



**TREATMENT OF AIDS**

**GUIDELINES FOR THE USE OF**

**ANTIRETROVIRAL THERAPY**

**IN MALAWI**

***Third Edition***

**April 2008**

**Ministry of Health, Malawi**



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## **FOREWORD TO THE THIRD 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 facility sites 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 Antiretroviral (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 2007, there were 109 facilities in the public sector (central, district, mission, and defence force hospitals and clinics) and 45 in the private sector delivering ART using national systems, and 145,000 patients had been registered for therapy.

The Ministry of Health developed a 5-year ART scale up plan (2006-2010) which lays out the path of how to deliver ART to over 250,000 HIV-infected eligible patients by the end of 2010. This will be a challenging time, as the field of HIV-treatment is continually changing.

With these thoughts in mind, I welcome the 2008 Third Edition of the “Guidelines for the Use of Antiretroviral Therapy in Malawi”. This has built on the first and second editions, and takes into account the experience developed in the country in the last 4 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 no less.

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## LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ABC	Abacavir (antiretroviral drug)
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine (antiretroviral drug)
CPT	Cotrimoxazole preventive therapy
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 counselling
IEC	Information, education and communication
KS	Kaposi's Sarcoma
LPV/r	Lopinavir/Ritonavir (antiretroviral drug)
MOH	Ministry of Health
MUAC	Mid- upper arm 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
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  $< 250/\text{mm}^3$
- iii) Assessed to be in WHO Clinical Stage 2 with TLC  $< 1200/\text{mm}^3$

### **Children (aged 14 years and below):**

#### ***Over the age of 18 months:***

Known to be HIV-seropositive and relatives or guardians 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 or guardians 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

Under the age of 12 months where virological testing has been done:  
All confirmed HIV-infected infants (confirmed by virological testing) irrespective of CD4-cell count or clinical stage

## **Antiretroviral Treatment Regimens:**

### **First Line regimen:**

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

Dose = one tablet in the morning and one tablet in the evening

Formulation for children depends on body weight

### **Alternative first line regimen substitutions in case of drug reactions:**

*Reactions due to stavudine:*

(severe peripheral neuropathy, pancreatitis, lactic acidosis, lypodystrophy)

Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP)

*Reactions due to nevirapine:*

(severe skin reactions, hepatitis)

Stavudine (d4T) + Lamivudine (3TC) + Efavirenz (EFV)

*Dual reactions to stavudine and nevirapine:*

Zidovudine (AZT) + 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 2007, 33.2 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 2007, it was estimated that there were 2.5 million people newly infected with HIV and there were 2.1 million AIDS deaths.

## HIV/AIDS in sub-Saharan Africa and Malawi

Sub-Saharan Africa is the epicentre of this epidemic, with 22.5 million people living with HIV/AIDS by the end of 2007. 68% of all HIV-infections and 85% of all estimated AIDS deaths occur in this region. During 2007, there were 1.7 million new infections in the region and 1.6 million deaths. Of the 2.5 million children estimated to be living with HIV/AIDS globally, 2.2 million (88%) live in sub-Saharan Africa.

Malawi has one of the highest HIV/AIDS prevalence rates in the world, with 12.0% of those aged 15 – 49 years infected. 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 2007 there were 898,888 adults and children living with HIV/AIDS and of these 89,025 were children aged less than 15 years. Of these, 100,000 HIV-infected adults and children were alive and on antiretroviral therapy by the end of 2007. HIV/AIDS is the leading cause of death in the most productive age group, resulting in 60,932 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 thus leaves countless numbers of grandparents to bring up children. Many orphans cannot attend school. They may 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. AIDS also causes high death rates in infected children, and 15% of under-5 deaths are directly attributable to HIV infection.

## **Combination antiretroviral therapy (ART)**

Combination antiretroviral therapy (ART), previously known as highly active antiretroviral therapy or 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 ART is an important component of a strategy to support people living with HIV/AIDS as well as preventing transmission of infection. People are more willing to undergo HIV testing and counselling and disclose their HIV status when 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 2005, it was estimated that 185,000 people in Malawi were 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 the first line ART regimen only (stavudine+lamivudine+nevirapine = “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 & AIDS Department of the Ministry of



Health as ready to deliver ART therapy. It was agreed that ART must be provided within a structured framework, “a public health approach”. The first edition of the Malawi ART Guidelines provided for such an approach, and the implementation of ARV delivery has been based on this document.

The Ministry of Health, the National AIDS Commission, other national stakeholders and donor institutions approved the scale up plan 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 on therapy), 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 was developed and approved by the Ministry of Health and its stakeholders. Malawi’s “aspirational” goal will be to provide “Universal Access” of ART 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 ART Programme, which is structured, organised and well monitored. On the road towards universal access, Malawi aims to have started 245,000 patients on ART by the end of 2010 and under the plan aims to achieve 50% or higher 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 is a more explicit scale up of ART for children. By the end of 2005, children comprised 5% of all patients, but by 2010 it is envisaged that they will comprise 10% or more of new patients.

**Table 1: ART Patient Targets 2006 - 2010**

<b>Year</b>	<b>Number of new patients – adults and children-registered on ART during the year (with number of new children shown in parenthesis)</b>	<b>Number of patients - adults and children- ever registered on ART by the end of the year (with number predicted to be alive by end of year)</b>
2005	20,000 (1,000)	38,000 (30,000)
2006	35,000 (2,625)	70,000 (60,000)
2007	40,000 (4,000)	110,000 (90,000)
2008	45,000 (4,500)	155,000 (130,000)
2009	45,000 (4,500)	200,000 (170,000)
2010	45,000 (4,500)	245,000 (208,000)

The numbers of patients placed on ART will be achieved by expanding ART scale up and bringing on new sites on a year to year basis. Following Round 1 scale up with 60 ART sites, Round 2 scale up in 2006 brought on another 49 new sites and Round 3 scale up starts at the beginning of 2008 with another 54 sites (predominately 54 rural health centres) starting to deliver ART. Further rounds of scale up will follow. The private sector has also come fully on board, and by the end of 2007, 45 facilities were delivering ART. Plans to reduce the burden of work include less frequent follow-up of stable patients, decentralising the initiation and follow up of ART to health centres, and the use of task-shifting.

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 THERAPY**

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

## **Strategy**

The strategy is to mobilise all existing ART sites and identify new ART 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.

## **ART Policy Package**

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

1. Government commitment to ART delivery
2. 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
3. Standardised combination ART to HIV-seropositive eligible patients (adults and children) under proper case management conditions with high levels of drug adherence
4. Regular, secure and uninterrupted supply of ARV drugs to units which are administering ART
5. 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 ART in the country
- The ART 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 ART delivery. All staff involved in ART delivery must have attended this training either as part of the undergraduate curriculum or part of in-service 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
- ART 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 ART 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 ART 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 ART delivery**

### **Input indicators:**

- An ART guideline manual (reflects government commitment)
- Number of districts providing ART (cumulative by year)
- Number of HIV-ART Clinics administering ART in public sector
- Number of HIV-ART 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

### **Output indicators:**

- The number of new patients (adults and children) registered on ART each year
- The number of patients (adults and children) who have ever registered on standardised ART
- The number of those registered on ART who are alive and taking therapy at any given time (i.e., under care): as part of an annual survey this will also include the number of children alive and taking therapy at any given time
- The number of patients alive and on ART according to first line, alternative first line and second line regimens
- The number (and proportion) of those starting ART who have died

- The number (and proportion) of those starting ART who have defaulted (i.e. have been lost to follow-up)
- 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 HTC, and to the Antiretroviral Clinic**

Referral for HIV testing and counselling (HTC) 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, the laboratory and the community. Persons can also self-refer.

All persons who test HIV-positive at the HTC unit should be referred to the Antiretroviral Clinic for further assessment and staging: this also includes measurement of CD4-lymphocyte counts where appropriate (see Figure). Those who do not need ART will be referred to the general health services for management and advice, for example initiation of cotrimoxazole preventive therapy (CPT).

