy ■ Hepatitis ■ Lactic acidosis ■ Mitochondrial toxicity 	<p>PIs</p> <ul style="list-style-type: none"> ■ Lipodystrophy ■ GI Intolerance ■ Hyperglycaemia ■ Lipid abnormalities
<p>NNRTIs</p> <ul style="list-style-type: none"> ■ Rash ■ Fever ■ Nausea ■ Diarrhea ■ Hepatotoxicity, CNS 	<p>Common Adverse Effects</p> <ul style="list-style-type: none"> ■ Peripheral Neuropathy – d4T,ddl ■ Hematotoxicity - AZT ■ Hepatotoxicity - NVP ■ Diarrhea – NFV ■ Skin rash – NVP ■ Lipodystrophy– PIs, NRTIs ■ CNS disturbance – EFV ■ Hypersensitivity – ABC ■ Hyperlipidemia-PIs, d4T

Considerations for changing therapy due to toxicity

- Establish whether the adverse event is due to ARV drug(s) or to other medication. For example, one should consider isoniazid as a cause of peripheral neuropathy in a patient on ARV drugs taking anti-TB drugs
- Not all problems that arise during treatment result from ARV drugs therefore, consider other disease processes, for example infectious hepatitis when there is transaminitis.
- **In the setting of good therapeutic response**, the development of a clearly definable toxicity permits single drug substitutions without compromising the overall regimen. For example, d4T or TDF can be substituted for AZT in patients with AZT related anaemia; TDF or ABC for d4T associated lipoatrophy; efavirenz can be substituted for Nevirapine-related symptoms and vice versa.
 - Where alternative drugs are available change of treatment for toxicity should be prompt; this is important because some ARV related side effects may



respond poorly to treatment discontinuation.

- For minor symptoms ART should be continued and the patient observed
- In some instances especially with severe ADRs, the entire drug regimen needs to be discontinued e.g. if lactic acidosis occurs, this often necessitates treatment discontinuation followed by re-instituting a regimen that contains drugs less likely to cause mitochondrial toxicity after full recovery of the patient. (Refer to ARV Clinical manual).
- If treatment failure is likely or suspected, single drug substitution should not be done; the entire regimen needs to be changed and the new regimen should take into account issues raised by the previous regimen.
- **Treatment should be stopped if severe reactions occur.** Manage the medical event prior to reintroducing ARV drugs using a modified regimen.

Stopping NNRTIs

NNRTIs have a long half-life. As a result, if treatment is discontinued, therapeutic drug levels may persist for up to 2-3 weeks during which time viral rebound occurs. This means that if the NRTI backbone (which consists of drugs with relatively short half lives) is also discontinued at the same time, the patient will effectively be on NNRTI monotherapy and is therefore likely to develop NNRTI drug resistance. There is emerging evidence that if NRTIs are continued for some time after stopping the NNRTI, the proportion of patients developing drug resistance can be reduced. It is therefore recommended that in the event that an NNRTI is likely to be used again in the future, on discontinuation of either EFV or NVP, the NRTI backbone (e.g. 3TC + d4T) should be continued for a period of 2 weeks where possible.

4.2.2 Treatment Failure

Definition

Antiretroviral treatment failure can be defined as a sub-optimal response to effective ART. Treatment failure can be defined clinically, immunologically and/or virologically.

Clinical Failure

Clinical failure is likely to be present when a patient develops recurrence of prior opportunistic conditions or onset or recurrence of WHO stage 3 or 4 conditions signifying clinical disease progression after a period during which the patient had no symptoms.

Failure is unlikely to be responsible for symptoms in an adherent patient in the first 6 months of treatment since immune recovery is still on-going and the patient may still develop OIs or the IRIS (See 8.1).

Patients who develop features suggestive of clinical failure are likely to have been failing their drug regimen for several months. Ideally, treatment failure should be diagnosed early to avoid morbidity and likely mortality associated with clinical failure and to enable construction of effective subsequent ARV drug regimens.



Immunological Failure

Immunological failure is defined as a failure to significantly increase CD4 count after a sustained period of effective ART or a persistent decline in CD4 count after a period of immune reconstitution.

- Failure of CD4 count to improve or further worsening of CD4 despite treatment
- Return of the CD4 count to pre-treatment levels
- Fall of >50% of CD4 from peak value

In patients with inter-current illnesses the CD4 count may drop substantially. Treatment change decisions should not be based on a single CD4 assessment or on one done during an episode of illness.

In patients with severe immune suppression at treatment initiation with very low CD4 counts, CD4 recovery may be very slow and/or less than expected. Care should therefore be taken that such patients, if stable and adherent, should not have their treatment changed unnecessarily.

Virological Failure

This can be defined as

- failure to reduce the viral load to undetectable levels after 24 weeks of effective ARV drug therapy or
- A sustained increase in viral load after a period of full suppression.

Occasionally patients with extremely high viral loads at treatment initiation may take longer than 24 weeks to fully suppress viral replication. This is why a baseline viral load assessment prior to treatment initiation is useful in interpreting subsequent results.

Viral load is the most sensitive way to assess response to treatment. Clinical and immunological assessments are useful; deterioration of these parameters in a patient failing treatment is however often preceded by a rise in viral load by several months. However since viral load measurement is not readily available at the moment, many clinicians will change therapy on the basis of clinical or immunological failure.

Causes of Treatment Failure

- Non-adherence to treatment
- Viral resistance to one or more drugs
- Regimens with low potency
- Impaired drug absorption
- Altered drug pharmacology including drug-drug and drug food interactions

Non-adherence is the main cause of treatment failure is.



Factors that increase the risk of treatment failure include:

- Factors that affect adherence such as lack of psycho-social support, depression, treatment regimen (pill burden, frequency, food or fluid restrictions)
- Poor patient-provider relationship
- Development of intolerance or toxicity
- Financial barriers to care
- Substance abuse

Considerations for Changing a Failing Regimen

As with the initiation of antiretroviral therapy, the decision to change regimens should be approached with careful consideration of several complex factors, which should be taken into account prior to changing treatment.

- Do not rush into second-line therapy. As much as possible, patients who need to change therapy should be discussed in a multi-disciplinary team.
- When changing therapy, determine whether poor adherence was responsible for the failure.
- If it is not possible to improve adherence, attempt directly observed therapy with a health worker, family member or a friend
- When initiating first- or second-line treatment always review ARV treatment history including previous preventive therapy for MCT
- The new therapy should include as many active drugs as possible and where possible, the regimen should be changed entirely to drugs that have not been taken previously.
- Class cross resistance should be considered; with triple combinations of drugs, at least two of the drugs selected should be drugs that are not subject to anticipated cross-resistance to drugs given previously.
- When changing therapy review all other medications for possible drug interactions
- In patients with weight loss always consider TB as a possible cause. HIV positive patients on treatment continue to be at risk for developing TB; this may therefore not necessarily be a result of treatment failure
- **Do not discontinue the failing regimen until the new regimen becomes available**

4.3 Drug Interactions (See Appendix Tables 7-10)

Frequent co-morbidity in HIV infected patients at the time ART initiation and less so during the course of ART means that they may also be on other medications that interact with ARV drugs. Potential for drug-drug interaction is therefore considerable. Apart from this, interactions between ARV drugs and food also exist and thus should also be taken into consideration when selecting antiretroviral regimens.-(See Appendix Tables 1-4) A thorough review of current medication can help in designing a regimen that minimizes undesirable interactions. Moreover review of drug interaction potential should be undertaken when any new drug, including over-the-counter pills, is added to an existing regimen.

4.3.1 Minimizing drug interactions

- Educate patient to consult before taking any other medicines and to avoid over



- counter pills and herbal preparations
- Always enquire at each visit what other medication the patient is taking.
 - Avoid drugs which interact wherever possible

4.3.2 Discontinuation of therapy

Currently, once a patient is on ARV drugs, they should continue with treatment without interruption, indefinitely. Since continuing sub-optimal ARV will lead to emergence of viral resistance, there are circumstances where it may be necessary to discontinue ARV. Such circumstances include extremely poor adherence, serious drug toxicities or reactions, intervening illnesses that preclude oral therapy, severe IRIS involving CNS or eyes and cases where the administration of medication is repeatedly interrupted. Consider discontinuation only after exploring all potentially corrective measures, including intensive counselling, additional caregiver education and family support.

4.3.3 Structured treatment interruptions

This is currently NOT recommended for routine management of patients.





CHAPTER 5

Guidelines on the Diagnosis and Staging of HIV in Children and Antiretroviral Therapy in Children

5.1 Overview

Most children acquire HIV infection in-utero, during delivery or through breastfeeding. Paediatric HIV disease progression can be rapid or slow. Rapidly progressing disease results in high mortality during the first few years of life. “Slow progressors” develop severe immunosuppression (AIDS) several years after initial infection.

Diagnosis of HIV in children differs according to age; children older than 18 months are confirmed HIV infected by a positive HIV antibody test. Children under 18 months may have maternal HIV antibody, and antibody (HIV ELISA) tests may give false positive results. HIV diagnosis in children < 18 months is by a positive virologic test such as HIV PCR; in the absence of virologic tests a diagnosis can also be made by using a combination of laboratory and clinical criteria.

Staging of severity of paediatric HIV disease classifies the disease using clinical criteria into four stages – asymptomatic, mild, moderate and severe disease. Degree of immunosuppression is also classified into three classes according to severity of CD4 depletion, and measured using CD4 percentage or absolute CD4 count. Because CD4 counts vary with age during the first 5 years of life, the cut-offs for this immunologic indicator differs from those cut-offs used for adults, and CD4 percentage (which does not vary with age) is preferred over absolute CD4 count. CD4 counts fall when children have mild infections or after vaccination. Accurate CD4 counts are therefore best determined when a child is stable (> 2 weeks after an infection). Total lymphocyte counts also decrease as HIV disease progresses and may be used as a surrogate at baseline to assess level of immunosuppression.

Cotrimoxazole prophylaxis reduces morbidity, hospital admissions and death in children infected with HIV. Cotrimoxazole should be administered routinely to **all HIV exposed children from the age of 6 weeks until HIV status is determined. Cotrimoxazole should also be given to all HIV infected children regardless of age, immune or treatment status.** All routine childhood vaccines are given to HIV infected children, however BCG and yellow fever vaccine should be avoided in children with symptomatic HIV disease.

Antiretroviral drugs should be used properly so as to avoid development of drug resistance and restore or maintain the immune status. Drug therapy in children is dependent on the development of processes needed for their metabolism and excretion. Drug doses are calculated according to weight and body surface area, and dosage adjusted upwards regularly as weight and body surface area increases. Nevirapine dose is adjusted 2 weeks after treatment initiation and also at the age of 8 years. Certain paediatric formulations require refrigerator storage (e.g. stavudine, ritonavir or ritonavir containing preparations). Tablets and syrups/suspensions may be used alone or in combination to achieve accurate doses and to reduce cost.

Adherence to treatment is dependent on the commitment of the caregiver. Children have special counselling needs; older children, especially adolescents, need to understand their



diagnosis if they are to adhere to antiretroviral therapy. Disclosure of HIV status to a child needs to be handled with care and with the involvement of the family or guardian.

5.2 Diagnosis and Staging of HIV Infection in Children.

Children born to HIV infected mothers passively acquire maternal antibodies in-utero which may persist up to the age of 18 months and interfere with HIV antibody tests (ELISA and rapid tests). After 18 months of age HIV infection is confirmed by a positive HIV antibody test. Before 18 months of age HIV infection is diagnosed by tests that demonstrate virus in blood (positive HIV PCR or ultra sensitive p24 antigen test). If virologic tests are not available or affordable, diagnosis in a child < 18 months may be made by a combination of laboratory and clinical criteria (positive HIV antibody test *plus* low CD4 percentage or absolute count *plus* symptomatic HIV – WHO stage 3 or 4 disease. **(See Table 5.2 and Appendix Table 14 for WHO Staging in Children).**

HIV testing of children is usually carried out for two reasons:

1. Identification of the HIV-exposed Child

- Children exposed to HIV infection should be identified as early as possible to enable interventions to prevent MCT (if <72hours post partum) or to allow entry into care.
- Where virological tests are not available, routine HIV antibody testing should be offered to children less than 18 months of age whose exposure status is unknown, as an entry point to CTX prophylaxis. This can be done during immunisation or other visits to the maternal and child health (MCH) clinics, in other out-patient settings and in paediatric wards. A negative HIV antibody test excludes HIV infection in an exposed child and may enable advice on infant feeding to reduce MCT.

2. Identification of the HIV Infected Child

- This is crucial to enable children to access timely ART, taking into account that a large proportion of HIV infected children will otherwise be dead by their second birthday. Where virological tests are available, HIV exposed infants should be tested as early as possible. DCT should be universal in all paediatric wards and out-patient facilities.

Table 5.1 HIV Diagnosis in Children

Age	HIV diagnosis confirmed as follows:
18 months and older	Positive HIV antibody test (long and rapid EIA)
Below 18 months	Positive HIV PCR* after age 1 month or positive ultra sensitive p24 Ag
Below 18 months <i>if PCR not possible</i>	If no PCR available – Presence of the following 3 criteria: 1. Positive HIV antibody test PLUS 2. Symptomatic HIV WHO Stage 3 or 4 disease PLUS 3. Low CD4 (CD4% < 20% or CD4 count < 750)



*Two available PCR tests available: (i) Qualitative HIV DNA PCR which reports presence or absence of viral DNA in child's white blood cells (test reported as positive or negative for HIV DNA), and is the gold standard test for diagnosis of HIV in children under 18 months (ii) Quantitative RNA PCR which reports viral load (number of copies of virus/ml of blood) and may also be used for diagnosis of HIV in children under 18 months although it has not been validated for this purpose. The ultra-sensitive p24 antigen test appears to be as good as HIV DNA PCR for diagnosis in children < 18 months. It is cheaper and easier to do; it is however not yet available for widespread use.

Figure 5.1 Presumptive HIV Diagnosis in Children

Presumptive Stage 4 HIV diagnosis in children less than eighteen months old where virological confirmation of infection is not available

Presumptive stage 4 HIV diagnosis may be made in a child < 18 months who is symptomatic with 2 or more of the following:

- o Oral candidiasis/thrush
- o Severe pneumonia requiring oxygen
- o Severe wasting/malnutrition
- o Severe sepsis requiring injectable antibiotics

Other factors that support the diagnosis of clinical stage 4 HIV infection in an HIV sero-positive infant are recent maternal death or advanced HIV disease in mother.

Table 5.2 Immunological categories based on age specific CD4+ T-lymphocyte counts and CD4 percent of total lymphocytes

Immune category	< 12 months		1-5 years		6-12 years	
	CD4Count*	CD4 %	CD4Count	CD4 %	CD4Count	CD4 %
1: Not immunosuppressed	> 1500	> 25%	> 1000	> 25%	> 500	> 25%
2: Moderately immunosuppressed	750-1,499	15-24%	500-999	15-24%	200-499	15-24%
3: Severely immunosuppressed	< 750	< 15%	< 500	< 15%	< 200	< 15%

*CD 4 count in cells/mm³

MMWR Morbidity Mortality Weekly Report 1994

5.3 When to Initiate Antiretroviral Therapy in Children

Antiretroviral therapy once commenced is life-long. A child depends on a reliable parent or guardian to regularly receive therapy. The following medical and psychosocial criteria should be met before initiating this lifelong therapy in a child.



Medical Criteria

Confirmed HIV infection of the child as outlined above, as well as **one or more** of the following:

- **WHO stage 3 or 4 disease** (irrespective of CD4 counts or %).
- **Recurrent hospitalizations** (> 2 admissions in previous year) for HIV-related disease, or prolonged hospitalization (> 4 weeks) in previous year.
- **Low CD4 count or percentage** as follows (irrespective of WHO stage):
 - **Child < 18 months - CD4 < 25%** or absolute CD4 count < 1500
 - **Child 18 months to 5 years - CD4 < 15%** or absolute CD4 count < 500
 - **Child older than 5 years - CD4 < 15%** or absolute CD4 count < 200

Viral load is highly variable in young children, and levels that predict rapid disease progression are not well defined for children. Therefore they are **not** recommended as a criterion for ART initiation

Table 5.3 Summary of Medical Criteria for Initiation of Antiretroviral Therapy in a Child (Clinical criteria alone and/or CD4%/count)

Age	Clinical Stage	CD4%	CD4 count
< 18 months	WHO 3 or 4	< 25%	< 1500
18 months – 5 years	WHO 3 or 4	< 15%	< 500
> 5 years	WHO 3 or 4	< 15%	< 200

Psychosocial criteria

- An identifiable parent or guardian who is
 - Able to understand the treatment requirements
 - Consistently and correctly administer the child’s medication.
 - Able to attend the HIV clinic appointments regularly.
- Sustainable long-term access to antiretroviral drugs (either through programs providing ART, or financially able to purchase ARV drugs).

A child who fulfils the above medical and psychosocial criteria for ART initiation should start ART.

5.3.1 How to Prepare a Child for Antiretroviral Therapy

Prior to initiating the child on ART, the following should take place:

Medical Preparation:

- Where possible, the following baseline tests to should be carried out to assess haematological, liver and kidney function, as well as immune status:
 - Full blood count (resources limited, do Haemoglobin)
 - Liver function tests (resources limited, do alanine transaminase or ALT)
 - Renal function tests (resources limited, do serum creatinine)
 - CD4 if possible
- Baseline viral load (RNA PCR) is optional and is **NOT** required to initiate ART



- **All** children enrolled into care or those being assessed for ART should be screened for TB. This should take into account history of TB in the child's immediate family. Since HIV infected individuals remain at high risk of developing TB disease regardless of treatment status a high level of vigilance for TB is required for patients in care. If TB is confirmed and dual treatment of TB/HIV required, see section on ART and TB.
- Treat any inter-current illnesses
- Initiate cotrimoxazole prophylaxis in all children unless it is contraindicated. (*see table below*)

Table 5.4 Dose of Prophylactic Cotrimoxazole (CTX)

Weight of Child (kg)	CTZ suspension 240mg per 5ml	CTZ tablets single strength 480mg (SS)	CTZ double strength tablets 960mg (DS)
1 – 4	2.5 ml	1/4 SS tab	—
5 – 8	5 ml	1/2 SS tab	1/4 DS tab
9 – 16	10 ml	1 SS tab	1/2 DS tab
17 – 30	15 ml	2 SS tabs	1 DS tab
> 30	20 ml	2 SS tabs	1 DS tab

Counselling Preparation

Counsel the parent/guardian on the following:

- Goals of ART
- Lifelong nature of therapy
- Importance of adherence to ART
- Importance of monitoring and need to attend clinic regularly as required and as well as for inter-current conditions
- When and how to administer the drugs
- Possible adverse effects of the ARV drugs intended for use, how to recognize them and what to do should they arise
- Carers should be encouraged to bring a child on treatment back to clinic if they have concerns or the child becomes ill.

