TREATMENT OF AIDS

GUIDELINES FOR THE USE OF ANTIRETROVIRAL THERAPY IN MALAWI

Second Edition:

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Ministry of Health, Malawi

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FOREWARD TO THE SECOND EDITION

In 2004, Malawi developed and started to implement a 2-year scale-up plan for antiretroviral therapy (ART) to HIV-infected patients who were eligible for treatment. In January 2004, about 3,000 – 4,000 patients were accessing ART in 9 public health facilities around the country. At that time, there was no standardised treatment, and no standardised system of training, monitoring, evaluation and drug procurement. However, this was about to change. The publication and dissemination of the 2003 First Edition of the ARV Treatment Guidelines provided the core material to ensure that Malawi moved forward to deliver ART to large numbers of HIV-infected eligible patients using a public health structured approach.

The country has done well. By the end of 2005, there were 60 facilities in the public sector (central, district, mission, and defence force hospitals and clinics) delivering ART using national systems, and 37,840 patients had ever been started on therapy. The private sector was also brought on board, and by the end of 2005, 23 private sector facilities were delivering ART using national guidelines to 932 patients.

The Ministry of Health has developed a 5-year ART scale- up plan (2006-2010) which lays out the path of how to deliver ART to over 200,000 HIV-infected eligible patients by the end of 2010. This will be a challenging time, as the drugs and the field of HIV-treatment are changing all the time.

With these thoughts in mind, I welcome the 2006 Second Edition of the "Guidelines for Antiretroviral therapy in Malawi". This has built on the first edition, but takes into account the experience developed in the country in the last 2 years as well as changes that have occurred in international recommendations. I thank all the people who have given their time in the writing committee, consultation groups and dissemination meetings, and who have worked together to ensure the successful completion of an excellent and useful booklet. What now remains is to distribute this booklet to all health care workers in the public and private sector, and to insist that health care workers read, understand, digest and adhere to the contents. If this can be done, then patients with AIDS in Malawi will be offered an excellent standard of care. They deserve nothing less.

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LIST OF ABBREVIATIONS

AIDS : Acquired immune defiency syndrome
ABC : Abacavir (antiretroviral drug)
ART : Antiretroviral therapy
ARV : Antiretroviral
AZT : Zidovudine (antiretroviral drug)
CPT : Cotrimoxazole preventive therapy
CT : HIV counseling and testing
CTX : Cotrimoxazole (antibiotic)
ddI : Didanosine (antiretroviral drug)
d4T : Stavudine
E : Ethambutol (anti-TB drug)
EFV : Efavirenz (antiretroviral drug)
EH : Ethambutol and isoniazid (anti-TB drugs)
ERT : Empowered reinforced therapy
GFATM : Global Fund to fight AIDS, tuberculosis and malaria
GST : Guardian supported therapy
HAART: Highly active antiretroviral therapy
HIV : Human immunodeficiency virus
HCW : Health care worker
HTC : HIV Testing and counseling
IEC : Information, education and communication
"Kaletra" : Trade name for Lopinavir/Ritonavir (antiretroviral drug)
KS : Kaposi's Sarcoma
LPV/r : Lopinavir/Ritonavir (antiretroviral drug)
MOH : Ministry of Health
MUAC : Mid-arm upper circumference
NNRTI : Non-nucleoside reverse transcriptase inhibitor
NRTI : Nucleoside reverse transcriptase inhibitor
NVP : Nevirapine (antiretroviral drug)
PEP : Post-exposure prophylaxis
PCR : Polymerase chain reaction
PMTCT: Prevention of mother to child transmission (of HIV)

PTB : Pulmonary Tuberculosis
RHZ : Rifampicin, isoniazid and pyrazinamide (anti-TB drugs)
STI : Sexually transmitted infection
3TC : Lamivudine (antiretroviral drug)
TB : Tuberculosis
TDF : Tenofovir (antiretroviral drug)
TLC : Total lymphocyte count
UNAIDS : United Nations Consortium for AIDS
VCT : Voluntary counseling and HIV testing
WHO : World Health Organization

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SUMMARY

Eligibility for ART:

Adult (aged 15 years and above):

Known to be HIV-seropositive and understand implications of ART PLUS one of the following

i) Assessed to be in WHO Clinical Stage 3 or 4

ii) Have a CD4-lymphocyte count < 250/mm^3

iii) Assessed to be in WHO Clinical Stage 2 with TLC < 1200/mm^3

Children (aged 14 years and below):

Over the age of 18 months:

Known to be HIV-seropositive and relatives understand implications of ART

PLUS one of the following

i) Assessed to be in WHO Paediatric Clinical Stage 3 or 4

ii) Have a CD4-lymphocyte percentage < threshold (age-based- see table 11)

iii) Assessed to be in WHO Paediatric Stage 2 with TLC < threshold (table 11)

Under the age of 18 months:

Known to be HIV-seropositive and relatives understand implications of ART

PLUS one of the following

i) Assessed to be in WHO Paediatric Clinical Stage 4

ii) Have 2 or more of a) oral candida, b) severe pneumonia or c) severe sepsis

Antiretroviral Treatment Regimens:

First Line regimen:

Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP)
Formulation depends on body weight
Dose = one tablet in the morning and one tablet in the evening

Alternative first line regimen substitutions in case of drug reactions:

Reactions due to stavudine:
(severe peripheral neuropathy, pancreatitis, lactic acidosis)
Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP)

Reactions due to nevirapine:
(severe skin reactions, hepatitis)
Stavudine (d4T) + Lamivudine (3TC) + Efavirenz (EFV)

Second line regimen switch in case of failure to first-line regimen:

Adults: Zidovudine (AZT) + Lamivudine (3TC) + Tenofovir (TDF) +
Lopinavir/ Ritonavir (LPV/r)

Children: Didanosine (ddI)+Abacavir (ABC)+ Lopinavir/Ritonavir (LPV/r)

INTRODUCTION

Global Burden of HIV/AIDS

At the end of 2005, 40 million adults and children were estimated to be living with HIV / AIDS in the world. Since the start of the epidemic in 1981, nearly 25 million people have died of AIDS. During the year 2005, it was estimated that there were 5 million people newly infected with HIV and there were 3 million AIDS deaths.

HIV/AIDS in sub-Saharan Africa and Malawi

Sub-Saharan Africa is the epicentre of this epidemic, with 26 million people living with HIV/AIDS by the end of 2005. 85% of all estimated deaths due to HIV/AIDS since the start of the pandemic have occurred in this region. There were 3.2 million new infections in the region in 2005 and there were 2.4 million deaths.

Malawi has one of the highest HIV/AIDS prevalence rates in the world, with 14% of those aged 15 – 49 years infected, while the national prevalence is estimated at 8 percent. These prevalence rates have remained stable for several years. Life expectancy has declined to 39 years from a projected 54 years without the HIV/AIDS epidemic. The National AIDS Commission estimated that in 2005 there were about 790,000 adults and children living with HIV/AIDS in the country (confidence intervals 780,000 – 1,120,000). HIV/AIDS is the leading cause of death in the most productive age group, resulting

in 85,000 adult and child deaths annually. The cumulative number of orphans, directly related to the AIDS epidemic, is approximately 700,000 and more than 60,000 are added to this pool each year.

AIDS kills young adults in their most productive years, depriving the region of the skills and knowledge base so essential to human and economic development. AIDS leaves countless numbers of grandparents to bring up children. Many orphans cannot attend school. They also suffer from poverty and malnutrition and become sucked into a spiral of crime, violence and commercial sex. AIDS retards development and creates the foundations for political instability.

Highly active antiretroviral therapy (HAART)

Combination antiretroviral therapy (ART), also known as highly active antiretroviral therapy (HAART), has dramatically improved the survival of patients living with HIV and AIDS in industrialised countries of the world. AIDS has been transformed from a fatal disease into a potentially treatable and chronic condition. Access to HAART is an important component of a strategy to support people living with HIV/AIDS as well as preventing transmission of infection. People may be more willing to undergo voluntary counselling and testing and disclose their HIV status if there is the possibility of getting effective treatment. By reducing viral load ARV drugs may, from a biological viewpoint, reduce the risk of sexual transmission. Sick people will be able to return to work. Parents will stay alive longer, thus delaying the time when

children become orphans. The rate of mother-to-child-transmission will be reduced.

ART in Malawi – Progress to 2005

In Malawi, it is estimated that 185,000 people are in immediate need of ART. At the beginning of 2004, there were 9 facilities in the public sector delivering ART, and an estimated 3,000 to 4,000 patients on treatment. As a result of this inadequate response, a major scale-up of ART was planned. Between January and February 2004, the Ministry of Health, working alongside its partners, developed an ambitious and bold 2-year scale-up plan for 2004 and 2005. The main elements of this plan were as follows:

i) 60 hospitals and clinics in the public health sector were selected for ART scale up providing broad geographical coverage throughout Malawi

ii) ART drugs were provided free of charge in the public sector

iii) Scale-up in new facilities involved the use of first line ART regimen only (stavudine+lamivudine+nevirapine i.e "Triomune"), but when health facilities showed capacity to properly deliver such treatment they were to be provided with alternative first line and second line therapy

iv) Facilities were only provided with ARV drugs if they had been formally assessed by the HIV Unit of the Ministry of Health as ready to deliver ARV therapy.

It was agreed that ARV drugs must be provided within a structured framework, "a public health approach". The first edition of the Malawi ARV Treatment Guidelines provided for such an approach, and the implementation of ARV delivery has been based on this document.

The scale up plan was approved by the Ministry and its partners in February 2004. Implementation then started with an intensive period of briefings and trainings for clinicians and nurses in each of the 60 health facilities. The private sector was also brought on board, and by December 2005, 1350 clinicians and nurses in the public and private sectors had completed a formal ART training and passed the formal examination. In the latter half of 2004, the HIV Unit started structured assessments of all health facilities about readiness to start ART; by the end of March 2005, all the health facilities had been assessed as ready to start ART.

The procurement and distribution of ARV drugs was planned in a phased approach, with the 60 health facilities given a "quota" of drugs according to whether they were low burden (starting 25 new patients per month), medium burden (50 new patients per month) or high burden units (150 new patients per month). ARV drugs were procured according to "Starter pack kits and Continuation pack kits", and these started to arrive in the latter half of 2004. By June

2005, all health facilities had received drugs and had started to treat patients.

A national monitoring system is in place and functioning. National and international stakeholders are kept briefed on progress by quarterly ART reports prepared by the HIV Unit. By the end of 2004, there were 13,183 patients who had ever started ART in the public sector in Malawi. By the end of 2005, this number had increased to 37,840. Of those ever started, 81% were alive and on ART by the end of December 2005.

ART in Malawi: 2006 – 2010

A five year plan (2006-2010) for ART scale up has been developed and approved by the Ministry of Health and its stakeholders. Malawi's "aspirational" goal will be to provide "Universal Access" of ARV therapy by 2010. Fulfilment of this goal means having 170,000 patients on treatment, and each year increasing this number by the number of patients becoming eligible for ART (i.e., 90,000 new patients per year). The goal of "Universal Access" is that adopted by the G8 countries in July 2005 and is the goal also adopted by the World Health Organization and UNAIDS.

However, the health sector works under considerable constraints in Malawi. The goal of "Universal Access" is ambitious and extremely demanding, and in reality cannot be reached, if Malawi wishes to run an ARV Programme, which is structured, organised and well monitored. On the road towards universal access, Malawi will aim to have started 245,000 patients on ART by the end of 2010, and from the third year on will aim to place 45,000 new patients on treatment each year (i.e., achieve 50% universal access). Based on the current successful "push" system of delivering ARV drugs and quotas given to hospitals, the table shows the estimated number of new patients starting ART per annum and the cumulative number of patients ever started on ART (and the number estimated to be alive) by the end of each year in the public and private sectors. There will be a more explicit scale-up of ART for children. By the end of 2005,

children comprised 5% of all patients, but by 2007 it is envisaged that they will comprise 10% of new patients.

Table: Numbers started and alive on ART from 2006 - 2010

Year	Number of new patients –adults and children- started on ART during the year	Number of patients - adults and children- ever started on ART by the end of the year (and number predicted to be alive by end of year)
2005	20,000	38,000 (30,000)
2006	35,000	70,000 (60,000)
2007	40,000	110,000 (90,000)
2008	45,000	155,000 (130,000)
2009	45,000	200,000 (170,000)
2010	45,000	245,000 (208,000)

The numbers of patients placed on ART will be achieved by continuing current scale-up in the 60 ART facilities in Round 1; by bringing 40 new sites in Round 2 in the first half of 2006; having more sites in Round 3 delivering therapy by 2007 and finally by involving the private sector. Plans to reduce the burden of work in established clinics include less frequent follow-up of stable patients, use of a lower cadre of health worker to follow-up patients and decentralising to health centres. It is acknowledged that ART scale up must be accompanied by HIV prevention strategies, both for adults and for children (e.g., PMTCT), otherwise the country will have no chance of containing and coming to grips with the HIV/AIDS epidemic.

FRAMEWORK FOR ANTIRETROVIRAL DRUG DELIVERY

This framework lays out the public health approach for the wide scale delivery of antiretroviral (ARV) drugs. The framework consists of the following:-

- Goal
- Objectives and targets of ART
- Strategy for ART
- ART Policy Package
- Key operations involving ART
- Indicators to measure progress with ART

Goal

The goal is to reduce morbidity and mortality of HIV in adults and children.

Objectives and Targets

The principal objectives of antiretroviral drug delivery are:

- To provide long term ART to eligible patients
- To monitor and report treatment outcomes on a quarterly basis

- To attain individual drug adherence rates of 95% for patients on ART

- To increase life span so that at least 50% of patients on ART are alive and ambulatory after three years of ART

- To ensure that 80% of patients on ART are engaged in productive activity within 6 months of starting ART

Strategy

The strategy is to mobilise all existing ARV delivery sites and identify new ARV delivery sites to provide standardised combination ART to HIV-positive persons who present to health facilities and who fulfil the eligibility criteria (see Chapter on Patients Eligible for ART), using wherever possible guardian supported treatment.

ARV Policy Package

The success of the ARV delivery framework depends on the implementation of a 5-point policy package:

- government commitment to ARV delivery
- detection of eligible cases (adults and children) who have undergone HIV testing and counselling, have a confirmed HIV-seropositive result and who fulfil eligibility criteria
- standardised combination ART to HIV-seropositive eligible patients (adults and children) under proper case management conditions with high levels of drug adherence
- regular, secure and uninterrupted supply of ARV drugs to units which are administering ART
- monitoring system for supervision of ART, effective patient tracing and follow-up and regular evaluation

Key Operations

- There is an HIV/AIDS Unit in the Ministry of Health, which has overall responsibility for the management of ARV therapy in the country
- The ARV treatment guidelines for adults and children are available in every treatment unit which administers ART, with these guidelines updated at regular intervals based on national experience and new international knowledge

- There is a standardised registration, recording and reporting system
- There is a combined training and examination programme, covering all aspects of ARV delivery. All staff involved in ARV delivery must have attended this training and must have passed the formal examination
- There is an HIV testing and counselling service linked to every unit providing ART, which is subject to regular quality assurance and quality control
- ARV treatment units are provided within the general health services, at hospital and also at health centre level
- There is a regular supply of ARV drugs and HIV testing materials
- There is a plan of supervision, mentorship, monitoring and evaluation
- There is a plan of regular reporting and evaluation
- HIV / AIDS research is fully regulated to support patient care and implementation of the ARV treatment guidelines
- There is a process to develop long-term and medium term plans with budget details, funding sources and responsibilities

Other important key operations essential to strengthen and sustain ARV delivery include information, education, communication and social mobilisation, involving private and voluntary health care providers, and operational research.

Indicators and Targets to measure progress with ARV delivery

Input indicators:

- An ARV treatment guideline manual (reflects government commitment)
- Number of districts providing ART (cumulative by year)
- Number of HIV-ARV Clinics administering ART in public sector
- Number of HIV-ARV Clinics administering ART in private sector
- Number of staff trained and accredited in use of ARV drugs in the public sector
- Number of staff trained and accredited in use of ARV drugs in the private sector
- No stock-outs of ARV drugs and uninterrupted supplies of ARV drugs to patients
- No stock-outs of HIV test kits

Output indicators:

- The number of new patients (adults and children) started on ART each year
- The number of patients (adults and children) who have ever started on standardised ART
- The number of those starting ART who are alive and taking therapy at any given time (ie, under care)
- The number (and proportion) of those starting ART who have died
- The number (and proportion) of those starting ART who have defaulted (ie have been lost to follow-up)
- The proportion of patients alive and on ART who are ambulatory
- The proportion of patients alive and on ART who are engaged in productive activities (or in the case of children engaged in age-related day time activities)
- The proportion of patients alive and on ART who show 95% adherence to ART
- In a sample of specimens assessed, the percentage of patients with undetectable viral load 12 months after the introduction of ART

The targets linked to these indicators are shown in **Annex 1.** For further reading about goals, objectives and targets, please see the "5-year ART scale up Plan 2006-2010".

THE HIV ANTIRETROVIRAL CLINIC AND STAFFING

Referral for HIV Testing and Counselling (HTC), and to the Antiretroviral Clinic

Referral for HIV testing and counselling can be from several sites such as the general outpatient departments of adult and paediatric medicine, the general adult and paediatric wards, the TB wards, the antenatal clinic, nutritional rehabilitation units or the laboratory. Persons can also self-refer.

Persons who test HIV-positive at the HCT unit need to be classified into a) asymptomatic and b) symptomatic. Those who are symptomatic or who are identified with other ART eligibility criteria such as a previous history of Pulmonary TB will be referred to the Antiretroviral Clinic for further assessment (see **Figure below**). Those who are asymptomatic will be referred to the general health services for management and advice, for example initiation of cotrimoxazole preventive therapy (CPT).