## **The Antiretroviral Clinic**

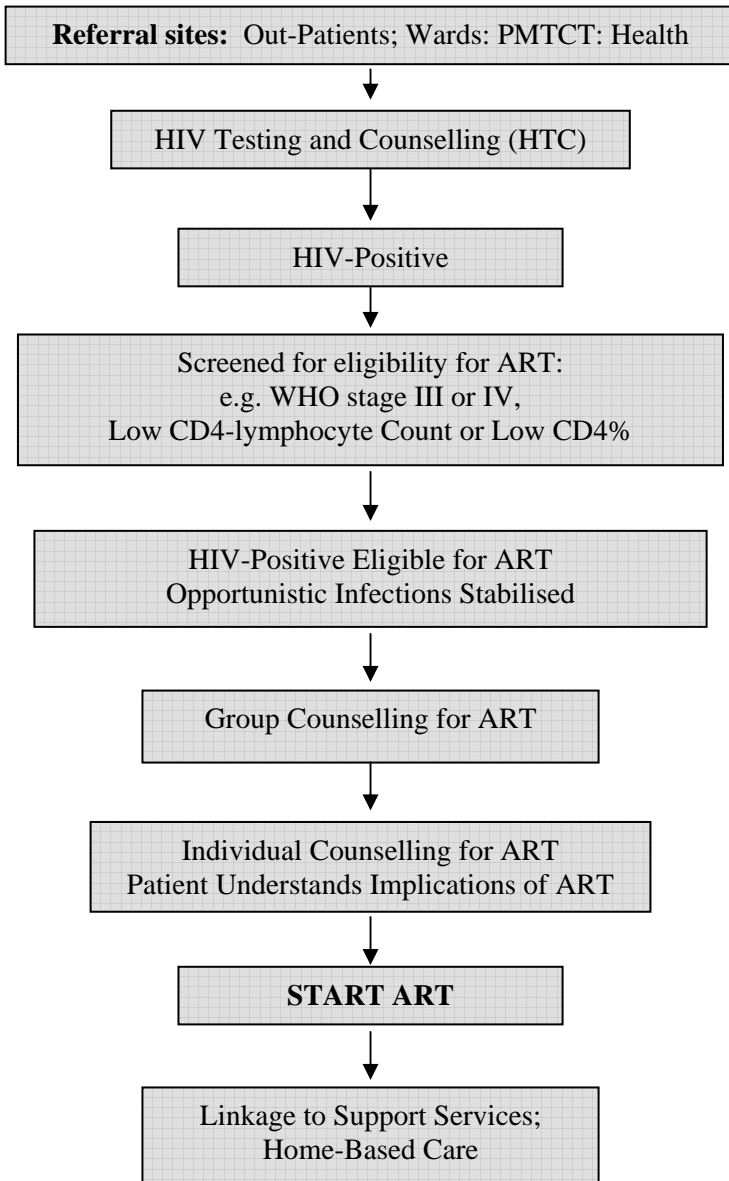
ART will be provided to HIV-positive eligible patients. The clinics will be situated in hospitals (central, district, mission, and rural), health centres or other stand-alone sites. These guidelines do not advocate any rigid or specific design. Clinics must be set up and adapted to the context in which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

- The Clinic should be physically integrated with the general outpatient services
- The Clinic must be linked to HIV counselling and testing services, PMTCT services, the wards and out-patient departments
- 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 supplemented 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 1 Essential Steps in the referral to and screening at the ART clinic**



## **HIV-Antiretroviral Clinic Staff for The Public And Private Sector**

The health facility will determine the number and type of staff needed to run the ART Clinic. Trained ART staff should always be available for assessment and staging, and this can be done outside of the ART clinic. The ART clinic itself (in terms of initiating and following up patients on therapy) 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

1 nurse

1 ward clerk equivalent

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

The criteria are that the staff have:- a) attended a pre-service ART training module and passed the final diploma or undergraduate examination, or b) attended an ART training course recognised by the Ministry of Health, Medical Council of Malawi and Nursing Council of Malawi and passed an examination based on this training course. Such health personnel will be certified as competent to manage ART. Details of the in-service certification mentioned under (b) 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 HIV testing and counselling sites and laboratories attached to ART 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 or in the case of infants through a positive DNA-PCR 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 2: WHO clinical Staging**

HIV-associated symptoms	WHO Clinical Stage
<i>Asymptomatic</i>	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 3: WHO Clinical Stage 1**

- Asymptomatic
- Persistent generalized lymphadenopathy

**Table 4: WHO Clinical Stage 2**

- Respiratory tract infections, recurrent (sinusitis, tonsillitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Oral ulcerations, recurrent
- Papular pruritic eruptions / Fungal nail infections
  
- Moderate weightloss <10%, unexplained
- Seborrhoeic dermatitis

**Table 5: WHO Clinical Stage 3**

- Fever, persistent unexplained (intermittent or constant, >1 month)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Pulmonary tuberculosis within the last 2 years
- Anaemia, unexplained < 8 g/dl
- Neutropaenia, unexplained < 500 /mm<sup>3</sup>
- Thrombocytopaenia, chronic < 50,000 /mm<sup>3</sup>
  
- Severe weightloss >10% and/or BMI <18.5kg/m<sup>2</sup>, unexplained
- Diarrhoea, chronic (>1 month) unexplained
- Oral candidiasis
- Severe bacterial infections (pneumonia, empyema, pyomyositis, bone/joint, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

**Table 6: WHO Clinical Stage 4**

- Pneumocystis pneumonia
- Candidiasis of oesophagus, trachea, bronchi or lungs
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- HIV encephalopathy
- Cryptococcal meningitis or other Extrapulmonary cryptococcosis
- Disseminated non-tuberculous mycobacterial infection
- Cryptosporidiosis, chronic with diarrhoea
- Isosporiasis >1 month
- Disseminated mycosis (coccidiomycosis or histoplasmosis)
- Symptomatic HIV-associated nephropathy or cardiomyopathy
- Progressive multifocal leukoencephalopathy
- Cerebral or B-cell non-Hodgkin lymphoma
  
- HIV wasting syndrome (severe weightloss + persistent fever of severe weight loss + chronic diarrhoea)
- Bacterial pneumonia, recurrent severe
- Chronic herpes simplex infection (orolabial, genital / anorectal >1 month or visceral at any site)
- Cytomegalovirus infection (retinitis or infection of other organs)
- Toxoplasmosis of the brain
- Non-typhoidal Salmonella bacteraemia, recurrent
- Invasive cancer of cervix
- Leishmaniasis, atypical disseminated

## **INFANTS AND CHILDREN (age range of less than 15 years):**

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

**Table 7: WHO Paediatric Clinical Stage 1**

- Asymptomatic
- Persistent generalized lymphadenopathy

**Table 8: WHO Paediatric Clinical Stage 2**

- Hepatosplenomegaly, persistent unexplained
- Lineal gingival erythema
- Wart virus infection, extensive
- Molluscum contagiosum, extensive
- Parotid enlargement, persistent unexplained
  
- Respiratory tract infections, recurrent (sinusitis, tonsillitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Oral ulcerations, recurrent
- Papular pruritic eruptions / Fungal nail infections

**Table 9: WHO Paediatric Clinical Stage 3**

- Moderate unexplained wasting / malnutrition not responding to treatment (weight-for-height 70-79% or MUAC 11-12cm)<sup>a</sup>
- Diarrhoea, persistent unexplained (14 days or more)
- Oral candidiasis (from age 2 months)
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Bacterial pneumonia, severe recurrent
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
  
- Fever, persistent unexplained (intermittent or constant, >1 month)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Pulmonary tuberculosis within the last 2 years
- Anaemia, unexplained < 8 g/dl
- Neutropaenia, unexplained < 500 /mm<sup>3</sup>
- Thrombocytopaenia, chronic < 50,000 /mm<sup>3</sup>

<sup>a</sup> **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 children under 5 years:** 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