5.3.2 Goals of Antiretroviral Therapy in Children

The goal of ART in children is to decrease HIV related morbidity and mortality. Successful treatment results in:

- Reduced frequency and severity of illnesses (inter-current and/or opportunistic illnesses)
- Achievement of normal or close to normal growth
- Sustained CD4 count or percentage increase
- Where viral load may be regularly measured, a decrease to undetectable levels by 6 months should be attained, (or < 400copies/ml) and remain undetectable as long as patient is taking their medication correctly. However in young children (< 5 years)



undetectable viral load may not always be achievable. In these children the goal of treatment should be at least a 5-fold drop in viral load, combined with sustained elevation of CD4 above baseline, and absence of inter-current and/or opportunistic infections.

5.4 First Line Therapy

Antiretroviral drugs should always be given as a combination of at least *three* drugs simultaneously (highly active antiretroviral therapy - HAART), and should never be given as mono-therapy. The following are the Kenyan National recommendations for initiation of ART in children:

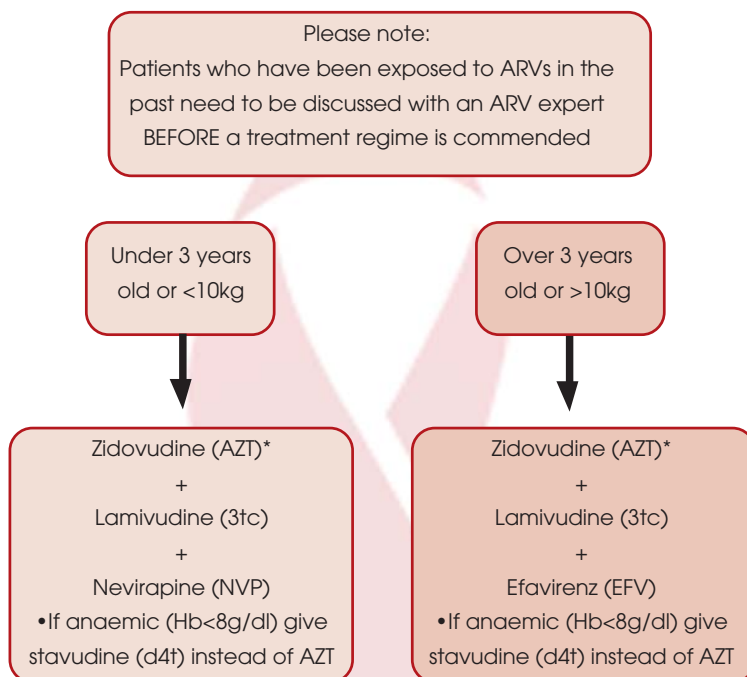
Table 5.5 National First Line Regimens for Antiretroviral Therapy in Children

Child Characteristics	Recommended Regimen
A. Child previously NOT exposed to Nevirapine for PMCT HIV transmission	
Age below 3 years or weight < 10kg	Zidovudine (AZT) ¹ + Lamivudine (3TC) + Nevirapine ² (NVP)
Age above 3 years and weight > 10kg	Zidovudine (AZT)* + Lamivudine (3TC) + Efavirenz (EFV)/Nevirapine (NVP) ²
B. Child exposed to single dose NVP (failed prophylaxis)⁴	
All ages	AZT ¹ + 3TC + Kaletra ³ (LPV/r)

1. In cases of severe anaemia (Hb < 8g/dl), give *stavudine* in place of *zidovudine* for first line therapy.
2. Nevirapine should be started at low dose for 14 days, then stepped up to full dose on day 15
3. Nelfinavir can be used instead of LPV/r in cases where refrigeration is not available or ambient temperatures prohibit its use. All pharmacies stocking ARV drugs should have a refrigerator. Kaletra can be kept at a maximum temperature of 25° C for up to 2 months and can therefore be dispensed to patients without refrigerators; in these circumstances patients should store the drugs in a cool dry place. (Compare insulin storage in homes without refrigerators)
4. Preliminary evidence to date suggests that many children exposed to SDNVP may develop resistance to NVP and as a result may not respond well to a NNRTI-based HAART regimen. This recommendation will be reviewed as more evidence becomes available



Flow Chart1: First-line Treatment of children



Points to note:

- o Recalculate doses according to the weight or body surface at every 3 monthly visit
- o Store stavudine capsules and solution in refrigerator if possible; can be stored by patient for 42 days if kept below 25 degrees Celsius.

Calculating Dosages

Children's ARV drug dosages are always calculated according to the child's body weight in kilograms, or according to the child's body surface area in metres². Surface area may be determined using a normogram or easily calculated as shown below:

Computation of body surface area of a child:

Body surface area in square metres = $\text{square root of } \frac{\text{weight in kg} \times \text{height in cm}}{3600}$

Appendix Table 12 provides a simpler approach to prescribing ARV drugs in children using weight bands and may therefore be preferred for centres with out the capacity to do the above. Details of paediatric drug dosages and formulations, and major side effects for each drug are shown in **Appendix Tables 11 a and b**.



5.5 Monitoring ART in Children

The frequency of visits, and the schedule of clinical and laboratory monitoring that should be performed during each visit is indicated below. At each visit plot the physical growth of the child on a growth chart. Address ongoing medical problems and treat any inter-current infections, if present. Continue cotrimoxazole prophylaxis and nutritional supplements (such as multivitamins and protein rich porridge flour) at each visit.

Greater than 95% adherence is necessary to prevent the emergence of drug resistance and ensure long-term good virological response with the first line regimen. If a child misses more than 1 dose in ten days it implies < 95% (suboptimal) adherence, and the health-worker should counsel parent or guardian to identify causes of missed doses and how to avoid this in the future.

Table 5.5 Follow-up, laboratory and clinical monitoring schedule for patients on ART

VISIT	Base-line	Wk 2	Months						Thereafter in
			1	2	3	6	9	12	
									stable patient
Weight, height Clinical evaluation	+	+	+	+	+	+	+	+	Every 3 months
Check adherence &side-effects	+	+	+	+	+	+	+	+	Every 3 months
Check ART drug dosages	+			+	+	+	+	+	Every 3 – 6 months
FBC*	+		+		+	+		+	Every 6 months
LFT or ALT**	+		+		+	+		+	Every 6 months
Creatinine	+							+	Every 12 months
CD4	+					+		+	Every 6 months
Viral load(HIV PCR)***	(+)					(+)		(+)	Every 6-12 months
Lipid profile/ fasting blood sugar****	+					+		+	Every 6 months

FBC = full blood count. HB essential if AZT used

** LFT = liver function tests. At a minimum perform alanine transaminase (ALT or SGPT).

*** RNA PCR for viral load.

****For children on protease inhibitors

() Parenthesis indicates test is optional, perform if finances available



NOTE: Stable patients under the care of a parent or guardian with an excellent grasp of treatment requirements, who have been on treatment for some time, can be followed up less frequently by clinicians. Clinics should still enable such patients to be seen when necessary.

5.6 Antiretroviral Therapy and Tuberculosis Treatment (Flow Chart 2)

Rifampicin interacts with both PIs and NNRTIs, which limits the use of rifampicin based anti-TB treatment and these ARV drugs. Dual treatment of TB/HIV co-infection is further complicated by the overlapping toxicities and high pill burden of combined ARV and anti-TB drugs. TB treatment should always be given priority in co-infected patients. The following general guidelines can be used to manage co-infected children as effectively as possible.

If TB infection is diagnosed prior to ART initiation:

Complete TB therapy first, if possible before starting ART

OR

Delay ART until patient has completed the first two months (intensive phase) of anti-TB treatment. Use EFV (if above 3 years and > 10kg) or Abacavir (if < 3 years or < 10kg). **Once child completes anti-TB treatment, they should switch from Abacavir back to Nevirapine.**

OR

In patients with advanced HIV disease who may succumb if ART is delayed, start ART as soon as feasible in the intensive phase of TB treatment. Use EFV (if above 3 years or > 10kg) or ABC (if < 3 years or < 10kg). Once a child completes anti-TB treatment, they should switch from Abacavir to Nevirapine.

If TB develops while on 1st Line ART

If on Nevirapine switch to Abacavir (if < 3 years or < 10kg) or Efavirenz (if above 3 years and/or > 10kg). Once the child completes anti-TB treatment, they should revert back to the national first line therapy regimen (switch from Abacavir back to Nevirapine).

OR

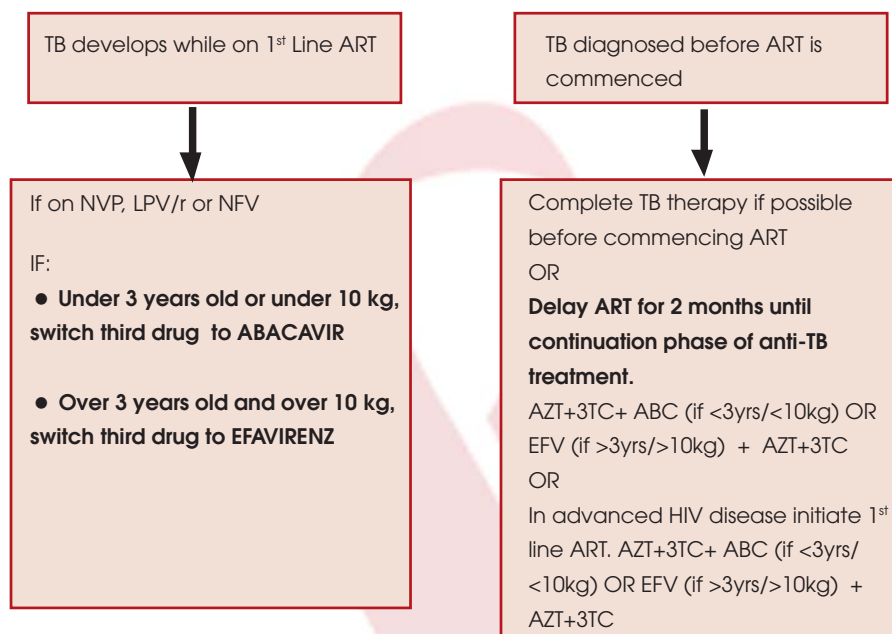
Where dual treatment is difficult and is likely to affect adherence to either the TB or the ARV treatment, or where toxicity of dual treatment is a problem, **consider interrupting ART**. Resume after completion of anti-TB therapy.

TB in patients on second line ART regimens

Patients on second line treatment who develop TB should be discussed with a senior consultant. Patients who have previously failed first line treatment should never be given triple nucleoside therapy.



Flowchart 2: How to treat HIV Positive children with Concomitant Tuberculosis



Remember:

- Patients on TB medication and ARV drugs are taking a large number of doses of medications:-provide intensive counseling and support to improve adherence.
- Check LFTs (ALT) monthly while on concomitant ARV/TB drugs
- Recalculate doses according to weight or body surface at 3 monthly visits.
- **When patient completes anti-TB treatment, those on abacavir should switch back to nevirapine, or to the protease inhibitor that they were previously on.**
- **Patients who are on second line ART who develop TB should be discussed with a senior clinician**

5.7 Indications for Changing or Stopping Antiretroviral Therapy

Treatment may need to be changed for reasons of toxicity, failure, co-morbidity with adherence implications and drug-drug interactions; interruption of drug supply; changes in guidelines; changes in access to drugs; cost of treatment.

5.7.1 Toxicity

Major severe adverse events may occur with the listed first and second line drugs, which warrant withdrawal of the offending drug, and its substitution with an alternative antiretroviral drug. Generally, if a specific drug causes a severe adverse effect, only the offending drug should be changed. Toxicity or intolerance is often the most likely cause of treatment change within the first year of treatment.



Table 5.6 Specific severe adverse effects, possible offending drug(s) and management

Adverse Effect/Possible Offending Drug(s)	Clinical Signs/Symptoms	Management
<p>Acute hepatitis Nevirapine (NVP); EFV less common; more uncommon with zidovudine (ZDV), didanosine (ddl), stavudine (d4T) (<1%), and protease inhibitors (PI); most frequently with ritonavir (RTV)</p>	<p>Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)</p>	<ul style="list-style-type: none"> • If possible, monitor serum transaminases, bilirubin. • All ARV should be stopped until symptoms resolve. • NVP should be permanently discontinued.
<p>Acute pancreatitis ddl; d4T; lamivudine (3TC) (infrequent)</p>	<p>Nausea, vomiting, and abdominal pain</p>	<ul style="list-style-type: none"> • If possible, monitor serum pancreatic amylase, lipase. • All ART should be stopped until symptoms resolve. • Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g., ZDV, ABC).
<p>Lactic acidosis All nucleoside analogue reverse transcriptase inhibitors (NRTIs)</p>	<p>Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnoea and dyspnoea) or neurological symptoms (including motor weakness)</p>	<ul style="list-style-type: none"> • Discontinue all ARV; symptoms may continue or worsen after discontinuation of ART. • Supportive therapy. • Regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly ABC.



Adverse Effect/Possible Offending Drug(s)	Clinical Signs/Symptoms	Management
<p>Hypersensitivity reaction Abacavir (ABC); nevirapine(NVP)</p>	<p>ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea (with or without rash). While these symptoms overlap those of common infectious illness, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash.</p>	<ul style="list-style-type: none"> • Discontinue all ARVs until symptoms resolve. • The reaction progressively worsens with drug administration and can be fatal. • Administer supportive therapy. • Do not re-challenge with ABC (or NVP), as anaphylactic reactions and death have been reported. • Once symptoms resolve, restart ARVs with change to different NRTI if ABC-associated or to PI- or NRTI-based regimen if NVP-associated.
<p>Severe rash/Stevens-Johnson syndrome Non-nucleoside reverse transcriptase inhibitors (NNRTIs); nevirapine (NVP); efavirenz (EFV)</p>	<p>Rash usually occurs during the first 2–4 weeks of treatment. The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson Syndrome or toxic epidermal necrolysis (SJS/TEN) has been reported in ~0.3% of infected individuals receiving NVP.</p>	<ul style="list-style-type: none"> • Discontinue all ARVs until symptoms resolve. • Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria or SJS/TEN. • Once resolved, switch ART regimen to different ARV class (e.g., 3 NRTIs or 2 NRTIs and PI). • If rash moderate but not severe and without mucosal or systemic symptoms, change in NNRTI (e.g., NVP to EFV) could be considered after rash resolves.
<p>Severe peripheral neuropathy ddI; d4T; 3TC</p>	<p>Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.</p>	<ul style="list-style-type: none"> • Stop suspect NRTI and switch to different NRTI that does not have neurotoxicity (e.g., ZDV, ABC). • Symptoms generally improve but may not resolve fully.



5.7.2 Treatment failure

There are certain clinical, immunological and virological conditions that might indicate that the first line regimen is failing, and a need to consider changing to second-line therapy.

Defining Treatment Failure

Clinical Indications for Change of ART

- Poor growth or decline in growth despite ART, after excluding other causes, such as TB, inadequate nutrition and the IRIS.
- Recurrence of infections that are *severe, persistent, or refractory* to treatment*.
- New opportunistic infections; patient progressing to a more advanced clinical stage than baseline stage.
- Neuro-developmental delay or deterioration.

*Short acute upper lower respiratory tract infections and gastroenteritis that respond promptly to treatment should not be regarded as clinical failure. Immune reconstitution inflammatory syndrome (IRIS) occurs during the first 3-6 months of ART and may present as TB, herpes zoster and other opportunistic infections; do not be hasty to diagnose clinical failure.

Immunological Indications for Change of ART

- Drop of CD4 (count or percentage) to baseline or below baseline levels. **
- Drop of CD4 (count or percentage) by more than one-third from peak level achieved on ART, in absence of other concurrent infection. Ideally a second CD4 count to confirm the drop in CD4 cells should be performed before deciding to change ART regimen.
- If CD4 percentile drops more than 5 percentiles

**Do not measure CD4 during an ongoing infection; wait until > 2 weeks after the infection.

Virological Indications for Change of ART

- Failure to achieve significant suppression of virus after 6 months of effective ART.
 - Child < 2 years less than 5-fold (0.7 log) drop in VL
 - Child > 2 years less than 3-fold (0.5 log) drop in VL
- Progressive increase in viral load after initial adequate VL suppression when adherence to medication is adequate.
 - a 5-fold (0.7 log) or more increase in children < 2 years, and
 - a 3-fold (0.5 log) or more increase in children 2 years and above.

However, an undetectable viral load may not always be achievable even in adherent young children and may therefore be tolerated, provided they are growing well, and their CD4 count is maintained at elevated level achieved on ART.

Second Line Antiretroviral Treatment

Principles of second-line antiretroviral therapy: (see section 2.5.3.2)

- Do not rush into second line therapy



- First check adherence;
 - If poor adherence is the cause of failure of the first regimen, unless adherence can be improved, do not start 2nd line ART, *withdraw ART altogether*.
- If problems causing poor adherence may be solved, then consider changing to 2nd line. One strategy is to attempt directly observed therapy (DOT), with a health care worker or trusted “other” family member or friend Adherence history on medication and likely adherence if a new and possibly more complex regimen is introduced
- **Patients should not discontinue a failing drug regimen until a new drug regimen is available and ready for use.**
- **In case of failure of treatment new drugs should never be introduced one at time.**

As a rule: CHANGE ALL THREE DRUGS if a patient has failed treatment

Table 5.7 Second Line Treatment

1 st line regimen	2 nd line regimen
zidovudine + lamivudine + nevirapine (AZT) (3TC) (NVP)	didanosine + abacavir + lopinavir/ritonavir (ddl) (ABC) (LPV/r)
zidovudine + lamivudine + efavirenz (AZT) (3TC) (EFV)	didanosine + abacavir + lopinavir/ritonavir (ddl) (ABC) (LPV/r)
Stavudine + lamivudine + nevirapine or efavirenz (D4T) (3TC) (NVP) (EFV)	didanosine + abacavir + lopinavir/ritonavir (ddl) (ABC) (LPV/r)
Zidovudine + lamivudine + lopinavir/ ritonavir (or NFV) AZT 3TC LPV/r	didanosine + abacavir + PI/ritonavir (ddl) (ABC) (LPV/r if NFV used)

Nelfinavir can be used instead of LPV/r in cases where refrigeration is not available or ambient temperatures prohibit the use of LPV/r. All pharmacies stocking ARV drugs should have a refrigerator. Kaletra can be kept at a maximum temperature of 25° C for up to 2 months and can therefore be dispensed to patients without refrigerators; in these circumstances patients should store the drugs in a cool dry place. (Compare insulin storage in homes without refrigerators)

5.8 Alternative Regimens

Sometimes children will have used first line treatment regimens that are different from those recommended in the current national guidelines. These include when patients from the private sector transfer in to the public sector services for care; these patients may have used or may be using regimens that are different from those recommended for use in the public sector. There are also patient categories (see above) who may not be able to use the standard recommended first line regimens for various reasons including toxicity, intolerance or co-infections. Examples are given of such regimens and suitable second line changes.