The Antiretroviral Clinic

ART will be provided to HIV-positive eligible patients. The clinics will be situated in hospitals (central, district, mission, and rural), health centres or other stand-alone sites. These guidelines do not advocate any rigid or specific design. Clinics must be set up and adapted to the context in which they are situated. However, there are a

few key points which should be followed in setting up ARV clinics:-

- The Clinic should be physically integrated with the general out-patient services

- The Clinic must be near HIV testing and counselling services, the wards and out-patient departments, and the hospital laboratory service where HIV testing is carried out

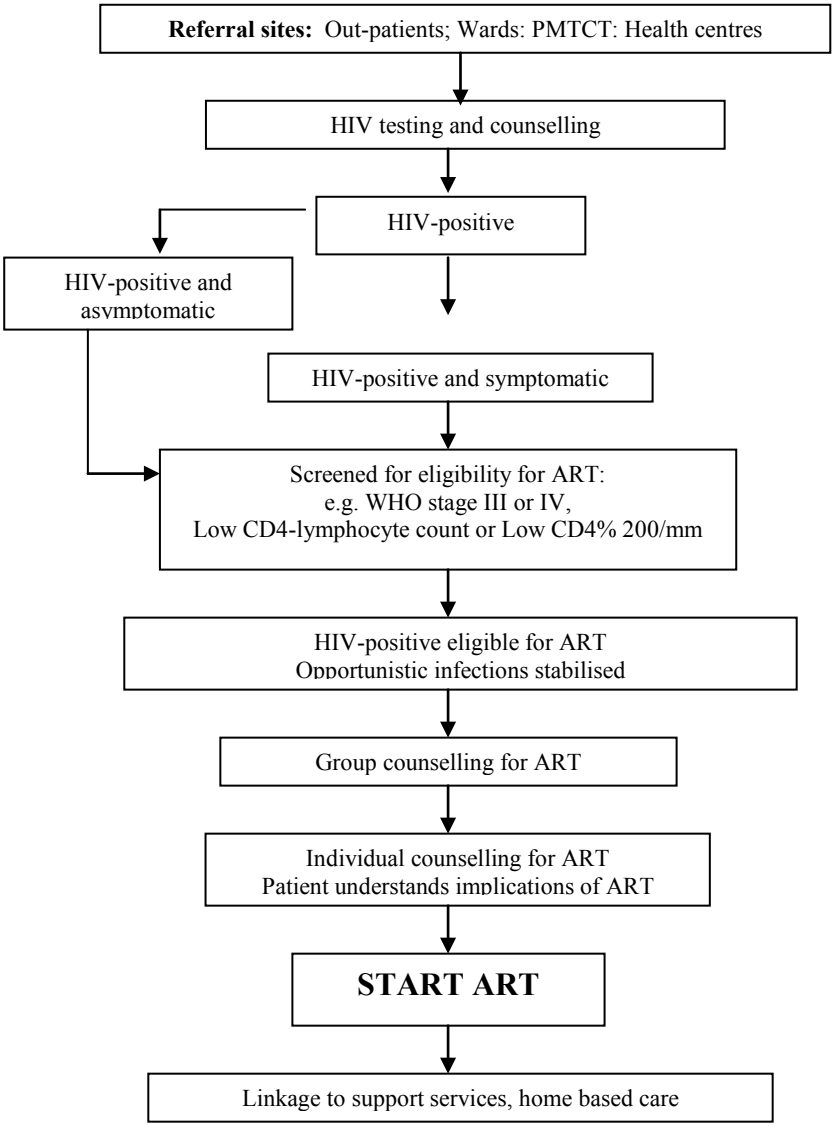
- The Clinic is specifically for HIV-positive patients, who need skilled care for the management of their opportunistic infections and malignancies and who need ART

- The Clinic will carry out the WHO Clinical Staging assessment in HIV-positive patients, as this staging determines whether or not the patient is eligible for ART. Where available, this assessment may be enhanced by CD4 count measurements.

- The Clinic needs space and possibly separate rooms for:-
  a) counselling, support and education of patients on ART
  b) clinical management of opportunistic infections, WHO clinical staging assessments, and clinical assessment of possible ART toxicity
  c) registration and initiation of ART and follow-up of patients on ART

- The Clinic will normally dispense ARV drugs, and in this way there will be a more robust accountability of drug usage. Patient visits will be planned and organised as discussed under Monitoring and Recording Treatment Response.

Figure: Essential Steps in the referral to and screening at the HIV-Antiretroviral Clinic



HIV-Antiretroviral Clinic Staff for the public sector

The health facility will determine the number and type of staff needed to run the ART Clinic. For example, the ART clinic may run on five days a week, two days a week, or one day a week. Whenever it is being run, the minimum staff requirement is:-

1 clinician	(full-time)
1 nurse	(full-time)
1 ward clerk equivalent	(full-time)

Provided certain criteria are met (see below), medical officers, clinical officers and medical assistants can initiate and prescribe ARV drugs within these clinics. All these officers and nurses can provide follow-up of ART

The criteria are that the staff have:- a) attended an ARV training course recognised by the Ministry of Health, Medical Council of Malawi and Nursing Council of Malawi, and b) passed an examination based on this training course. Such health personnel will be certified as competent to manage ARV therapy. Details of this certification are maintained in databases with the Medical Council of Malawi and Nursing Council of Malawi.

Laboratory Back-up: minimum requirements

An essential laboratory investigation is the HIV-antibody test. All laboratories attached to ARV Clinics must be able to do quality-assured HIV-antibody tests. If zidovudine (AZT) is to be used, then the laboratory must also be able to carry out a Haemoglobin test.

WHO-CLINICAL STAGING OF ADULTS AND CHILDREN

The World Health Organization (WHO) staging system is for use where HIV infection has been confirmed through a positive HIV-antibody test. The clinical stage is useful for a baseline assessment of a patient being considered for ART and also for follow-up. The clinical stages relate to survival, prognosis and progression of clinical disease without ART.

The table shows how symptoms relate to WHO Staging category.

Table: WHO clinical staging of established HIV infection

HIV-associated symptoms	WHO Clinical Stage
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe/very advanced symptoms	4

ADULTS AND ADOLESCENTS: (age range 15 years and above)

The tables below provide the features in each Stage category for adults infected with HIV.

Table: WHO Clinical Stage 1

Asymptomatic Persistent generalised lymphadenopathy

Table: WHO Clinical Stage 2

- Moderate unexplained weight loss (< 10% of presumed or measured body weight
- Recurrent respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular itchy dermatitis
- Seborrhoeic dermatitis
- Fungal nail infections

Table: WHO Clinical Stage 3

- Unexplained severe weight loss
  (> 10% of presumed or measured body weight
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever
  (intermittent or constant for longer than one month
- Persistent oral candida
- Oral hairy leukoplakia
- Pulmonary tuberculosis (active or within the previous 2 years)
- Severe presumed bacterial infections (eg, pneumonia, empyema,
  pyomyositis, bone/joint infections, meningitis, sepsis)
- Acute necrotising ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (<8g/dl), neutropenia (<500/mm^3) or thrombocytopenia (<50,000/ mm^3)

Table: WHO Clinical Stage 4

- HIV Wasting syndrome (unexplained severe weight loss >10% plus either chronic diarrhoea or fever in the absence of concurrent illness)
- Pneumocystis jiroveci (formerly: carinii) pneumonia [PCP]
- Recurrent severe or radiological presumed bacterial pneumonia
- Recurrent bacteraemia or sepsis
- Toxoplasmosis of the brain
- Cryptosporidiosis
- Isosporiasis
- Cryptococcosis, extrapulmonary
- Cytomegalovirus of an organ other than liver, spleen or lymph node
- Herpes simplex infection, mucocutaneous for > 1 month or visceral
- Progressive multifocal leucoencephalopathy
- Any disseminated endemic mycosis
- Candidiasis of oesophagus, trachea and bronchus
- Atypical mycobacteriosis, disseminated or lungs
- Extrapulmonary tuberculosis
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Kaposi's sarcoma
- HIV encephalopathy
- Visceral leishmaniasis

INFANTS AND CHILDREN (age range 14 years and below):

The tables below provide the features in each Stage category for children with HIV.

Table: WHO Paediatric Clinical Stage 1

Asymptomatic
Persistent generalised lymphadenopathy

Table: WHO Paediatric Clinical Stage 2

- Unexplained persistent hepatomegaly and splenomegaly
- Papular itchy skin eruptions
- Extensive skin warts (human papilloma virus infection)
- Extensive molluscum contagiosum
- Recurrent oral ulcerations
- Unexplained persistent parotid gland enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic respiratory tract infections
- (sinusitis, otorrhoea, tonsillitis, otitis media)
- Fungal nail infections

Table: WHO Paediatric Clinical Stage 3

- Moderate unexplained malnutrition not responding to standard therapy [a]
- Unexplained persistent diarrhoea for longer than 14 days
- Unexplained persistent fever above 37.5 (intermittent or constant for longer than one month
- Persistent oral candida (outside the first 6-8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotising ulcerative gingivitis or periodontitis
- TB lymphadenopathy
- Pulmonary tuberculosis
- Severe recurrent presumed bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease, including bronchiectasis
- Unexplained anaemia (<8g/dl), neutropaenia (<500/mm^3) or thrombocytopaenia (<50,000/ mm^3)
- HIV-associated cardiomyopathy or HIV-associated nephropathy

[a] **in general:** defined by weight for height 70-79%; weight for age 70-79% (or below the third percentile in weight for age chart in health passport) on 2 measurements 3 months apart; weight loss >10% sustained over 3 months. **in under 5s:** defined as failure to gain weight over a period of 6 months. **in children 1-5 years,** defined as MUAC of 11-11.9cm. Simple anthropometric charts can be obtained from MOH, Nutrition Unit, or Action against Hunger, Malawi

Table: WHO Paediatric Clinical Stage 4

- Unexplained severe wasting, stunting, or severe malnutrition not responding to standard therapy [a]
- Pneumocystis carinii (jeroveci) pneumonia
- Recurrent severe presumed bacterial infections (eg, empyema, pyomyositis, bone or joint infections, meningitis, sepsis, but excluding pneumonia)
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea > 1 month
- Isosporiasis with diarrhoea > 1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus of an organ other than liver, spleen or lymph node
- Chronic herpes simplex infection (orolabial or cutaneous for > 1 month) or visceral at any site
- Progressive multifocal leucoencephalopathy
- Any disseminated endemic mycosis
- Candidiasis of oesophagus, trachea and bronchus
- Atypical mycobacteriosis, disseminated or lungs
- Extrapulmonary tuberculosis, excluding TB lymphadenopathy
- Lymphoma (cerebral or B cell non-Hodgkin)
- Acquired HIV associated rectal fistula
- Kaposi's sarcoma
- HIV encephalopathy

[a] **in general:** defined by weight for height < 70%; weight for age <70%; bilateral oedema of both feet. **in children aged 1-5 years:** defined as MUAC of < 11 cm.
Simple anthropometric charts can be obtained from MOH, Nutrition Unit, or Action against Hunger, Malawi

MEASUREMENT OF CD4-LYMPHOCYTE COUNT

HIV infection causes a progressive decline in cell-mediated immunity. This is manifested by a decrease in the number of T-cell lymphocytes that bear the CD4 receptor, and these are known as CD4-lymphocytes. The immunological status of the HIV-infected infant, child, adolescent or adult can be assessed by measurement of the absolute number or % of CD4-lymphoctes, and this is regarded as the standard way to define the severity of HIV-related immunodeficiency.

Immunological status in adults and adolescents

Normal CD4 counts in adults and adolescents range from 500 – 1,500 cells per cubic millimetre of blood. HIV-associated immunodeficiency is advanced if the CD4 count is between 250- 349/mm^3. HIV-associated immunodeficiency is severe or very advanced if the CD4 count is < 250/mm^3.

Immunological status in children

The absolute CD4 counts and the percentage of CD4-lymphocytes in healthy infants, not infected with HIV, are much higher than those observed in uninfected adults, and slowly decline to adult values by 5 years of age. In considering absolute CD4 counts and CD4 percentages, age must therefore be taken into account. In children less than 5 years of age, the absolute CD4 count varies more than the CD4 percentage, and therefore measurement of

CD4 percentage is more valuable in younger children. Not all equipment in Malawi is able to measure CD4 percentage, and measurements may have to rely on back calculation of the CD4% from an absolute CD4 count and the total lymphocyte count using the formula:
"Relative CD4% = absolute CD4 lymphocyte count x WBC x Lymphocytes (%)"

The proposed classification of immunodeficiency based on CD4-counts or CD4-percentages is shown in the Table below.

Table: WHO proposed immunological classification of established HIV infection

HIV-Immune Deficiency	**Age-related CD4-lymphocyte values**			
	< 1 year CD4%	**1 yr to < 3 yrs CD4%**	**3 yrs to < 5 yrs CD4 %**	**5 yrs and > (per mm^3)**
Not significant	> 35	> 30	> 25	> 500
Mild	30-35	25-30	20-25	350-499
Advanced	25-30	20-25	15-20	250-349
Severe	< 25 (CD4<1500) (TLC <4000)	< 20 (CD4 < 750) (TLC <3000)	< 15 (CD4 < 350) (TLC <2500)	<15 (CD4 < 250) (TLC <2000)

Priority for CD4-lymphocyte count testing

At the time of writing the Guidelines, only 14 facilities in Malawi have capacity for CD4 testing. Priority for CD4 testing should go to:- i) patients in WHO Stage 2, ii) HIV-infected children and iii) HIV-positive pregnant women identified through the PMTCT programme and who on clinical staging are not eligible for ART.

PATIENTS ELIGIBLE FOR ART

ADULTS [persons aged 15 years and above]:

Asymptomatic patients who are HIV-positive are in general not eligible for ART because there is no evidence that early institution of ART benefits the patient. Adult patients will therefore be eligible for ART if they fulfil condition 1 and 2 PLUS either conditions 3, 4, 5 or 6:-

1. Patients are known to be HIV-seropositive

Patients must have undergone HIV testing and counselling, and must provide written evidence of a positive HIV-test result from a reputable and quality assured VCT counselling site.

Patients who provide verbal confirmation only of a positive HIV-test result are not eligible for ART.

2. Patients understand the implications of ART

Patients must have undergone counselling sessions (group and individual) during which the implications of ART have been discussed, in particular that ART requires high adherence and compliance and is a life long commitment.

Patients who are ill with an opportunistic infection or HIV-related malignancy should be treated appropriately and stabilised before considering the possible use of ART. ART is **not** an emergency treatment.

3. Patients are assessed as being in WHO Clinical Stage 3

Patients who have any of the features listed in Stage 3 (see the Table on page 37) should receive ART, but be stabilised **before** treatment commences.

There must be documented written evidence of a history of a) pulmonary tuberculosis within the past year or b) severe bacterial infections. Verbal reports of pulmonary TB or bacterial infections will not be acceptable as evidence for starting ART.

4. Patients are assessed as being in WHO Clinical Stage 4

Patients who have any of the features listed in Stage 4 (see the Table on page 38) should receive ART, but be stabilised **before** treatment commences.

5. Patients are assessed as being in WHO Clinical Stage 2 with a total lymphocyte count < 1200/mm^3

A total lymphocyte count < 1200/ mm^3 in conjunction with clinical staging has useful prognostic significance. Therefore, patients with a low total lymphocyte count and any features in WHO Stage 2 (shown in the Table on page 36) are eligible for ART.

6. Patients have a CD4 lymphocyte below 250/mm^3

Any patient HIV-seropositive with a CD4 count below 250/mm^3 is eligible for ART regardless of WHO Staging or symptoms.

These constitute the medical criteria for adult eligibility to ART. It is beyond the scope of this document to discuss social criteria for eligibility.

CHILDREN [persons aged 14 years or below]:

Asymptomatic children who are HIV-positive are in general not eligible for ART because there is no evidence that early institution of ART benefits the patient.

General Principles:

Although the pathogenesis of HIV and the underlying principles of antiretroviral therapy (ART) are similar in adults and children, there are specific physiologic, clinical, practical and social issues to consider when starting children on ART. Paediatric patients will be eligible for ART if their care-givers have received appropriate counselling and understand the implications of ART and if they fulfil the age-related criteria set out below:

Children who are acutely unwell should be treated appropriately and stabilised before being considered for ART.

HIV testing in children will be provided in the presence of a caregiver. However, older children and adolescents will need to be actively involved in HIV testing and counselling. The process of disclosure of the diagnosis to a child and an adolescent requires close co-operation with the caregiver and an experienced counsellor. Likewise, the implications of ART need to be explained to the caregiver and the child in an age-adapted fashion.

The presence of trans-placental maternal antibody means that HIV infection cannot be diagnosed using antibody-based HIV tests in children less than 18 months of age. Furthermore, as discussed earlier, normal lymphocyte counts and the proportion of lymphocytes expressing CD4 vary with age, particularly in young children. In children aged less than 5 years, the CD4 percentage is generally preferred as a measure of immune-status in HIV-infected children. However, from 5 years and above the absolute CD4 lymphocyte count can be used.

Eligibility for ART in children over the age of 18 months

Children over the age of 18 months will be eligible for ART if they are HIV-seropositive and they and/or their care givers understand the implication of ART, in the same way as for adults plus the following conditions shown below:-

- **WHO Paediatric Clinical Stage 4**

- **WHO Paediatric Clinical Stage 3**

  In these situations, the presence of a CD4 lymphocyte count may add guidance to the decision-making. In children with TB, lymphocytic interstitial pneumonia, oral hairy leukoplakia or thrombocytopenia, ART may be deferred if the CD4 count or CD4 percentage is above the threshold value for starting ART (see Table on page 43)

- **WHO Paediatric Clinical Stage 2 with a total lymphocyte count at or below the threshold value (**see Table on page 43)

- **Children with a CD4 lymphocyte count or CD4 percentage below the threshold value for starting ART (**see Table on page 43**)**

Eligibility for ART in children under the age of 18 months

For infants and children less than 18 months of age, the diagnosis of HIV infection is difficult because of passage of maternal antibody. In most situations in Malawi, there will be no access to virological testing. In these situations, clinical criteria (shown below) can be used for making the diagnosis of severe HIV disease requiring ART.