**Table 10: WHO Paediatric Clinical Stage 4**

- Severe unexplained wasting / malnutrition not responding to treatment (weight-for-height/age <70% or MUAC <11cm or oedema)<sup>a</sup>
  - Bacterial infections, severe recurrent (empyema, pyomyositis, bone/joint, meningitis, but excluding pneumonia)
  - Chronic herpes simplex infection (orolabial or cutaneous >1 month or visceral at any site)
  - Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ (from age 1 month)
  - Toxoplasmosis of the brain (from age 1 month)
  - Recto-vaginal fistula, HIV-associated
- 
- Pneumocystis pneumonia
  - Candidiasis of oesophagus, trachea, bronchi or lungs
  - Extrapulmonary tuberculosis
  - Kaposi's sarcoma
  - HIV encephalopathy
  - Cryptococcal meningitis or other Extrapulmonary cryptococcosis
  - Disseminated non-tuberculous mycobacterial infection
  - Cryptosporidiosis, chronic with diarrhoea
  - Isosporiasis >1 month
  - Disseminated mycosis (coccidiomycosis or histoplasmosis)
  - Symptomatic HIV-associated nephropathy or cardiomyopathy
  - Progressive multifocal leukoencephalopathy
  - Cerebral or B-cell non-Hodgkin lymphoma

<sup>a</sup> **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

# 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-lymphocytes, 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<sup>3</sup>. HIV-associated immunodeficiency is severe or very advanced if the CD4 count is < 250/mm<sup>3</sup>.

## 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 (from a full blood count).

In order to calculate the CD4%, a full blood count with differential white cell count and an absolute CD4 count must be obtained. To calculate a total lymphocyte count (TLC) a full blood count must be obtained. Below are the formulae used to calculate the TLC and CD4%:

*TLC = absolute white blood cell count x % lymphocytes*

*CD4% = absolute CD4 lymphocyte count / total lymphocyte count (%)”*

Example: The following are FBC and CD4 counts in a 2 year old infected child

**Table 11: CD4% Calculation**

<b>FBC</b>	
WBC	9,000 cells/mm <sup>3</sup>
Neutrophils	60%
Lymphocytes	30%
Eosinophils	5%
Monocytes:	5%
<b>CD4 count</b> =	400 cells/mm <sup>3</sup>
TLC =	9,000 cells/m <sup>3</sup> x 0.30= 2700/mm <sup>3</sup>
<b>CD4%</b> =	<b>400/2700 = 0.14 = 14%</b>

This represents severe immuno-suppression in any child < 5 years of age. In a setting where CD4 counts are not available, this child is eligible for ART. The proposed classification of immunodeficiency based on CD4-counts or CD4-percentages is shown in the Table below.

**Table 12: WHO Proposed Immunological Classification of established HIV infection**

<b>HIV-Immune Deficiency</b>	<b>Age-related CD4-lymphocyte values</b>			
	<b>&lt; 1 year CD4%</b>	<b>1 yr to &lt; 3 yrs CD4%</b>	<b>3 yrs to &lt; 5 yrs CD4 %</b>	<b>≥ 5 years (per mm<sup>3</sup>)</b>
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)	< 20 (CD4 < 350) (TLC <2500)	<15 (CD4 < 250) (TLC <2000)

Patients with severe immunodeficiency are eligible for ART

## **Priorities for CD4-lymphocyte count testing**

The first priority for CD4 count testing is to identify patients who are eligible for ART. Priority for CD4 testing should go to:-

- i. HIV-positive pregnant women identified through the PMTCT programme and who on clinical staging are not eligible for ART
- ii. patients in WHO Stage 2
- iii. HIV-infected children

The second priority for CD4 count testing is to support the identification of patients on ART who might have treatment failure. In these situations, CD4-lymphocyte counts should be measured at:-

- i. Base-line
- ii. Whenever failure on ART is suspected

The third priority is to do regular follow-up CD4 counts on a) patients already on ART and b) persons who are HIV-positive but are not yet eligible for treatment. This should only be done once the first and second priorities have been adequately covered:-

- i. Follow-up every 12 months for people living with HIV with a CD4-count of  $\geq 500$  cells/mm<sup>3</sup> and follow up every 6 months for people with a CD4 count of less than 500 cells/mm<sup>3</sup>
- ii. Follow-up every 6-12 months of patients on ART depending on capability of CD4-testing at the ART facility

# 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 regardless of CD4 lymphocyte count

Patients who have any of the features listed in Stage 3 (see the Table on page 18) should receive ART, but be stabilised **before** treatment commences.

There must be documented 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 regardless of CD4 lymphocyte count**

Patients who have any of the features listed in Stage 4 (see the Table on page 18) 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<sup>3</sup>**

A total lymphocyte count < 1200/ mm<sup>3</sup> 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 17) are eligible for ART.

#### **6. Patients have a CD4 lymphocyte below 250/mm<sup>3</sup>**

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

### **Children [persons aged 14 years or below]:**

**Asymptomatic children over 12 months of age who are HIV-positive are in general not eligible for ART because there is no evidence that early institution of ART benefits these patients.**

### **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.

HIV progresses very rapidly in children infected through vertical transmission. Without intervention, almost 40% of vertically infected

infants will die by 12 months of age, and over 50% will die by 24 months. Recent data has shown significant mortality benefit in starting children < 12 months of age on ART irrespective of CD4 count or clinical stage. Therefore these guidelines recommend starting ART on all HIV infected infants (<12 months of age) in whom the diagnosis of HIV has been confirmed.

The presence of trans-placental maternal antibody means that HIV infection cannot reliably be diagnosed using antibody-based HIV tests in children less than 18 months of age. Therefore, in such children, if available, a virological test called a DNA PCR is done to diagnose HIV infection. Blood samples for this test can be collected on filter paper which is sent to a central lab for analysis.

**A positive DNA PCR result indicates that the child is HIV positive.**

A negative DNA PCR result needs to be interpreted with consideration as to whether the child has breast fed in the 6 weeks prior to the DNA PCR test. If the child has breast fed in the 6 weeks before testing then the child is defined as HIV exposed. This child needs to be retested with a DNA PCR 6 weeks after weaning from breast milk. If the child has not breast fed in the 6 weeks before testing then the child is HIV negative. This service is becoming more widely available in Malawi, and can be used to diagnose children as young as 6 weeks of age. All infants born to an HIV infected mother should be tested by DNA PCR at 6 weeks of age.

All children born to HIV infected women must start CPT at 6 weeks of age.

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.

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.

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**
- **Children with a TLC, CD4 lymphocyte count or CD4 percentage below the threshold value for starting ART (see Table 12)**

### **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 the passage of maternal antibody. Virological testing is becoming more widely available in Malawi, and is being rolled out nationally, but it has not yet reached all health facilities. In these situations, clinical criteria (shown below) can be used for making the diagnosis of severe HIV disease requiring ART. Eligibility criteria then depend on a) no DNA-PCR available or b) a positive DNA-PCR test



## **Where no DNA-PCR test has been done:**

The following are the criteria for eligibility for ART:-

- 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;**
    - iii) severe sepsis**

Other factors that support the diagnosis of severe HIV disease and ART eligibility in an HIV-seropositive infant include:

- a) recent HIV-related maternal death;
- b) advanced HIV disease in the mother;
- c) CD4 < 20% in children 12-18 months, and <25% in children less than 12 months.

The HIV rapid test needs to be repeated at an age of 18 months. If the test is positive ART should be continued; if the test is negative ART (and CPT) should be discontinued. There is no risk for the development of HIV drug resistance.

## **Where a DNA-PCR test has been done and is Positive:**

The following are the criteria for eligibility for ART:

- **All HIV infected children with positive DNA-PCR < 12 months of age**  
This is irrespective of clinical or immunologic status
- **Any child > 12 months with WHO Paediatric Clinical Stage 3 or 4**
- **Any child > 12 months with CD4 or TLC counts below threshold values for starting ART** (see Table 12)

These are the paediatric criteria for eligibility to ART. 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 below.

**Table 13: Classes of Antiretroviral Drugs Approved by WHO in 2006**

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

[There are also several ritonavir-boosted PIs: eg lopinavir-ritonavir]

These drugs, used in combination, act by blocking the action of enzymes, which are important for replication and functioning of HIV.