Alternative First line	Subsequent Second Line
ddl/d4T/EFV or NVP	ABC/3TC/Kaletra ¹
ABC/3TC/AZT	NNRTI/Kaletra ¹ /ddl



1. LPV/r preferred but Nelfinavir can be used in case there is no cold storage for Kaletra or where the ambient temperature is too high. All pharmacies stocking ARV drugs should have a refrigerator. Kaletra syrup can be kept at a maximum room temperature of 25° C for up to 2 months and can therefore be dispensed to patients without refrigerators; in these circumstances patients should store the drugs in a cool place.

Flowchart 3: Second-line Treatment of children.

Consider a move to second-line therapy under the following conditions:

Clinical	Immunological	Virological
<ul style="list-style-type: none"> • Poor growth or decline in growth • Recurrence of infections that are <i>severe persistent</i>, or <i>refractory</i> to treatment*. • New opportunistic infections: new stage 3 disease • Neuro-developmental deterioration. <p>Note: Short inter-current episode of pneumonia, LRTI and gastroenteritis should not be regarded as clinical failure. TB is not a reason to move to second-line therapy. TB can present as progression to stage 3 disease and must first be excluded before changing to second-line therapy.</p>	<ul style="list-style-type: none"> • Decline in the CD 4 count or % to baseline or below baseline • Rapid decline, loss of > 1/3 CD4 cells in the absence of TB • Fall of > 5 percentiles from previous one if below 15% <p>Note: The CD4 percentage should NOT be measured during an inter-current Infection –but preferably a month post resolution.</p> <p>If there is a modest decline in CD4 percentage and if no failure to thrive, do not change medication, but monitor closely.</p>	<ul style="list-style-type: none"> • Failure to achieve initial suppression of virus after 6 months of ART. • Progressive increase in viral load after initial adequate VL suppression when adherence to medication is adequate. <p>Note: A detectable viral load may be tolerated in children, providing that growth and elevated CD4 count are sustained.</p>

Procedure for introduction of second-line therapy:

- Do not rush into second-line therapy
- First check adherence- If it is not possible to improve adherence, attempt directly observed Therapy (DOT), with a health care worker or trusted “other” family member or friend
- Always make sure second-line therapy does not include any drugs to which resistance is likely to have developed during first-line therapy
- Table below shows specific second line regimen for each of the possible 1st regimens

Remember to recalculate doses according to weight or body surface area at every 3 monthly visit.



Discontinuation of Therapy

Under certain circumstances it may be necessary to discontinue ART, this includes the following situations:

- Consistently poor adherence for whatever reason
- Repeated treatment interruptions
- Severe toxicity such as severe hepatotoxicity, Stevens Johnson syndrome or lactic acidosis
- Child develops tuberculosis while on ART and cannot tolerate the combination of anti-TB as well as antiretroviral drugs.

For patients on NNRTIs if therapy must be discontinued *and it is intended that a NNRTI be used in the future*, where possible the NRTI backbone (AZT or d4t + 3TC) should be continued for a further two weeks after the NNRTI is discontinued. This is due to the long half life of both NNRTIs; if all treatment is discontinued simultaneously sufficient NNRTI will persist in circulation long enough to increase the likelihood of NNRTI drug resistance development. Only consider discontinuation of therapy after exploring all potentially corrective measures with child, caregiver and family.



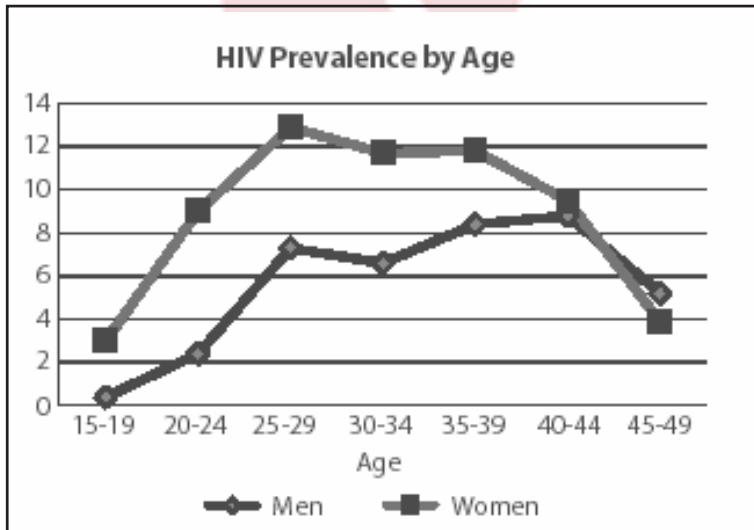
CHAPTER 6

Antiretroviral Therapy in the Management of HIV-Infected Pregnant

6.1 Overview

HIV sero-prevalence among women remains high in Sub Saharan Africa. In Kenya the 2003 population based survey showed that women in the reproductive age group are particularly vulnerable to HIV infection, with women being on average twice as likely as men to be HIV positive. Overall 4-35% of antenatal attendees are HIV positive in Kenya.

Kenya Demographic Health Survey 2003 Central Bureau of Statistics, Kenya



Although the prevalence of HIV is declining, these statistics would suggest that mother to child transmission (MTCT) is likely to remain a significant source of infection for children in Kenya as in much of Africa, unless effective interventions are used to prevent it. In Kenya, MTCT accounts for more than 90% of HIV infection in children. Currently it is estimated that there are about 150,000 children living with HIV in Kenya and an annual 50-60,000 new infections in children mostly as a result of MTCT.

Transmission of HIV from infected mothers to their babies can occur during the antenatal period (10 -20%), labour and delivery (35 - 50%), and breastfeeding (40 - 50%). Overall the risk of transmission in breast feeding populations is 25-40%. Factors that affect transmission include:

- Maternal health and HIV disease status (high viral load and low CD4 count; presence of chorioamnionitis, genital infections, mastitis when breast feeding, all correlate with higher rates of transmission)
- Obstetric factors (mode of delivery - elective pre-labour CS halves transmission (probably except in patients with fully suppressed viral replication) compared to vaginal delivery; duration of membrane rupture >4 hours associated with increased transmission)



- Infant factors: premature delivery at less than 34 weeks associated with increased transmission rates; infant feeding –breast feeding increases the transmission rate

Interventions to reduce MTCT should target each of these key areas and include

- Optimized antenatal and obstetric care (see PMCT Guidelines)
- Assessment of **ALL** HIV positive pregnant women, by clinical staging and CD4 measurement where possible, and use of antiretroviral drugs for treatment and/or prevention as appropriate
- Modified infant feeding (see PMCT Guidelines)

As well as the above, efforts to prevent HIV infection should start earlier in women at risk with education of young girls and women on primary prevention of HIV infection; prevention and treatment of STIs; voluntary counselling and testing and knowledge of HIV status pre-pregnancy; prevention of unplanned pregnancies in HIV positive women; universal HIV testing of all pregnant women and provision of appropriate interventions.

6.2 Rationale for ARV Drug Use in Pregnancy for PMCT

The efficacy of ARV drug use to prevent MTCT has been demonstrated in various randomized control trials as well as in observational studies. Different short course ARV drug regimens used in late pregnancy and during labour reduce MTCT by 2-3 fold. Observational studies have shown that the more complex or potent the ARV drug regimen used in treating HIV positive pregnant women, the more effective the reduction in MTCT. In countries where effective interventions against MTCT have been successfully implemented, new HIV infection in children is now extremely rare. This has largely been achieved through the universal testing of pregnant women and use of effective ARV drugs both for prevention of MTCT and treatment in HIV+ pregnant women.

In Kenya, up till much of 2005, single dose Nevirapine (SDNVP) has effectively been the method of choice for PMCT mainly for reasons of deliverability. Although single dose Nevirapine is efficacious, it has significant drawbacks. These include failure to prevent transmission in about 50% of instances and drug resistance development in a significant proportion of women who use it as well as in most of the infants in whom prophylaxis fails.

Over the past 2 years ART has become increasingly more accessible to ordinary Kenyans. As such, **all pregnant women who need ART should be offered effective ART for their own health.** This will also serve the purpose of more effectively reducing MTCT. Since the majority of pregnant women do not have symptomatic HIV disease, many would not qualify for treatment on the clinical criteria currently used to determine entry into treatment for adults and adolescents. There has therefore been a need to include severe immunosuppression as measured by a CD4 count of less than 350 cells/mm³ as part of the treatment initiation criteria for pregnant women. Below this CD4 count, there is a high likelihood of transmission of HIV infection to the infant; apart from this the mother would benefit from ART for her own health. It is therefore important that CD4 measurements be carried out in pregnant women, particularly in asymptomatic women. The other factor that is addressed in these guidelines is an alternative choice of ARV drug regimen specifically for prevention that would be tolerable and yet more effective than single dose nevirapine (SDNVP) when used in pregnancy.



6.3 Challenges of ARV Drug Use for PMCT

If implemented correctly, single dose Nevirapine to mother and baby for PMCT while not perfect would have a tremendous impact on childhood HIV related disease and mortality. More complex ART regimens used either for maternal treatment or for prevention of infection transmission would result in markedly lower rates of MTCT and would also probably have less of a negative impact on future treatment options of the mother (and infant with failed prophylaxis).

Effective universal delivery of PMCT may be difficult unless antenatal and post natal services undergo considerable improvement. Currently, 90% of pregnant women in Kenya receive some element of antenatal care from medical professional (70% nurse or midwife 18% from a doctor). Despite the relatively high rate of contact with medical personnel, only a small proportion of pregnant women get the recommended antenatal interventions, such as the tetanus toxoid vaccination, iron supplementation or malaria prophylaxis. Apart from this a significant proportion of births still occur at home.

Clearly delivery of effective PMCT will be a considerable challenge that requires improvement of both basic pre- and post- natal care of women. It is important that an effort to implement more effective but complex ARV drug interventions should not result in a situation where poorer or no ARV related PMCT services are offered. For these reasons, single dose Nevirapine will still have a role in PMCT particularly in peripheral health care settings where other interventions are neither feasible nor available.

As ART becomes more accessible in Kenya it is quite likely that increasingly more HIV infected women may conceive while on ART. Consequently these guidelines address issues related to ART use in pregnancy. Because of the potential risks of some ARV drugs in pregnancy, it is important that the choice of treatment for women of child bearing potential takes into account the possibility of planned or unplanned pregnancy and offers a high margin of safety. It is also essential that ART clinics are able to offer contraceptive advice and link up with appropriate contraceptive services.

Nevirapine resistance after PMCT

NVP resistance has been documented in varying proportions of women who have used SDNVP for PMCT. Resistance is more likely to develop in women with severe immunosuppression and high viral load. The impact of SDNVP-related NNRTI resistance on future treatment is not yet clearly defined. From early studies poor outcome with early treatment failure to subsequent NVP-based regimen is more likely in exposed women, especially if ART is started soon after delivery (often indicating severe HIV disease). **For this reason it is recommended that for women who have had SDNVP who require ART if a NNRTI based regimen is used monitoring be carried out to enable early detection of treatment failure. A PI-based regimen may be preferred.**

6.4 Choice of ARV Drug Regimen in Pregnancy (See table below)

The choice of ARV drug regimen used in pregnancy is influenced by Maternal clinical and immunological status

- ARV drug regimen properties including efficacy, potential adverse effects, pharmacokinetics, potential for drug resistance developing. It should be



remembered that drugs may adversely affect both foetus and mother. Thus the following should be considered:

- o ddI combined with d4T has been associated with increased risk of life-threatening lactic acidosis and pancreatitis in pregnancy
 - o Nevirapine associated hepatotoxicity more likely especially if started in women with a CD4 >250
 - o Potential for drug resistance (mother's and infant's future treatment). Single dose Nevirapine associated with high levels of drug resistance in mothers who use it for PMCT as well as in infants in whom prophylaxis fails. This may impact on future treatment outcomes in both mother and child. It is essential that *where a mother qualifies for ARV drug treatment this is started during pregnancy* to limit the likelihood of the above.
 - o Use of Lamivudine for periods >4 weeks as part of a short course regimen PMCT also associated with high level of drug resistance and should therefore be avoided.
- Maternal choice
 - Availability, accessibility and costs of services.

6.5 When to start HAART in pregnant women

CD4 NOT available: ALL patients with WHO Stage 3 and 4 disease

CD4 available: ALL patients with CD4 count < 350 regardless of clinical status

If HAART is not used in HIV positive pregnant women then one of the short course ARV drug regimens for PMCT should be used as appropriate. (See table below)

Conclusion

PMCT should take into account both current and future maternal health needs as well as the need to have a healthy baby. Thus, as much as possible, **all pregnant women with HIV infection should be assessed for treatment as early in the pregnancy as possible.** Where possible, CD4 counts should be done to support treatment decisions. Positive pregnant women should be offered ART in line with these treatment guidelines where possible. Selected short course ARV drug regimens should continue to be used where ART is neither appropriate nor available. For adequate assessment of HIV positive pregnant mothers, to enable effective ART use as part of PMCT, it is necessary to have reliable CD4 measurements available. In the absence of this, clinical indicators for treatment should be used as per National Treatment Guidelines as indicated above.



Table 6.1 Antiretroviral Drugs for Treatment and Prevention of Mother to Child Transmission of HIV Infection

Mother's Presentation (Scenario)	On ART?	Intervention where possible	Infant intervention	Follow up after delivery
<p>1. Pregnancy at any gestation: Any clinical or immunological category</p>	Yes	<p>Review treatment. Check adherence Assess for failure (clinically, immunological and VL if possible); if failing optimize ART Continue cotrimoxazole¹; Standard antenatal care package²</p>	<p>If mother confirmed to be failing treatment close to delivery seek senior opinion NVP 2mg/Kg immediately after birth + AZT 4mg/Kg BD for 1 week</p>	<p>Mother to continue ART. Discuss and offer dual contraception infant to start CTX at 4-6 weeks and be enrolled into care Infant feeding as per PMCT guidelines Infant HIV status to be determined as early as possible to inform subsequent care.</p>
<p>2. Gestation < 36 weeks: Treatment indicated (Clinical Stage 3 or 4 OR CD4 < 350 regardless of clinical stage)</p>	No	<p>Prepare for ART³; Start CTX¹ Standard antenatal care package² Start on NVP⁴/3TC/d4T (or AZT). Best initiate ART after 1st trimester unless benefits outweigh risks.</p>	<p>Nevirapine 2mg/Kg immediately after birth + AZT 4mg/Kg BD for 1 week</p>	<p>Mother to continue ART and regular monitoring Discuss and offer dual contraception infant to start CTX at 4-6 weeks and be enrolled into care Infant feeding as per PMCT guidelines Infant HIV status to be determined as early as possible to inform subsequent care.</p>
<p>3. Gestation >36 weeks and Mother needs treatment (Clinical Stage 3 or 4 OR CD4 < 350 regardless of clinical stage)</p>	No	<p>Prepare for ART³; Start CTX¹; Standard antenatal care package². It is better to start HAART but it may not be possible to start ART at this stage. If treatment possible: use scenario 2. Treatment not possible: use scenario 4 and consider options A or B as feasible.</p>	<p>Single dose Nevirapine 2mg/Kg immediately after birth + AZT 4mg/Kg BD for 1 week</p>	<p>If mother is not started on ART in pregnancy and SDNVP used as in scenario 4; assess for ART as per adult national guidelines (CD4 < 200 or WHO 3 or 4). If ART is indicated immediately use a PI-based regimen⁵. If ART started, management and follow up as indicated in 2 above. Infant care as above</p>



Table 6.1 Antiretroviral Drugs for Treatment and Prevention of Mother to Child Transmission of HIV Infection

Mother's Presentation	On ART?	Intervention where possible	Infant intervention	Follow up after delivery
4. A symptomatic plus CD4>350 Any gestation (treatment not indicated)	No	Start CTX ¹ . Standard antenatal care package ² Option A preferred: Start on AZT 300mg BD from 28 weeks on, plus AZT 600mg at onset of labour PLUS NVP 200mg start during labour Option B: Single dose 200mg NVP to be taken at onset of labour	Single dose Nevirapine 2mg/Kg immediately after birth + AZT 4mg/Kg BD for 1 week	Mother to continue care and follow up. Discuss and offer dual contraception Infant to start CTX at 4-6 weeks and be enrolled into care Infant feeding as per PMCT guidelines Infant HIV status to be determined as early as possible to inform subsequent care Note use of NVP +/- AZT for future reference.
5. Mother presents at any gestation in primary care setting; No access to ART OR mother presents early in labour (> 1 hour before delivery)	No	Single dose 200mg NVP to be used in established labour at least 1hr before delivery	Single dose NVP 2mg/Kg immediately after birth + AZT 4mg/Kg BD for 1 week	Mother to be referred to nearest CCC for assessment and Care. If possible, this should always be done before delivery to allow optimal antenatal care. Note use of NVP +/- AZT for future reference. Discuss and offer dual contraception Infant to start CTX at 4-6 weeks and enrolled into care Infant feeding as per PMCT guidelines Infant HIV status to be determined as early as possible to inform subsequent care
6. Mother presents in late labour (< 1 hr before delivery) or <72 hours post delivery	No	N/A	Single dose NVP 2mg/Kg PLUS 1 week of AZT 4mg/Kg BD.	If mother's status is unknown a rapid HIV test should be carried out as soon as possible to enable infant PEP to be administered and entry into appropriate care for both. Assess mother's clinical and immunological status. Treatment as per national guidelines. Start CTX. Discuss and offer dual contraception Infant to start CTX at 4-6 weeks and enrolled into care Infant feeding as per PMCT guidelines Infant HIV status to be determined as early as possible to inform subsequent care



1. **Fansidar should not be used for malaria prevention in patients already on cotrimoxazole** (additive toxicity and CTX is effective as prophylaxis for malaria)
2. Manage STIs; partner to be offered testing; optimize antenatal care as per PMCT guidelines
3. It is important to prepare pregnant women for ART through patient education, counselling and support to avoid non-adherence and treatment failure. Many of these patients are likely to be relatively well and may thus not feel that they need ART.
4. NVP is more likely to cause hepatotoxicity in women with pre-treatment CD4>250. It is therefore essential that, if it is used in such patients, regular clinical and LFT monitoring be carried out. Where available a LPV/r-based regimen may be preferred
5. Early evidence suggests that women who have used single dose NVP for PMCT who subsequently use a NVP based regimen for treatment are more likely to fail treatment than women not exposed to SDNVP; they should therefore be given a Kaletra (PI) based regimen where this is available. Nelfinavir can be used instead of LPV/r in cases where refrigeration is not available or ambient temperatures prohibit its use. All pharmacies stocking ARV drugs should have a refrigerator. Kaletra can be kept at a maximum temperature of 25° C for up to 2 months and can therefore be dispensed to patients without refrigerators; in these circumstances patients should store the drugs in a cool dry place. (Compare insulin storage in homes without refrigerators). **Where PIs are not accessible a NNRTI-based regimen should be used with close monitoring of treatment response.**

Notes

- (i) Efavirenz should **not** be used in women of child bearing potential unless effective contraception is used. If a woman using EFV falls pregnant then it should be switched to an alternative drug as early as possible during the 1st trimester. The CD4 count at change of treatment should be considered (see (iii) below).
- (ii) ART should not be discontinued in patients planning a pregnancy or in those with an established pregnancy. If patients are on EFV this should be switched to an alternative ARV as (i) above.
- (iii) For pregnant women who need to start ART the choice of drug depends on the CD4 at the time treatment initiation: if CD4<250 then NVP can be used. If CD4>251 then LPV/r or NFV should be used instead. In the absence of these options a NVP based regimen can be used with careful monitoring for hepatotoxicity.
- (iv) Generally initiation of ART should be delayed until women are in the 2nd trimester of pregnancy. However the benefits may outweigh the risks of starting treatment in the 1st trimester in the severely ill patient.
- (v) Hyperemesis gravidarum may sometimes necessitate discontinuation of ART in women receiving treatment prior to the pregnancy.
- (vi) ART should be continued during labour in women already on treatment
- (vii) Where possible AZT should be used instead of d4T for initiating treatment in pregnant women
- (viii) All HIV positive pregnant women should be screened for TB (history, examination and sputum; CXR only where essential); if TB disease is found anti-Tb treatment



should be prioritized and started immediately. If a pregnant woman on TB treatment needs ART in the intensive phase then a triple nucleoside regimen should be used (ABC or TDF + 3TC + AZT). Triple therapy should be discontinued after delivery and immediately replaced with a standard regimen. In the event that a triple nucleoside regimen is not available, a NVP based regimen can be used during the continuation phase of TB treatment instead.