A presumptive diagnosis of severe HIV disease requiring ART is made if:-

- **The infant is confirmed HIV antibody positive**

and

- **The infant is categorised in WHO Paediatric Clinical Stage 4** (this includes severe malnutrition)

or

- **The infant is symptomatic with two or more of the following conditions:- i) oral candidiasis, ii) severe pneumonia and iii) severe sepsis**

Other factors which support the diagnosis of severe HIV disease in an HIV-seropositive infant include:- a) recent HIV-related maternal death, b) advanced HIV disease in the mother, and c) CD4 < 20% in children 12-18months, and <25% in children less than 12 months.

These constitute the paediatric criteria for eligibility to ARV therapy. It is beyond the scope of this document to discuss social criteria for eligibility.

ANTIRETROVIRAL DRUGS: GENERAL PRINCIPLES

Aims of Treatment

The three main aims of ART are to:-

- Reduce HIV-related morbidity and mortality
- Prolong good quality life
- Assist the patient in being able to return to previous work or employment

The Two Commonly Used Classes and their Drugs

The commonly used antiretroviral drugs belong to two major classes:

1. Reverse Transcriptase Inhibitors (RTIs)
2. Protease Inhibitors (PIs)

Reverse transcriptase Inhibitors are further divided into 3 groups:

1.1. Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)
1.2. Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)
1.3. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Examples of antiretroviral drugs in each of these classes are shown in the Table.

Table: Different classes of antiretroviral drugs, approved by WHO in 2006

NsRTI	NtRTI	NNRTI	PI
Zidovudine (ZDV) **Didanosine (ddI)** **Lamivudine (3TC)** **Stavudine (d4T)** **Zalcitabine (ddC)** **Abacavir (ABC)** **Emtricitabine (FTC)**	**Tenofovir (TDF)**	**Nevirapine (NVP)** **Efavirenz (EFV)** **Delavirdine (DLV)**	**Nelfinavir (NFV)** **Saquinavir (SQV)** **Ritonavir (RTV)** **Lopinavir (LPV)** **Indinavir (IDV)** **Amprenavir (APV)** **Tipranavir (TPV)** **Atazanavir (ATV)**

All these drugs act by blocking the action of enzymes, which are important for replication and functioning of HIV. The drugs must be used in combination, usually three drugs together.

Monotherapy (using one drug) is not recommended because of the inevitable development of drug resistance. However, for the specific indication of prevention of mother to child transmission of HIV infection, short course monotherapy may still be indicated.

Dual nucleoside therapy is also not recommended because it does not have a beneficial effect at a population level in terms of reducing HIV-related mortality and because dual therapy is also associated with rapid development of drug resistance. However, for post-exposure prophylaxis, short course dual therapy for 30 days is still indicated (see page 43).

Class-specific and drug-related side effects:

Class-specific side effects:

NsRTI	Mitochondrial toxicity Lipodystrophy syndrome with long usage
NtRTI	Mitochondrial toxicity
NNRTI	Skin rash Hepatitis
PI	Lipodystrophy syndrome Hyperlipidaemia Hyperglycaemia

Drug specific side effects:

Table: Some of the side effects of antiretroviral drugs

NsRTIs:	
Zidovudine	Anaemia, nausea, headache, fatigue, muscle pains, agranulocytosis
Didanosine	Nausea, diarrhoea, neuropathy, pancreatitis
Lamivudine	Nausea, headache, fatigue, muscle pains
Stavudine	Neuropathy, pancreatitis, diarrhoea, insomnia, lipodystrophy
Zalcitabine	Neuropathy, pancreatitis, oral ulcers
Abacavir	Nausea, fatigue, sleep disturbance, hypersensitivity reaction
Emtricitabine	Nausea, headache
NtRTI:	
Tenofovir	Renal failure, osteoporosis
NNRTIs:	
Nevirapine	Skin rash, Stephen Johnson Syndrome, hepatitis
Efavirenz	Skin rash, central nervous system disorders, teratogenicity
PIs:	" all PIs can give rise to lipodystrophy syndrome"
Nelfinavir	Diarrhoea, nausea, skin rash
Saquinavir	Diarrhoea, nausea, headache
Lopinavir/ ritonavir	Diarrhoea, nausea, headache, abnormal taste, peri-oral numbness, pancreatitis
Indinavir	Nephrolithiasis, diarrhoea, nausea, abdominal pain, headache
Amprenavir	Diarrhoea, nausea, abnormal taste, peri-oral numbness
Tipranavir	Diarrhoea, nausea, abdominal pain, rash
Atazanavir	Diarrhoea, nausea, jaundice (due to indirect hyperbilirubinemia)

Drug Doses

Table: Standard adult doses of antiretroviral drugs

Drug class / drug	Dose
NsRTIs:	
Zidovudine	300 mg twice daily
Didanosine	400 mg once daily (250 mg once daily if < 60Kg)
Lamivudine	150 mg twice daily
Stavudine	40 mg twice daily (30 mg twice daily if < 60Kg)
Zalcitabine	0.75 mg three times daily
Abacavir	300 mg twice daily
Emtricitabine	200 mg once daily
NtRTI:	
Tenofovir	300 mg once daily
NNRTIs:	
Nevirapine	200 mg once daily for 14 days, then 200 mg twice daily
Efavirenz	600 mg once daily
PIs:	
Nelfinavir	1250 mg twice daily
Saquinavir / ritonavir	1000 mg / 100 mg twice daily
Lopinavir / ritonavir	133 mg / 33 mg – three capsules twice daily
Indinavir / ritonavir	800 mg / 100 mg twice daily
Atazanavir	400 mg once daily
Atazanavir/ritonavir	300 mg/ 100 mg once daily

Novel classes of ARV drugs, which may become available in Malawi in the future

- Integrase inhibitors, which work on blocking the integrase enzyme and preventing HIV-DNA from inserting into the nucleus of the host cell

- Cell attachment inhibitors, which work by preventing the HIV from attaching to the cell.

- CCR5 co-receptor inhibitors, which work by preventing the HIV from binding to the important CCR5 co-receptor

- Fusion inhibitors, which work by preventing the HIV from fusing with the cell membrane and gaining entry to the cell cytoplasm. There is already an approved drug called "enfuvirtide or T-20", currently given by injection.

STANDARDISED TREATMENT FOR MALAWI: PRINCIPLES

The First Line Regimen:

Basic principles for choosing the regimen:

The basic principles for choosing the first line regimen were:-

- need for standardised therapy across the country
- ease of administration (eg. once or twice a day)
- few side effects, especially side effect needing laboratory monitoring
- lack of interaction, where possible, with rifampicin
- previous experience with use
- price

Using these principles:-

NsRTIs:

- zidovudine was not a good choice because of the tendency to cause anaemia, and therefore the need for haematological monitoring
- didanosine was not a good choice because it has to be taken on an empty stomach

NNRTIs:

- efavirenz was not a good choice because of the risk of teratogenicity

PIs:

- the whole class not a good choice because they have to be taken in relation to food, gastro-intestinal side effects are common and they all interact with rifampicin

The choice of the first line regimen and the components:

Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP)

Stavudine (d4T)

This is a nucleoside reverse transcriptase inhibitor.
It is easy to administer and generally well tolerated except in patients with peripheral neuropathy. d4T should **not** be combined with zidovudine (AZT) due to pharmacologic antagonism.

Side effects: the main immediate side effect is peripheral neuropathy: long term side effects include the lipodystrophy syndrome, lactic acidosis and other manifestations of mitochondrial dysfunction that also include peripheral neuropathy.

Stavudine is combined with Lamivudine as a dual therapy drug.

Stavudine is combined with Lamivudine and Nevirapine as a triple therapy drug.

Lamivudine (3TC)

This is a nucleoside reverse transcriptase inhibitor.
It is easy to administer and generally well tolerated.
The drug should never be given as monotherapy as high grade resistance rapidly develops. The drug has useful activity against hepatitis B.

Side effects are infrequent, and mainly consist of headaches, nausea, diarrhoea, abdominal pain and insomnia.

Lamivudine is combined with Stavudine as a dual therapy drug.
Lamivudine is combined with Stavudine and Nevirapine as a triple therapy drug.

Nevirapine (NVP)

This is a non-nucleoside reverse transcriptase inhibitor.
It is easy to administer. It has a long half life.

It is advisable not to give the drug as monotherapy as high-grade resistance rapidly develops. NVP is currently being given as monotherapy for PMTCT, although the use of single dose NVP is currently under review.

There is a lead in dose for the first two weeks to reduce the frequency of skin rash. After the first two weeks the standard dose is administered.

There are two major side effects, which occur principally during the initial 8 weeks of treatment. The first major effect is a cutaneous hypersensitivity reaction (fever, rash, arthralgia and myalgia), which can lead to a life-threatening Stevens Johnson syndrome. The second major effect is drug-induced hepatitis. Women with a CD4 count > 250 and men with CD4 count > 400 may be at increased risk of hepatitis.

Nevirapine is combined with Stavudine and Lamivudine, as triple therapy.

Interactions with other drugs: Nevirapine induces cytochrome p450, and has some important drug interaction problems.

- There is an interaction with rifampicin, a drug which also induces cytochrome p450. Rifampicin decreases the levels of nevirapine by 30-40% and may therefore decrease its effectiveness and increase the risk of inducing NVP resistance (see section on TB and ART)

- There is an interaction with ketoconazole leading to a 30% increase in nevirapine levels and a 60% reduction in ketoconazole levels: the two drugs should not be used together.

- There is an interaction with oestradiol leading to a 20% decrease in effectiveness of oral contraception. Alternative or additional methods of contraception should be used.

Alternative First-line regimens to be substituted in case of drug reactions

Patients may experience adverse reactions to the first-line regimen (see Monitoring and Managing Drug Toxicity), and some of these may be serious enough to require stopping the first line regimen.

There are three main types of adverse drug reaction requiring stoppage of the first line regimen. In these situations, the following changes in drug treatment are recommended:-

Reactions due to the Stavudine Component:

These are in order of frequency: -

i) Severe peripheral neuropathy
ii) Pancreatitis
iii) Lactic acidosis / Lipodystrophy syndrome

In these situations, the regimen is changed to

zidovudine plus lamivudine plus nevirapine (AZT + 3TC + NVP)

The patient will need regular monitoring every 3 months with measurements of Haemoglobin. Anaemia from AZT tends to occur within the first three months of treatment. Therefore consider Haemoglobin measurements at 1 month and then every 3 months after starting AZT or if there are clinical features suggesting anaemia.

Reactions due to the Nevirapine Component:

These are in order of frequency:-

i) skin reactions
ii) hepatitis

In these situations, the regimen is changed to

stavudine plus lamivudine plus efavirenz (d4T + 3TC + EFV)

Women of child-bearing age will need to take precautions to avoid pregnancy because of the risk of teratogenicity of EFV. EFV may cross-react with nevirapine in being associated with skin reactions, and this drug may need to be introduced cautiously.

All HIV-Antiretroviral clinics should be able to manage these problems, and implement a change to an alternative first line regimen if indicated. In addition to triple therapy (d4T/3TC/NVP-30 and d4T/3TC/NVP-40) and dual therapy
(d4T/3TC-30 and d4T/3TC-40), such clinics will either have available sufficient supplies of alternative first line therapy or be able to obtain these drugs from one of the central hospitals according to the referral systems already set up.

The Second line Regimen to be used in case of ART drug failure:

The second line regimen is used when patients have failed the first line regimen. Failure is defined as either the development of a new WHO Clinical Stage 4 feature or a CD4 count / CD4% which has declined to pre-treatment values or declined to <50% of peak value. These CD4 measurements need to be confirmed one month later in a patient who has been on ARV therapy for 6 months or more and adhering to therapy.

The decision to change to the second line regimen must be made in consultation with a specialist at one of the central hospitals, because the regimen is more difficult for patients to take and requires more management. This is particularly the case for patients with EPTB.

Replacement of d4T/3TC:

In Adults:
Zidovudine + lamivudine + tenofovir will be the NRTI backbone to replace d4T and 3TC. AZT+3TC is a dual combination – If there is the K65R mutation then AZT retains some activity to this – If there is the M184 mutation from 3TC, then it is advantageous to maintain this mutation, as this mutated virus is poorly replicative and susceptible to other NRTIs. TDF is a useful NRTI and relatively easy to take

In Children:
In children abacavir and didanosine will be the NRTI backbone to replace d4T and 3TC. Unfortunately, there is little information regarding the use of tenofovir in children. Tenofovir causes decreased bone mineral density in children, and given the high rate of nutritional deficiencies in this population, this adverse effect counterbalances the benefits of using this potent drug. Zidovudine is also of concern for children because of the effects of AZT-induced anaemia.

Replacement of NVP:

Because of cross-resistance with other members of the NNRTI class, nevirapine has to be replaced with a protease inhibitor. Lopinavir/Ritonavir is a powerful PI, but the drug must be stored in a fridge in the hospital or treatment unit as the capsules deteriorate in the hot weather. From mid-2007 a new heat-stable tablet of Lopinavir/ Ritonavir will become available. Failure in Malawi will be diagnosed in a late stage, based mainly on clinical features, and thus there is a need for this powerful PI.

The second line regimens

In adults the following drug regimen is the chosen second line option:
Zidovudine (AZT) + Lamivudine (3TC) + Tenofovir (TDF) + Lopinavir/Ritonavir (LPV/r)

In children the following drug regimen is the chosen second line option:
Didanosine (ddI) + Abacavir (ABC) + Lopinavir/Ritonavir (LPV/r)
[ddI in Malawi will be procured as enteric coated capsules, which can be taken with food, in contrast to non-enteric coated tablets which are taken on an empty stomach]

IMPLEMENTING STANDARDISED ART IN ADULTS

First Line Regimen:

Introduction of the first line regimen for individual adult patients

- *Staging and management of HIV-related disease:* Eligible patients who are staged in the ARV Clinic will receive treatment and care for any HIV-related disease. The patient will be asked to choose a guardian to provide support for what will be life-long treatment. Both patient and guardian will return to the Clinic on another day to attend a formal group counselling session.

- *Group Counselling:* At the group counselling session, the patient and guardian will be educated about ART - the drugs, the importance of strict adherence to therapy, what to do in case of side effects, the importance of continuing to practice safe sex, the need to attend the clinic on the appointed dates and the responsibility of Clinic staff and facility support staff to follow-up the patient in the community in the event of "default" (see Chapter on Education). The patient, and if possible with the guardian, will be asked to return to the clinic in a few days to one week for individual counselling and start of ART

- *Individual counselling and assessment of contraindications for ART:* The patient will be

assessed for any contraindications to d4T/3TC/NVP. The main contraindications are obvious liver disease [jaundice or ascites] and renal failure. The understanding of the main messages from group counselling will be assessed and reinforced.

- *Weight:* The patient will be weighed, and then prescribed either the stavudine-30mg or stavudine-40mg depending on body weight.
  If the weight of the patients is 59Kg or less, the formulation is stavudine-30mg
  If the weight of the patient is 60Kg or above, the formulation is stavudine-40mg

- *Other blood tests:* If facilities permit, blood may be taken for Full blood count, Liver Function tests and Serum creatinine: however, these tests are not mandatory.

- *The first two weeks:* Patients will be given drugs for two weeks as follows:
  d4T/3TC/NVP 1 tablet morning plus d4T/3TC 1 tablet evening
  The introduction of d4T/3TC/NVP in this fashion is because of the need to reduce the frequency of rash caused by Nevirapine.

- *The two-week review:* Patients will be reviewed back at the treatment unit after two weeks. At that time, provided there are no side effects, patients will be given drugs for 30 days (d4T/3TC/NVP comes in tins of 60 tablets, which is sufficient for 30 days)

d4T/3TC/NVP 1 tablet morning plus 1 tablet evening

- *Four-week reviews:* Patients will be seen every four weeks, and if there are no problems, will be prescribed drugs again for 30 days. If any side effects occur between reviews, patients must be told about the need to report to a health facility

- *Two-month reviews:* After 6 months, if the patient is stable and doing well, the patient will be asked to attend a formal group counselling session on drug adherence after which clinic reviews can be every two months

  Adjustment of drug formulation: If the weight of the patient increases from below 60Kg to 60Kg or above, the formulation of d4T-30mg/3TC/NVP will be changed to d4T-40mg/3TC/NVP

Table: Steps in Administering First line ARV therapy

First two weeks	d4T/3TC/NVP 1 tablet in the morning Plus d4T / 3TC 1 tablet in the evening
Next month	d4T/3TC/NVP 1 tablet in the morning Plus d4T/3TC/NVP 1 tablet in the evening
Monthly reviews for first 6 months	d4T/3TC/NVP 1 tablet in the morning Plus d4T/3TC/NVP 1 tablet in the evening
2-monthly reviews after 6 months if patient is stable, adherent and attends a 6-monthly group counselling session	d4T/3TC/NVP 1 tablet in the morning Plus d4T/3TC/NVP 1 tablet in the evening

Alternative First-line regimens to be substituted in case of drug reactions

Change needed due to the Stavudine Component:

This change will be because of severe peripheral neuropathy, pancreatitis or lactic acidosis. The patient is changed to

zidovudine plus lamivudine plus nevirapine (AZT + 3TC + NVP)
The dose of medication is:-

AZT+3TC 1 tablet morning and 1 tablet evening
NVP 1 tablet morning and 1 tablet evening

At the time of writing these guidelines, this medication is administered as a dual combination tablet of AZT and 3TC (one tablet in the morning and one tablet in the evening, from bottles of 60 tablets) and tablets of NVP (one tablet in the morning and one tablet in the evening, from bottles of 60 tablets).
Thus, the patient takes 4 tablets a day.