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 and for prevention of maternal to child transmission, short course dual therapy for 30 days is still indicated (see page 43).

### **Class-Specific and Drug-Related Side Effects:**

**Table 14: Class-Specific Side Effects:**

<b>NsRTI</b>	Mitochondrial toxicity Lipodystrophy syndrome with long usage
<b>NtRTI</b>	Renal toxicity
<b>NNRTI</b>	Skin rash Hepatitis
<b>PI</b>	Lipodystrophy syndrome Hyperlipidaemia Hyperglycaemia

## Drug specific side effects:

**Table 15: Some Side Effects of Antiretroviral Drugs**

<b><i>NsRTIs:</i></b>	
Zidovudine	Anaemia, nausea, headache, fatigue, muscle pains,
Didanosine	agranulocytosis
Lamivudine	Nausea, diarrhoea, neuropathy, pancreatitis
Stavudine	Nausea, headache, fatigue, muscle pains
Zalcitabine	Neuropathy, pancreatitis, diarrhoea, insomnia, lipodystrophy
Abacavir	Neuropathy, pancreatitis, oral ulcers
Emtricitabine	Nausea, fatigue, sleep disturbance, hypersensitivity reaction
	Nausea, headache
<b><i>NtRTI:</i></b>	
Tenofovir	Renal failure, osteoporosis
<b><i>NNRTIs:</i></b>	
Nevirapine	Skin rash, Stephen Johnson Syndrome, hepatitis
Efavirenz	Skin rash, central nervous system disorders, teratogenicity
<b><i>PIs:</i></b> “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,
Amprenavir	headache
Tipranavir	Diarrhoea, nausea, abnormal taste, peri-oral numbness
Atazanavir	Diarrhoea, nausea, abdominal pain, rash
	Diarrhoea, nausea, jaundice (due to indirect hyperbilirubinemia)

## Drug Doses

**Table 16: Standard Adult Doses of Antiretroviral Drugs**

Drug Class / Drug	Dose
<b>NsRTIs:</b> Zidovudine Didanosine Lamivudine Stavudine Zalcitabine Abacavir Emtricitabine	300 mg twice daily 400 mg once daily (250 mg once daily if < 60Kg) 150 mg twice daily 30 mg twice daily (weight in adults is no longer an issue) 0.75 mg three times daily 300 mg twice daily 200 mg once daily
<b>NtRTI:</b> Tenofovir	300 mg once daily
<b>NNRTIs:</b> Nevirapine Efavirenz	200 mg once daily for 14 days, then 200 mg twice daily 600 mg once daily
<b>PIs:</b> Nelfinavir Saquinavir / ritonavir Lopinavir / ritonavir Indinavir / ritonavir Atazanavir Atazanavir/ritonavir	1250 mg twice daily 1000 mg / 100 mg twice daily 200 mg / 50 mg – two tablets twice daily 800 mg / 100 mg twice daily 400 mg once daily 300 mg/ 100 mg once daily

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

- Integrase inhibitors (e.g. raltegravir), 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 (e.g. maraviroc) , 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 ( e.g. 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

#### **NNRTIs:**

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

#### **PIs:**

- The whole class not a good choice because gastro-intestinal side effects are common, they all interact with rifampicin, they are expensive and are to be reserved for second line therapy

### **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. Stavudine 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 used as monotherapy for PMTCT. Nevirapine-based regimens may be used after the drug has been used as monotherapy for PMTCT.



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 (rash, fever, 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 various adverse drug reactions requiring change of the first line regimen:-

### **Reactions due to the Stavudine Component:**

These are in order of frequency: -

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

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.

### **Less common reactions:**

- reactions due to stavudine and nevirapine, change the regimen to **zidovudine plus lamivudine plus efavirenz (AZT + 3TC + EFV)**
- reactions due to stavudine and zidovudine (most commonly anaemia), change the regimen to **tenofovir plus lamivudine plus efavirenz (TDF + 3TC + EFV)**

- reactions due to nevirapine and efavirenz, change the regimen to **stavudine plus lamivudine plus lopinavir/ritonavir (AZT + 3TC + LPV/r)**

## **Second line Regimen for ART Drug Failure:**

The second line regimen is used when patients have failed the first line regimen. The final diagnosis of ART drug failure is made by a specialist or experienced clinician in dedicated clinics with access to viral load tests. Patients with Suspected ART Drug Failure need to be referred to these clinics.

### **Suspected ART Drug Failure:**

This is defined as fulfilling conditions A, B and C:

- A. On ART for at least one year and adhering to therapy
- B. Fulfil at least one of the following three criteria:
  - i. the development of a new WHO Clinical Stage 4 feature
  - ii. a CD4 count / CD4% which has declined to pre-treatment values or less
  - iii. a CD4 count /CD4% which has declined to <50% of peak value on ART
- C. a CD4 count < 200 cells/mm<sup>3</sup>

The CD4 count needs to be repeated after one month and the patient is referred only if the result supports the earlier CD4 test.

The decision to change to the second line regimen must be made in consultation with a specialist or experienced clinician at one of the dedicated clinics, with access to viral load tests, because the regimen is more difficult for patients to take and requires more management.

### **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 M184V 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. The new heat stable tablet of Lopinavir/Ritonavir has now become available, removing the need to store the drugs in the fridge. 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 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 ART 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, using wherever possible a standard Flip Chart - 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] and renal failure. The understanding of the main messages from group counselling will be assessed and reinforced.

*Weight and Height:* The patient will be weighed and have the height measured. This enables calculation of the body mass index (BMI) =  $\text{wt in kg} / \text{ht in cm}^2$ . All adults will now receive the stavudine-30mg regimen, which has been shown to be as effective as stavudine-40mg and with less toxicity.

*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 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. If after one year, the patient is still stable, then consideration can be given to extending follow-up to three-monthly.

**Table 17: Steps in Administering First Line ART**

<b>Time Period</b>	<b>ART</b>
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 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 two tables twice a day, morning and evening

*LPV/r and TDF can be taken independently of 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.

A new paediatric fixed dose combination of d4T 6mg/3TC 30mg/NVP 50mg (known as Triomune-Baby) should be used for children less than 10 kg (**Annex 2a**). Please note that the dosage table given in **Annex 2a** is in line with current WHO recommendations but different from the dosage table found in the package insert by the time of writing. Compared to the split adult T30 regimen in Annex 2b, the new formulation provides higher NVP concentrations (target NVP dose is 300mg/mm<sup>2</sup>/d); especially for children <10kg of body weight.

If the new formulation is unavailable children less than 10 kg should receive split adult T30 regimen as set out in **Annex 2b**.

Children 10 kg and above should generally receive split adult T30 regimen as set out in Annex 2b.

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**

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.

## **ART in children younger than 1 year of age**

The writing committee supports universal ART for DNA PCR confirmed HIV infected children younger than 1 year of age in line with current evidence of high mortality in this age group. However, operational research is being conducted to determine the best ART regimen for these children in Malawi in accordance with locally available resources and also taking into consideration the current PMTCT regime. Until more guidance is available, it is strongly recommended that a low threshold for ART treatment is practiced, especially in children not exposed to nevirapine prophylaxis

## **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 18: CPT prescription criteria**

**CPT offered to the following adults and children who are known to be HIV-positive**

<b>Category</b>	<b>Conditions for prescription</b>
Adults	Any person with symptomatic HIV disease [Stages 2,3 and 4] Any person who has a CD4 count of 500/mm <sup>3</sup> or less, regardless of symptoms Pregnant women irrespective of duration of pregnancy
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

CPT is also offered to DNA-PCR- negative children who continue to breast feed.