- (ix) Pregnant women who are on PI based treatment who develop TB should be discussed with a senior clinician. PIs should not be given together with Rifampicin.
- (x) The alternative approach of providing potent combinations of antiretroviral agents to all pregnant women (regardless of clinical, immunological or virological status) to achieve full virologic suppression has the potential to reduce neonatal HIV infection to the levels seen in the developed world while preventing emergence of drug resistance in the mothers. In Kenya this is not yet a feasible option on a national scale and is therefore not recommended.
- (xi) For management of labour and the use of caesarean section for PMCT, refer to the PMCT guidelines. C/s in addition to ARV drug use has been shown to be effective at further reducing MCT regardless of viral load.



CHAPTER 7

Prevention of HIV Transmission

7.1 Antiretroviral Drugs for the Prevention of HIV Transmission

7.1.1 Post- exposure prophylaxis (PEP) in the occupational setting:

Introduction

Management of infectious diseases of public health concern has traditionally involved different approaches including avoiding exposure, immunization, prophylaxis and treatment. With particular regard to prophylaxis, drug treatment has been used successfully in different settings to prevent infection from developing following exposure. It is therefore not surprising that these same principles have been applied in the prevention and control of HIV infection.

About 100 documented and 200 possible cases of HIV infection in health care workers (HCWs) have been reported worldwide. The risk of transmission has been estimated on average to be 0.3% after a percutaneous exposure to HIV infected blood, and 0.09% after a mucous membrane exposure; the risk can be higher following an exposure to a large volume of blood or to a high titre of HIV.

Health care workers are at risk of exposure to HIV through contact with contaminated blood and other body fluids containing HIV through

- needle stick injuries and injuries by other sharp objects
- non-intact skin and mucous membranes

The risk of exposure to HIV contaminated blood or body fluids should be minimized by using universal precautions. This means that all blood should be treated **as if contaminated with HIV**. The same conditions apply to hepatitis B & C which are also blood borne viruses. To avoid exposure to these viruses precautions should be taken when handling possibly contaminated body fluids including the use of appropriate barriers such as gloves, gowns and goggles; care with sharps including minimizing blind surgical procedures and proper handling and disposal of sharps; safe disposal of contaminated waste; safe handling of soiled linen; adequate disinfection procedures and universal Hepatitis B vaccination of non-immune at risk groups including HCWs, police, prison staff and rescue workers.

Indications for and considerations prior to prescribing PEP

Whether or not antiretroviral prophylaxis is prescribed after an occupational exposure to HIV is based on a risk assessment, which takes into account the type of exposure, the characteristics of the source patient and the material to which the HCW is exposed, as summarized in the table below:



Table 7.1 Risk Assessment Following Exposure to Various Body Fluids

	Low Risk	Medium Risk	High Risk
Type of Exposure	Intact skin	Mucus membrane/ non-intact skin	Percutaneous injury
Source	HIV negative	HIV status unknown; clinically well/unwell*	HIV positive with advanced disease. (Consider treatment history)
Material	Saliva, tears, sweat, faeces, urine, sputum, vomit	Semen, vaginal secretions, synovial, pleural, pericardial, peritoneal, amniotic fluids	Blood and bloody bodily fluids; CSF; viral cultures in labs

Other Considerations

- Local capacity to offer treatment as soon as possible after risk exposure
 - Once the decision to give PEP has been made, treatment should be started as soon after the exposure as possible and administered for 4 weeks. (Goal: within 1 hour of exposure)
 - Efforts should be made to have rapid HIV test kits available to avoid delay in initiating PEP. Lack of such tests should not be a reason not to start PEP as soon as possible.
 - PEP should be discouraged more than 72 hours after exposure. (Ensure early referral to nearest centre offering PEP if no local services)
- Pre-existing medical conditions and any medications that an exposed HCW may be taking.
- Choice of a simplified regimen whenever possible to increase adherence by reducing number of pills and frequency of dosing.
- Capacity to follow up the HCW, provide on-going counselling and monitor treatment
 - Once treatment is started constitutional adverse reactions if reported, can be managed symptomatically. This could enhance adherence to the prescribed regimen with the ultimate goal of achieving treatment completion in the exposed HCW.
- Links to a unit where ART is provided should this be necessary in the HCW (as well as source)
- Recording and reporting of data

Post-Exposure Management

- Provide immediate care to exposure site
- Encourage bleeding
- Wash with soap and water
- Do not scrub or cut the site



- Determine risk associated with exposure
 - Evaluate the source and exposed person
 - Assess the potential risk of infection
 - Both source and exposed HCW need to be counselled for HIV-testing. Known source should be tested for HIV; if the source declines to be tested they should not be coerced into having the test.
 - Discarded sharps/needles should not be tested
 - The exposed HCW should not receive ARV drugs without being tested. *However where immediate testing is not possible treatment **must not be delayed*** since HIV testing can be carried out within the next day or as soon as possible. Counselling and support should be provided and HCWs who decline testing should be offered appropriate support.
 - HIV test for person exposed should be done at baseline, at 3 months and at 6 months. Other baseline tests to be carried out where possible include FBC, LFT and renal function.
- Offer PEP as appropriate (see below)
- The first doses should not be delayed by baseline HIV Testing
- Treatment should not be continued if status of exposed individual remains undetermined
- Hepatitis B vaccination should be offered to the non-immune.
- Review of staff health and safety: evaluate exposure and determine whether local preventive strategies could be improved
- Provide follow up testing and counselling for the HCW
- Proper documentation and reporting of event and patient management

Choice of treatment regimen

PEP is recommended following exposures judged to be of high and medium risk.

The ideal regimen for PEP is not yet defined and in fact most of the information guiding drug use for PEP is based on animal studies and studies on prevention of maternal to child transmission. The choice of ARV drugs used for PEP should be made only after careful assessment of the nature of the exposure and the source patient's characteristics, including previous and current ART history.

While any combination of antiretroviral drugs approved for the treatment of HIV-infected patients can be used in PEP regimens at the recommended dose and for the recommended period, local guidelines and practice should take into consideration current limitations.

Recommendations

- **Dual Nucleoside Reverse Transcriptase Inhibitor combination is recommended as first line PEP.**
- **PI-based triple regimens should be used in cases judged to involve particularly high risk exposure**
- **Exposures involving source patients on ART should be discussed with a clinician**



experienced in HIV management (by phone as soon as possible)

- **NNRTI-based regimens are NOT recommended for PEP.** (Severe NVP toxicity has been reported and should be anticipated in the immunocompetent. There is no biological reason why EFV should not be used; however EFV and the risk of teratogenicity in early pregnancy and short term toxicity may pose problems. Furthermore, these drugs are part of standard first line treatment and should therefore not be used in circumstances where PEP may be used following exposure to patients on NNRTI treatment, HIV sero-conversion may occur or treatment discontinuation is likely to be high)

For **any** exposure deemed to be significant:

AZT 300 mg + 3TC 150 mg OR d4T 40mg (30 mg if WT<60kg) + 3TC 150mg

Twice a day for 28 days

Use FDCs if available, to reduce pill burden and increase adherence

For high risk exposures

Kaletra (LPV/r) + AZT (or d4T) + 3TC

Give as soon as possible after exposure

Follow up, adherence counselling and support also necessary. Management of side effects may facilitate adherence.

7.1.2 PEP in cases of Sexual Assault

- The case for providing antiviral treatment as post-exposure prophylaxis after sexual exposure is an extension of the case for providing it in occupational settings.
- The argument is based on a comparison of per-exposure risks. Transmission rates in men receiving unprotected anal sex or a woman's exposure during rape or receptive vaginal intercourse with a partner likely or known to be HIV positive are comparable to transmission rates associated with most needle-stick injuries

Table 7.2 Probability of HIV acquisition after different exposures

Exposure	Probability of disease acquisition (%)
Receptive anal intercourse	0.008-0.032 (0.8-3.2)
Receptive vaginal	0.0005-0.0015 (0.05-0.15)
IVDU	0.0067 (0.67)
Needle stick injury	0.0032 (0.32)
Insertive vaginal intercourse	0.0003-0.0009 (0.03-0.09)

The risk of HIV transmission is probably significantly higher in rape because of trauma due to lack of lubrication and forceful penetration. Other factors that increase transmission risk include disease



status of rapist (risk increases with viral load) and presence of STIs in the source or the person assaulted.

NB: in a high HIV prevalence population rapists should be **assumed to be HIV positive unless proven otherwise**

Management of sexual assault

- Provide appropriate first aid and emotional support
- Provide baseline and follow up counselling for HIV test
- Offer PEP as appropriate
- The first doses should not be delayed by baseline HIV Testing
- Treatment should not be continued if status of patient remains undetermined
- Offer Emergency Contraception in women at risk of pregnancy
- Document clinical evidence of assault, take appropriate swabs and forensic specimens should be handled appropriately (see Guidelines on PEP)
- Consider STI prophylaxis and hepatitis B vaccination if indicated
- Offer trauma counselling
- Alert authorities as appropriate
- Refer as appropriate for legal services

Once a decision to provide PEP is reached, ARV regimens for adults and adolescents are the same as above. For children the following regimens should be used.

Children > 25 kg: treatment as in adults

Children 15-24 kg: (+/-syrup) AZT 200mg BD + 3TC 75mg BD

Children 10-14 kg: syrup AZT 100mg TDS + syrup 3TC 75mg BD

Because of severe trauma often sustained by children following sexual defilement Nelfinavir may be added to the above, where possible.

(See Table 12 for dosages)

Other situations where non-occupational PEP may be considered:

Following RTA where there has been exposure to other people's blood; among police and prison staff who may be injured in the course of their work.

7.2 Prevention of Transmission of HIV Infection

Even as ART services are expanded, HIV prevention should become and remain a routine part of primary health care in all health care settings, whether ARV drugs are being provided or not. Community and public sector HIV prevention programs should promote HIV testing and educate people about HIV treatment at the same time. They should also develop close links with antiretroviral treatment facilities and other providers of care for people with HIV. There should be increased diagnostic testing in health care facilities; basing this on risk profile of individuals is not of benefit in high prevalence area such as Kenya and a move to universal testing in the health care setting should be the goal. HIV testing should remain voluntary, but the offer of an



HIV test must be encountered in *all* health care settings, as should education about HIV, access to condoms and other prevention tools, and screening for sexually transmitted infections.

Prevention of HIV is largely through

- Education
- Knowledge of status through voluntary counselling and testing
- Abstinence/fidelity/fewer sexual partners
- Condom use – correctly and consistently
- Prevention and timely treatment of STIs
- Screening of blood for transfusion
- Proper precautions in medical and other settings where contact with bodily fluids likely (including IVDU)
- PMTCT through
 - Primary prevention of HIV in women
 - Prevention of unwanted pregnancy in HIV + women
 - Provision of adequate antenatal care of positive women
 - ART and ARV drugs for the PMTCT
 - Treatment of HIV infection

STIs and HIV

STIs are important cofactors in the transmission of HIV infection as has been shown in several trials including cross-sectional, case control, prospective, interventional, biological and randomized controlled trials. Both genital ulcerative diseases, inflammatory (Gonococcal or chlamydial disease) and non-inflammatory (bacterial vaginosis) genital infections increase the risk of both HIV transmission and acquisition, by increasing genital tract viral load as well as impairing mucosal integrity.

Lack of male circumcision is also an important co-factor in STI and HIV transmission/acquisition.

Prevention and control of STIs would therefore have an impact on the incidence of HIV infection. It is therefore essential that prevention and control of STIs continues in order to prevent these conditions that cause significant morbidity as well as mitigate their impact on transmission of HIV infection. Since HIV is largely a sexually transmitted infection in our setting, all adult and adolescent patients accessing care should be routinely assessed for possible concomitant STIs which if found should be treated during clinic appointments. Patients should also be advised on the need for partner assessment both for STIs and for HIV infection.

Prevention in positives and in discordant couples

HIV positive patients in care should be encouraged to minimize the risk of both HIV transmission and STI acquisition as indicated above. Partners of HIV positive individuals should be encouraged to attend care for assessment of status and support with prevention efforts where discordance exists. Adequate information should be available for these purposes and condoms should be made available in all CCCs for use by clientele as required. HIV infected women may choose to engage in unprotected sexual intercourse for purposes of pregnancy. HCWs should be proactive in discussing patient's reproductive concerns to enable risk reduction behaviour to be adopted.



CHAPTER 8

Special Considerations

8.1 Immune Reconstitution Inflammatory Syndrome (IRIS)

Antiretroviral therapy is associated with a decrease in viral load, an increase in CD4 count with improvement in pathogen-specific immunity, reductions in opportunistic infections and decreased morbidity and mortality. During the early phase of immune recovery, exaggerated immune response to pre-existing untreated opportunistic infections may occur, a reaction similar to the type IV hypersensitivity reaction. This reaction is termed the Immune reconstitution inflammatory syndrome (IRIS); it is most likely to occur in individuals who start HAART with very advanced immune suppression. This paradoxical clinical deterioration after starting ART results from immune system interaction with organisms that have colonised the body prior to treatment initiation. It is characterized by persistent or worsening constitutional symptoms and severe inflammation of the affected organ. The pathogenesis is unclear but it is thought to be the result of restoration of pathogen-specific immune reactivity against pre-existing pathogens leading to inflammatory reactions in infected tissues. The risk factors for IRIS according to observational studies include

- initiation of concurrent HAART while treating an OI such as TB, CMV or Cryptococcal meningitis
- low CD4 cell count at ARV treatment initiation
- for TB patients extra-pulmonary site of disease
- greater reductions in viral loads as a result of HAART

Clinical presentation of IRIS varies, and depends on the causative organism and the organ system that is affected. In our setting IRIS commonly involves TB, often extrapulmonary. In such patients there will be persistent or increasing fever despite effective anti-TB treatment; worsening pulmonary inflammation where the lungs are involved and increasing lymphadenopathy. It may be associated with recovery of PPD-positivity. Other conditions associated with IRIS include PCP, Cryptococcal meningitis, CMV retinitis and hepatitis B.

There are as yet no figures for the incidence of IRIS in Kenyan patients; documented reports from elsewhere show a variable incidence of 7-35%.

IRIS usually develops 1-3 months after initiation of effective ART and should not be confused with treatment failure.

Management

In patients already on treatment for an OI it is necessary to determine whether this is a progression of disease (e.g. drug failure) or IRIS. Treatment of the disease to reduce the antigenic burden should be continued and effective HAART should also be continued. The suspected immune basis of the syndrome suggests that therapy with anti-inflammatory agents or steroids may be helpful and should therefore be used.



Unmasking of sub-clinical infection, that was previously not apparent, necessitates specific antimicrobial therapy and supportive treatment including antipyretics and anti-inflammatory drugs. Adjunctive steroid therapy may be necessary in case of severe reactions especially where vital organs are involved (e.g. CNS, eyes).

As much as possible ART should be continued at the same time. Occasionally ART has to be temporarily withheld if a patient is unable to adequately adhere to all treatment, drug-drug interactions occur or the inflammatory reaction is severe and involves vital organs (e. CNS with rising ICP or retinal disease).

8.2 Acute or Primary HIV Infection (PHI)

An estimated 40% - 90% of patients acutely infected with HIV will experience symptoms of acute retroviral syndrome. However, acute HIV infection is often not recognized by clinicians because of the non-specific nature of the symptoms which are similar to those of other viral and non-viral infectious conditions. Clinicians should therefore maintain a high level of suspicion especially in a high prevalence area as Kenya.

Symptoms include:

- Fever 96%
- Lymphadenopathy 74%
- Pharyngitis 70%
- Rash 70%
 - Erythematous maculopapular with lesions on face, trunk and sometimes extremities (including palms and soles)
 - Mucocutaneous ulceration involving mouth, oesophagus, or genitals
- Myalgia or arthralgia 54%

Less common presentations include gastrointestinal (nausea, vomiting diarrhoea); neurological (aseptic meningitis, meningoencephalitis, neuropathies)

Diagnosis of Primary HIV infection (PHI).

Clinicians should maintain a high level of suspicion especially where there are compatible clinical syndromes. Acute HIV infection is defined by recent known sero-conversion or HIV RNA > 10,000 with a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/ml) may represent a false-positive test, since values in acute infection are generally very high (> 100,000 copies/ml)

Fourth generation EIA assays are very sensitive and allow for diagnosis as early as 2-4 weeks after infection thus reducing the window period during which the serologic diagnosis of acute HIV infection can be in doubt. It should be remembered that some patients may not seroconvert for periods longer than this.