Change needed due to the Nevirapine Component:

This change will be because of skin reactions or hepatitis. The patient is changed to:

stavudine plus lamivudine plus efavirenz (d4T + 3TC + EFV)
The dose of medication is: d4T+3TC 1 tablet morning and 1 tablet evening
EFV 1 tablet evening

At the time of writing these guidelines, this medication is administered as a dual combination tablet of d4T and 3TC (one tablet in the morning and one tablet in the evening, provided in bottles of 60 tablets) and one additional tablet of EFV (one tablet taken last thing at night to prevent neuro-psychiatric side effects, provided in bottles of 30 tablets).
Thus, the patient takes 3 tablets a day

This substitution is complicated by the fact that nevirapine has a long half life and the triple therapy drug should not be stopped completely at once, otherwise NVP drug resistance may be allowed to occur. The following steps are therefore recommended:

- Stop triple therapy drug
- Immediately start d4T and 3TC, one tablet twice a day, and continue for one week
- Then stop d4T and 3TC, and wait until the rash or hepatitis has settled
- Then start d4T and 3TC and EFV

The Second line Regimen:

The following drug regimen is the chosen second line option:

Zidovudine (AZT) + Lamivudine (3TC) + Tenofovir (TDF) + Lopinavir/Ritonavir (LPV/r)

The drugs are taken as: AZT+3TC one tablet morning and one tablet evening
TDF one tablet morning
LPV/r three capsules twice a day, morning and evening

Wherever possible it is advised that LPV/r is kept in a fridge, or if this is not possible, in as cold a place as possible in the house. LPV/r and TDF should be taken with food. Thus for simplicity the entire regimen should be taken with food.

IMPLEMENTING STANDARDISED ART IN CHILDREN

ART will be initiated at an HIV-Antiretroviral Clinic. This clinic will not replace regular services of under 5 clinics, and on-going attention should be paid to vaccinations, weight monitoring, diagnosis and treatment of opportunistic infections. Staff providing ART for children must have received appropriate training in the use of paediatric ART.

First line Regimen

Ideally, antiretroviral drugs for children should be available as paediatric formulations, i.e. palatable syrups for administration in appropriate volumes. However, liquid preparations present their own particular problems, including increased bulk and weight (for storage and transport), increased cost, limited shelf-life and the need for caregivers to measure volumes. There is currently no liquid combination formulation available for d4T/3TC/NVP, and although individual syrups are available for 3TC and NVP, d4T syrup needs to be kept refrigerated.

There are considerable advantages in using the same treatment options for adults and children. It is recommended therefore that children receive d4T + 3TC + NVP given as divided tablets according to weight as set out in **Annex 2.** There is now evidence that split dose triple therapy is effective and also feasible.

The initiation of treatment should follow the same general steps as shown earlier for adults. Treatment should be initiated with a single daily dose of d4T/3TC/NVP with once daily d4T/3TC given for the first two weeks. Caregivers should be asked to re-attend promptly if the child develops a rash or becomes unwell. Guardians should be instructed not to stop therapy without authorisation from clinic staff.

Alternative First-line regimens to be substituted in case of drug reactions

Children, like adults, may experience adverse reactions to the first-line regimen, and some of these may be serious enough to require stopping the first line regimen. The same recommendations, as for adults, apply to children. Doses and guides to starting alternative first line ART are given in **Annex 3**:-

In children under 3 years of age, the triple combination with EFV cannot be recommended in view of lack of pharmacokinetic data before this age: in these situations, the first line regimen is stopped, not substituted and specialist opinion must be sought.

The Second line Regimen:

Children may fail first line treatment. However, different recommendations about the regimen apply to children compared with adults. Doses and advice about starting second line ART are given in **Annex 3.** Specialist opinion must be sought.

COTRIMOXAZOLE PREVENTIVE THERAPY WITH ART

There is a national policy on use of cotrimoxazole preventive therapy (CPT). The main indications for CPT are shown in the Table below

Table: CPT is offered to the following adults and children

Adults	Any person with symptomatic HIV disease [Stages 2,3 and 4] Any person who has a CD4 count of 500/mm^3 or less, regardless of symptoms
Children	Any child, aged 6 weeks or more, born to an HIV-positive woman irrespective of whether the woman received ART in pregnancy Any child, 6 weeks or more, who is HIV-positive regardless of symptoms

Thus, all patients eligible for ART are also eligible for CPT. Every attempt should be made to place such patients on CPT either before or at the same time as starting ART.

The dosages of CPT are shown in the Table below

Table: Dosages of CPT

Category	**Dosage of CPT (480mg tablets)**
Adults	One tablet (480mg) twice a day
Children aged 5- 14 years	One tablet (480mg) once a day
Children aged 6 months to 4 years	Half a tablet once a day (240mg daily)
Children aged 6 weeks to 5 months	Quarter of a tablet once a day (125 mg daily)

EDUCATION FOR THE PATIENT AND GENERAL PUBLIC

Education for the patient and the care giver/ guardian

Before patients start on ART they must understand the implications of therapy and be prepared to accept therapy as a life long commitment. Group counselling sessions must be conducted on HIV /AIDS with due reference to the benefits and dangers of ART followed by individual counselling sessions.

Counsellors and clinicians must be trained in providing key messages about ART, and regular counselling sessions should be a routine part of the service provided at the HIV Clinic. Staff at the HIV clinic should encourage HIV-positive patients who are on ART to enrol as "educators" and counsellors, for these patients can provide valuable information about ART to the patients who are starting therapy.

Patient education must occur at the start of ART and during therapy. It is recommended that 6 months after therapy, patients routinely attend a group counselling session, and if adherent and stable, these patients can be recommended for 2 monthly follow-up visits. Adherence counselling in groups should occur every 6 months

IEC materials on ART, which have been distributed to health facilities and public places (e.g. ART patient calendars), must be used to educate patients and care

givers. Radio broadcasts will also be a regular feature, so that patients and the general public are made aware of the benefits and dangers of ART.

Wherever possible, support groups, including national organizations such as NAPHAM, MANET and MANASO should be used to help patients and their caregivers in ensuring adherence to ART

The key messages about ARV drugs and ART are:-

- The drugs are not a cure and have to be taken for life
- Patients remain infective and therefore need to practice safe sex and use condoms
- Only drugs prescribed from certified practitioners should be taken
- All the drugs have to be taken daily according to prescription advice, otherwise they will become ineffective because of resistance. Guardians and care givers must support drug administration for children
- Drugs must not be shared with relatives or friends
- If an adverse effect occurs while on the drugs, a clinician must be consulted. If the side effect is jaundice or a severe skin rash with blisters in the mouth or around the genitalia, the drugs must be stopped and a clinician seen as quickly as possible

- In the event of not showing at the clinic, the ART clinic staff and the support services will try and trace the patient or the guardian to find out what has happened – the master card has a field that explicitly requests patient consent for defaulter tracing

- At every clinic visit, the patient or the guardian must bring back the pill container so that clinic staff can count the remaining number of pills in the container (see section on patient monitoring and drug adherence)

- If there is evidence that drugs are being sold in market places this must be reported to the health authorities in order for action to be taken - such practices will lead to the development of widespread resistance to ARV therapy

- ARV drugs in the first line regimen and alternative first line regimens can be taken independently of food. It is important that patients try and get as good nutrition as possible (see Nutrition guidelines). It is best to avoid alcohol

- If the patient dies, the remaining ARV drugs must be returned to the ARV Clinic. These drugs must then be destroyed in accordance with standard pharmaceutical practices

Education for the general public

Key messages for the general public are:-

- ARV drugs are not a cure for patients and have to be taken for life
- Patients remain infective and therefore need to practice safe sex and use condoms where appropriate
- Only drugs prescribed from certified practitioners should be taken
- All the drugs have to be taken according to the prescription advice, otherwise they will become ineffective because of resistance
- Drugs must not be shared with relatives or friends
- If a person is raped, then the nearest health facility must be approached as soon as possible regarding implementation of post-exposure prophylaxis

ART IN SPECIAL SITUATIONS

WOMEN OF CHILDBEARING POTENTIAL AND WHO ARE PREGNANT

ART is a priority for pregnant women who are eligible for ART, because a) triple therapy is very effective in reducing mother to child transmission of HIV, b) triple therapy reduces the risk of HIV transmission during breast feeding. Wherever possible, HIV-positive pregnant women should have a CD4-lymphocyte count performed to determine eligibility for ART even in the absence of symptoms. In the event of waiting lists, HIV-positive eligible pregnant women should be given priority.

Nevirapine, one of the components of d4T/3TC/NVP, can lower the blood concentration of oral contraceptives, and additional or alternative contraceptive methods (such as medroxyprogesterone for women or condoms for men) should be considered to avoid pregnancy in women using these drugs. If efavirenz is used as an alternative first line drug, this is teratogenic: women who are taking efavirenz must take appropriate contraception to avoid getting pregnant.

d4T/3TC/NVP is not contraindicated in pregnancy, and can be safely given. Thus if a woman becomes pregnant while on d4T/3TC/NVP, this can be continued.

Any woman who is taking triple ART and becomes pregnant should continue with the first line regimen, and not be given nevirapine at the onset of labour. However, the child born to such a woman should be given the standard recommended ARV prophylaxis within 72 hours of birth (see PMTCT Guidelines).

D4T/3TC/NVP can be given to lactating mothers and reduces the risk of HIV transmission during breastfeeding.

PATIENTS WITH LIVER DISEASE

Patients with acute hepatitis (manifested by jaundice) or with established chronic liver disease should not be given d4T/3TC/NVP.

PATIENTS WITH RENAL FAILURE

Both stavudine and lamivudine are eliminated by the renal route, and need dose reductions as renal failure progresses. NVP does not require dose adjustment in renal failure. Specialist advice is needed for the administration of ART in case of renal failure. As d4T/3TC/NVP cannot be reduced in relation to creatinine clearance individual drugs have to be given. This treatment might be considered at central hospital level, although the individual drugs will have to be obtained on a named patient basis.

Renal failure will not automatically exclude patients from treatment, because patients with HIV nephropathy can directly benefit from ART.

TDF is also excreted through the renal route and may need dose adjustment in renal failure.

TREATMENT OF HIV-POSITIVE ADULTS AND CHILDREN WITH TUBERCULOSIS

Background:

Patients with tuberculosis are treated with standardised regimens in Malawi. All regimens include an Initial Phase of Treatment with 3 to 5 drugs, and a continuation phase usually with two drugs (see TB Treatment Manual, 2002, Edition 5). In the initial phase of treatment, all drug combinations include rifampicin, which interacts with nevirapine. In the continuation phase of treatment for new patients with smear-positive pulmonary TB (PTB), smear-negative PTB and extrapulmonary TB, the treatment is daily ethambutol and isoniazid for 6 months. In new patients with TB meningitis and patients being treated for recurrent TB, the continuation phase includes rifampicin.

New developments:

Malawi will introduce rifampicin and isoniazid (RH), as combination therapy, for the continuation phase of anti-TB treatment. This has the following advantages for both HIV-positive and HIV-negative patients with TB:- a) a stronger regimen with a better eventual treatment outcome; b) a reduced risk of recurrent TB after treatment is completed; c) a shorter duration of chemotherapy which will be for a total of 6 months instead of 8 months. However, the introduction of this shorter rifampicin-throughout regimen poses some problems when it comes

to ART (see below). RH as continuation treatment will be introduced in a phased approach.

The problem: rifampicin and non-nucleoside reverse transcriptase inhibitors:

Non-nucleoside reverse transcriptase inhibitors are metabolised mainly through cytochrome P450 (CYP450) enzymes. Rifampicin induces CYP450, leading to a reduction in the plasma concentration of nevirapine by 30-40% and efavirenz by
20% - 25%. There is concern that reduced nevirapine concentrations will lead to emerging drug resistance and treatment failure. Increasing the dose of nevirapine to compensate for this interaction increases the risk of toxicity, and the risk of hepatotoxicity is already increased in patients with a low body mass index or with high CD4-lymphocyte counts.

It is therefore usually advised that nevirapine and rifampicin should not be used together, and that efavirenz be substituted for nevirapine. The problem is that efavirenz is teratogenic (and nationally over half of treated patients are women), there is currently no fixed dose combination with stavudine and lamivudine, and efavirenz based-treatment is more expensive. Moreover, evidence is accumulating that, although plasma nevirapine levels are reduced by rifampicin, they still remain in the effective range, and outcomes in patients on rifampicin and nevirapine are still good.

As a result of this uncertainty, certain districts are going to implement the use of nevirapine-based regimens in association with rifampicin, and closely monitor the outcomes of patients. One district, Chiradzulu, will use efavirenz at a dose of 600mg daily. This approach has the support and backing of the World Health Organization.

Eligibility for treatment:

All patients with tuberculosis are potentially eligible for ART, because they are either categorised as WHO Clinical Stage 3 or 4. However, it is well known that TB can occur in HIV-positive patients with high CD4 counts (who therefore may not need ART). Operational research will be conducted into whether the addition of a CD4 lymphocyte count improves patient management.

When to start ART in a patient on anti-TB treatment:

In the initial phase of anti-TB treatment, ART will not be given because the patient is still sick, the pill burden will be high and there is a danger of immune reconstitution disease (see below). In severely immuno-compromised patients in specialist centres, consideration may be given to starting ART within 2 weeks of initial phase anti-TB treatment.

Once the patient has completed the initial phase of treatment and started on the continuation phase of anti-TB treatment with either isoniazid and ethambutol (EH) or rifampicin and ethambutol (RH), the patient will then be eligible for ART.

In the case of EH, it is advised that ART with d4T/3TC/NVP is started after the patient has been on continuation therapy for two weeks, so that both monthly continuation phases of ART and anti-TB treatment can be synchronised.

Provision of ART for TB patients on EH

The following steps are recommended:-

- Upon registration for anti-TB treatment, TB patients will receive HIV testing and counselling (provider-initiated HIV testing). HIV-positive TB patients will start or continue on cotrimoxazole according to the current cotrimoxazole policy

- Once HIV-positive TB patients have completed their initial phase of anti-TB treatment, they will be started on EH. They will be referred to the ART clinic for staging, group counselling and individual counselling. This process will take two weeks, at which time the patients will start ART in the usual way.

- At the end of the two-week starter pack phase, patients will come back to the ART clinic to collect their monthly supplies of d4T/3TC/NVP. These visits will coincide with visits to the TB office, so that patients can collect their monthly supplies of anti-TB treatment on the same day. CTX will be continued along with ART: [it is not known definitely whether CTX should be continued or stopped in these circumstances, and relevant operational research will be carried out to answer this question]. Because of the added adverse effects of stavudine and isoniazid in causing peripheral neuropathy, patients should be given ½ tablet of pyridoxine daily (12.5mg daily)

Provision of ART for TB patients on RH

The following steps are recommended:-

- Upon registration for anti-TB treatment, TB patients will receive HIV testing and counselling (provider-initiated HIV testing). HIV-positive TB patients will start on cotrimoxazole according to the current cotrimoxazole policy

- Once HIV-positive TB patients have completed their initial phase of anti-TB treatment, they will be started on RH. During the initial phase of anti-TB treatment, eligible patients should have been staged, group counselled and individually counselled.

- Patients will start straight away with the continuation phase of d4T/3TC/NVP. This is because rifampicin reduces plasma levels of NVP, and use of the starter pack will result in sub-therapeutic NVP levels. Patients will collect the monthly supply of d4T/3TC/NVP and also collect their monthly supplies of anti-TB treatment on the same day. CTX will be continued along with ART. Because of the added adverse effects of stavudine and isoniazid in causing peripheral neuropathy, patients should be given ½ tablet of pyridoxine daily (12.5mg daily)

Table: ART with anti-tuberculosis treatment

Phase of Anti-TB Treatment	**ARV therapy**
Initial Phase [RHZ(E)]	No ART
Continuation Phase (EH)	Wait for 2 weeks Two weeks starter pack Then, four weeks continuation pack of d4T/3TC/NVP
Continuation Phase (RH)	Prepare the patient with group counselling in initial phase Start at continuation phase with four-weeks continuation pack of d4T/3TC/NVP Every month the patient collects one month's supply of RH and d4T/3TC/NVP

Management of patients already on ART who develop TB:

It has been observed that a proportion of patients who start ART for other reasons may develop TB. If this does happen, it most frequently occurs during the first three months of ART. The risk is higher if patients have a previous history of TB.

In these cases, it is advised that ART continues with d4T/3TC/NVP, and anti-TB treatment started in the usual way.

This advice is different from that offered in the first edition, when it was recommended to stop ART until the initial phase of anti-TB treatment had been completed. Stoppage of ART at this early stage runs a risk of creating drug resistance, and it is felt to be better practice to continue ART. This action has the support and backing of the World Health Organization.

Some of the patients who develop TB soon after starting ART may have had undiagnosed TB at the time of starting ART. Clinicians must have a low threshold for suspecting TB in both adults and children. If there is any suspicion of TB, the appropriate investigations (sputum smears, chest x-ray) must be undertaken.

TREATMENT OF HIV-POSITIVE PATIENTS WITH MALIGNANCY

HIV-infected patients have a dramatically increased risk of developing malignancies during the course of their illness, particularly Kaposi's Sarcoma, and lymphomas.

The presence of Kaposi sarcoma is usually ascertained clinically, whereas the diagnosis of lymphoma requires histological confirmation, only feasible at central level in Malawi.

One of the core elements of treatment for HIV-related malignancy is the provision of ART. In fact, in patients with benign, non-aggressive cutaneous forms of Kaposi' s sarcoma ARV therapy on its own is sufficient enough treatment. However, for most patients treatment of HIV-related malignancies should also include the use of cytotoxic drugs, if these are available. This strategy applies to patients with **aggressive Kaposi's Sarcoma** (in which lesions are associated with a significant impact on functional and/or vital prognosis) **or lymphoma**. Even though not curative, the addition of cytotoxic therapy can significantly increase the patients' quality of life and length of survival, although these drugs in their own right suppress immunity.