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 for tablets and for solutions for children are shown in the Tables below

**Table 19: Dosages of CPT**

<b>Category</b>	<b>CPT (480mg tablets)</b>	<b>CPT dispersable (120mg) tablets</b>	<b>CPT suspension</b>
<b>Children aged 6 weeks to 5 months</b>	Quarter of a tablet once a day (120 mg daily)	One tablet once a day (120mg daily)	2.5ml once a day
<b>Children aged 6 months to 4 years</b>	Half a tablet once a day (240mg daily)	One tablet twice a day (240mg daily)	5ml once a day
<b>Children aged 5- 14 years</b>	One tablet (480mg) once a day		
<b>Adults</b>	One tablet (480mg) twice a day		

## **Contra-indications to CPT:**

Known allergy to cotrimoxazole for adults and children

## **Duration of therapy:**

### **Adults:**

CPT should be lifelong. If antiretroviral therapy is started, then CPT should be continued. If CD4 counts are monitored on ART and the CD4 count rises above  $500/\text{mm}^3$ , then CPT may be discontinued. CPT should be **discontinued** in the event of severe cutaneous reactions, renal or hepatic toxicity or severe haematological toxicity. In these situations, dapsone can be considered as an alternative prophylaxis.

### **Children:**

In HIV-exposed infants (i.e. children born to HIV-positive women) CPT should be taken until HIV infection can be confidently excluded. At 18 months of age and provided the child has stopped breast-feeding, the child should have an HIV test. If the child continues to breast feed after 18 months, CPT is continued until 3 months after breast-feeding has stopped and the child is then offered an HIV test. In both situations, if the HIV test is positive, then the child continues on CPT indefinitely. If the HIV test is negative, then the child discontinues CPT.

HIV-positive children take CPT life-long. If antiretroviral therapy is started, then CPT should be continued. CPT should be **discontinued** in the event of severe cutaneous reactions, renal or hepatic toxicity or severe haematological toxicity

## **Pregnant women on CPT:**

If a pregnant woman is on CPT, then there is no need for her to take intermittent anti-malarial prophylaxis with sulfadoxine-pyrimethamine (SP).

# **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 up 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 drugs
- ARV drugs in the first line regimen, alternative first line and second 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 ART 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
- 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: Childbearing Age & Pregnant Women

ART is a priority for pregnant women who are eligible for ART, because triple therapy is very effective in reducing mother to child transmission of HIV. 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. HIV-positive women should also be started on CPT.

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 Second Edition of PMTCT Guidelines).

D4T/3TC/NVP can be given to lactating mothers and reduces the risk of HIV transmission during breastfeeding. Breastfeeding should be exclusive for the first 6 months according to the Second Edition of PMTCT Guidelines.

## Patients with Liver Disease

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



disease should be referred for specialist opinion about whether they can start ART.

## **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: HIV-Positive Adults and Children with TB**

### **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, 2007, Edition 6). In the initial phase and continuation phase of treatment, all drug combinations include rifampicin, which interacts with nevirapine.

### **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, there is evidence 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. Malawi will therefore continue to use nevirapine-based regimens in association with rifampicin, and closely monitor the outcomes of patients.

### **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). Specialist opinion may dictate that some HIV-positive TB patients have ART deferred if the CD4 count is felt to be too high.

### **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. Thus, in general, once the patient has completed the initial phase of treatment and started on the continuation phase of anti-TB treatment with rifampicin and isoniazid (RH), the patient will then be eligible for ART.

## Provision of ART for TB patients on continuation phase RH

The following steps are recommended:

- During 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 CPT policy
- Once HIV-positive TB patients have completed their initial phase of anti-TB treatment, they will be started on RH
- 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. CPT 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 20: ART with Anti-Tuberculosis Treatment**

<b>Phase of Anti-TB Treatment</b>	<b>ART</b>
Initial Phase [RHZ(E)]	No ART  Prepare the patient with group counselling in initial phase
Continuation Phase (RH)	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:**

A proportion of patients who start ART for other reasons may develop TB. This most frequently occurs during the first three months of ART. The risk is higher if patients have a previous history of TB. 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. If TB develops when the patient is on ART, ART continues with d4T/3TC/NVP, and anti-TB treatment started in the usual way.

### **Other ART and anti-TB issues**

- If patients on first line ART develop drug-resistant TB and need a second line anti-TB treatment regimen, then this can be given. Second line anti-TB treatment regimens do not contain rifampicin, and consequently there are no serious drug-drug interactions to be concerned about
- If patients on second line ART (which contains protease inhibitors) develop TB, then the second line ART regimen will have to be modified as rifampicin and protease inhibitors cannot be given together with any degree of safety or efficacy. Specialist opinion must be sought about what this modified second line ART should be.
- If patients on second line ART develop drug-resistant TB and need a second line anti-TB treatment regimen, then this can be given. Second line anti-TB treatment regimens do not contain rifampicin, and consequently there are no serious drug-drug interactions to be concerned about

## 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 (KS) 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 ART 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 (to name only those available in Malawi) figure among the drugs ordinarily used in various protocols of mono- or preferably poly-chemotherapy. Steroids (prednisolone/dexamethasone) may also be used in combination. Apart from vincristine, the other drugs are usually only available at central hospitals in Malawi. Radiotherapy, not currently available in Malawi, is occasionally indicated.

The 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 and Etoposide are myelotoxic, like Zidovudine (AZT). This association requires more frequent measurements of the full blood count. These drugs should only be used at sites with oncology expertise.

Management of Kaposi 's sarcoma: ART in combination with vincristine monotherapy is the standard regime for aggressive and/or progressive disease in Malawi. In patients with mild to moderate disease which does not limit function ART can be given alone. For others, six weekly doses of vincristine may be started either before or concurrently with ART. (For more information refer to the Malawi HIV- management guidelines). KS immune reconstitution disease may occur at initiation of ART but has been found to be rare (1-2%) in a Western setting.

## **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 clean 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. ART 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 must be 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 (e.g., 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 21: The PEP Regimen**

<b>DRUG</b>	<b>DOSE</b>	<b>FREQUENCY</b>	<b>DURATION</b>
Zidovudine (AZT) 300mg/ Lamivudine (3TC) 150mg	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 two tablets twice a day can be added to the dual NRTI therapy: specialist advice is necessary in these cases.

*Documentation of PEP:*

Whenever PEP is given there should be formal documentation in a register that is kept centrally in the ART clinic. See **Annex 8**. Every quarter, the number of persons in whom PEP is given should be recorded as part of the ART supervision.

**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 PEP. As with PEP after occupational injuries, 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, criminal investigations).

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, and the HIV Testing and Counselling Guidelines of the Ministry of Health.

# MONITORING ART

## Registration of Patients on ART

Each patient who starts ART will be given a unique treatment unit ART Registration Number. Each facility has a code for ART (e.g., MCH for Mchinji District Hospital), and patients are given a unique number. This number is increased sequentially. This number will be written on the patient master card and the patient identity card, and put into the ART Register.

The system of patient registration is as follows:

### ART 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:- Patient details, status at ART initiation, date and place of first positive HIV test and ART regimes. Ensure that all required data are filled out. It is important to ask the patient if there has been previous exposure to ARV drugs and if the patient agrees to follow up in case of missed clinic visits. Adherence to ART is critical to good treatment outcomes and clinics must ask patients if they agree to be contacted by telephone or in person in case they miss their appointments at the ART 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 (maximum 100) 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.

### ART Patient Register

Each facility has its own ART patient register. The Register has a left hand page and a right hand page (**Annex 5**). The left hand page

consists of :- ART number, year, quarter and date of registration, name, address, occupation, age and age group. The right hand page consists of ART status at registration, reason for starting, TB and KS status at initiation, primary outcomes and dates, date of starting ART regimens, number of times re-started ART and comments. Both pages are completed at the time of registration

### **Patient Identity Cards**

Patient identity cards (**Annex 6**) will be smaller and will contain basic information from the patient master card. This will include:- treatment unit, patient name, ART number, age, sex, and current ART regimen. Patients will be given their own ART 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.

### **“Transfer-in”**

Patients who transfer in from another site are registered as follows. A transfer in patient should always bring the ART patient master card from the previous facility. At the new facility, the new ART number assigned to the patient replaces the previous number on the master card and the patient is indicated on the master card as a “transfer-in”.

In the ART register, the transfer-in patient is written into the next available row with the new number and the demographic and clinical details. The date of registration is recorded in the appropriate column. The date first started on ARV drugs is the date the patient was first started on ART in the previous facility. Under reason for ART, the staging condition by which the patient started ART at the previous facility is recorded and the patient is also indicated in this column as a “transfer-in”.