If standard EIA tests are positive, then PHI can not be diagnosed with certainty unless a previous blood sample is available for testing or patient knows when they were last HIV negative. Patients with PHI diagnosed by HIV RNA testing should have confirmatory serologic testing performed 2 to 4 months later.



It is important to recognize primary HIV disease because of the high risk of HIV transmission associated with this period of the infection. The potential to be able to reduce HIV transmission by individuals with PHI exist. In the future, special tests may become available that make it easier to identify patients with PHI with the potential importance in counselling newly infected patients regarding high rates of transmission.

Treatment for Acute HIV Infection.

Currently it is not recommended that ART is started during PHI. Clinical trials information regarding treatment of acute HIV infection is limited. Potential benefits and risks of treating are as follows:

- Potential benefits of treating PHI:
 1. Theoretically, early intervention could decrease the severity of acute disease in the symptomatic
 2. Alter the initial viral set point, which can affect disease progression rates; reduce the rate of viral mutation as a result of suppression of viral replication
 3. Preserve immune function; and reduce the risk of viral transmission.
- Potential Risks of Treating Acute HIV Infection:
 1. Exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy, and adverse effect on quality of life.

8.3 Hepatitis B (HBV)/HIV Co-infection

- HIV infected patients co-infected with HBV have higher rates of chronic hepatitis B infection, higher frequency of HB e antigenaemia, higher levels of HBV DNA and higher rates of HBV-associated liver diseases.
 - HBV/HIV co-infection is associated with a higher mortality when compared to HIV only infected patients. It is unclear if chronic HBV-infection increases HIV disease progression, but it does increase the frequency of antiretroviral-associated hepatotoxicity.
 - Patients with HIV/HBV should be advised to avoid or limit alcohol consumption and use appropriate precautions to prevent transmission of both viruses.
 - They should receive hepatitis A virus (HAV) vaccine if found to be susceptible, as determined by the absence of HAV antibody.
 - Patients with HBV should be considered for HBV therapy. Antiviral therapy is recommended for those patients with active HBV replication, defined as HB e Ag positive and necroinflammation in the liver (a serum alanine amino transferase (ALT) at least 2 x upper limit of normal (ULN) or histological evidence of moderate disease activity or fibrosis).
 - Response to HBV therapy is generally poor in patients with baseline ALT levels < 2 x ULN
 - Treatment: There are two forms of therapy for HBV infection, but unfortunately access to these drugs is limited for the majority of Kenyans with HBV infection. There are now several NRTIs and NtRTIs which are active against hepatitis B; these drugs may in the future be made available to HBV infected patients in resource limited settings.
- a) Interferon alfa 2a or 2b given subcutaneously in doses of 5 MU per day or 10 MU three times weekly for 16 – 24 weeks (for HB e Ag positive individuals) or > 48 weeks (for HB e



Ag negative individuals).

- b) Nucleoside or Nucleotide analogues can be used. Lamivudine, emtricitabine, and tenofovir are active against both HIV and HBV. All of these drugs have the potential of serious hepatotoxicity due to a flare in hepatitis B when they are discontinued.

- Scenarios for treating HBV/HIV co-infection:

- a) Need to treat HIV and not HBV

- Consider withholding tenofovir, emtricitabine and lamivudine for future use if necessary
- Avoid using Lamivudine or tenofovir as the single drug with anti-HBV activity in this setting; i.e. use the two drugs together.

- b) Need to treat HIV & HBV

- Consider using tenofovir, emtricitabine, or lamivudine
- Due to high rates of HBV resistance to lamivudine or emtricitabine, combining either of these with tenofovir is recommended

- c) Need to treat HBV and not HIV

- Consider adefovir or interferon α (pegylated preferred)
- Avoid emtricitabine, lamivudine and tenofovir since these drugs should only be used as components of a fully suppressive combination antiretroviral regimen, unless HIV resistance to these specific agents has been previously documented

- d) Need to discontinue lamivudine, tenofovir or emtricitabine.

- Monitor clinical course and liver function tests carefully and consider use of adefovir to prevent flares especially in patients who have marginal hepatic reserve.

Inclusion of HBV vaccination in the Expanded Program on Immunization should help reduce future disease burden attributable to HBV.

8.4 Hepatitis C (HCV)/HIV co-infection

- 2 – 20% of patients with chronic HCV infection develop cirrhosis in 20 years
- This rate of progression increases with older age, alcoholism, and HIV infection.
- Chronic HCV infection also complicates HIV treatment by the increased frequency of antiretroviral-associated hepatotoxicity.
- Patients with HIV/HCV should be advised to avoid or limit alcohol consumption and use appropriate precautions to prevent transmission of both viruses and should be given hepatitis A and B vaccine if found to be susceptible.
- There is generally a poor response to treatment which in any case is not accessible to the majority in resource limited settings.
- Standard indications for HCV therapy in the absence of HIV infection are:



- a) Detectable plasma HCV RNA
- b) A liver biopsy showing bridging or portal fibrosis.

- ALT levels may be elevated in association with HCV infection. However, ALT levels do not accurately reflect the severity of HCV-associated liver disease.
- Liver biopsy is important for therapeutic decision-making but is indicated only if the patient is considered a treatment candidate based on multiple other variables including severity and stability of HIV disease, other co-morbidities, probability of adherence, and if there are contraindications to interferon-alpha.
- Using Pegylated interferon plus ribavirin for 48 weeks showed sustained virologic response (SVR) rates of 60-70% for HCV genotype 2/3 but only 15-28% for genotype 1. These were based on patients with CD4 cell counts > 200/mm³.

8.4.1 Treatment of HCV/HIV Co-infection.

- Preference given to those with higher CD4 cell counts > 200/mm³. For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible, but may be complicated by pill burden, drug toxicities and drug interactions.
- Scenarios for treating HCV/HIV Co-infection:
 - a) Ribavirin should not be given with didanosine due to the potential for drug-drug interactions leading to pancreatitis and lactic acidosis
 - b) Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic so that monitoring of serum transaminase levels is important
 - c) Zidovudine combined with ribavirin is associated with higher rates of anaemia suggesting this combination should be avoided when possible.
 - d) Growth factors to manage interferon-associated neutropenia and ribavirin-associated anaemia may be required.

8.5 Management of Patients Failing Second Line Treatment

- Current first line treatment regimens are effective and convenient to take; as much as possible patients should be supported to be able to stay on these treatments for as long as possible. Despite this some of our patients will fail both first and subsequently, second line treatment. In our setting where failure is likely to be diagnosed late (i.e. clinical failure) these patients will most likely have failed all 3 classes of ARV drugs. Following second line treatment failure constructing a new regimen with fully active new drugs will depend on prior treatment history and may not be possible with the drugs available in resource limited settings.
- The following principles will be useful in the management of patients failing a second-line regimen;
 - Adherence is key to treatment success; patient readiness and understanding of treatment requirements should always be part of the process of treatment initiation or change. Adherence counseling should be an ongoing part of the care of patients on ART



- Managed well patients on post second-line (salvage) therapy can survive for long periods
- Knowledge of drug history including adherence behaviour and toxicity is essential for the management of these patients.
- Resistance testing is still not accessible to most patients in Kenya and will for the time being not inform treatment in these circumstances; where available it may assist in the choice of an effective regimen. (see Chapter 4)
- For better clinical outcomes in salvage therapy it is best to change treatment “early”; this may not be possible where viral loads are not routinely available
- Either use of drug classes to which patient has not been exposed or use of drugs from classes already used but to which resistance is unlikely to have developed is likely to give better results; this may be a problem in resource limited settings where availability of newer ARV drugs is likely to be limited.
- Once failure is confirmed (trends in clinical status, CD4 count, viral load) ascertain factors responsible for failure of the most recent regimen
 - Correct these prior to initiation of new regimen
 - Choose appropriate regimen based on drug history, adherence, tolerability and feasibility (and resistance testing)
- **Where treatment options are limited, a stable patient who is failing treatment should be continued on the failing regimen until other options become available.**
- Where a patient is unstable available options should be discussed with a senior clinician
- Managing patients with multiple ARV drug experience in resource limited settings will be a considerable challenge because of the individualized nature of treatment of such patients; more costly regimens which are likely to be inaccessible; more laboratory requirements for the more complex regimens; greater adherence demands from the patient; lack of effective monitoring tools (viral load) and the expertise required. The likelihood of drug interactions also is expected to be greater. **For these reasons clinicians and their patients should aim to get the maximum mileage out of initial treatment.**



APPENDIX

Table 1 Nucleoside & Nucleotide Reverse Transcriptase Inhibitors (NRTIs & NRTI)

(Key: A: Available in Kenya, NA (Not available in Kenya))

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Stavudine (d4T) Available in 15mg, 20mg, 30mg, 40mg capsules (A)	40mg BD for patients > 60kg; 30mg BD for patients < 60kg;	Take without regard to meals	Peripheral neuropathy; Pancreatitis; Lipodystrophy; Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported); Headache; gastrointestinal disturbances; skin rashes;	Avoid combination with ddI especially in pregnancy. Decrease dosage in patients with renal impairment
Zidovudine (AZT or ZDV) Available in 100mg capsules, 300mg tablets (A)	300mg/dose BD	Take without regard to meals	Haematological toxicity (bone marrow suppression), including Anaemia; Granulocytopenia; Headache; gastrointestinal intolerance; myopathy; myositis; liver toxicity; discoloured nails; Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported).	Monitor for anaemia in the first 3 months of treatment
Lamivudine (3TC) . Available in 150mg tablet (A), 300mg (NA)	150mg/dose BD	Take without regard to meals	Headache; fatigue; nausea; diarrhoea; skin rash; Pancreatitis; Peripheral neuropathy; Liver disease/hepatitis; Lactic acidosis and severe hepatomegaly with steatosis (rare fatal cases have been reported).	A well-tolerated drug. Adjust dose in renal impairment. Can also be used in the treatment of chronic Hepatitis B. Ideally, patients should be screened for chronic Hepatitis B virus (HBV) before starting therapy; exacerbation of Hepatitis B has been reported in patients on discontinuation of 3TC.





Table 1

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Stavudine Didanosine (ddI) Available in 25mg, 50mg, 100mg, 200mg tablets (A), 150mg (NA) Enteric coated tablets; 125mg, 200mg, 250mg, 400mg (A)	>60kg: 200mg/dose BD or 400mg/dose OD<60kg: 125mg/dose BD or 250mg OD	Take on an empty stomach at least 30 minutes before or 2 hours after eating (food decreases absorption). For EC tablets take at least 1 hour before or 2 hours after meals	Pancreatitis; Peripheral neuropathy; Nausea; Diarrhoea; Abdominal pain and vomiting; Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported); Hyperuricaemia; electrolyte abnormalities;	Avoid combination with d4T especially in pregnancy. Do not use with Tenofovir; high virological failure rate and increased toxicity. Requires dosing separation from most Requires dosing separation from most Pls
Abacavir (ABC) Available in 300mg tablets (A)	300mg/dose BD	Take without regard to meals. Alcohol increases ABC levels to 41%	Hypersensitivity reaction (potentially fatal) whose symptoms include fever, fatigue, malaise, nausea, vomiting, diarrhoea and abdominal pain or respiratory symptoms such as shortness of breath, lymphadenopathy, ulceration of mucous membranes and skin rash. Patients suspected of having hypersensitivity reaction should have ABC stopped and never be restarted. Pancreatitis: Lactic acidosis with hepatic steatosis is rare.	Educate patient on hypersensitivity reaction. Once hypersensitivity has occurred, the patient should never be re-challenged. Avoid alcohol while on ABC.

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Stavudine Emtricitabine (FTC) Available in 200mg capsules (NA)	200mg/dose OD	Take without regard to meals.	Well tolerated. Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported); headache; diarrhoea; nausea; rash; skin discoloration.	Effective against Hepatitis B. Ideally, patients should be screened for chronic Hepatitis B virus (HBV) before starting therapy; exacerbation of Hepatitis B has been reported in patients on discontinuation of FTC. Decrease dosage in patients with renal impairment. Monitor renal function if combined with TDF. When used in combination with TDF, should not be given to patients with a creatinine clearance of <30ml/min. Should not be used with or after failure of 3TC
Tenofovir disoproxil fumarate (TDF) Available in 300mg tablets (A)	300mg/dose OD	Take without regard to meals.	Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported with nucleoside analogues); renal toxicity; Pancreatitis	Should not be used with ddI. Should never be used in triple nucleoside combinations with 3TC+ddI/ABC. Renal function should be monitored while on TDF. Ideally, patients should be screened for chronic Hepatitis B virus (HBV) before starting therapy; Exacerbation of Hepatitis B has been reported in patients on discontinuation of TDF. When used in combination with 3TC, should not be given to patients with a creatinine clearance of <30ml/min. When used with ATV levels of ATV reduced significantly therefore combine with RTV





Table 1

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Stavudine Zalcitabine (ddC)/Available in 0.375mg, 0.75mg tablets (NA)	0.75mg TDS	Take on an empty stomach at least 30 minutes before or 2 hours after eating (food may decrease absorption). Antacids decrease absorption of ddC	Peripheral neuropathy; Pancreatitis; hepatic toxicity; oral or oesophageal ulcers; headache; gastrointestinal disturbances; malaise; Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported).	Decrease dosage in patients with renal impairment. Should not be used with ddI or d4T

Table 2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Nevirapine(NVP) Available in 200mg tablets (A)	200mg/dose OD for first 2weeks Then 200mg/dose BD	Take without regard to meals.	Skin rash (may be severe, requiring hospitalization, and life-threatening, including Stevens-Johnson syndrome, toxic epidermal necrolysis); hepatitis; fever, nausea, headache.	Avoid in women with baseline CD4>250 or in men with baseline CD4>400. Liver function tests in the first 3 months of treatment. Should not be used with Rifampicin in TB patients.Avoid NVP in patients requiring prolonged treatment with Fluconazole because of increased NVP levels with possibility of increased toxicity. Use alternative antifungal drugs for treatment of oral candidiasis in patients on NVP
Efavirenz (EFV) Available in 50, 100, 200mg capsules, 600mg tablets (A)	600mg ODBest given at bedtime, especially for the first two weeks to avoid CNS effects	Can be given with food, but avoid high fat meals which increase absorption. Preferably taken on an empty stomach.	CNS symptoms (somnia, insomnia, abnormal dreams, confusion, hallucination, amnesia, etc. Avoid in patients with history of psychiatric disease); Skin rash; teratogenic in primates (avoid use in women of child-bearing potential)	Can be used with Rifampicin in TB patients
Delavirdine (DLV) Available as 100, 200mg tablets (NA)	400mg TDS	Can be given with food, but should be taken one hour before or one hour after ddi or antacids.	Skin rash (may be severe); headache; fatigue; gastrointestinal complaints.	




Table 3 Protease Inhibitors (PIs)

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Lopinavir/ritonavir (LPV/r, Kaletra) Available as 133.3mg LPV + 33.3mg RTV	(LPV 400 mg + RTV 100 mg) 3 capsules BD With EFV or NVP (LPV 533 mg + RTV 133 mg) (4 capsules) BD	Take with food. Moderate fat increases bioavailability.	GI intolerance; nausea; vomiting; diarrhoea	Capsules should be refrigerated, however can be stored at room temperature (up to 25°C) for 2 months. Preliminary data show lower drug exposure in pregnancy
Indinavir (IDV) Available as 200mg, 400mg (A) capsules	800mg/dose TDS with RTV: IDV 800mg BD + RTV 100mg BD preferred	For unboosted IDV: Take on an empty stomach, one hour before or two hours after meals; may take with skim milk or low-fat meal. For RTV-boosted IDV: Take with or without food Plenty of fluids to be taken (> 2 litres per day)	Nephrolithiasis; exacerbation of chronic liver disease; fat redistribution and lipid abnormalities; nausea; abdominal pain; headache; metallic taste; dizziness; asymptomatic hyperbilirubinaemia	Separate dosing if given with ddI Ritonavir-boosted IDV preferred because of better pharmacokinetics, no food restrictions and increased efficacy
Nelfinavir (NFV) Available as 250mg tablets (A)	750mg TDS or 1250mg BD	Take with meal (high fat meal preferred)	Diarrhoea; asthenia; abdominal pain; rash; exacerbation of liver disease; fat redistribution and lipid abnormalities; possible increased bleeding episodes in patients with haemophilia.	Manage diarrhoea symptomatically. Failure likely if inadequate food is taken with drug. Higher rate of virological failure when compared to other PIs (LPV/r & Fosamprenavir) and Efavirenz in clinical trials. Favourable safety and pharmacokinetic profile for pregnant women when compared to other PIs.

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Saquinavir (hard gel formulation)(SQV) Available as 200mg capsules (A)	Only for combination with Ritonavir in dose of SQV 1000mg and RTV 100g BD	Take within 2 hours of a meal	Exacerbation of liver disease; fat redistribution and lipid abnormalities; diarrhoea; abdominal discomfort; headache; nausea; paraesthesia; skin rash; spontaneous bleeding episodes in haemophiliacs.	Unboosted SQV not recommended.
Saquinavir (soft gel formulation)(SQV) Available as 200mg capsules (A)	Not recommended: 1,200mg TDS or 1,600mg BD <u>With RTV:</u> • (RTV 100 mg +SQV-sgc 1,000mg) two times/day	Take with large meal.	As above	Refrigerate or store at room temperature (< 25°C) for upto 3 months)
Ritonavir(RTV) Available as 100mg capsules (A) Capsules should be refrigerated until dispensed; stable at room (up to 25°C) for 30 days	WHO recommends that RTV be used only as a booster for other PIs at low dosage?	Administration with food increases absorption and helps reduce gastrointestinal side effects.	Exacerbation of liver disease; fat redistribution and lipid abnormalities; diarrhoea; abdominal discomfort; headache; nausea; paraesthesia; skin rash; spontaneous bleeding episodes in haemophiliacs.	Potent CYP450 inhibitor, thus its use as a booster of other PIs




Table 3 Protease Inhibitors (PIs)

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Amprenavir (APV) Available as 50mg capsules (A)	1200mg BD	Can be taken with or without food but high fat meal should be avoided (decreases absorption).	Fat redistribution and lipid abnormalities; Life-threatening rash, including Stevens-Johnson syndrome in 1% of patients; exacerbation of pre-existing diabetes mellitus, haemolytic anaemia, spontaneous bleeding episodes in haemophiliacs.	Hepatic, Renal function; Routine blood chemistry. AMP oral solution and RTV oral solution should not be co-administered together.
Atazanavir (ATV) Available in 100mg, 150mg, 200 mg capsules (A)	400mg OD	Take 2 hours before or 1 hour after antacids and buffered medications such as buffered ddI (reduced ATV concentrations if administered together) Take with food.	Jaundice; headache; fever; depression; nausea; diarrhoea and vomiting; paraesthesia; spontaneous bleeding episodes in haemophiliacs.	Indirect hyperbilirubinaemia. When used with TDF should always be given with RTV. Experienced patients should also be given ATV/RTV.
Preferred boosted with Ritonavir (ATV/RTV)	ATV 300mg /RTV 100mg OD			
Fosamprenavir (f-APV) Available as 700mg tablets (NA)	ARV-naive patients: f-APV 1400mg BD (without RTV); f-APV 1400mg + 200mg RTV OD; f-APV 700mg + 100mg RTV BD PI-experienced pts (concedaily regimen not recommended): f-APV 700mg + 100mg RTV BD	Take with or without food. Take 1 hour before or 1 hour after antacids or ddI use	Fat redistribution and lipid abnormalities; Life-threatening rash, including Stevens-Johnson syndrome in 1% of patients;	Dosage adjustment in hepatic insufficiency recommended

Table 4 Fusion Inhibitors

Drug name	Dose	Dietary restrictions	Major side effects	Comments
Enfuvirtide (T-20) Available in 108mg injection (when reconstituted, delivers 90mg/ml) (NA)	90mg (1ml) BD injected subcutaneously into upper arm, anterior thigh or abdomen.	N/A	Local injection site reactions; increased rate of bacterial pneumonia; hypersensitivity reactions including fever, nausea and vomiting.	Mainly for salvage treatment. Store at room temperature (up to 25°C). Reconstituted solution should be stored under refrigeration at 2°C to 8°C and used within 24 hours.