Cytotoxic drugs:

Bleomycine, Vincristine, Etoposide, Cyclophosphamide, Methotrexate (to name only those available in Malawi) figure among the drugs ordinarily used in various protocols of mono- or preferably poly-chemotherapy. Apart from vincristine, the other drugs are usually only available at central hospitals in Malawi. Radiotherapy, which is not currently available in Malawi, is also frequently recommended.

The five drugs, mentioned above, can be used with ART: there are no contraindications. However, some of the drugs are associated with a toxicity profile similar to ART, and this may require particular attention and monitoring.

The common principal toxicities caused by the available cytotoxic and ARV drugs are shown below:-

- Vincristine and Etoposide may induce peripheral neuropathy, like Stavudine (d4T) and Didanosine (ddI)

- Bleomycine may cause muco-cutaneous reactions, like Nevirapine (NVP)

- Cyclophosphamide, Methotrexate, Etoposide are all myelotoxic, like Zidovudine (AZT). This association requires more frequent measurements of the full blood count

Management of Kaposi's Sarcoma: In patients with bulky tumours, vincristine should be given as weekly doses for about 2-3 weeks prior to the start of ART. This may allow some shrinkage of the tumour before ART starts, and this in turn reduces some enlargement of the KS lesions that sometimes occurs in the early weeks of ART.

MANAGEMENT OF OCCUPATIONAL AND ACCIDENTAL EXPOSURE

Occupational exposure might place a health care worker (HCW) at a risk of HIV infection. Needle-stick injury is the most common occupational exposure, although exposure to other body fluids such as pleural, pericardial, ascitic, amniotic, synovial, cerebral spinal fluids, semen and vaginal secretions pose a risk for HIV infection.

The overall risk of HIV infection from occupational exposure is low. For example, from needle sticks the overall risk of becoming HIV-infected is 1 in 300. From mucous membrane exposure it is less than 1 in 1000.

HIV exposure for the purposes of interventions is classified as either:-
low risk or *high risk.*

High risk: Percutaneous injuries with hollow needles and large volumes of blood on to a mucosal surface from a source person who is known to be HIV-seropositive, or if there is a strong suspicion that the source is HIV-seropositive, are considered *high risk exposures.*

Low risk: All other exposures, including percutaneous injuries with solid needles, exposures to fluids other than blood, and exposures to the non-intact skin, are considered *low risk exposures.*

Exposure of blood or other fluids to the intact skin is not a risk in this context and does not require Post-exposure Prophylaxis (PEP)

Although there are several options for Post Exposure Prophylaxis (PEP), it is critical that health care workers minimise their risk of exposure to HIV infection. Therefore all body fluids should be considered potentially infectious and it is important to follow all universal infection control precautions.

What to do after occupational exposure: low risk and high risk

Immediate measures:

- Use soap and water to rinse any wound or skin site in contact with infected blood or fluid
- Rinse exposed mucous membranes thoroughly with water
- Irrigate generously any open wound with sterile saline or disinfectant solution (2-5 min)
- Eyes should be irrigated with clear water, saline or sterile eye irrigants.
- Report to the clinician on duty as soon as possible

Post-exposure prophylaxis (PEP): low risk and high risk

"**PEP**" refers to treatment of occupational exposures using ARV drugs. ARV therapy started immediately after exposure to HIV may prevent HIV infection, although this protection is not 100%. Treatment should be initiated within 1-2 hours of exposure, but if there are delays, PEP can still be started up to 72 hours after the exposure.

Operational considerations:

- Each *health facility* should have a bottle of **AZT/3TC** (60 tablets) kept in an agreed designated unit for easy, but secure, access

- Following occupational exposure, a HCW should immediately report to the senior member of his/her unit and the designated PEP location where initial risk assessment will be done: a 3-day supply of AZT/3TC will be given. This should be started as soon as possible after the needle stick injury.

- The HIV status of the source patient should be determined whenever possible. If the source patient is HIV-positive, then PEP is indicated. If the source patient is HIV-negative, then this may be because the patient is in the window period of HIV-infection or in hospital because of primary HIV infection. Specialist advice may be sought

about the need to continue or stop PEP, but in general the advice will be to continue the PEP because of the risk

- The HCW must be strongly encouraged to undergo counselling and testing immediately or within 72 hours of exposure. If the HCW is HIV-positive, then PEP is not necessary and should be stopped. Moreover, taking dual therapy in an already HIV-infected patient may lead to the development of drug resistance. HIV-positive HCWs need to assessed for eligibility for ART.

- If the HCW is HIV-negative, then PEP is continued for a total duration of 30 days. HCWs must be counselled about side effects. Side effects are monitored clinically, and laboratory tests (eg, haemoglobin measurements for zidovudine) may be done according to indications.

- Follow-up HIV testing is done at 3 and 6 months. If the HIV test remains negative at 6 months, the HCW can be counselled that he/she has not been infected with HIV as a result of the exposure.

Table: The PEP Regimen

DRUG	DOSE	FREQUENCY	DURATION
Zidovudine (AZT) 300mg/ Lamivudine (3TC) 150mg (Duovir)	One tablet	Twice a day (BD)	30 days

Dual therapy should be available at every health facility and at central medical stores. In cases of high risk exposure or when the source patient is already on ART, lopinavir/ritonavir three capsules twice a day can be added to the dual NRTI therapy: specialist advice is necessary in these cases.

MANAGEMENT OF HIV EXPOSURE THROUGH RAPE

Another group of persons to be offered **post-exposure prophylaxis (PEP)** is women, men and children who have been raped. Although the risk of acquiring infection from a single act of sexual intercourse is low, this kind of exposure (i.e., rape) is commonly associated with violence and genital tract trauma, which increases the risk of HIV transmission.

All persons who are HIV-seronegative and who have been raped, should be offered post -exposure prophylaxis. As with PEP, the earlier it is administered the more effective it is. Clinicians must also ensure appropriate referral or treatment for other aspects of sexual assault (e.g., STI, emergency contraception, psycho-social support).

The same procedures for PEP that have been described earlier in this section should be followed. If the victim is found to already be HIV-seropositive, then PEP should not be started or be stopped, and appropriate counselling and clinical referral made.

All persons involved with rape victims, including the police, must ensure that the rape victim is brought to hospital as an emergency before detailed questioning takes place in order not to delay PEP initiation. Health care workers must make their own decisions about the need for PEP, based on a history of penetrative sexual

violence, and not be bound by the police report on whether rape has occurred or not.

The regimen is the same as PEP for occupational exposure. Zidovudine 300 mg plus Lamivudine 150 mg are given twice a day for 30 days: the appropriate dose schedules are followed for children as shown in **Annex 3**. Follow-up HIV testing is done at 3 months and 6 months.

For more information, please refer to Guidelines on Sexual Abuse and Rape from the Reproductive Health Unit, Ministry of Health.

MONITORING ART

REGISTRATION OF PATIENTS ON ARV THERAPY

Each patient who starts ART will be given a unique treatment unit ARV Registration Number. Each facility has a code for ARV (e.g., MCH for Mchinji District Hospital), and patients are given a unique number. This number is increased sequentially. For example, the first patient in a facility is given the number "01". The thousandth patient is given the number "1000". This number will be stamped on the patient master card and the patient identity card, and put into the ARV Register.

The system of patient registration is as follows:

ARV Patient Master Cards:

Each patient has a patient master card: for new patients and for follow-up patients. Cards for new patients (**Annex 4**) should have all registration data entered at the time when the patient starts ART. This includes:- ARV registration number, name, address, age, sex, weight, height, whether the patient is a "transfer in" from another treatment unit, name of identifiable guardian, reason for starting ART, date of starting first line ART, dose of d4T/3TC/NVP, initial outcome status and concomitant use of cotrimoxazole preventive therapy. It is important to ask the patient if there has been previous exposure to ARV drugs.

The address is very important for follow-up purposes. The address wherever possible should be a physical address and should include a phone number. At the end of the address row, there is a yes/no box to be ticked where the patient agrees to be followed-up in the community in the event of a no-show at the clinic.

Patient master cards will be placed in a cellophane sleeve and these will be kept sequentially in hard back lever arch files. It is vital that these master cards are kept in an ordered sequence in arch back files. It is recommended that 50 master cards in their polythene sleeves be kept in one arch back file. All follow-up data are also recorded in the master card. At the end of the first year, a follow-up master card (also see **Annex 4**) is given to the patient and filed away in the same polythene sleeve as the first master card.

ARV Patient Register:

Each facility has its own unique ARV patient register. The Register has a left hand page and a right hand page (**Annex 5**). The left hand page consists of case registration data, and this includes:- ARV number, year of registration, quarter, date of registration, name, age, sex, address, reason for ART, date of starting ART, name of guardian and treatment unit. The right hand page consists of patient outcomes (see below) and also at the end a column for the patient's occupation and remarks. At the time of registration, the left hand page and right hand page is completed, with patients being registered as "Alive" and on "Start". (See below).

Patient Identity Cards:

Patient identity cards (**Annex 6**) will be smaller and will contain the same basic information as the patient master card. This will include:- ARV registration number, name, address, age, sex, weight, whether the patient is a "transfer in" from another treatment unit, name of identifiable guardian, the reason for starting ARV therapy, the date of starting first line ART, the dose of d4T/3TC/NVP, the date of starting second line ART and the reason. Patients will be given their own ARV identity cards, which serve as a reference for all follow-up visits and if and when the patient becomes ill and is admitted to another facility for treatment.

Patient stamps in Health Passports:

An alternative identity reference is a stamp placed in the health passport. Special stamps are provided in each facility, which exactly mirror the patient identity card. The relevant information is written into the stamp in the passport.

MONITORING AND RECORDING TREATMENT RESPONSE

Patient visits:

Patients will be seen two weeks after starting ART, and then 4-weekly.
After 6 months, if stable and adherent and if they have attended another formal group counselling session, review visits can be increased to once every two months

At monthly visits, patients will:

- Have their weight recorded and in children the height as well
- Be asked about their general health
- Be asked about whether they are ambulant or in bed
- Be asked about whether they are working
- Be asked about side effects and symptoms (see Table below)
- Have their returned pill bottles inspected to count the remaining drugs
- Collect another 30 day supply of drugs or have ARV therapy stopped
- Be reminded about the importance of strict adherence to therapy
- Be asked about CPT

At these monthly visits, if the patient is well then there is no need to see a clinician. However, it is recommended that all adults, regardless of symptoms, see a clinician once every three months if attending monthly and once every four months if attending 2-monthly. Children will always see a clinician at least once every three months.

Table: Check List of Symptoms for patient attending the Clinic

Did you experience any new or worsening symptoms since your last visit such as:-		
Fever	YES	NO
Abdominal Pain	YES	NO
Vomiting	YES	NO
Diarrhoea	YES	NO
Weight loss	YES	NO
Rash	YES	NO
Pain or numbness in your legs	YES	NO
Cough	YES	NO
Yellow eyes	YES	NO
Any unwanted changes in body shape	YES	NO
Any other new symptoms	YES	NO
If any of the symptoms are recorded as YES, then the patient must be seen by a clinician and be assessed *If all symptoms are recorded as NO then the patient can be dispensed a bottle of ARV drugs*		

The information about weight and the answers to questions will be recorded in the patient master cards (**Annex 4**). In order to avoid "ghost patients", patients themselves or their identifiable guardians will collect their own supply of drugs. Guardians are permitted to collect drugs on behalf of a patient for a maximum of two months: after this the patient must be seen at the clinic and must collect his/her own supply of drugs. Thus, on two monthly follow-up visits it is expected that a guardian can only collect drugs once and the next visit the patient must attend.

Definition of Standardised monthly outcomes:

Standardised outcomes will be monitored monthly. The Tables below show and explain the standardised outcomes.

Table: Outcome status:-

Alive and on ART (A) [note 1]	Patient who is alive, on ART at the facility where he/she is registered, and has collected his/her own 30-day supply of drugs
Dead (D)	Patient who has died for any reason while on ARV therapy
Defaulted (DF) [note 2]	Patient who is not seen at all during a period of 3 months
Stopped (Stop) [note 3]	Patient who has stopped treatment completely either because of side effects or other reasons
Transfer-out (TO) [note 4]	Patient who has transferred out permanently to another treatment unit

Note 1:

A patient who is alive is further categorised according to the type of ARV treatment regimen he/she is taking.

Start (Start): i.e., the patient is on the first line regimen

Substituted (Sbs): i.e., the patient experienced side effects from the first line regimen and has changed to an alternative first line ARV regimen

Switch (Switch): i.e., the patient has switched to the second line regimen because of treatment failure. The patient must have been on first line ART for 6 months or more, and must have been adhering to therapy, before he/she can be recorded as "Failed". Specialist opinion must always be sought before classifying a patient as “Failure”. A patient may be deemed to have failed ART in the following situations:-

a) Where no CD4 count is possible, the development of a new WHO Clinical Stage 4 feature

b) Where CD4 count is possible, a CD4 count < 50% of the peak value or less than the pre-treatment value obtained before ART was started provided there is no concomitant infection to explain the decrease. Appropriate

low values (e.g., CD4%) apply to children. These low CD4 counts must be confirmed one month later. The first CD4 count should, where facilities exist, be carried out 6 months after starting ART and every 6 months thereafter.

Note 2:

A patient who has not come for review for 3 months is classified as a defaulter, the date of default being 3 months from the time that the patient was last seen (see below). Every attempt must be made to try and find such patients before they become defaulters.

Note 3:

A patient may stop or be withdrawn from treatment because of a) unacceptable side effects despite substituting an alternative first line regimen, b) poor adherence with medication, c) other reasons such as not wishing to continue any longer on ART. Patients are to be recorded as "STOP" and the reasons for stopping or withdrawal are to be indicated in the patient master card

Note 4:

If a patient transfers permanently out of a district to another ARV treatment facility, this is recorded in the patient master card. The patient takes that master card to the new district, where it is indicated that he/she is a transfer-in. The patient is

given a new ARV registration number, and is placed in the cohort of the new district at the time that the patient registers in the new district. The ARV Programme realises that this patient is counted twice in terms of case finding.

Table: Ambulatory status:-

Ambulatory (Amb)	Able to walk to the treatment unit and walks around at home unaided or in the case of a child able to perform age-specific daytime activities
Bed (Bed)	Unable to walk to the treatment unit and spends most of the time in bed at home

Table: Work (or school) status:-

Yes (Yes)	Engaged in productive work, or in the case of children being at school. Productive work also applies to work which is not paid, i.e., being a housewife
No (No)	Not engaged in previous work or employment

Table: Side effects:-

Yes (Yes) : specify side effects Eg (Yes-PN) (Yes-HP) (Yes-SK) (Yes-LA) (Yes-LD) (Yes-AN)	Side effects stated by patient after questioning from health worker:- PN = peripheral neuropathy HP = jaundice, liver failure SK = cutaneous hypersensitivity LA= lactic acidosis LD=lipodystrophy AN = anaemia
No	No side effects stated by patient

Pills left in ARV container:-

Counting the pills remaining in the pill container only applies to adult patients and to patients on the standardised first line regimen. This task is too difficult to do in the case of children (except in the case of specialist paediatric clinics) and in the case of patients taking other treatment regimens.

The number of ARV pills, left in the container at the next visit, is counted: if the patient comes at 4 weeks, there should be 4 pills left. The number of pills in the container is indicated in the column box (ie, 4, 6, 8). If pill counts are 8 or less, this is equivalent of 95% drug adherence. If the patient comes early, the number of days on ART is calculated, multiplied by two and used to determine the number of tablets which should have been taken to be measured against pills left. If the container is not returned to clinic or the patient comes late to clinic, self-reporting of drug adherence will be carried out: in these circumstances the registration officer will decide whether or not there is 95% adherence. At every visit, health personnel must talk to the patient about the importance of drug adherence.

The patient may come to the clinic several days after the ARV drugs have finished, and the patient is then no longer on ART. In this case, there is also poor drug adherence. Clinic staff must estimate the number of pills that the patient has been without and indicate a MINUS number in the pill count column.

Managing the remaining pills in the container:

There are two ways of managing the remaining pills:-

a) In ARV clinics operating 4 or 5 days a week, the patient is asked to finish the remaining pills, a new container is given to the patient and the patient rescheduled to be seen 28+2 days later, if there were 4 tablets remaining. In this way, pill counts can be done.

b) In ARV clinics operating once or twice a week, the ARV pills remaining in the container are given back to the patient and he/she is asked to keep them at home. A new container is given to the patient, who is asked to take tablets from this container straight away. The remaining tablets at the next visit are treated in the same way until three months have elapsed. At this time, the patient will have 12 or so tablets remaining at home, and is asked to take these tablets plus the new tablets and to report at the clinic at 5 weeks instead of 4 weeks.

Recording standardised treatment outcomes:

Standardised outcomes and weight, with the date of the visit, are recorded in the appropriate row in the patient master card every time the patient reports to the clinic.

If the patient's outcome changes from "Alive and from "Start", this is recorded in the master card and also recorded in the ARV Register with the **date or month** of the change. If a patient is not seen for 3 months, he/she is recorded in the master card and the register as "default" with the date being three months since the last recorded visit.

Outcomes are dynamic. If a patient is recorded as "default" and subsequently the outcome is discovered to be "death" or "transferred out", then the outcome is changed to "death" or "transfer out" with the date or month of this outcome.

If the patient transfers out to another district and sometime in the future transfers back to the first district where he/she was registered, the patient maintains the original ARV number and the outcome is changed back from "transfer out" to "alive and on ART".