## 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 and sometimes to once every three months

At these follow-up visits, patients will:

- Have their weight recorded and in children the height as well
- Be asked about their general health
- Be asked about side effects and symptoms (see Table below)
- Be asked about signs of TB (cough, fever, night sweat)
- Be asked about the number of doses missed since last visit
- Have their returned pill bottles inspected to count the remaining drugs
- Collect another one-, two- or three- month supply of drugs
- Be reminded about the importance of adherence to therapy
- Be asked about CPT

**Table 22: Check List of Symptoms for Patients Attending the Clinic**

Did you experience any new or worsening symptoms since you 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 refer to a clinician. If all symptoms are recorded as NO then the patient can be dispensed ARVs		

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. At three-monthly visits, the patient must attend.

**Definition of Standardised monthly outcomes:**

Standardised outcomes will be monitored at every follow-up visit. The Tables below show and explain the standardised outcomes.

**Table 23: Outcome Status**

<b>Category</b>	<b>Definition</b>
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 supply of drugs
Dead (D)	Patient who has died for any reason while being registered on ART
Defaulted (Def) [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 ART regimen he/she is taking.

*1<sup>st</sup> Line (1L):* i.e., the patient is on the first line regimen

*Alternative 1<sup>st</sup> Line (AZT, EFV or AZT +EFV containing alternative first line regime):* i.e., the patient experienced side effects from the

first line regimen and has changed to an alternative first line ART regimen

*2<sup>nd</sup> Line (2Ad for adults or 2Ch for children):* i.e., the patient has switched to the second line regimen because of ART failure (see definition of Suspected ART Failure on page 39). Specialist opinion must always be sought before classifying a patient as “Failure”.

**Note 2:**

A patient is declared a defaulter if he/she has not appeared at the clinic 2 months after the next appointed date. The date of default is the date at which the default classification is made. The box shows how to define defaults depending on whether follow-up is 1-, 2- or 3-monthly. Clinics should follow up patients when they miss their appointment. Telephone calls to the patient or guardian could be made within a few days of missing the appointment. Follow up visits should be initiated not later than 14 days after the missed appointment.

**Table 24: Default Status Definitions**

<b>Follow-up</b>	<b>Definition of Default</b>
One-monthly	3 months after last recorded visit made by patient
Two-monthly	4 months after last recorded visit made by patient
Three-monthly	5 months after last recorded visit made by patient

**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 on the patient master card

**Note 4:**

If a patient transfers permanently out to another ART facility, this is recorded on the patient master card and also in the ART Register. 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 ART registration number, and is placed in the cohort of the new district at the time that the patient registers in the new district. The ART Programme realises that this patient is counted twice in terms of case finding.

**Table 25: Side Effects**

No	No side effects stated by patient or identified after clinical assessment
PN HP SK  Other (specify under comments column)	Side effects stated by patient after questioning from health worker or identified after clinical assessment: PN = peripheral neuropathy HP = jaundice, liver failure SK = cutaneous hypersensitivity  LA = lactic acidosis LD = lipodystrophy AN = anaemia

**Pills left in ARV container and doses missed:**

Given the great importance of near-perfect adherence<sup>1</sup>, 2 complimentary methods should be used at every visit to assess if the patient has taken the expected number of doses.

1. Ask the patient if s/he has missed any doses since the last visit and record the number of doses missed on the master card.

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<sup>1</sup> More than 95% of doses should always be taken to avoid development of drug-resistant virus



This question should encourage an open relationship with the patient that will permit a constructive discussion of any adherence problems the patient may experience.

2. Physically count ARV tablets remaining from the last visit each time and check if the pill count is consistent with the reported number of doses missed. Separately record the pill count on the master card.

This strategy serves a) to remind the patient that it is crucial that tablets are taken regularly and b) to measure adherence in order to counsel the patient if there is a problem. Insist that all remaining tablets are always brought back to the clinic for a physical count. It is useful to ask for any additional tablets left at home. Tablets left at home should be included for the calculation of adherence and the next appointment if this information is believed to be reliable, but should be ignored otherwise.

There are two ways of measuring adherence from pill counts, which should be 95% or more to prevent the development of drug resistance:

The simple way (used in sites with no electronic register) is to count the number of pills in the container in adults on first line regimen only. It is too difficult to do this for other regimens or with children. The table below shows the number of tablets left in a container that indicate whether adherence is 95% or greater.

**Table 26: Pill Count Adherence Estimation**

<b>Appointment interval</b>	<b>Tablets dispensed at previous visit</b>	<b>100% adherence (tablets remaining at current visit)</b>	<b>95% adherence (tablets remaining at current visit)</b>
4 weeks	60	3	6
8 weeks	120	6	12
12 weeks	180	9	18

If the container is not returned to clinic or the patient comes late to clinic, adherence can only be assessed from self-reporting of doses missed.

The more complicated way (used in sites with an electronic register or with a calendar and calculator) is to calculate adherence as a percentage: *actual consumption of tablets since last visit / Expected consumption of tablets since last visit*. The general adherence calculation uses the following information:

A: Number of days since the last visit

B: Total number of tablets available at last visit (= tablets remaining from previous visit + tablets newly dispensed at last visit)

C: Number of tablets to be taken per day

D: Number of tablets remaining at current visit

Adherence % = (B-D) / (A x C)

Low calculated drug adherence can be due to the following reasons:

- a. Visit on or before the appointment date but too many tablets remaining
- b. Late visit, even if no tablets are remaining. In this case, calculate the number of tablets missed and indicate as negative pill count on patient master card (e.g. '-14' if 7 days late after running out of tablets)

Calculated adherence will be greater than 100% if there are fewer than expected tablets remaining. This can be due to poor adherence (overdosing, patient has taken more tablets than prescribed) or an indication for tablet loss or sharing.

### **Managing the remaining pills in the container:**

Patients should not be allowed to accumulate large numbers of tablets in the course of their visits because they will eventually be at risk of taking expired drugs. Even if patients are 100% adherent, accumulation will occur unless appointments are delayed to allow patients to 'use up' remaining pills before the next dispensing. Patients should usually be given a new bottle and instructed to take all remaining before opening the new bottle.

The strategy for delaying appointments has to take account of the days that the clinic is open for follow-up visits. As a general rule, delayed appointments should only be given once the patient has accumulated more than 8 tablets and at least as many tablets as are needed to

‘reach’ a later clinic day. In any case, the patient should be left with 2 days worth of tablets on the new appointment date as a ‘safety-buffer’. When calculating delayed appointments, great care has to be taken not to schedule appointments for weekends or public holidays.

### **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 “1<sup>st</sup> Line”, this is recorded in the master card and also recorded in the ART Register with the **date or month** of the change. If a patient is not seen for 3 months, 4 months or 5 months depending on the time period of follow-up, he/she is recorded in the master card and the register as “default” with the date being 3 months, 4 months or 5 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 ART number and the outcome is changed back from “transfer out” to “alive and on ART”.

### **Strategies to increase 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 at least 95% adherent to therapy. Adherence is measured at each visit by self reporting of the number of doses missed, validated by a physical pill count.