Table 5A: Pharmacokinetic properties of Antiretroviral Drugs RTIs

Drug	Oral Bioavailability	Serum half-life	Intracellular half-life	Elimination
Stavudine	86%	1.0 hour	3.5 hours	Renal excretion 50%
Zidovudine	60%	1.1 hours	3 hours	Metabolized to AZT glucuronide (GAZT). Renal excretion of GAZT
Lamivudine	86%	3-6 hours	12 hours	Renal excretion
Didanosine	30-40%	1.6 hours	25-40 hours	Renal excretion 50%
Abacavir	83%	1.5 hours	3.3 hours	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82%
Zalcitabine	85%	1.2 hours	3 hours	Renal excretion 70%
Tenofovir	25% in fasting state; 39% with high-fat meal	17 hours	10-50 hours	Primarily renal excretion by glomerular filtration and active tubular secretion
Nevirapine	>90%	25-30 hours	Data not available	Metabolized by cytochrome P450 (3A inducer): 80% excreted in urine (glucuronidated metabolites; <5% unchanged); 10% in faeces




Table 5A: Pharmacokinetic properties of Antiretroviral Drugs RTIs

Drug	Oral Bioavailability	Serum half-life	Intracellular half-life	Elimination
Efavirenz	Data not available	40-55 hours	Data not available	Metabolized by cytochrome P450 (3A mixed inducer/ inhibitor); 14%–34% excreted in urine (glucuronidated metabolites, < 1% unchanged); 16%–61% in faeces.
Delavirdine	85%	5.8 hours	Data not available	Metabolized by cytochrome P450 (3A inhibitor); 51% excreted in urine (< 5% unchanged); 44% in faeces

Table 5B: Pharmacokinetic properties of Antiretroviral Drugs PIs and FI

Drug	Oral Bioavailability	Serum half-life	Route of Metabolism
Indinavir	65%	1.5-2 hours	P450 cytochrome 3A4 inhibitor (less than ritonavir)
Nelfinavir	20-80%	3.5-5 hours	Cytochrome P450 (3A4 inhibitor; less than ritonavir)
Saquinavir (soft gel capsules)	4% erratic	1 – 2 hours	Cytochrome P450 (3A4 inhibitor (less than ritonavir)
Saquinavir (hard gel capsules)	Not determined	1 – 2 hours	Cytochrome P450 (3A4 inhibitor (less than ritonavir)
Ritonavir	Not determined	3 – 5 hours	Cytochrome P450 (3A4 > 2D6; Potent 3A4 inhibitor)
Amprenavir	Not determined in humans	7.1 – 10.6 hours	Cytochrome P450 (3A4 inhibitor (less than ritonavir; similar to indinavir, nelfinavir)
Lopinavir/ritonavir	Not determined in humans	5 – 6 hours	Cytochrome P450 (3A4 inhibitor)
Enfuvirtide	84, 3%	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool

Table 6: Summary of ARV Drug Adverse Effects and Management (see Kenya National Clinical Manual for ART Providers)

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Hepatic Events (Nevirapine-associated symptomatic events, including hepatocarcinoma)	Nevirapine	<p>Onset: Greatest risk within 1st few weeks of therapy; can occur through 18 weeks</p> <p>Symptoms: Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure with encephalopathy</p> <p>Approximately 1/2 of the cases have accompanying skin rash.</p> <p>Some may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)</p>	<ul style="list-style-type: none"> Higher CD4 cell count at initiation (>250 cells/mm³ in women & >400 cells/mm³ in men) Female gender (including pregnant women) Elevated ALT or AST at baseline; HBV and/or HCV co-infection; Alcoholic liver disease HIV (-) individuals when NVP is used for post-exposure prophylaxis High NVP concentration 	<ul style="list-style-type: none"> Counsel pts re: signs & symptoms of hepatitis; stop NVP & seek medical attention if: signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions Monitoring of ALT & AST (every 2 weeks x 1st month, then monthly x 3 months, then every 3 months) Obtain AST/ALT in patients with rash 2-week dose escalation may reduce incidence of hepatic events 	<ul style="list-style-type: none"> Discontinue ARV including nevirapine (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV co-infected patients) Discontinue all other hepatotoxic agents if possible Rule out other causes of hepatitis Aggressive supportive care as indicated Note: Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. Do not re-challenge patient with NVP The safety of other NNRTIs (EFV or DLV) in patients who experience significant hepatic event from NVP is unknown – use with caution. Refer to Kenya National clinical manual for ARV providers





Table 6: Summary of ARV Drug Adverse Effects and Management

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Hepatotoxicity (clinical or asymptomatic serum transaminase elevation)	All NNRTIs All PIs All NRTIs	<p>NNRTI – for NVP - 2/3 within 1st 12 weeks NRTI – over months to years PI – generally after weeks to months</p> <p>Symptoms/Findings: NNRTI – asymptomatic to non-specific symptoms such as anorexia, weight loss, or fatigue. Approximately 1/2 of patients with NVP-associated symptomatic hepatic events present with skin rash.</p> <p>NRTI – • ART, ddl, d4T - may cause hepatotoxicity associated with lactic acidosis with micro-vesicular or macro-vesicular hepatic steatosis due to mitochondrial toxicity. 3TC, FTC, or tenofovir – HBV co-infected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops.</p> <p>PI – • Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.</p>	<p>Hepatitis B or C co-infection</p> <ul style="list-style-type: none"> Alcoholism Concomitant hepatotoxic drugs For NVP-associated hepatic events – female w/ pre-NVPCD4 >250 cells/mm³ or male w/ pre-NVPCD4 >400 cells/mm³ 	<p>NVP – monitor liver associated enzymes at baseline, 2 & 4 weeks, then monthly for 1st 3 months; then every 3 months</p> <p>Other agents: monitor liver associated enzymes at least every 3–4 months or more frequently in patients at risk</p>	<ul style="list-style-type: none"> Rule out other causes of hepatotoxicity – alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC or TDF withdrawal, or HBV resistance, etc. For symptomatic patients: Discontinue all ARV (with caution in patients with chronic HBV infection treated w/ 3TC, FTC and/or TDF) and other potential hepatotoxic agents After symptoms subside & serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) <p>For asymptomatic patients:</p> <ul style="list-style-type: none"> If ALT > 5-10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring After serum transaminases returned to normal, construct a new ARV regimen <p>Refer to Kenya national clinical manual for ARV providers page 33 and 34</p>

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Skin rash	NVP EFV ABC ATV APV	Onset: within first few days to weeks after initiation of therapy Symptoms: most rashes are mild to moderate in nature; diffuse maculopapular rash without pruritus; severe rash, rash with fever or with mucous membrane involvement warrants immediate discontinuation of ARV Note: Please also see sections on Stevens-Johnson Syndrome & Systemic Hypersensitivity	<ul style="list-style-type: none"> NVP – female, Black, Asian, Hispanic f-APV, APV – sulphoramidate derivative – potential for cross hypersensitivity with other sulphamides EFV – higher in 	<p>NVP – always use a 2-week low dose lead-in period</p> <ul style="list-style-type: none"> Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash Patient education – advise to report first sign of rash Most experts suggest avoidance of EFV or DLV in patients with history of severe rash from NVP, and vice 	<ul style="list-style-type: none"> Mild to moderate rash may be managed by symptomatic treatment with antihistamine and continuation of offending agent Discontinue therapy if skin rash progresses to severe in nature (accompanied by blisters, fever, mucous membrane involvement, conjunctivitis, oedema, or arthralgia) or presence of systemic symptoms (including fever) Do not restart offending medication in case of severe rash If rash develops during first 18 weeks of NVP treatment obtain serum transaminases to rule out symptomatic hepatic event. <p>Refer to Kenya national clinical manual for ARV</p>





Table 6: Summary of ARV Drug Adverse Effects and Management

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Stevens Johnson's syndrome	NVP EFV DLV	<p><u>Onset</u>: first few days to weeks after initiation of therapy</p> <p><u>Symptoms</u>:</p> <p><i>Cutaneous involvement</i>:</p> <ul style="list-style-type: none"> • Skin eruption with mucosal ulcerations (may involve orolingival mucosa, conjunctiva, ano-genital area); • Can rapidly evolve with blister or bullae formation; • May eventually evolve to epidermal detachment and/or necrosis <p><i>Systemic Symptoms</i>:</p> <p>fever, tachycardia, malaise, myalgia, arthralgia</p> <p><i>Complications</i>: fluid depletion; bacterial or fungal superinfection; multi-organ failure</p>	NVP-Female, Black, Asian, Hispanic	<ul style="list-style-type: none"> • 2-week lead in period with 200mg once daily, then escalate to 200mg twice daily • Educate patients to report symptoms as soon as they appear • Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash 	<ul style="list-style-type: none"> • Discontinue all ARVs and any other possible agent (s) (e.g. of trimoxazole) Aggressive symptomatic support may include: • Intensive care support • Aggressive local wound care (e.g. in aburn unit) • Intravenous hydration • Parenteral nutrition, if necessary • Pain management • Antipyretics • Empiric broad-spectrum antimicrobial therapy if superinfection is suspected <p>Controversial management strategies:</p> <ul style="list-style-type: none"> • Corticosteroid • Intravenous immunoglobulin <p>Do not re-challenge patients with offending agent. It is unknown whether patients who experience SJS while on NNRTI are most susceptible from another NNRTI-most experts would suggest avoiding this unless no option</p>

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Peripheral neuropathy	D4T DDI DDC	Onset: weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) Symptoms: • Begins with numbness & paraesthesia of toes and feet; • May progress to painful neuropathy of feet and calf; • Upper extremities less frequently involved • Can be debilitating for some patients. • May be irreversible despite discontinuation of offending agent(s)	<ul style="list-style-type: none"> • Pre-existing peripheral neuropathy; • Combined use of these NRTIs or concomitant use of other drugs which may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs which may increase ddl intracellular activities (e.g. HU or RBV) 	<ul style="list-style-type: none"> • Avoid using these agents in patients at risk – if possible • Avoid combined use of these agents • Patient query at each encounter 	<p>May consider discontinuing offending agent before pain becomes disabling – may halt further progression, but symptoms may be irreversible</p> <p>Pharmacological management (with variable successes):</p> <ul style="list-style-type: none"> • Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol • Narcotic analgesics • Capsaicin cream • Topical lidocaine
Pancreatitis	D4T DDI 3TC-in children	Onset: usually weeks to months Laboratory abnormalities: increased serum amylase and lipase Symptoms: post-prandial abdominal pain, nausea, vomiting	<p>High intracellular and/or serum ddl concentrations</p> <ul style="list-style-type: none"> • History of pancreatitis • Alcoholism • hypertriglyceridaemia • Concomitant use of ddl with d4T, HU, or RBV • Use of ddl + TDF without ddl dose reduction 	<p>ddl should not be used in patients with history of pancreatitis</p> <ul style="list-style-type: none"> • Avoid concomitant use of ddl with d4T, HU or RBV • Reduce ddl dose when used with TDF • Monitoring of amylase/lipase in asymptomatic patients is generally not recommended 	<p>Discontinue offending agent(s)</p> <ul style="list-style-type: none"> • Symptomatic management of pancreatitis – bowel rest, IV hydration, pain control, then gradual resumption of oral intake • Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake





Table 6: Summary of ARV Drug Adverse Effects and Management

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Lactic acidosis	D4T DDI	<p><u>Onset</u>: months after initiation of ARV; then dramatic motor weakness occurring within days to weeks</p> <p><u>Symptom</u>: very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré Syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; resulted in deaths in some patients</p> <p>Laboratory findings may include:</p> <ul style="list-style-type: none"> • Low arterial pH • Increased lactate • Low serum bicarbonate • Increased anion gap • Markedly increased CPK 	Prolonged D4T use	Early recognition and discontinuation of ARVs may avoid further progression	<p>-Discontinuation of ARVs</p> <p>Supportive care including mechanical ventilation if needed</p> <p>-Other measures attempted with success:</p> <ul style="list-style-type: none"> • plasmapheresis, high dose corticosteroids, intravenous immunoglobulin. <p>Recovery often takes months</p> <p>-ranging from complete recovery to substantial residual deficits</p> <p>Do not re-challenge patient with the offending agent</p>
Hypersensitivity reactions	ABV	<p><u>Onset of 1st reaction</u>: median onset – 9 days; approximately 90% within 1st 6 weeks</p> <p><u>Onset of re-challenge reactions</u>: within hours of re-challenge dose</p> <p><u>Symptoms</u>: acute onset of symptoms (in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhoea, vomiting, abdominal pain, dyspnoea,</p>	<ul style="list-style-type: none"> • HLA-B*5701, HLA-DR7, HLADQ3 (from Australian data) • ARV-native patients • Higher incidence of grade 3 or 4HSR with 600mg once daily dose than 	<ul style="list-style-type: none"> • Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly • Wallet card with warning information for patients 	<ul style="list-style-type: none"> • Discontinue ABC and other ARVs • Rule out other causes of symptoms (e.g., inter-current illnesses such as viral syndromes, and other causes of skin rash, etc) • Most signs and symptoms resolve 48hours after discontinuation of ABC <p><i>More severe cases:</i></p>

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Bone marrow suppression	AZT	<p>tachypnoea) <i>With continuation of ABC, symptoms may worsen to include:</i> hypotension, respiratory distress, vascular collapse <i>Re-challenge reactions:</i> generally greater intensity than 1st reaction, can mimic anaphylaxis <u>Onset:</u> 1st 3 months of treatment</p> <p>Laboratory abnormalities:</p> <ul style="list-style-type: none"> Anaemia Neutropenia <p><u>Symptoms:</u> fatigue due to anaemia; potential for increase bacterial infections due to neutropenia</p>	<p>300mg twice daily dose in onestudy (5% vs. 2%)</p> <p>-Advanced HIV - High dose of AZT- Pre-existing anaemia or neutropenia- Concomitant use of bone marrow suppressants e.g. ganciclovir, cotrimoxazole, ribavirin</p>	<p>-Avoid use in patients at risk-Avoid other bone marrow suppressants if possible-Monitor CBC with differential.</p>	<ul style="list-style-type: none"> Symptomatic support - antipyretic, fluid resuscitation, pressure support (if necessary) Do not re-challenge patients with ABC after suspected HSR <p>Switch to d4T or TDF or ABC patients at risk)</p> <ul style="list-style-type: none"> Discontinue concomitant bone marrow suppressant if there is alternative option; otherwise: <p>For neutropenia:</p> <ul style="list-style-type: none"> Identify and treat other causes Consider treatment with filgrastim <p>For anaemia:</p> <ul style="list-style-type: none"> Identify and treat other causes of anaemia(if present) Blood transfusion if indicated Consider erythropoietin therapy <p>Refer to Kenya national clinical manual for ARV providers page 36</p>


Table 6: Summary of ARV Drug Adverse Effects and Management

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Nephrotoxicity	IDV; potentially TDF	<u>Onset:</u> IDV – months after therapy TDF – weeks to months after therapy <u>Laboratory and other findings:</u> IDV: serum creatinine, pyuria; hydronephrosis or renal atrophy TDF: serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis <u>Symptoms:</u> IDV: asymptomatic rarely develop to end stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus; Fanconi's Syndrome	<ul style="list-style-type: none"> History of renal disease Concomitant use of nephrotoxic drugs 	Avoid use of other nephrotoxic drugs <ul style="list-style-type: none"> Adequate hydration if on IDV therapy Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk 	Stop offending agent, generally reversible <ul style="list-style-type: none"> Supportive care Electrolyte replacement as indicated
Central nervous system effects	EFV	<u>Onset:</u> begin with first few doses <u>Symptoms:</u> may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation. Most symptoms subside or diminish after 2-4 weeks	Pre-existing or unstable psychiatric illnesses; <ul style="list-style-type: none"> Use of concomitant drugs with CNS effects 	Take at bedtime or 2-3 hours before bedtime; <ul style="list-style-type: none"> Take on an empty stomach to reduce drug concentration & CNS effects Warn patients regarding restriction of risky activities – such as operating heavy machinery during the 1st 2-4 weeks of therapy 	Symptoms usually diminish or disappear after 2-4 weeks <ul style="list-style-type: none"> May consider discontinuing therapy if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Fat mal-distribution	PIs, d4T, AZT	<p>d4T Onset: gradual - months after initiation of therapy</p> <p>Symptoms:</p> <ul style="list-style-type: none"> Lipoatrophy – peripheral fat loss manifested as facial thinning, thinning of extremities and buttocks (d4T) Increase in abdominal girth, breast size, and dorso-cervical fatpad (buffalo hump) 	Lipoatrophy – lowbaseline body mass index	None to date	<p>Where possible, switching to other agents – may slow or halt progression, however, may not reverse effects:</p> <p>substitution of d4T with TDF or ABC result in reversal of fat loss.</p> <ul style="list-style-type: none"> Diet and exercise may improve lipoatrophy associated with PI use Injectable poly-L-lactic acid for treatment of facial lipoatrophy
Gastrointestinal intolerance	All PIs, ZDV/DDI	<p>Onset: Begin within first doses</p> <p>Symptoms:</p> <ul style="list-style-type: none"> Nausea, vomiting, abdominal pain – all listed agents Diarrhoea – commonly seen with NFV, LPV/r, & ddI buffered formulations 	All patients	<p>Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV)</p> <ul style="list-style-type: none"> Some patients may require anti-emetics or anti-diarrhoeal pre-emptively to reduce symptoms 	<p>May spontaneously resolve or become tolerable with time; if not:</p> <p>For nausea & vomiting, consider:</p> <ul style="list-style-type: none"> Anti-emetic prior to dosing Switch to less emetogenic ARV or diarrhoea, consider: Anti-motility agents – such as loperamide, diphenoxylate/atropine Calcium tablets Bulk-forming agents, such as psyllium products Pancreatic enzymes in case of severe GI loss: Rehydration & electrolyte replacement as indicated