ADHERENCE TO ART

Patient adherence is a key factor in the success of ART. Every attempt should be made to ensure that the patient is 95% adherent to therapy. Adherence is measured monthly either by a) pill counts or b) by self-reporting.

Every patient is strongly encouraged to identify a guardian to remind, facilitate and support the patient in taking medications on a regular and timely basis. This form of treatment is termed "ERT", empowered reinforced therapy, or "GST", guardian supported therapy, which both may include directly observed treatment. At each clinic visit, the returned bottle must be counted for "pills", and a record made of the number of pills left in the container. If pills are not counted because the patient is late or has left the pill container behind, self–reporting of adherence is carried out. At the same time, the patient must be counselled about the importance of strict adherence to treatment. Treatment units should have an ample supply of IEC (Information, Education and Communication) patient leaflets, explaining the importance of good drug adherence and the dangers of poor adherence.

If, despite consultation with the patient and guardians, adherence to treatment is a problem or the patient is not compliant with monthly visits, the clinician can decide to withdraw the patient from therapy

Operational research should be conducted on a regular basis to determine drug adherence at community level.

Drug Adherence in Children

To promote drug adherence the following steps are recommended:

A. At HIV-ARV clinics ARV-drugs must always be available

B. Before initiating ART in children
    a. A person responsible for drug administration should be clearly identified
    b. Caregivers should be provided with a written medication-schedule emphasising the need for a modified dosing scheme during the first two weeks of therapy, together with the need to report promptly the appearance of rash or other new symptoms
    c. Caregivers should repeat the dosing schedule to make sure that the schedule is understood
    d. Caregivers should attend education sessions focusing on
        i. Understanding the medication rationale and schedule
        ii. Practising pill swallowing
        iii. Integrating medication intake into the regular routines of the child and family

iv. Providing information about opportunities to further improve adherence (e.g. patient support groups, positive reinforcement of good medication intake, reminder systems, etc.)

C. At each subsequent visit
   a. The dose of d4T/3TC/NVP should be reviewed and updated if necessary according to body weight
   b. The dose and schedule should be repeated by the caregiver
   c. Caregivers should be asked about the potential adverse effects of therapy
   d. Treatment adherence needs to be explored by a health care worker
   e. Medicine containers (with or without remaining tablets) must be brought to the clinic at every visit
   f. Caregivers should be instructed to return to clinic one week before it is anticipated that ARV drugs will run out

MONITORING AND MANAGING DRUG TOXICITY

Adverse effects of ARV therapy using the First Line Regimen

Clinical monitoring of side effects will be carried out during treatment. Routine laboratory monitoring is not required. Health personnel can monitor adverse effects in the following two ways. First, they can teach patients how to recognise symptoms of common adverse effects and to report if they develop such symptoms. Second, they can specifically ask about symptoms when patients report to collect drugs.

Side effects can be minor or major:

Minor side effects include headaches, nausea, abdominal pain, diarrhoea and difficult in sleeping at night. These should be managed symptomatically.

Major side effects are divided into immediate and long term.

Immediate side effects include peripheral neuropathy, hepatitis, pancreatitis and cutaneous hypersensitivity. *Long-term side effects* include lactic acidosis, lipodystrophy syndrome and also peripheral neuropathy.

Management of major side effects is discussed below.

Table: Major side effects with d4T/3TC/NVP

Immediate Side Effects
Peripheral Neuropathy
Hepatitis
Pancreatitis
Cutaneous hypersenstivity
Long Term Side Effects
Peripheral Neuropathy
Lactic acidosis
Lipodystrophy syndrome

Management of peripheral neuropathy

This is due to the stavudine (d4T) component.

Peripheral neuropathy should be diagnosed if the patient complains of pain, paraesthesiae, numbness or weakness of the lower limbs. The usual presentation is gradual worsening over several months and is predominately sensory in nature.

Risk factors for peripheral neuropathy should be minimised. For example, TB patients on isoniazid should be given pyridoxine 10 mg (or 12.5mg, depending on the formulation available) daily before starting ART. Patients should be advised not to take alcohol.

The following are recommended steps in the management of peripheral neuropathy:-

- First, treat the patient with multi-vitamins and amitryptiline 25 mg in the evening, increasing to 50mg in the evening if no response after 4 weeks
- If this combination is unsuccessful, then an anti-inflammatory drug such as indomethacin 50 – 75 mg nocte or ibuprofen 400 mg three times a day should be added to the symptomatic treatment regimen
- If symptomatic treatment is unsuccessful, then the dose of d4T/3TC/NVP should be reduced from d4T/3TC/NVP-40 to d4T/3TC/NVP-30 if the patient is on the higher dose
- If peripheral neuropathy continues to be severe and progressing, the ARV regimen may have to be stopped and replaced with an alternative first line regimen: Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP). The dose for adults is one tablet of AZT+3TC twice a day plus one tablet of NVP twice a day (ie, four tablets a day). The dose for children is shown in **Annex 3**
- If the Haemoglobin is less than 8g/dl at the time of substitution, consult with a specialist before commencing therapy because AZT is not recommended

[severe, rapidly progressive neuropathy with weakness or upper limb involvement should prompt a suspicion of lactic acidosis – see below]

Management of pancreatitis

This is usually due to the stavudine or, more rarely, the lamivudine component.

Pancreatitis should be suspected if the patient develops severe upper abdominal pain, nausea and vomiting. Confirmation of the diagnosis is by finding a raised serum or urine amylase (or lipase), abnormal abdominal ultrasound and abnormal abdominal CT scan. In the absence of these investigations the diagnosis must be made clinically.

A diagnosis of pancreatitis requires that the d4T/3TC/NVP regimen be **stopped and this must not be re-introduced.** Once the pancreatitis has resolved, treatment is changed to: Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP).
The dose for adults is one tablet of AZT+3TC twice a day plus one tablet of NVP twice a day (ie, four tablets a day). The dose for children is shown in **Annex 3.**
If the Haemoglobin is < 8g/dl at the time of substitution, consult with a specialist before starting therapy because AZT is not recommended.

Management of hepatitis

This is due to the nevirapine component.

Hepatitis should be diagnosed if the patient is jaundiced, or suspected if the patient develops anorexia and vomiting particularly if the patient becomes confused as well.
In the case of jaundice or high suspicion of hepatitis with impending liver failure, d4T/3TC/NVP should be **stopped**. If possible liver function tests should be performed to determine the degree of abnormality of the liver enzymes. If the transaminases are higher than 5 times the upper limit of normal, this is an indication to stop ART.

ART must be stopped and d4T/3TC/NVP should **not** be restarted. Another ART regimen needs to be given once the hepatitis has resolved. This substitution is complicated by the fact that nevirapine has a long half life and the triple therapy drug should not be stopped completely at once, otherwise NVP drug resistance may be allowed to occur. The following steps are therefore recommended:

- Stop d4T/3TC/NVP and immediately
- Start d4T and 3TC, one tablet twice a day, and continue for one week, then
- Stop d4T and 3TC, and wait until hepatitis has settled – in general wait for 4 weeks after the jaundice has settled, then
- Start stavudine (d4T) + lamivudine (3TC) + efavirenz (EFV). The dose for adults is d4T+3TC one tablet twice a day (from the 60-tablet bottles) and EFV one tablet daily. The dose for children is shown in **Annex 3.**

Management of cutaneous hypersensitivity

This is due to the nevirapine component.

In the first two weeks: If a rash occurs in the first two weeks, then the patient must be closely observed either in or out of hospital. There should be no escalation of the dose of nevirapine, which remains at 200 mg once a day. If the rash improves or remains stable, then the dose of nevirapine can be increased to 200 mg twice a day, again being carried out under careful observation.

After the first two weeks: Any new skin manifestation requires that the patient be assessed at hospital ART clinic. If itching occurs then d4T/3TC/NVP should be continued and an antihistamine added, such as chlorpheniramine 4mg three times a day. If a rash develops in addition to itching, the patient should be carefully assessed. Other causes for a rash should be ruled out, eg scabies, CTX. If the rash becomes worse, and if there is mucosal membrane involvement, the ART must be stopped.

If the skin reaction is severe and accompanied by any of the following, the patient must be admitted to hospital:

a) exfoliative dermatitis or toxic epidermal necrolysis
b) mucous membrane involvement
c) hypotension

The patient should be cared for in a side ward. The patient may need intravenous fluids and antibiotics to cover secondary infections, which almost invariably arise in these circumstances. Good nursing care is essential: blisters must not be opened; clean bedding must be provided daily, if possible, from theatre. Many physicians give steroid treatment, although there is no firm evidence that this helps. A typical dose schedule consists of 60 mg daily of oral prednisolone for 1 –2 weeks. Initially, if a patient is unable to swallow, the patient can be given intravenous hydrocortisone 100-200 mg daily (instead of oral prednisolone).

Once the rash has resolved, d4T/3TC/NVP should **not** be restarted. Another ART regimen needs to be given. This substitution is complicated by the fact that nevirapine has a long half life and the triple therapy drug should not be stopped completely at once, otherwise NVP drug resistance may be allowed to occur. The following steps are therefore recommended:

- Stop d4T/3TC/NVP and immediately
- Start d4T and 3TC, one tablet twice a day, and continue for one week, then
- Stop d4T and 3TC, and wait until the rash has settled, then
- Start stavudine (d4T) + lamivudine (3TC) + efavirenz (EFV).
  The dose for adults is d4T+3TC one tablet twice a day (from the 60-tablet bottles) and EFV one tablet daily. The dose for children is shown in **Annex 3.**

Long term side effects:

d4T/3TC/NVP may be associated with long term side effects, such as lactic acidosis and lipodystrophy syndrome. These effects do not usually occur until the patient has been on ART for at least 6 months.

Lactic acidosis:

This is a rare, but potentially fatal side effect with a 50% mortality rate. It is difficult to diagnose under resource-poor conditions. The pathogenesis is believed to be due to mitochondrial toxicity of NRTIs. Stavudine has the highest risk, zidovudine a lower risk and tenofovir the lowest risk.

Patients typically present with fatigue, nausea, vomiting, abdominal pain or distension, muscle pains, weight loss, palpitations and shortness of breath. There may also be an acute onset sensory or motor neuropathy with rapid ascending weakness. In particular, the triad of abdominal complaints, weight loss and severe neuropathy in a previously stable patient should make the clinician suspect lactic acidosis. The diagnosis should be considered if the above symptoms develop fairly rapidly over a few days to weeks in a previously stable patient, although weight loss may have occurred over a period of several months.

Confirmation of the diagnosis is by a low serum bicarbonate, elevated blood lactate and high creatine phosphokinase, all of which are difficult to measure in Malawi. If the diagnosis is suspected clinically, specialist or HIV Unit advice should be sought. The most important therapeutic intervention is to STOP the ART. Symptoms and signs can take several weeks to resolve.

Once the symptoms have resolved, the patient can be started on AZT+3TC +NVP, and must be carefully observed. If there are any recurrences of the same symptoms or signs, the ART must be stopped and specialist opinion sought. Specialists might consider restarting the patient on tenofovir (TDF) + NVP + Lopinavir/Ritonovir – but this is an unusual combination, and requires 2 additional doses of Lopinavir/Ritonavir.

The risk of lactic acidosis in increased in a) pregnancy, b) obesity, c) concomitant use of metformin, d) heavy alcohol consumption, and e) alcohol binge drinking.

Lipodystrophy syndrome or fat redistribution syndrome:

This is usually seen in patients taking protease inhibitors, although it can occur with any antiretroviral drug and particularly stavudine (d4T). Clinical features include central obesity and peripheral fat wasting of the face, limbs and buttocks. There is often associated hyperglycaemia and hyperlipidaemia. If the diagnosis is suspected, this should be discussed with a specialist. One

possible treatment option is to substitute AZT for d4T, and change the patient to AZT+3TC+NVP.

Adverse effects and their management of Alternative and Second Line Regimens

Antiretroviral drug	Side effect	Management
Zidovudine	Anaemia Myopathy Lactic acidosis	Stop and consider other management if HB drops below 8g/dl Stop and replace the drug Management as with NRTIs
Efavirenz	CNS effects eg, confusion Rash Hepatitis Teratogenicity	Take the drug last thing at night Management as with NVP Management as with NVP Avoid pregnancy
Tenofovir	Renal injury Osteoporosis (children esp)	Stop TDF Stop TDF
Lopinavir/ritonavir	Gastro-intestinal Teratogenicity Interaction with other drugs – rifampicin, oestrogen	Symptomatic Avoid in pregnancy Avoid drug-drug combinations

If patients develop severe toxicity to efavirenz, they may need to change to a protease inhibitor. If AZT or TDF have to be stopped, specialist opinion must be sought about alternative medications or alternative ways of managing the patient.

DRUG – DRUG INTERACTIONS

ARV drugs may interact with other medications. The table below shows the significant interactions.

Table: drug-drug interactions

ARV Drug	Contra-indicated	Use with great care/ specialist advice	Dose adjustment required (of either ARV, combined drug or both)
"Triomune"	ketoconazole, zidovudine	Oral anti-contraceptives	
Zidovudine	Stavudine	Ganciclovir	
Efavirenz	astemizole, terfenadine, midazolam, triazolam, cisapride, ergot alkoids, St. John's wort, voriconazole	simvastatin (and other statins), rifabutin, warfarin, claritromycin	phenobarbitone, fenytoin, carbamazepine, rifabutin, methadone, most protease inhibitors (including Kaletra)

Table: drug-drug interactions (continued)

ARV Drug	Contra-indicated	Use with great care/ specialist advice	Dose adjustment required (of either ARV, combined drug or both)
Tenofovir		didanosine	Didanosine
"Kaletra"	rifampicin, astemizole, terfenadine, fleceanide, propafenone, simvastatine, lovastatine, midazolam, triazolam, pimozide, cisapride, ergot alkoids, St. John's wort, rifapentine, phenytoin	rifabutin, clarithromycin, methadone, atorvastatine, pravastatine, ketoconazole, drugs for erectile dysfunction, carbamazepine, phenobarbitone, warfarine, atovaquone, oral anti-contraceptives (additional method)	rifabutin, clarithromycin, methadone, atorvastatine, ketoconazole, drugs for erectile dysfunction, carbamazepine, phenobarbitone, warfarine, atovaquone, nevirapine, efavirenz, most other protease inhibitors

MONITORING AND MANAGING IMMUNE RECONSTITUTION

In patients who are severely immunocompromised (for example, with a CD4 lymphocyte count < 50/mm^3), the initiation of ART may be associated in the first one to three months with an increase in the inflammatory response as a result of immune reconstitution.

There are two types of Immune Reconstitution Disease (IRD).

1. Infections which were latent before the start of ART and develop into clinical illness on ART; for example, TB or cryptococcal meningitis

2. Infections and diseases that were already diagnosed and even treated before the start of ART and which become clinically worse on ART: for example, TB and KS

The clinical illness resulting from immune reconstitution is termed a paradoxical response. The clinical spectrum of paradoxical responses includes fever, lymphadenopathy, lung and central nervous system involvement, depending on the infection or disease in question.

Paradoxical reactions should be managed according to the presenting illness, and may aspirin and anti-inflammatory drugs, antibiotics and even consideration of cortico-steroids. First line ART should be continued.

One special example of immune reconstitution is a patient developing overt tuberculosis soon after starting ART. In this situation, the first line ART with d4T/3TC/NVP can be continued and anti-TB treatment commenced. This advice is different from that recommended in the first edition.

COHORT ANALYSIS OF TREATMENT OUTCOME

Monitoring may be done manually and electronically.

Monitoring will be done every quarter. In the month following the end of one quarter, the monitoring forms will be completed. For example, for the quarter 1st January to 31st March, the monitoring forms will be completed in April.

For ARV treatment, there are two monitoring forms:-

1) Quarterly ARV Cohort Analysis Form. The updated quarterly information for the most recent quarterly cohort of patients started on ART will be entered into the form (**Annex 7**). The health care worker in charge of the ARV clinic treatment unit will be responsible for completion of this form. Details will be checked during supervisory visits.

2) Cumulative ARV Quarterly Analysis Form. This form is completed every quarter, and represents a cumulative analysis of case finding data and treatment outcome data on all patients ever started on ART (**Annex 7**). The health care worker in charge of the ARV clinic treatment unit will be responsible for completion of this form. Details will be checked during supervisory visits.

The HIV Unit and the ARV team at the facility will keep copies of the completed quarterly and cumulative cohort analyses. The ARV team will keep the originals in a special hard arch-back file.

Notes on completing the cohort analysis:

An example of a completed cumulative cohort analysis is provided in **Annex 8.**

Case finding data:

For the number of patients registered in the quarter and in the cumulative cohort,
Males and females must add up to the total number
Adults and children must add up to the total number
Occupation details must add up to the total number
Number with Stage 3 + Stage 4 + CD4 count must add up to the total number

In addition, the number of patients with PTB, EPTB and referred from PMTCT are put into the forms

The MOH also obtains data on the number of patients with Kaposi's Sarcoma treated with ART in the most recent quarterly cohort.

Treatment outcome data:

Outcomes are censored on the last day of the quarter in question. Thus, in the quarterly analysis form October to December and cumulative analysis up to December, the last day of census is 31st December. Also outcomes such as ambulatory, at work, side effects and pill counts are done for the last month of the quarter.

Notes on the calculations:

For the number of patients registered in the quarter and in the cumulative cohort,
the number alive on ART+ deaths + defaults + stops + transfer-outs must add up to the total number registered

For patients alive and on ART,
the number on Start + Substitute + Switch must add up to the number alive

For patients alive and on ART,
the number ambulatory, at work, and with side effects are recorded
the number with a pill count done and the number with pill count 8 or less is recorded

For patients who have died, the number dying in month 1, month 2, month 3 and month 4 and beyond is documented. These numbers must add up to the total number of patients who have died.