At the ART staging assessment, 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. The patient and the guardian should attend, wherever possible, the first group counselling session at which the ART staff with the help of the Standard Flip

Chart provides education about ART and the importance of adherence. 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 and calendar booklets, 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 may decide, after appropriate consultation, 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. Before ART initiation**

- Two persons responsible for drug administration should be clearly identified, so that if one is ill or away there is always a caregiver available
- 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
- Caregivers should repeat the dosing schedule to make sure that the schedule is understood
- Health care worker hands out and explains to caregivers and children the paediatric ART calendar booklet

- Caregivers attend an education session focusing on
  - Understanding the medication rationale and schedule
  - Practising pill swallowing
  - Integrating medication intake into the regular routines of the child and family
  - Providing information about opportunities to further improve adherence (e.g. patient support groups, positive reinforcement of good medication intake, reminder systems, etc.)
- Facilitators of the education sessions should use the National Paediatric ART Flip Chart

### **B. At each subsequent visit**

- Check if the caregiver can recite the prescribed schedule and dosage of ART
- Check if the caregivers can recite the potential adverse effects of therapy
  - “2 books and bottle”: together with the health passport and the calendar booklet the ART bottles, either empty or with remaining tablets, need to be brought to the clinic
  - Treatment adherence needs to be explored by a health care worker using pill counts. In addition, the health care worker should check ticks in the ART Calendar booklet
  - Caregivers are instructed to follow given appointments (table provided in the last page of the calendar booklet) or return to the clinic one week before it is anticipated that ARV drugs will run out

### **C. Advice about pill taking**

- If the child vomits the tablets or solutions within half an hour of ingestion, then the dose must be repeated
- Tablets are not to be pre-cut
- Caregivers should be given regular supplies of pill cutters and the ART staff must explain how to use them to cut pills at home

## **Monitoring and Managing Drug Toxicity**

### **Adverse Effects of ART 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 must teach patients how to recognise symptoms of common adverse effects and to report if they develop such symptoms. Second, they must 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 27: Major Side Effects with d4T/3TC/NVP**

<b>Immediate Side Effects</b>
<ul style="list-style-type: none"> <li>• Peripheral Neuropathy</li> <li>• Hepatitis</li> <li>• Pancreatitis</li> <li>• Cutaneous hypersensitivity</li> </ul>
<b>Long Term Side Effects</b>
<ul style="list-style-type: none"> <li>• Peripheral Neuropathy</li> <li>• Lactic acidosis</li> <li>• Lipodystrophy syndrome</li> </ul>

## **Management of peripheral neuropathy**

This is due to the stavudine (d4T) component. Patients may have pre-existing peripheral neuropathy before starting ART, but this should not stop the initiation of ART as it may get better with treatment.

Peripheral neuropathy should be diagnosed if the patient complains of pain, paraesthesia, 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, although clinical judgement must be used about how to progress through these steps:-

- 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 and the peripheral neuropathy continues to be severe and progressing, the ART 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 (i.e. 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. In this situation, the usual alternative regimen will be Tenofovir (TDF) + Lamivudine (3TC) + Nevirapine (NVP)

*[Severe, rapidly progressive neuropathy of late onset 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. In this situation, the usual alternative regimen will be Tenofovir (TDF) + Lamivudine (3TC) + Nevirapine (NVP)

### **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.

*After the first two weeks:* Any new skin manifestation requires that the patient be assessed at an ART clinic or in a hospital. 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, e.g. scabies, cotrimoxazole. 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, ART must be stopped and 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 and it may do harm.

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, which is correlated to the lactic acid level in the blood. It is difficult to diagnose under resource-poor conditions and collection methods are challenging. For example, blood sampling needs to be without tourniquet and blood needs to be delivered to the lab on ice for processing within 4 hours. Overdiagnosis due to faulty collection methods may occur. 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, weakness, nausea, vomiting, abdominal pain or distension, muscle pains, weight loss, palpitations and shortness of breath. There may also be an acute or sub-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, particularly if they are at high risk (e.g. female, obesity).

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. The substituted regimen should usually be started no sooner than 2 months after stopping the first line ART regimen. If there are any recurrences of the same symptoms or signs, the ART must be stopped and specialist opinion sought. In this situation, the usual alternative regimen will be Tenofovir (TDF) + Lamivudine (3TC) + Nevirapine (NVP).

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

A mild elevation of lactic acid levels without symptoms can occur (asymptomatic lactic acidemia) which may be due to a faulty collection method. Treatment in asymptomatic patients should not be changed.

### **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. One possible treatment option is to substitute AZT for d4T, and change the patient to AZT+3TC+NVP or again consider Tenofovir (TDF) + Lamivudine (3TC) + Nevirapine (NVP).

Table 28: Adverse Effects & Management

Alternative and Second Line Regimens

<b>Antiretroviral Drug</b>	<b>Side Effect</b>	<b>Management</b>
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  Interaction with other drugs – rifampicin, oestrogen	Symptomatic Avoid drug-drug combinations
Abacavir	Hypersensitivity reaction (multi-organ syndrome with fever, rash, gastrointestinal effects, malaise and respiratory symptoms)	Stop Abacavir and other ART drugs  Do NOT rechallenge after suspected hypersensitivity
Didanosine	Neuropathy Pancreatitis	Management as with stavudine Management as with stavudine

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 Interactions

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

**Table 29: ARV Drugs – Significant Interactions**

ARV Drug	Contra-indicated	Use with great care/ specialist advice	Dose adjustment required (of either ARV, combined drug or both)
<b>Stavudine-Lamivudine-Nevirapine</b>	ketoconazole, zidovudine, St. John's wort	oral anti-contraceptives (additional method required), ganciclovir, amodiaquine, lumefantrine*	
<b>Zidovudine</b>	stavudine	ganciclovir	
<b>Efavirenz</b>	astemizole, terfenadine, midazolam, triazolam, cisapride, ergot alkoids, St. John's wort, voriconazole, amodiaquine	simvastatin (and other statins), rifabutin, warfarin, claritromycin, lumefantrine*	phenobarbitone, fenytoin, carbamazepine, rifabutin, methadone, most protease inhibitors (including lopinavir/r)
<b>Tenofovir DF</b>		didanosine	didanosine
<b>“Aluvia” (Lopinavir/Ritonavir)</b>	rifampicin, astemizole, terfenadine, fleceanide, propafenone, simvastatine, lovastatine, midazolam, triazolam, pimozide, cisapride, ergot alkoids,	rifabutin, clarithromycin, methadone, atorvastatine, pravastatine, ketoconazole, drugs for erectile dysfunction, carbamazepine, phenobarbitone, warfarine,	rifabutin, clarithromycin, methadone, atorvastatine, ketoconazole, drugs for erectile dysfunction, carbamazepine, phenobarbitone, warfarine,

ARV Drug	Contra-indications	Use With Care	Dose Adjustment
<b>“Aluvia” (Lopinavir/ Ritonavir)</b> <i>continued</i>	St. John's wort, rifapentine, phenytoin	atovaquone, amodiaquine, halofantrine, lumefantrine* oral anti- contraceptives (additional method required)	atovaquone, nevirapine, efavirenz, most other protease inhibitors
<b>Abacavir</b>			
<b>Didanosine</b>	stavudine, ribavirin tenofovir DF	tenofovir DF, ketoconazole, fluoro-quinolones	tenofovir DF ganciclovir

\* part of Malawi’s first line anti-malaria treatment, lumefantrine + artemether (LA)

## Monitoring and Managing Immune Reconstitution Disease

In patients who are severely immunocompromised (for example, with a CD4 lymphocyte count  $< 50/\text{mm}^3$ ), 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 require aspirin and non-steroidal anti-inflammatory drugs (such as ibuprofen), antibiotics and sometimes cortico-steroids. In general, 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.

## **ART reporting and Cohort Analysis**

The national ART program relies heavily on accurate and timely data for drug procurement, monitoring of patient outcomes and prevention of wide-spread ARV drug resistance.

Data analysis for ART monitoring is usually done manually. Electronic systems for monitoring will increasingly be used at sites with many patients.

Monitoring is done every quarter. ART reporting forms are filled by the clinic staff within 2 weeks after the end of every quarter. For example, for the quarter 1<sup>st</sup> January to 31<sup>st</sup> March, the supervision and monitoring forms will be completed in April.

The cohort analysis consists of 2 parts:

- Registration details (patient status at time of registration)
  - Analysis of patients registered in the last quarter
  - Analysis of patients ever registered (done by addition)
- Patient outcomes at the end of the quarter evaluated
  - Cumulative for all patients ever registered only

(See ART reporting form in **Annex 7** for details)

The clinic's own analysis will be checked by the supervision team each quarter. Copies of the checked reports are kept at the clinic.

### **Analysis of registration details (status at registration)**

Registration details are written in the register at the time of patient registration. Tallying of these data needs to be done only once for



every new quarterly cohort, because these data will never change over time. From version 3 of the ART register, page summaries should be filled as soon as the page is filled and quarterly total will be obtained from page summaries.