Table 6: Summary of ARV Drug Adverse Effects and Management

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Cardiovascular events	Possibly all PIs except ATV	<u>Onset</u> : months to years after beginning of therapy <u>Presentation</u> : premature coronary artery disease	Other risk factors for cardio vascular disease such as smoking, age, hyperlipidaemia, hypertension, diabetes mellitus, family history of premature coronary artery disease and personal history of coronary artery disease	<ul style="list-style-type: none"> Assess each patient's cardiac risk factors Consider non-PI based regimen Monitor & identify pts w/hyperlipidaemia or hyperglycaemia Counselling for lifestyle modification- smoking cessation, diet, and exercise 	<ul style="list-style-type: none"> Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors such as hyperlipidaemia, hypertension, and insulin resistance/diabetes mellitus Assess cardiac risk factors Lifestyle modifications: diet, exercise, and/or smoking cessation Switch to agents with less propensity for increasing cardiovascular risk factors, i.e. NNRTI- or ATV-based regimen & avoid d4T use
Hyperlipidemia	All PIs except ATZ D4T EFV to a lesser extent	Onset: weeks to months after beginning of therapy Presentation: All PIs except ATV -- in LDL & total cholesterol (TC) & triglyceride (TG), in HDLPPV/r & RTV – disproportionate in TGd4T – mostly in TG; may also have in LDL & total cholesterol (TC) EFV or NVP: in HDL, slight TG	Underlying hyperlipidaemia <ul style="list-style-type: none"> Risk based on ARV therapy PI: LPV/r & RTV >NFV & APV >IDV & SQV >ATV; NNRTI: less than PIs; NNRTI: d4T > ZDV & TDF 	<ul style="list-style-type: none"> Use ATV-based regimen Fasting lipid profile at baseline, 3-6 months after starting new regimen, then annually or more frequently if indicated (in high risk patients, or patients with abnormal baseline levels) 	<p>Follow ACTG guidelines recommendations for management (1)</p> <ul style="list-style-type: none"> Assess cardiac risk factor Lifestyle modification: diet, exercise, and/or smoking cessation Switching to agents with less propensity for causing hyperlipidaemia <p>Pharmacologic Management:</p> <ul style="list-style-type: none"> Total cholesterol, LDL, TG 200-500mg/dl: "statins" – pravastatin or atorvastatin TG > 500 mg/dl – gemfibrozil or micronized fenofibrate

Adverse Events	Causative ARV	Onset, Clinical Manifestation	Risk Factors	Prevention/Monitoring	Management
Insulin resistance/ diabetes mellitus	All PIs All PIs	Onset: weeks to months after beginning of therapy Presentation: Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycaemia in patients with underlying diabetes	Underlying hyperglycaemia, family history of diabetes mellitus	Use PI-sparing regimens • Fasting blood glucose 1-3 months after starting new regimen, then at least every 3-6 months	Diet and exercise • Consider switching to an NNRTI-based regimen • Metformin • "gliflozines" • Sulfonylurea • Insulin
Nephrolithiasis / urolithiasis/ crystalluria	IDV-most frequent	Onset: any time after beginning of therapy – especially at times of reduced fluid intake Laboratory abnormalities: pyuria, haematuria, crystalluria; rarely – rise in serum creatinine & acute renal failure Symptoms: flank pain and/or abdominal pain (can be severe), dysuria, frequency	History of nephrolithiasis • Patients unable to maintain adequate fluid intake • High peak IDV concentration • duration of exposure	Drink at least 1.5 to 2 litres of non caffeinated fluid (preferably water) per day • Increase fluid intake at first sign of darkened urine • Monitor urinalysis and serum creatinine every 3-6 months	Increase hydration • Pain control • May consider switching to alternative agent or therapeutic drug monitoring if treatment option is limited • Stent placement may be required


Table 7: Drug-drug interactions: overlapping drug toxicity

Bone marrow suppression	Peripheral neuropathy	Pancreatitis	Nephrotoxicity	Hepatotoxicity	Rash	Diarrhoea	Ocular effects
Amphotericin B	Didanosine	Didanosine	Indinavir Acyclovir (IV; high dose)	Abacavir	Abacavir	Atovaquone	Cidofovir
Cotrimoxazole	Isoniazid	Lamivudine in children	Adefovir high dose	Amprenavir	Amprenavir	Clindamycin	Didanosine
Dapsone	Stavudine	Stavudine	Aminoglycosides	Atazanavir	Atazanavir	Didanosine (buffered formulations)	Ethambutol
Flucytosine	Zalcitabine	Cotrimoxazole	Amphotericin B	Atovaquone	Atovaquone		Linezolid
Ganciclovir		Ritonavir	Cidofovir	Cotrimoxazole	Cotrimoxazole		Rifabutin
Hydroxyurea		Pentamidine	Foscarnet	Dapsone	Dapsone	Lopinavir/	Voriconazole
Interferon-		Zalcitabine	Indinavir	Delavirdine	Delavirdine	Ritonavir	
Primaquine			Pentamidine	Efavirenz	Efavirenz	Nelfinavir	
Pyrimethamine			Tenofovir	Fosamprenavir	Fosamprenavir	Ritonavir	
Zidovudine				Nevirapine	Nevirapine		
				Sulfadiazine	Sulfadiazine		
				Voriconazole	Voriconazole		

Table 8: Drug-drug interactions requiring dose modification or cautious use- NRTIs

Drugs Affected	Zidovudine (ZDV)	Stavudine (d4T)	Didanosine (ddI)	Tenofovir (TDF)
Methadone	ZDV AUC increase 43%. Monitor for ZDV related adverse effects.	Levels: d4T ↓ 27%, methadone unchanged. No dose adjustment.	Levels: EC ddI unchanged. Buffered ddI AUC ↓ 63%, methadone unchanged. Dose: No change EC ddI. May consider buffered ddI dose increase or maintain standard.	No change in methadone or TDF levels. Sulfadiazine. Voriconazole

Drugs Affected	Zidovudine (ZDV)	Stavudine (d4T)	Didanosine (ddI)	Tenofovir (TDF)
Ribavirin	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible or closely monitor virologic response.	No data	Co-administration not recommended. Ribavirin increases the intracellular levels of the active metabolite of ddI and may cause serious toxicities.	Level: Ribavirin unchanged, no data on TDF level
Didanosine	No significant interactions	Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; use with caution and only if potential benefit outweighs potential risks.	No data	Levels: ddI EC AUC ↑ by 48-60%, Cmax ↑ by 48-64%. Monitor for ddI-associated toxicities; For patients > 60kg, 250 mg/day of ddI EC is recommended.
Atazanavir (ATV)	ZDV: No change in AUC but 30% ↓ in Cmin. Significance unknown	No data	Buffered ddI + ATV simultaneously: Level: ↓ AUC of TV 87%; take ATV (with food) 2 hrs before or 1 hr after buffered ddI. No interaction is expected with ddI-EC; however, dosing should be at different times at TV should be taken with fold and ddI-EC on an empty stomach.	ATV 400 + TDF 300 Levels: ATV AUC ↓ 25% and Cmin ↓ by 40%. TDF AUC was by ↑24%. Avoid concomitant use. ATV + RTV 300/100MG QD + TDF 300 MG QD. Levels: ATV AUC was ↓ by 25% and Cmin by 23%; ATV Cmin was higher with RTV than ATV without RTV; Consider ATV + RTV (300/100 mg QD) For Co-administration with TDF (300 mg QD); however, pharmacokinetic, safety and virologic data are limited.





Table 8: Drug-drug interactions requiring dose modification or cautious use- NRTIs

Drugs Affected	Zidovudine (ZDV)	Stavudine (d4T)	Didanosine (ddl)	Tenofovir (TDF)
Indinavir (IDV)	No significant PK interaction.	No significant PK interaction.	Buffered ddl and IDV simultaneously: Levels: ↓ AUC of IDV; take IDV 1 hr before or after buffered ddl. Enteric coated ddl can be taken together with IDV	Levels: IDV Cmax ↑ 14% Dose: Standard
Lopinavir/ ritonavir (LPV/r)	No data	No data	No data	LPV/r 400/100 AUC ↓ 15%; TDF AUC ↑ 34%; clinical significance of interaction is unknown; monitor for tenofovir toxicities
Cidofovir, valganciclovir	Ganciclovir + ZDV: no significant changes in levels for either drug Potential increase in haematological toxicities	No data	ddl + oral ganciclovir (GCV): ddl AUC ↑ 11%; GCV AUC ↓ 21%; Appropriate doses for the combination of ddl and oral GCV have not been established	Serum concentration of these drugs and/or tenofovir may be increased; Monitor for dose-related toxicities.

Table 9: Drug Interactions requiring dose modification or cautious use - NNRTIs

Drugs Affected	Nevirapine (NVP)	Efavirenz (EFV)
ANTIFUNGALS		
Ketoconazole	Levels: ketoconazole ↓ 63% NVP ↑ 15 – 30% Dose: Not recommended	No data
Voriconazole	Metabolism of Voriconazole may be induced by NVP. Voriconazole may inhibit NNRTI metabolism. Frequently monitor for NNRTI toxicity and antifungal outcome.	Levels: EFV ↑ 44% Voriconazole ↓ 77% This combination is not recommended.
Fluconazole	NVP Levels: Cmax, AUC, and Cmin ↑ 100% Fluconazole Levels: No change Risk of hepatotoxicity may increase with this combination. If concomitant use is necessary, recommend monitoring NVP toxicity.	No clinically significant changes in EFV or Fluconazole concentrations.
ANTI-MYCOBACTERIALS		
Rifampicin	Levels: NVP ↓ 20%-58%. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. Use of this combination is not recommended; however, if used, co administration should be done with careful monitoring.	Levels: EFV ↓ 25%. Dose: Consider ↑ EFV to 800 mg QD.
Clarithromycin	Levels: NVP ↑ 26%. Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent.	Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent.
ORAL CONTRACEPTIVES		
	Levels: ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.	Levels: Ethinyl estradiol ↑ 37%. No data on other components. Use alternative or additional methods.





Table 9: Drug Interactions requiring dose modification or cautious use - NNRTIs

Drugs Affected	Nevirapine (NVP)	Efavirenz (EFV)
IPID-LOWERING AGENTS		
Simvastatin Lovastatin	No data	Levels: Simvastatin AUC ↓ by 58%; EFV unchanged. Dose: Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose.
Atorvastatin	No data	Levels: Atorvastatin AUC ↓ 43%; EFV unchanged. Dose: Adjust atorvastatin dose according to lipid responses, not to exceed the maximum recommended dose.
Pravastatin	No data	No data
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Unknown Use with caution. Monitor anticonvulsant levels.	Use with caution. Monitor anticonvulsant levels.
METHADONE	Levels: NVP unchanged. Methadone ↓ significantly. Opiate withdrawal common when this combination is used. Increased methadone dose often necessary. Titrated methadone dose to effect.	Levels: Methadone ↓ 60%. Opiate withdrawal common, increase methadone dose often necessary. Titrated methadone dose to effect.
MISCELLANEOUS	No data	Monitor warfarin when used concomitantly.

Table 10: Drug-drug Interactions requiring dose modification or cautious use - Pls

Drugs Affected	Indinavir (IDV)	Ritonavir (RTV)	Saquinavir (SQV)	Nelfinavir (NFV)	Lopinavir (LPV)
ANTIFUNGALS					
Itraconazole	<p>Level: When IDV 600 mg q8h given with Itraconazole 200 mg bid, IDV AUC similar to IDV 800 mg q8h</p> <p>Dose: IDV 600 mg q8h; Itraconazole: do not exceed 200 mg bid.</p>	<p>No data, but potential for bi-directional inhibition between Itraconazole and RTV, monitor for toxicities.</p> <p>Dose: dose adjustment for patients receiving >400 mg Itraconazole may be needed, or consider monitoring Itraconazole level.</p>	<p>Bi-directional interaction between Itraconazole & SQV has been observed.</p> <p>Dose: Not established, but decreased Itraconazole dosage may be warranted. Consider therapeutic drug monitoring for both SQV (if unboosted) and Itraconazole.</p>	<p>No data, but potential for bi-directional inhibition between Itraconazole and Pls, monitor for toxicities.</p>	<p>Levels: Itraconazole ↑ when administered with LPV/r. Dose: Itraconazole – consider not to exceed 200 mg/day or monitor level and toxicity</p>
Ketoconazole	<p>Levels: IDV ↑ 68%.</p> <p>Dose: IDV 600 mg TDS.</p>	<p>Levels: Ketoconazole ↑ 3X.</p> <p>Dose: Use with caution; do not exceed 200 mg ketoconazole daily.</p>	<p>Levels: SQV ↑ 3X</p> <p>Dose: No dosage adjustment necessary.</p>	<p>No dose adjustment necessary.</p>	<p>Levels: LPV AUC ↓ 13% Azole ↑ 3-fold. Dose: Use with caution; do not exceed 200 mg ketoconazole daily.</p>



Table 10: Drug-drug Interactions requiring dose modification or cautious use - PIs

Drugs Affected	Indinavir (IDV)	Ritonavir (RTV)	Saquinavir (SQV)	Nelfinavir (NFV)	Lopinavir (LPV)
ANTI-MYCOBACTERIALS					
Rifampicin^s	Levels: IDV (unboosted) ↓ 89%; IDV (boosted) ↓ 87%; Contraindicated.	Levels: RTV ↓ 35%. Dose: No change. Increased liver toxicity possible. Co-administration may lead to loss of virologic response is RTV sole PI. Alternate anti-mycobacterial agents, such as rifabutin, should be considered.	Levels: SQV ↓ 84%. Contraindicated. Marked elevation of transaminases was seen in a pharmacokinetic study where healthy volunteers received a combination of rifampicin 600 mg QD + RTV 100 mg/SQV 1000mg BID. This combination should not be used.	Levels: NFV ↓ 82%. Should not be co-administered.	Levels: LPV AUC ↓ 75%. Should not be co-administered as a safe and effective dose of LPV/r that can be given with rifampicin has not been established. ⁵
Clarithromycin	Levels: Clarithromycin ↑ 53%. No dose adjustment.	Levels: Clarithromycin ↑ 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.	Levels: Clarithromycin ↑ 45%. SQV ↑ 177%. No dose adjustment.	No data	Levels: ↑ Clarithromycin AUC 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.

Drugs Affected	Indinavir (IDV)	Ritonavir (RTV)	Saquinavir* (SQV)	Nelfinavir (NFV)	Lopinavir (LPV)
ORAL CONTRACEPTIVES					
	Levels: norethindrone ↑ 26%. Ethinyl estradiol ↑ 24%. No dose adjustment.	Levels: Ethinyl estradiol ↓ 40%. Use alternative or additional method.	No data	Levels: Norethindrone ↓ 18%. Ethinyl estradiol ↓ 47%. Use alternative or additional methods.	Levels: Ethinyl estradiol ↓ 42%. Use alternative or additional method.
LIPID-LOWERING AGENTS					
Simvastatin Lovastatin	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: potential for large increase in statin levels. Avoid concomitant use.	No data	Simvastatin AUC ↑ 505%. Potential for large increase in lovastatin AUC. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
Atorvastatin	Levels: potential for increase in AUC Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 74% - use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 5.88-fold. Use lowest possible starting dose of atorvastatin with careful monitoring.



Table 10: Drug-drug Interactions requiring dose modification or cautious use - Pls

Drugs Affected	Indinavir (IDV)	Ritonavir (RTV)	Saquinavir (SQV)	Nelfinavir (NFV)	Lopinavir (LPV)
Pravastatin	No data	Levels: 50% ↓ when administered with SQV/RTV combination. Dose: Pravastatin dosage adjustment based on lipid response.	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. Dose: pravastatin dosage adjustment based on lipid response.	No data	Pravastatin AUC ↑ 33%; no dosage adjustment necessary.
ANTICONVULSANTS					
Carbamazepine Phenobarbital Phenytoin	Carbamazepine markedly ↓ DVAUC. Consider alternative agent or monitoring IDV level.	Carbamazepine; ↑ serum levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels.	Unknown, but may markedly ↓ SQV levels. Monitor anticonvulsant levels and consider obtaining SQV level.	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virologic response. Consider obtaining NFV levels.	Many possible interactions: Carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: levels of LPV, RTV, and ↓ levels of Phenytoin when administered together. Avoid concomitant use or monitor LPV level.

Drugs Affected	Infinavir (IDV)	Ritonavir (RTV)	Saquinavir (SQV)	Nelfinavir (NFV)	Lopinavir (LPV)
METHADONE	No change in methadone levels.	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone AUC ↓ 20%. When co-administered with SQV/RTV 400/400 mg BID. Dose: No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary.	NFV may decrease methadone levels, but opiate withdrawal rarely occurs. Monitor and titrate dose if needed. May require methadone dose.	Methadone AUC ↓ 53%. Opiate withdrawal may occur. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTION AGENTS					
Sildenafil	Sildenafil AUC ↑ 3 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects	Sildenafil AUC ↑ 2 fold. Use a 25 mg starting dose of sildenafil.	Sildenafil AUC ↑ 2-11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11-fold in combination with RTV. Do not exceed 25 mg every 48 hours.





Table 10: Drug-drug Interactions requiring dose modification or cautious use - Pls

Drugs Affected	Indinavir (IDV)	Ritonavir (RTV)	Saquinavir* (SQV)	Nelfinavir (NFV)	Lopinavir (LPV)
MISCELLANEOUS	<p>Grapefruit juice ↓ IDV levels by 26%. Vitamin C ≥ 1 gram/day ↓ IDV AUC by 14% and Crmin by 32%. Amlodipine: Amlodipine AUC ↑ 90% when co-administered with IDV/RTV. No change in IDV/RTV levels. Monitor closely.</p>	<p>Many possible interactions Desipramine ↑ 145%, reduce dose. Trazodone AUC ↑ 2.4 fold when given with 200 mg BID or RTV. Use lowest dose of trazodone and monitor for CNS and CV adverse effects. Theophylline ↓ 47%, monitor theophylline levels. RTV 100 mg bid significantly increase systemic exposure of inhaled (oral or nasal fluticasone, may predispose patients to systemic corticosteroid effects. Co-administration not recommended unless benefit of fluticasone outweighs the risk.</p>	<p>Grapefruit juice ↑ SQV levels. Dexamethasone ↓ SQV levels.</p>		

- There are limited data on RTV-SQV and; PV-RTV demonstrating that RTV compensates, to a degree, for rifampicin induction. In one small study, higher doses of ritonavir (up to 400 mg per dose) or an increased dose of LPV/RTV 800/200 mg were needed to offset rifampicin-inducing activity of LPV; the standard dose of rifampicin was used in these studies. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is not established. If co-administered, close monitoring is recommended, as is measuring LPV concentrations.