The quarterly cohort analysis provides data on the number of new patients started on ART in the previous quarter, and enables the facility and HIV Unit to check whether the units (low burden, medium burden, high burden) are meeting their targets. This helps with drug procurement. It also allows the unit and facility to see trends in the type of patients being enrolled to ART

The cumulative Analysis Form provides data on all patients ever started on ART, and enables the facility and HIV Unit to have regular up to date information on:-

- number of patients ever started on ARV drugs
- number of patients alive and currently taking ARV drugs
- number of patients currently taking drugs who have drug adherence rates > 95%
- number of patients who have died since starting ARV drugs
- number of patients who have defaulted since starting ARV drugs
- number of patients who have been substituted to an alternative first line regimen
- number of patients who have failed ARV drugs and been switched to a second line regimen, indicating problems with the first line ARV regimen
- number of patients on ART who are ambulant or in the case of children who are engaging in age-specific daily activities
- number of patients on ART who are engaged in productive work

This information is used for quarterly and annual reports. It allows the HIV Unit to work out drug orders for patients on ART from previous cohorts. It also enables the HIV Unit to assess the effectiveness of ART in Malawi, and allows problems to be identified and appropriate measures to overcome these problems to be found.

SURVEILLANCE FOR ARV DRUG RESISTANCE

Resistance testing is carried out, either by genotype testing or phenotype testing. Genotype testing looks for mutations on the reverse transcriptase or protease genes that impart partial or complete resistance to NRTIs or PIs. Phenotype testing looks at the concentration of ARV drugs necessary to inhibit a certain percentage of the HIV isolates. Both techniques require sophisticated technology and skilled staff, and are very expensive

In Malawi, it will not be possible to monitor for drug resistance on an individual level.
However, two surveillance systems are being set up at sentinel sites around the country.

First, there will be monitoring of patients on ART. The selected sites include Mzuzu Central Hospital, Lighthouse Clinic, Thyolo District Hospital and Queen Elizabeth Central Hospital. On an annual basis, patients who have never been exposed to ART and who are about to start treatment will have blood taken for viral load and genotype testing. 12 months later, the same patients will

have another sample of blood taken for viral load and viral genotype resistance testing in those with detectable virus. The data will provide information on a) the proportion of patients with complete viral suppression 12 months after the start of therapy and b) the pattern of genotype resistance patterns in those with detectable virus

Second, in young women presenting at antenatal clinics with a first pregnancy, blood will be taken for viral load and viral genotype patterns. The selected sites include Lilongwe Bottom Hospital and Chiradzulu District Hospital. The data will provide information on the resistance patterns of HIV circulating currently in persons in the Malawian population who have not been exposed to ART.

For both surveillance systems, the epidemiology unit of CHSU is the co-ordinating body. Blood samples will be sent to CHSU for onward transmission to USA for the genotype testing. Results will be fed back to the MOH and disseminated nationally.

SUPERVISION AND NATIONAL DATA COLLECTION

Supervision is currently co-ordinated by the HIV Unit, working with partners to provide supervision, mentorship, monitoring and evaluation every three months to all ART delivery sites in the country.

A structured form is used (**Annex 9**), in which qualitative data are collected on a) the use of ARV Registers and ARV patient master cards, ART clinic functions, b) ARV and specific OI drug stocks, c) quarterly and cumulative analysis, d) specific HIV-related diseases such as TB,. KS, cryptococcal meningitis and oesophageal candidiasis, e) use of CD4 machines and f) 6-month and 12-month survival analysis.

ANTIRETROVIRAL DRUG SUPPLY AND USE

All ARV drugs for use in Malawi have a WHO pre-qualification status. The regular supply of ARV drugs, their appropriate storage and use and the monitoring of drug security are three essential prerequisites for success of ARV treatment units.

Drug Procurement and distribution:

First line ART:
Each ART facility in Malawi is designated as a low burden (starting a maximum of 25 new patients per month), medium burden (starting a maximum of 50 new patients per month), high burden (starting a maximum of 150 new patients per month) or very high burden unit (starting a maximum of 250 new patients per month). This classification is based on size of facility, area of population served, HIV-prevalence rate in the population (if known) and TB case burden (as a proxy for AIDS cases).

The HIV Unit orders first line ARV drugs for each facility for 6 months. The drug orders are calculated for a) the number of new patients to start ART in the 6-month period, based on the category of the facility, b) the number of patients already placed on ART and alive and taking drugs from the facility and c) the drug stocks in the pharmacy. Drugs are ordered as "Starter Pack kits" and "Continuation Pack kits".

A starter pack kit contains antiretroviral drugs to start 75 new patients on treatment, and is based on a low burden unit starting 25 new patients every month for 3 months. A continuation pack kit contains antiretroviral drugs to maintain these 75 patients on treatment for 3 months. The composition of these kits is shown in the Table below.

Table: Starter pack kits and continuation pack kits

Starter pack kit	Continuation pack kit
Provides drugs for 75 new patients starting ART for 14 days	Provides drugs for 75 patients to continue on ART for 3 months, and receiving drug tins every 28 days
150 tins of ART:	**225 tins of ART**
60 tins of d4T-30mg/ 3TC (15 tablets) 15 tins of d4T-40mg/ 3TC (15 tablets)	180 tins of d4T-30mg/ 3TC/ NVP (60 tablets) 45 tins of d4T-40mg/ 3TC/ NVP (60 tablets)
60 tins of d4T-30mg/ 3TC/ NVP (15 tablets) 15 tins of d4T-40mg/ 3TC/ NVP (15 tablets)	

ARV drugs are provided as d4T-30mg or d4T-40mg, 3TC-150mg and NVP-200mg. The use of d4T-30mg or d4T-40mg depends on the patient's weight: those less than 60 Kg receive d4T-30mg and those 60 Kg and above receive d4T-40mg. Based on previous experience it was

estimated that 80% of patients would weigh less than 60Kg and 20% 60Kg or above.

In its first six-month period a low burden facility needs 2 starter pack kits (1 for each quarter) and 3 continuation pack kits (1 for the first three months and 2 for the next three months to cater for those placed on treatment in the first quarter and those coming on to treatment in the second quarter). A medium burden unit in its first six months needs 4 starter pack kits and 6 continuation pack kits, while a high burden unit needs 12 starter pack kits and 18 continuation pack kits.

Alternative first line ART and second line ART:
These drugs are currently supplied to central hospitals and to experienced district hospitals, such as Thyolo and Chiradzulu. Approximately, 5% of patients on ART need alternative first line treatment while 1% need second line treatment within one to two years of starting ART. This distributions may change as the ART programme matures.

Drug Security:

Once the drugs have arrived at the hospital (or in later years at the health centre) there has to be a robust system of ensuring that patient consumption matches drug usage (see Table). Otherwise, there may be leakage of ARV drugs out of the hospital.

Table: Drug security

Drug consumption by patients = drug usage from the treatment unit

Drug security is checked every quarter during the routine supervisory visits. Most ARV clinic facilities use an **ARV Drug Register** to record drugs given to patients and this is checked during supervisory visits.

Drug formulations needed for Malawi

The drug formulations used in Malawi are shown in the Table below.

Table: Drug formulations, with examples of trade names, for Malawi:

D4T/3TC/NVP (both -30 and -40 formulations, "Triomiune") – 15 and 60 tabs
D4T/3TC (both -30 and -40 formulations)- 15 and 60 tabs
AZT/3TC (dual combination "Duovir") – 60 tabs
EFV – 30 tabs
ABC – 60 tabs
ddI-EC (enteric coated) – 30 capsules
NVP – 60 tabs
Tenofovir (TDF, "Viread") – 30 tabs
Lopinavir/Ritonavir (LPV/r, "Kaletra") – 90 capsules / tablets

TRAINING IN USE OF ART

Background:

It is essential that staff who are to manage patients with ART are well trained. The core material for the modules will be the "ARV Treatment Guidelines" and "the Management of HIV-related diseases".

Training:

There will be two types of training:-

a) Pre-service training.
Medical students, paramedical students and nursing students will all undergo a modular training in use of ART and management of opportunistic infections. These modules have been developed and have been integrated into the curricula of the various training institutions.

b) In-service training.
All staff in the public sector who deliver ART must have undertaken the formal 5-day ART and HIV-related diseases training course and passed the formal examination. For those who are going to deliver ART, it is expected that they do a formal attachment at one of the experienced clinical centres or at their own facility once experience has been developed.

Certification in the use of ARV therapy:

A formal certificate, signed by the Secretary for Health, is given to every staff member who has completed the course and passed the examination. This certification is recognised with the Medical Council of Malawi and the Nurses and Midwives Council of Malawi. At the end of every training course, the names and addresses of those who have passed the examination are passed to the two regulatory bodies. In service ARV staff will receive refresher courses every year.

ART AND PRIVATE PRACTITIONERS

Private practitioners are a valuable part of the health delivery system in Malawi. The government sector is working with private practitioners to ensure that ARV drug regimens, systems of delivering ARV drugs, monitoring and evaluation are standardised throughout the country and are the same as in the public sector.

One of the pre-requisites of being able to prescribe subsidised ARV drugs is that the private health care worker should have a) undergone a formal training course in ART and b) be formally certified as competent in managing ART. This opportunity for training and certification is available for health care workers in the private sector in the same way as for the public sector. Training courses are done quarterly at the weekend for 2 days.

SUGGESTIONS FOR FURTHER READING

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ANNEX 1: TARGETS FOR ART SCALE UP

Strategy Indicator	Baseline (End 2005)	2006	2007	2008	2009	2010
Input Indicators:						
Up to date ART Manual Which is in circulation	Yes	Yes	Yes	Yes	Yes	Yes
Number of districts providing ART (cumulative)	28	30	30	30	30	30
Number of public health facilities providing ART (cum)	60	90	90	110	120	120
Number of private health facilities providing ART (cum)	30	40	50	60	70	80
Number of public HCW trained and accredited in ART (cum)	1000	1400	1800	2200	2600	3000
Number of private HCW trained and accredited in ART (cum)	200	300	400	450	500	550
Number of facilities with stock-outs of ARV drugs	0	0	0	0	0	0

Output Indicators:						
Number of new patients started on ART each year	20,000	35,000	40,000	45,000	45,000	45,000
Number of new children started on ART each year	1,000 (5%)	2,625 (7.5%)	4,000 (10%)	4,500 (10%)	4,500 (10%)	4,500 (10%)
Number of patients ever started on ART by end of year (cum)	35,000	70,000	110,000	155,000	200,000	245,000
Number of children ever started on ART by end of year (cum)	1,750 (5%)	4,375 (6.25%)	8,375 (7.6%)	12,875 (8.3%)	17,375 (8.7%)	21,875 (8.9%)
Number who are alive and on ART at end of each year (cum)	30,000	60,000	90,000	130,000	170,000	208,000
Proportion of those ever started who have died (cum)	8%	12%	12%	17%	17%	17%
Proportion of those ever started who are lost to follow-up (cum)	8%	10%	10%	10%	10%	10%
Proportion of patients alive who are ambulatory (cum	85%	85%	85%	85%	85%	85%
Proportion of patients alive who are at work (cum)	80%	80%	80%	80%	80%	80%
Proportion of patients alive with 95% drug adherence (cum)	90%	90%	90%	90%	90%	90%

ANNEX 2: DOSAGE GUIDELINES FOR FIRST LINE ART IN CHILDREN IN MALAWI[1],[2],[3]

Lamivir S 30 (LS30): 30mgd4T/150mg3TC ;

Triomune 30 (T30): 30mg d4T/150mg 3TC/200mg NVP

Target dosages: **d4T : 2mg/kg/d** **3TC : 8mg/kg/d**

NVP: 7mg/kg/d OD (lead in), 14mg/kg/d (up to 8yrs), 8mg/kg/d (above 8yrs)

Starter Phase (1st 2 weeks)

Weight (kg)	Dose LS30 am	Dose T30 pm	D4T daily dose mg/d	Range d4T mg/kg/d	3TC daily dose mg/d	Range 3TC mg/kg/d	NVP daily dose mg/d	Range NVPmg/kg/d	Number of tablets LS30/ T30 for 15 days
<5	-	¼	7,5	1,5-	37,5	7,5-	50	10-	-/4
5 - <8	¼	¼	15,0	1,9 – 3	75	9,4 -15	50	6,25 – 10	4/4
8 - <12	½	¼	22,5	1,9 – 2,8	112,5	9,4 - 14,1	50	4,2 – 6,25	8/4
12 - <14	½	½	30,0	2,1- 2,5	150,0	10,7 - 12,5	100	7,1 – 8,3	8/8

[1] Pre-packing and Pill count: Starter- and continuation packs can be pre-pack using the number of tablets given in the tables. Adherence can be assessed by comparing remaining tablets in the bottle with number in last column in the table (continuation phase). Appointments can be adjusted according to remaining tablets in the bottle and the new supply.

[2] Cutting tablets: Since T30 tablets are not scored, the use of commercial tablet cutters, provided by the HIV unit, is recommended.

[3] Pre-cutting tablets: Particularly quartered T30 tablets are not firm, and make break down over time. Therefore, pre-cutting of tablets is discouraged.

ANNEX 2: DOSAGE GUIDELINES FOR FIRST LINE ART IN CHILDREN IN MALAWI

Weight (kg)	Dose LS30 am	Dose T30 pm	d4T daily dose mg/d	Range d4T mg/kg/d	3TC daily dose mg/d	Range 3TC mg/kg/d	NVP daily dose mg/d	Range NVPmg/kg/d	Number of tablets LS30/ T30 for 15 days
14 - <19	¾	½	37,5	2 – 2,7	187,5	9,9 - 13,4	100	5,3 – 7,1	12/8
19 - <26	¾	¾	45,5	1,8 – 2,4	225,0	8,7 - 11,8	150	5,8 – 7,9	12/12
26 - <30	1	¾	52,5	1,8 – 2	262,5	8,8 - 10,1	150	5 – 5,8	15/12
≥30	1	1	60,0	-2,0	300,0	-10,0	200	- 6,7	15/15

ANNEX 2: Continuation phase

Weight (kg)	Dose LS30 am	Dose T30 pm	d4T daily dose mg/d	Range d4T mg/kg/d	3TC daily dose mg/d	Range 3TC mg/kg/d	NVP daily dose mg/d	Range NVPmg/kg/d	Number of tablets LS30/ T30 for 15 days
<5	-	¼	7,5	1,5-	37,5	7,5-	50	10-	-/4
5 - <8	¼	¼	15,0	1,9 – 3	75	9,4 -15	50	6,25 – 10	4/4
8 - <12	½	¼	22,5	1,9 – 2,8	112,5	9,4 - 14,1	50	4,2 – 6,25	8/4
12 - <14	½	½	30,0	2,1- 2,5	150,0	10,7 - 12,5	100	7,1 – 8,3	8/8
14 - <19	¾	½	37,5	2 - 2,7	187,5	9,9 - 13,4	100	5,3 – 7,1	12/8
19 - <26	¾	¾	45,5	1,8 – 2,4	225,0	8,7 - 11,8	150	5,8 – 7,9	12/12
26 - <30	1	¾	52,5	1,8 – 2	262,5	8,8 - 10,1	150	5 – 5,8	15/12
≥30	1	1	60,0	-2,0	300,0	-10,0	200	- 6,7	15/15

ANNEX 3: DOSAGE GUIDELINES FOR ALTERNATIVE FIRST LINE ART AND SECOND LINE ART FOR CHILDREN

Alternative 1st line for children for NVP related cutaneous reactions and hepatotoxicity

Target dose EFV: 10- <15kg- 200mg OD; 15-<20kg- 250mg OD; 20-<25Kg-300mg OD; 25-<33kg-350mg OD; 33-<40kg: 400mg OD; Maximum daily dose: 600mgOD

Weight	**Dose**			**d4T**		**3TC**		**EFV**[4],[5]	
(kg)	**d4T30mg /3TC (LS30)**	**d4T30mg/ 3TC (LS30)**	**EFV 600mg**	d4T daily dose mg/d	Range d4T mg/kg/d	3TC daily dose mg/d	Range 3TC mg/kg/d	EFV daily dose mg/kg	Range EFV mg/kg/d
	Am	Pm	Pm						
10- <12	½	¼	1/3	22,5	1,9 – 2,8	112,5	9,4 - 14,1	200	16,7- 20,0
12 - <14	½	½	1/3	30	2,1- 2,5	150	10,7 - 12,5	200	14,3- 16,7
14 - <19	¾	½	1/3	37,5	2 - 2,7	187,5	9,9 - 13,4	200	10,5- 14,3
19 - <26	¾	¾	1/2	45,5	1,8 – 2,4	225	8,7 - 11,8	300	11,5- 15,8
26 - <30	1	¾	2/3	52,5	1,8 – 2	262,5	8,8 - 10,1	400	13,3- 15,4
30- < 40	1	1	2/3	60	1,5 -2	300	7,5 -10	400	10- 13,3
≥40	1	1	1	60	-1,5	300	-7,5	600	-15

[4] EFV is not licensed for children <3 years of age and <10kg
[5] there are no pharmokokinetic data on the use of split EFV 600mg tablets; use of tablet cutters is encouraged

ANNEX 3: Alternative 1st line for children for peripheral neuropathy

Target dosage for AZT: 360-480 mg/m^2/day (= 180-240 mg/m^2 12 hourly)