Table 11a: Anti-retroviral Drugs in Paediatric Practice

Drug	Formulation	Dosage	Adverse Events	Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)				
Zidovudine AZT,ZDV, or Retrovirus	Suspension 10mg/ml Capsules 100mg, 250mg Tablets 300mg	180mg/m ² BD or 90-180mg/m ² toads Neonatal dose: 2mg/kg QID	Neutropaenia, anaemia, headache; Myopathy, lactic acidosis (rare)	Can be given with food store at room temperature
Lamivudine 3TC	Suspension 10mg/ml Tablets 150mg	4mg/kg BD neonatal dose: 2mg/kg BD	Headache, abdominal pain, fatigue, pancreatitis, peripheral neuropathy; ↑ neutropaenia, . LFTs, lactic acidosis (rare)	Can be given with food store at room temperature
Stavudine d4T; Zerit	Suspension 1mg/ mlCapsules 20mg,30mg,40mg	1mg/kg BD	Headache, GI upset; rash, peripheral neuropathy, ↑ LFTs, pancreatitis, lactic acidosis	Can be given with foodKeep suspension refrigerated
Didanosine ddI; Videx	Suspension 10mg/ml Tablets 25mg, 50mg,100mg,150mg	90-120mg/m ² BD	Diarrhoea, abdominal pain, nausea; peripheral neuropathy, pancreatitis, lactic acidosis ↑ LFTs	Give on empty stomach Keep suspension refrigerated
Abacavir ABC, Ziagen	Suspension 20mg/ mlTablets 300mg	8mg/kg BD	Hypersensitivity rash (5%), fever, malaise, mucositis, pancreatitis, lactic acidosis	Can be given with food store at room temperature Do not re- challenge after hypersensitivity
Non - nucleoside reverse transcriptase inhibitors (NNRTIs)				
Nevirapine NVP; Viramune	Suspension 10mg/ml Tablets 200mg	Start with 120mg/m ² once daily for 14 days increase to full dose (120-200mg/m ²) every 12 hours (maximum 200mg every 12 hrs) if no rash or severe adverse events	Rashes, Stevens-Johnson syndrome, ↑ LFTs; hypersensitivity and hepatitis	Can be given with food store at room temperature Watch for liver toxicity





Table 11b: Antiretroviral Dugs in Paediatric Practice

Drug	Formulation	Dosage	Adverse Events	Comments
Efavirenz EFV, Stocrin	Capsules 50mg, 200mg	Single daily dose 10-15kg:200mg 15-20kg:250mg 20-25kg:300mg 25-32.5kg:350mg 32.5-0kg:400mg >40kg:600mg	Rash (mild), somnolence, abnormal dreams, insomnia, confusion, hallucinations, euphoria, amnesia, agitation, abnormal thinking	Can be given with food Administer at night Store at room temperature No pharmacokinetic data <10kg and <3years of age
Protease Inhibitors (PIs)				
Ritonavir RTV, Norvir	Suspension 80mg/ml Capsules 100mg	Initial dose of 250 mg/ m ² BD BD.increase by 50mg/ m ² BD at 2-3 day intervals to 400mg/ m ² BD. if < 2 yrs of age, maximum dose 450mg/ m ² bd	GI intolerance, Headache, anorexia, ↑ LFTs; Abnormal lipids (rare)	Give with food palatability improved by mixing with milk, honey, ice cream, yogurt or chocolate milkshake store in refrigerator or room temperature
Nelfinavir	Suspension 50mg/ml/ 1gm spoon tablets 250mg	Paediatrics: 55mg/kg BD Adolescent: 750 mg TDS or 1250mg BD	Diarrhoea, vomiting, rash, abnormal lipids, exacerbation of chronic liver disease (rare)	Administer with food. Suspension may be mixed with water, milk, pudding, ice cream, formula
Lopinavir/ ritonavir LPV/ RTV, Kaletra	Suspension 80mg LPV and 20mg RTV per ml Capsules 133.3mg LPV and 33.3 mg RTV	230mg/ m ² LPV/57.5/ m ² RTV BD up to a maximum of 400mg LPV/100mg RTV BD Increase dose with NVP or EFV co-administration (refer package insert)	GI intolerance, rash; headache, abnormal lipids, hyperglycaemia, pancreatitis (rare)	Give with food store. A high fat meal increases absorption Refrigerate suspension or keep at room temperature for 2 months
Fixed drug combinations				
D4T/3TC/NVP (Tricomune) (syrups becoming available)	Tablet 40mg/50mg/ 200mg	1 tablet twice daily depending on child's weight		Tablet broken as per weight of child. Attainment of accurate dosage difficult with breakage of tablet

BD = twice a day, TDS = three times a day, qid = four times a day, m² = body surface area (BSA) metre squared

BSA in m² = $\sqrt{\text{Height (cm)} \times \text{Weight (kg)}}$
36000

Table 12 Antiretroviral Drugs and TMP/SMZ Paediatric Dose Chart for use in Resource-constrained Settings.

Weight	Abacavir (Zigen®)		Stavudine (Zerit®, ddI)	Lamivudine (EpiVir®, 3TC)	Zidovudine (Retrovir®, ZDV, AZI)	Didanosine (Videx®, DDJ)	Nevirapine (Viramune®, NVP)				Efavirenz (Stocrin®, Sustiva®, EFV)		Lopinavir/ritonavir (Kaletra®)		Nelfinavir (Viracept)	
	Liquid 20 mg/ml	Tablet 300 mg	Capsules 15, 20, 30 mg	Liquid 10 mg/ml	Tablet 150 mg	Liquid 10 mg/ml	Chewable tablets 25, 50, 100 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 30 mg/ml	Capsules 50, 100, 200 mg	Liquid lopinavir/mf	Capsule 133.3/33.3 mg	Tablet 250 mg
5-6.9	2 ml			2 ml	7 ml		2 ml									2 tabs ^a
7-9.9	3 ml		15 mg	3 ml	9 ml	25mg + 25mg	3 ml						1.5 ml			2 tabs ^a
10-11.9	4 ml		15 mg or (20 mg)	4 ml	12 ml	25mg + 25mg	4 ml			½ tab			9 ml			2 tabs
12-14.9	5 ml		15 mg or (20 mg)	5 ml	14 ml	50mg + 25mg	5 ml			½ tab			9 ml			3 tabs
15-16.9	6 ml		15 mg or (20 mg)	6 ml	15 ml	50mg + 25mg	6 ml			½ tab			10 ml			3 tabs
17-19.9	7 ml	½ tab	20 mg	7 ml	17 ml	50mg + 50mg	7 ml			1 tab AM + ½ tab PM ^d			10 ml			4 tabs
20-24.9	9 ml	½ tab	20 mg	9 ml	20 ml	50mg + 50mg	9 ml	½ tab		1 tab AM + ½ tab PM ^d			12 ml			5 tabs
25-29.9	25 - 21.9 KG	11 ½ tab	30 mg	11 ml	24 ml	100mg + 25mg	11 ml	½ tab		1 tab			15 ml			5 tabs
	28 - 29.9 KG	12 1 tab														
30-34.9	13 ml	1 tab	30 mg	13 ml	27 ml	100mg + 25mg	13 ml	1 tab ^b		1 tab ^b			13 ml			5 tabs
35-40	15 ml	1 tab	30 mg	15 ml	30 ml	100mg + 25mg	15 ml	1 tab ^b		1 tab ^b			15 ml			5 tabs

Abacavir - Tablets may be swallowed whole or crushed and dispersed in water or onto a small amount of food and immediately ingested.

Abacavir – Tablets may be swallowed whole or crushed and dispersed in water or onto a small amount of food and immediately ingested.

Stavudine - Capsules may be opened and dispersed in water or onto a small amount of food and immediately ingested. Stavudine capsules are not recommended for use in children < 7 KG since dose size from smallest capsule would be too large. Stavudine oral solution is stable at room temperature for 24 hours or under refrigeration for 30 days. In settings where households do not have access to refrigeration, the oral solution should not be used. ¹In the event that 15 mg capsules are not available, consider giving the 20 mg capsule to children in the 10-16.9 KG range. Though these may result in doses higher than the recommended 1mg/ Kg dose, higher doses than this have been used in clinical trials and these doses were generally well tolerated by children. However, for children < 10 KG a capsule size larger than 15 mg is not advised.

Lamivudine – Tablets are not scored, but can be divided into two equal halves with a pill splitter in the pharmacy. Tablet may be crushed and dispersed in water or onto a small amount of food and immediately ingested. Oral solution should be used in children < 15 KG since accurate dosing with tablets is not practical in smaller children. Oral solution is stable at room temperature. ²The dose changes from Ω to 1 tablet as a child enters this weight range, however, lamivudine has few adverse effects and this dose should be generally well tolerated.

Zidovudine –Capsules may be opened and dispersed in water or onto a small amount of food and immediately ingested. Tablets may be crushed and dispersed in water or onto a small amount of food and immediately ingested. Oral solution should be used in children < 7 KG since accurate dosing with capsules is not practical in smaller children. Oral solution is stable at room temperature. Weight based doses were determined by using body surface area values calculated from typical heights for weight.

Didanosine –Must use 2 tablets with each dose to provide adequate antacid to buffer stomach acid to allow absorption. The tablets may be dispersed in water before administering. Alternatively, the tablets may be chewed and swallowed. Must be administered on an empty stomach at least 30 minute before or 2 hours after eating. Oral suspension requires addition of antacid and water and is stable at room temperature for only 24 hours or under refrigeration for 30 days. In settings where households do not have access to refrigeration, the oral suspension should not be used. If taken with indinavir the drugs must be separated by one hour. Weight based doses were determined by using body surface area values calculated from typical heights for weight.

Nevirapine – Tablet is scored and may be divided into equal parts. Tablet may be crushed and dispersed in water or onto a small amount of food and immediately ingested. Oral solution is stable at room temperature. Nevirapine induction dose is 4 mg/KG once daily for 14 days and if no rash develops is followed by a maintenance dose of for children < 8 yrs old of 7mg/KG twice daily or for children \geq 8 yrs old of 4 mg/KG twice daily. ³Consider using liquid for the induction dose in children in this weight range to give a more precise dose. ⁴If using tablets for children in this weight range, this chart suggests 1 tablet in the AM and Ω tablet in the PM to yield a dose that approximates that of the liquid — the half-life of nevirapine is long enough that the fluctuation in drug levels from this staggered dose is considered clinically acceptable.

Efavirenz – Capsules may be opened and dispersed in water or onto a small amount of food and immediately ingested. Oral solution is stable at room temperature. Dose for oral solution is greater than that for capsules or tablets. The dose and pharmacokinetics of the oral solution is not as well established as with the capsules and tablet. Thus, although the liquid may be available in some areas, it is advisable to use the capsule or tablet forms when possible.

Lopinavir/ritonavir – Dose is calculated based on lopinavir component. Capsules may NOT be opened or crushed and must be swallowed whole, but may be used for children who can swallow capsules. Capsules or oral solution should be taken with food. Capsules and oral solution must be refrigerated until dispensed.



After removing from refrigeration capsules and oral solution are only stable for 60 days at room temperature (up to 25° C). Where temperatures are expected to exceed 25^AC, the feasibility of dispensing smaller amounts and giving more frequent refills should be considered (for instance, no more than monthly supplies dispensed at one time). Lopinavir/ritonavir is not recommended for children < 6 months old. ⁵The amount of solution has been rounded up to nearest 2 ml from manufacturer's recommendation for easier measurement. ⁶In the 17 - 19.9 KG range, two capsules twice daily would result in a dose that is ~40-60% higher than recommended, however, using only one capsule twice daily would result in a dose that is ~20-30% lower than recommended. Consider using liquid for children in this weight range.

Nelfinavir - Tablets may be crushed and dispersed in water or onto a small amount of food and immediately ingested. Must be taken with food to improve absorption. Oral powder for administration requires complicated administration technique that may not be practical in resource-poor settings. ⁷Doses for children < 2 years of age are not well established. The dose listed for children < 10 KG is within a range of up to 75 mg/KG/dose twice daily that has been used for small children by some clinicians.

Indinavir - Capsules may be opened and dispersed in water or onto a small amount of food and immediately ingested. Must be taken on an empty stomach (1 hour before or 2 hours after a meal). Patients must drink lots of water during the day while taking indinavir to prevent development of kidney problems. If taking didanosine, the drugs must be separated by one hour. Weight based doses were determined by using body surface area values calculated from typical heights for weight.

Trimethoprim/sulfamethoxazole - Recommendations for prophylaxis against opportunistic infections for HIV-infected children are to give 5 mg/kg given twice daily for 3 consecutive days/week. Considering the dosage strength of the TMP/SMZ suspension and in efforts to support medication adherence, dosing children once daily every day of the week may be a simpler alternative. The dose of 4 mg/kg is an easy conversion from the child's weight to the millilitres of suspension because the 8 mg/ml dosage strength of the TMP/SMZ suspension allows the dose to be calculated as 2 ml of suspension per KG. Doses are higher for treatment of bacterial and protozoal infections and other sources should be consulted.

Table 13 Revised WHO Clinical Staging for Adults and Adolescents

Clinical stage	Selected symptoms
Primary HIV infection	<ol style="list-style-type: none"> 1. Unrecognized 2. Acute Retroviral syndrome
Stage I	<ol style="list-style-type: none"> 1. Asymptomatic 2. Persistent Generalized Lymphadenopathy (PGL)
Stage II	<ol style="list-style-type: none"> 1. Moderate weight loss (< 10% of presumed or measured body weight) 2. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal infection, recurrent oral ulcerations, angular cheilitis) 3. Herpes Zoster, past or recurrent within last 2 years 4. Recurrent upper respiratory tract infections (bacterial sinusitis, bronchitis, otitis media, pharyngitis)
Stage III	<ol style="list-style-type: none"> 1. Severe weight loss (> 10% of presumed or measured body weight) 2. Unexplained chronic diarrhoea > 1 month 3. Unexplained prolonged fever > 1 month 4. Oral candidiasis (Thrush) 5. Oral Hairy Leucoplakia (OHL) 6. Pulmonary tuberculosis (PTB) in past 1 year 7. Severe bacterial infections (e.g. pneumonia, pyomyositis, empyema, bone or joint infections)
Stage IV	<p><i>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:</i></p> <ol style="list-style-type: none"> 1. HIV wasting syndrome 2. <i>Pneumocystis jiroveci</i> pneumonia (PCP) 3. Recurrent severe bacterial pneumonia (>= 2 episodes within 1 year) 4. Cryptococcal meningitis 5. Toxoplasmosis of the brain 6. Chronic orolabial, genital or ano-rectal herpes simplex infection for > 1 month 7. Kaposi's sarcoma (KS) 8. HIV encephalopathy 9. Extra pulmonary tuberculosis (EPTB)



Conditions where confirmatory diagnostic testing is necessary:

1. Cryptosporidiosis, with diarrhoea > 1 month
2. Isosporiasis
3. Cryptococcosis (extra pulmonary)
4. Disseminated non-tuberculous mycobacterial infection
5. Cytomegalovirus (CMV) retinitis or disease of the organs (other than liver, spleen, or lymph nodes)
6. Progressive Multifocal Leucoencephalopathy (PML)
7. Any disseminated endemic mycosis (e.g. histoplasmosis)
8. Candidiasis of the oesophagus or airways
9. Non-typhoid salmonella (NTS) septicaemia
10. Lymphoma cerebral or B cell NHL
11. Invasive cervical cancer
12. Visceral leishmaniasis



Table 14 Revised WHO Staging of Paediatric HIV/AIDS Disease

<p>WHO Stage 1</p>	<ul style="list-style-type: none"> • Asymptomatic • Persistent generalized lymphadenopathy (PGL) • Hepatosplenomegaly
<p>WHO Stage 2</p>	<ul style="list-style-type: none"> • Papular pruritic eruptions (PPE) • Seborrheic dermatitis • Fungal nail infections • Angular cheilitis • Linear gingival erythema • Extensive HPV or Molluscum infection (>5% of body area/face) • Recurrent oral ulcerations (>2 episodes/ in 6 months) • Parotid enlargement • Herpes zoster (>1 episode/12 months) • Recurrent or chronic upper respiratory infection (URI): otitis media, otorrhoea, sinusitis (>2 episodes/6 months)
<p>WHO Stage 3</p>	<ul style="list-style-type: none"> • <i>Unexplained</i> moderate malnutrition (-2SD or Z score) not responding to standard therapy • <i>Unexplained</i> persistent diarrhoea (>14 days) • <i>Unexplained</i> persistent fever (intermittent or constant, > 1 mo) • Oral candidiasis (outside neonatal period) • Oral hairy Leucoplakia • Pulmonary tuberculosis • Severe recurrent presumed bacterial pneumonia (>2 episodes/ 12 months) • Acute necrotizing ulcerative gingivitis/periodontitis • Lymphoid interstitial pneumonitis (LIP) • <i>Unexplained</i> anaemia (<8g/dL), neutropenia (<1000/mm³), or thrombocytopenia (<30,000/mm³) for >1 mo. • HIV-related cardiomyopathy • HIV-related nephropathy
<p>WHO Stage 4</p>	<ul style="list-style-type: none"> • <i>Unexplained</i> severe wasting or severe malnutrition (-3 SD or Z score) not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe bacterial infections (>2 episodes/12 months, <i>excluding</i> pneumonia) • Chronic orolabial or cutaneous HSV (lasting > 1 mo) • Extra-pulmonary tuberculosis



- Kaposi's sarcoma
- Oesophageal candidiasis
- CNS toxoplasmosis
- Cryptococcal meningitis
- Any disseminated endemic mycosis
- Cryptosporidiosis or Isosporiasis (with diarrhoea > 1 month)
- CMV infection of organ other than liver, spleen, lymph nodes (and onset age >1 month)
- Disseminated mycobacterial disease other than tuberculosis
- Candida of trachea, bronchi or lungs
- Acquired recto-vesicular fistula
- Cerebral or b cell non-Hodgkin's lymphoma
- Progressive Multifocal Leucoencephalopathy (PML)
- HIV encephalopathy

Drugs for which plasma concentration may be decreased by co-administration with ritonavir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

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Some drug interaction studies were conducted with Invirase®. May not necessarily apply to use with Fortovase.