Weight	Dose				AZT[6]			3TC		NVP	
(kg)	AZT/3TC[7]	AZT/3TC	NVP	NVP	daily dose (mg)	BSA estimated from weight (m^2)	Approximate Range (mg/m^2/d)	daily dose (mg)	Range (mg/kg/d)	daily dose (mg)	Range (mg/kg/d)
	am	pm	am	pm							
8-< 10	¼	¼	½	¼	150	0,40- < 0,47	320 – 375	75	4,7 – 9,4	150	15 - 18,7
10-<15	½	¼	½	½	225	0,47 -<0,64	350 – 480	112,5	6,2 – 9,4	200	13,3 - 20
15-<20	½	½	¾	½	300	0,64 -<0,80	375 – 470	150	6,2 – 9,4	250	12,5 - 16,7
20-<25	¾	½	¾	¾	375	0,80 -<0,93	403 – 470	187,5	6,8 – 8,3	300	12,0- 15,0
25-<30	¾	¾	1	¾	450	0,9 -<1,1	410 – 483	225	6,7 – 8,5	350	11,7- 14,0
30-<35	1	¾	1	1	525	1,1 -<1,2	435 – 475	262,5	6,9 – 8,2	400	11,4- 13,3
> 35	1	1	1	1	600	> 1,2	– 500	300	– 7,9	400	-11,4

[6] BSA was calculated from the bwt in kg (W) using the following formula: BSA (m^2)= 4W+7 devided by (90+W)
[7] the dosage guidelines for AZT/3TC (Duovir) can be also used for PEP in children. AZT should not be started if Haemoglobin < 8g/dl

ANNEX 3: Second Line Treatment for children

Target doses:

ABC: 16mg/kg/d, ideally 8mg/kg BD
ddI enteric capsules: 3 months- <13 years: 90-120mg/sqm BD or 240mg/sqm OD, maximal 200mg BD or 400mg OD
Lopinavir/r (Kaletra):

- 225mg/sqm BD **or** weight band based: 7-<15kg 12mg/kg BD
- 15-<40kg 10mg/kg BD
- >40kg 400mg BD

Weight	**Dose**						**ABC**[8][9]		**ddI**			**LPV/r**	
(kg)	**ABC 300mg tablets**		**ddI-EC 125mg, ddI-EC 200mg capsules**		**LPV/r 133mg/33mg capsules**		daily dose (mg)	Range (mg/kg/d)	daily dose (mg)	BSA estimated from weight (m^2)	Approximate Range ($mg/m^2/d$)	daily dose LPV/r (mg)	Approx Range ($mg/m^2/d$)
	am	pm	Am	pm	am	Pm							
10-< 12	¼	¼	125mg	—	1	1	150	12,5-15	125	0,47-0,54	231-266	266	493-566
12-<15	½	¼	125mg	—	1	1	225	15- 18,7	125	0,54-0,64	195-231	266	416-493
15-<20	½	½	200mg	—	2	1	300	15- 20	200	0,64-0,80	250-312	400	500-625
20-<25	¾	½	200mg	—	2	1	375	15-18,7	200	0,80-0,93	215-250	400	430-500

[8] ABC can cause a hypersensitivity reaction, which can be serious and live-threatening if ABC is re-challenged
[9] There are no PK data on split ABC tablets

25-<30	¾	¾	250mg	—	2	2	450	15-18	250	0,93-1,06	236-269	532	502-572
30-<35	1	¾	250mg	—	3	2	525	15-17,5	250	1,06-1,18	212-236	665	563-627
35- <45	1	1	250mg	—	3	3	600	13,3-17,1	250	1,18-1,39	180-212	800	575-678
45-<50	1	1	325mg	—	3	3	600	12-13,3	325	1,39-1,48	219-233	800	540-575
50-<60	1	1	400mg	—	3	3	600	10,0- 12,0	400	1,48-1,63	245-270	800	491-540

ANNEX 4: NEW PATIENT MASTER CARD FOR ARV [front]: ARV Number___ Year_____

Name_____ Age ____ Sex____ Initial Wt (Kg)_____ Initial Ht (cm)_____ Transfer-In (Y/N)_____

Address (physical address and phone)_____ Follow-up agreement (Y/N)_____

Name of identifiable guardian_____ Date and place of positive HIV test_____

Date of starting 1st line ARV regimen _____ Reason for ARV: Stage _____; PTB_____ EPTB____; KS_____; PMTCT____

Date of starting alternative 1st line ARV regimen (specify) _____ Date of starting 2nd line ARV regimen (specify)_____

Month	Date	Wt Kg	Ht cm	Outcome status					Of those alive			Ambulatory		Work/school		Side effects		No. Pills in Bottle	ARV Given		CPT	Other
				A	D	DF	Stop	TO	Start	Sbs	Switch	Amb	Bed	Yes	No	Y	N		P	G		
Jan																						
Feb																						
Mar																						
Apr																						
May																						
Jun																						
Jul																						
Aug																						
Sep																						
Oct																						
Nov																						
Dec																						

ANNEX 4: NEW PATIENT MASTER CARD FOR ARV [back]: Clinical Record Form

Indicate in the columns below what disease(s) the patients has by placing a ring around the bullet point next to the disease or clinical problem

WHO Clinical Stage I	WHO Clinical Stage II	WHO Clinical Stage III	WHO Clinical Stage IV
For adults and children • Asymptomatic • Persistent Generalised lymphadenopathy	For adults • Unintentional weight loss< 10% of body weight in the absence of concurrent illness • Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) • Herpes zoster • Recurrent upper respiratory tract infections (ie, bacterial sinusitis) For children • Unexplained persistent hepatomegaly and	For adults and children ▪ Oral candidiasis ▪ Oral hairy leukoplakia • Unintentional weight loss > 10% of body weight in the absence of concurrent illness • Chronic diarrhoea > 1 month • Prolonged fever (intermittent or constant) > 1 month • Active Pulmonary Tuberculosis • PTB within the past 2 years • Severe bacterial infections (eg pneumonia, pyomyositis, sepsis) • Acute ulcerative mouth infections • Unexplained anaemia,	For adults and children • HIV wasting syndrome (weight loss > 10% of body weight and either chronic fever or diarrhoea in the absence of concurrent illness) • Pneumocystis carinii pneumonia • Toxoplasmosis of the brain • Cryptosporidiosis or Isosporiasis • Recurrent severe presumed pneumonia • Cryptococcosis, extrapulmonary • Cytomegalovirus of an organ other than liver, spleen or lymph node • Herpes simplex infection, mucocutaneous for > 1 month or visceral • Progressive multifocal leucoencephalopathy • Any disseminated endemic mycosis • Candidiasis of oesophagus /trachea / bronchus

	splenomegaly • Papular itchy skin eruptions • Extensive wart virus infection • Extensive molluscum contagiosum • Recurrent oral ulcerations • Unexplained persistent parotid gland enlargement • Lineal gingival erythema • Herpes zoster • Recurrent or chronic respiratory tract infections (sinusitis, otorrhoea, tonsillitis, otitis media) • Fungal nail infections	neutropenia or thrombocytopenia <u>Additional for children</u> • Moderate unexplained malnutrition • TB lymphadenopathy • Severe recurrent bacterial pneumonia • Symptomatic lymphoid interstitial pneumonia • Chronic HIV lung disease, including bronchiectasis • HIV-associated cardiomyopathy • HIV-associated nephropathy	• Atypical mycobacteriosis, disseminated or lung • Recurrent bacteraemia or sepsis with NTS • Extrapulmonary tuberculosis (EPTB) • Lymphoma (cerebral or B-cell Non Hodgkin) • Kaposi's sarcoma • HIV encephalopathy • Other (Cancer cervix, visceral leishmaniasis) <u>Additional for children</u> • Unexplained severe wasting, stunting or malnutrition not responding to treatment • Recurrent severe presumed bacterial infections (eg empyema, sepsis, meningitis, bone or joint) • EPTB but excluding TB lymphadenopathy

ANNEX 4: FOLLOW UP PATIENT MASTER CARD FOR ARV [front and back are similar]:

Name_____ **ARV Number**_____

Year_____:

Month	Date	Wt Kg	Ht cm	Outcome status					Of those alive			Ambulatory		Work/school		Side effects		No. Pills in Bottle	ARV Given		CPT
				A	D	DF	Stop	TO	Start	Sbs	Switch	Amb	Bed	Yes	No	Y	N		P	G	
Jan																					
Feb																					
Mar																					
Apr																					
May																					
Jun																					
Jul																					
Aug																					
Sep																					
Oct																					
Nov																					
Dec																					

This box is repeated on the same page.

Thus, each page serves the patient for 2 years

ANNEX 5: PATIENT ARV REGISTER [left hand page]

ARV Registration Number	Year	Quarter	Date of registration	Name	Sex	Age	Address	Date first started ARV drugs	Reason for starting ARV drugs	Name / address of Guardian	ARV Treatment Unit

Reason for starting ARV Drugs: Stage III, Stage IV, CD4 count < 250/mm^3, Stage II with TLC < 1200/mm^3
Also indicate under Reasons for ART – PTB, EPTB, KS and Transfer In (TI
Quarters: 1 = January to March: 2 = April to June: 3 = July to September: 4 = October - December

ANNEX 5: PATIENT ARV REGISTER [right hand page]

Outcome (provide date when change from alive)					Of those alive (provide date when change from start)			Ambulant		At work or (in children) at school		Remarks (including occupation, BMI, ITN)
Alive	Dead	Default	Stop	Transfer	Start	Substitute	Switch	Yes	No	Yes	No	

Alive - alive and on ARV drugs: Dead - whatever the cause: Default - not seen in three months: Stop - stopped treatment due to side effects/other:
Transfer - transfer-out to another ARV treatment unit

Start - on first line regimen: Substitute - changed to alternative first line regimen: Switch - changed to second line regimen
Ambulant - yes/no: At work or school - at previous or new employment for adults

ANNEX 6: ARV PATIENT IDENTITY CARD

ARV IDENTITY CARD

Current Treatment Unit_____

Name of Patient_____

Unique ARV Number_____ _____

Age__ Sex__ Weight (Kg)____ Height (cm)____

Name of Guardian_____

Start 1st line ARV therapy (date) _____

Reason for ARV therapy_____

Start alternative 1st line ARV therapy (date)_____

Start 2nd line ARV therapy (date)_____

ANNEX 7: COHORT ANALYSIS FORM [same data for quarterly and cumulative]

Case Data:

Number of patients started on ARV therapy in the last quarter_____

Number of men started_____ Number of women started_____

Number of adults (15 and above)_____ Number of children (14 and below)____

Occupation: Housewives_____ Farmers _____ Soldiers/Police_____ Teachers____
Business_____ Health care workers____ Students/school_____ Other_____

Reasons for starting: Stage III_____ Stage IV_____ CD4 count_____

Indicate number started because of TB_____ (PTB_____ EPTB_____ Not known__)
Indicate number of pregnant women started on ART from PMTCT_____

Outcome Data:

Number alive and on ART_____

(Number alive and on first line regimen (Start)_____)
(Number alive and on alternative first line regimen (Substituted)_____)
(Number alive and on second line regimen (Switch)_____)

Number who have died_____

Number who have defaulted *[no defaults in a quarterly analysis]*_____

Number who have stopped_____

Number who have transferred out_____

Of the number alive and on ARV therapy:

Number who are ambulatory_____
Number who are at work_____
Number who have side effects_____
Number adults on 1st line regimen with pill count done in last month of quarter_____
Number with the pill count in the last month of the quarter at 8 or less_____

Of those who died: Number in month 1_____ Number in month 2____

Number in Month 3___ Number after month 3_____

ANNEX 8: CUMULATIVE ANALYSIS - AN EXAMPLE

Case Data:

Total number of patients ever started on ARV therapy 200

Number of men started 50 Number of women started 150

Number of adults (15 and above) 180 Number of children (14 and below) 20

Occupation: Housewives 40 Farmers 50 Soldiers/Police 2 Teachers 10
Business 30 Health care workers 3 Students/school 10 Other 55

Reasons for starting: Stage III 140 Stage IV 50 CD4 count 10

Indicate number started because of TB 35 (PTB 30 EPTB 5 Not known 0)
Indicate number of pregnant women started on ART from PMTCT 5

Outcome Data:

Number alive and on ART 140

(Number alive and on first line regimen (Start) 130
(Number alive and on alternative first line regimen (Substituted) 10
(Number alive and on second line regimen (Switch) 0

Number who have died 30

Number who have defaulted 20

Number who have stopped 5

Number who have transferred out 5

Of the total number alive and on ARV therapy (140)

Number who are ambulatory 135
Number who are at work 130
Number who have side effects 25
Number adults on 1st line regimen with pill count done in last month of quarter 100
Number with the pill count in the last month of the quarter at 8 or less 90

Of those who died: Number in month 1 (15) Number in month 2 (5)

Number in Month 3 (5) Number after month 3 (5)

ANNEX 9: ARV SUPERVISION FORM

Hospital_____ **Date**_____

Year_____ **Quarter evaluated**_____

ARV Clinic (orderly and tidy)_____
ARV Filing system in place_____

ARV Register:

Registration numbers are correct and match the master card numbers_____

Transfer-in patients are registered with the next site registration number_____

Patient registration is a continuous process and not one month per page_____

All columns are filled in (age, sex, reason for ART, ambulatory, work)_____

Transfer-in patients recorded under "Reason for ART"_____

Dates of outcomes are properly recorded under outcome columns_____

Patients' occupation is recorded in "Remarks"_____

If patient is pregnant and referred from PMTCT this is indicated in "Remarks"___

TB is indicated under "Reason for ART" – also PTB and EPTB_____

All ARV outcomes are updated every three months_____

ARV Register is up to date and in line with Master Cards_____

ARV Master Cards:

The case finding data is properly completed on each Patient Master Card_____

TB indicated "PTB or EPTB" under reason for ART next to Stage_____

The 2-week visit after the start of ART is written at the bottom of the card_____

Regular record of Weight done at every visit_____

Each monthly visit has all columns completed_____

Pill counts done according to previous directives_____

Back of master card is completed_____

ARV Drug Register

Being used_____

ARV Cohort Analysis:

Cohort analysis done for the quarter_____

Cohort analysis done for the cumulative number on ART_____

Check that outcomes are for the period of the quarter being assessed_____

ARV Clinic Days (M, Tu, W, Th, F)

New patients_____Follow-up patients_____

Group Counselling (and check the time between GC and start of ART)_____

On a clinic day, number of clinicians ___ number of nurses____ number of clerks____

VCT Register

Properly completed and monthly summaries done properly_____

Number of people tested in the quarter_____

Number of people HIV positive in the quarter_____

Number of people referred to ART in the quarter_____

Pharmacy:

ARV Drugs	Number Tins In	Tins in stock
D4T/3TC (D4T-30mg) [15 tablets]		
D4T/3TC (D4T-40mg) [15 tablets]		
D4T/3TC/NVP (D4T-30mg) [15 tablets]		
D4T/3TC/NVP (D4T-40mg) [15 tablets]		
D4T/3TC/NVP (D4T-30mg) [60 tablets]		
D4T/3TC/NVP (D4T-40mg) [60 tablets]		
"Duovir" for PEP		
AZT/3TC [60 tablets] – Alternative/ 2nd line		
NVP [60 tablets[- alternative		
D4T/3TC-30/40 [60 tablets] -Alternative		
Efavirenz [30 tablets] – Alternative		
Tenofovir [30 tablets] Second Line		
"Kaletra" [180 capusles] – Second Line		
OI Drugs		
Fluconazole (Diflucan programme)		
Cotrimoxazole		
Acyclovir		
Ceftriaxone		
Ciprofloxacin		
Vincrsitine		
Morphine		

Laboratory:

CD4 Machine installed (specify yes/no and type) _____

Quarterly ARV Assessment: (assess for the quarter being evaluated)_____

(see Annex 6)

Cumulative ARV assessment: for patients registered up to_____

(see Annex 7)

Number of HIV-related diseases diagnosed in the quarter:

Specify the quarter:_____

TB patients registered in TB Register_____

Kaposi's Sarcoma patients_____

Cryptococcal meningitis patients in Diflucan Register_____

Oesophageal candida patients in Diflucan Register_____

Survival analysis: 6-month and 12-month survival on cohorts

12 month survival: outcomes by end of December 2005

New patients registered for ART between October and December 2004:_____

Number Alive and on ART_____

Number Dead_____

Number Defaulted_____

Number Stopped Treatment_____

Number Transferred Out_____

6 month survival: outcomes by end of December 2005

New patients registered for ART between April to June 2005:_____

Number Alive and on ART_____

Number Dead_____

Number Defaulted_____

Number Stopped Treatment_____

Number Transferred Out_____

This manual is for use by doctors, clinical officers, nurses and other health workers responsible for the provision of ART to people living with HIV/AIDS. It presents up-to-date clinical guidelines, prepared by experts for the initiation and follow-up of patients on ART in clinical settings with limited laboratory backup as well as where laboratory plays a major role in facilitating clinical decision making.

The manual should be used at all levels of clinical services delivery in Malawi; in outpatient or inpatient settings having providers certified in the initiation and follow-up of patients /clients on ART. Certification of providers will follow a Medical Council approved training programme.

The guidelines require the clinic or inpatient setting that will be used to deliver ART to have:

- The capacity to do HIV counseling and testing, WHO clinical AIDS staging, treatment of HIV/AIDS related conditions, ARV compliance counseling, patient ART registration and follow-up.;
- Able to directly dispense ARV drugs or linked to dispensing facilities with adequate capacity and security to dispense ARVs and completing of patient follow-up questionnaire.

Guidelines for the treatment of HIV/AIDS related conditions are covered in a separate document and not described in this document although it is expected that all clinic or inpatient settings that will be used to deliver ART will need to have capacity to manage all common HIV/AIDS related conditions in line with the standard protocols provided.

The manual compliments standard, more comprehensive ART textbooks, which should be consulted for information on the management of rarer complications. However, it is important to note that this manual superior as far as the Malawian setting is concerned and will be routinely updated to remain up-to-date.

This manual is part of a series of documents and tools that support the Integrated HIV/AIDS management in a continuum of care and support. It is consistent with STI, VCT, PMTCT, HIV/AIDS related conditions and other clinical guidelines for outpatient and inpatient management of AIDS.

For any inconsistencies or clarification, users are encouraged to consult Secretary for Health, P.O. Box 30377, Lilongwe 3; Tel. 01 789 400; Attention: The Head of HIV Unit.