For the cumulative analysis, the new quarterly registration data can simply be added to the previous cumulative data.

Note that patients in each of the categories in each section should add up to the respective total:

- Males, non-pregnant females and pregnant females must add up to the total number registered
- Age groups must add up to the total number registered
- ART status (first time initiation, re-initiation, and transfer in) must add up to the total number registered
- The 7 categories for reason for starting ART must add up to the number registered.

In order to capture data on the frequency of 2 leading clinical stage-defining conditions, patients presenting with TB or Kaposi's Sarcoma (KS) are counted separately in the analysis. (These categories are not expected to add up to the total number registered)

### **Analysis of treatment outcomes**

Treatment outcomes are separated into:

- Primary outcomes (for all patients ever registered)
  - alive on ART
  - died
  - defaulted
  - stopped ART
  - transferred out
- Secondary outcomes (only for patients alive on ART)
  - Current ART regimen
  - Adherence
  - TB status

Primary outcomes must add up to the total patients registered.

Secondary outcomes must add up to the total patients alive and on ART.

All deaths must be classified according the time after ART initiation when entering in the register. (Death within 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, month after ART initiation or after 3<sup>rd</sup> month of ART initiation)

It is essential that the ART register is updated from the Master cards before performing the cohort analysis, because outcomes will change over time. For this reason, outcomes have to be newly tallied each quarter for all patients ever registered – correct outcomes can not be obtained by addition from the previous quarterly outcome data.

Outcome dates are crucial for the analysis: any outcome that occurred after the end of the quarter evaluated must be excluded when tallying.

For the secondary outcomes of the patients alive and on ART, look at the last visit before the end of the quarter evaluated. This visit might be several months before the end of the quarter if the patient on extended ARV dispensing intervals.

From version 3 of the Master card, monitoring of adherence will only be based on the number of doses missed. The translation of the number of doses missed into adherence % obviously depends on the number of days since the last visit. In practice, it is too complicated to consider varying intervals when analysing cohort adherence. Therefore, assuming most patients now come every 2 months, any patient who had more than 6 doses missed at the last visit before the end of the quarter must be tallied under ‘adherence <95%’

## **Group Cohort Analysis**

Because cumulative cohort outcomes depend on the duration of patient follow-up, it is difficult to compare cumulative outcomes between clinics. In addition to the regular cumulative cohort outcome analysis, separate outcome analyses are done for discrete quarterly cohorts of patients that registered 12, 24, 36, etc. months before the end of the quarter evaluated. This helps to standardise the observation period and therefore makes outcome analysis comparable between clinics.

- For example, the 12-month cohort survival analysis done for quarter 4 in 2008 will consider the outcomes (by 31st Dec 2008) of the patient cohort registered during quarter 4 in 2007 (between 1st Oct and 31st Dec 2007).
- The 12-month cohort survival analysis is done separately for children

The MOH also obtains data on the number of patients who received Post Exposure Prophylaxis (PEP) in the quarter.

## 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, NNRTIs 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 most sites in Malawi, it is not currently possible to monitor for drug resistance on an individual level. However, two surveillance systems have been set up at sentinel sites around the country.

**First**, there is monitoring of patients who have been on ART for 12 months. They have blood taken for viral load and genotype testing at 12 months after starting the first line ART regimen. The data 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.

**Secondly**, in young women presenting at antenatal clinics with a first pregnancy, blood is taken for viral load and viral genotype patterns. The data 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 8**), in which qualitative data are collected on a) the use of ART Registers and ART 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, f) number of persons receiving PEP in a quarter, and g) 12-month, 24-month and 36-month group cohort treatment outcome 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 ART units.

### **Drug Procurement and distribution:**

#### *First line ART:*

Each ART facility in Malawi is designated in a particular category, 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). Facilities can also be upgraded or downgraded depending on performance

**Table 30: ART Site Burden Classification**

<b>Site Classification</b>	<b>Criteria</b>
Low Burden	25 new patients placed on ART in a month
Medium Burden	50 new patients placed on ART in a month
Medium/ High Burden	100 new patients placed on ART in a month
High Burden	150 new patients placed on ART in a month
Very High Burden	250 new patients placed on ART in a month
Super High Burden	400 new patients placed on ART in a month

The HIV and AIDS Department 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 31: Starter Pack Kits and Continuation Pack Kits**

Starter Pack Kit	Continuation Pack Kit
<p>Provides drugs for 75 new patients starting ART for 14 days</p> <p><b>150 tins of ART:</b></p> <p>75 tins of d4T-30mg/ 3TC (15 tablets) 75 tins of d4T-30mg/ 3TC/ NVP (15 tablets)</p>	<p>Provides drugs for 75 patients to continue on ART for 3 months, and receiving drug tins every 28 days</p> <p><b>225 tins of ART</b></p> <p>225 tins of d4T-30mg/ 3TC/ NVP (60 tablets)</p>

*Alternative first line ART and second line ART:*

These drugs used to be supplied to central hospitals and to experienced district hospitals. However, this has now changed and all ART facilities now receive alternative first line ART. Second-line ART is supplied to all central hospitals, selected district hospitals and a few private hospitals.

**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 32: Drug Security Definition

Drug consumption by patients	=	Drug usage from the treatment unit
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Drug security is checked every quarter during the routine supervisory visits. Most ART 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 33: Current Drug Formulations with Examples of Trade Names**

<ul style="list-style-type: none"> <li>• d4T/3TC/NVP - 15 and 60 tabs</li> <li>• d4T/3TC - 15 and 60 tabs</li> <li>• AZT/3TC (dual combination “Zodolam” or “Duovir”) – 60 tabs</li> <li>• EFV – 30 tabs</li> <li>• ABC – 60 tabs</li> <li>• ddI-EC (enteric coated) – 30 capsules</li> <li>• NVP – 60 tabs</li> <li>• 3TC – 60 tablets</li> <li>• Tenofovir (TDF, “Viread”) – 30 tabs</li> <li>• Lopinavir/Ritonavir (LPV/r, “Aluvia”) – 120 tablets</li> </ul>
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Consideration is being given to other regimens for future use, and these are listed in the Table

**Table 34: Future Drug Formulations with Examples of Trade Names, which may be used in Malawi**

<ul style="list-style-type: none"> <li>• TDF/FTC/EFV (triple combination, “Atripla”) – 60 tablets</li> <li>• Atazanavir/Ritonavir (ATZ/r) – 60 tablets</li> </ul>
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# 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 “ART 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. If these students qualify from the training institutions, they will be considered to have been trained in ART

### b. In-service training.

All staff in the public sector who deliver ART, and who have not been trained in the pre-service years, must undertake the formal 5-day ART and HIV-related diseases training course and pass 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. Refresher ART training courses will be run on an annual basis for these in-service staff.

## **Certification in the use of ART:**

A formal certificate, signed by the Secretary for Health, is given to every staff member who has completed the in-service ART 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.



## **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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National HIV/AIDS Policy. A call to renewed action. ISBN No: 99908-73-07-0 Office of the President and Cabinet, National AIDS Commission, October 2003

Prevention of Mother-to-Child Transmission of HIV in Malawi. Guidelines for implementers. Second Edition, 2008.

## ANNEX 1: TARGETS FOR ART SCALE UP

Strategy Indicator	Baseline (End 2005)	2006	2007	2008	2009	2010
<b>Input Indicators:</b>						
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
<b>Output Indicators:</b>						
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 2a: Dosage guidelines for first line ART in children

### Presentation of Drugs

Trade name	Ingredients	Pack sizes
<i>Lamivir-S Baby</i>	6mg d4T + 30mg 3TC	14 tabs blister pack 60 tabs bottle
<i>Triomune Baby</i>	6mg d4T + 30mg 3TC + 50mg NVP	30 tabs bottle 60 tabs bottle
<i>Lamivir S 30</i>	30mg d4T + 150mg 3TC	15 tabs bottle 60 tabs bottle
<i>Triomune-30</i> <i>Nevilast-30</i>	30mg d4T + 150mg 3TC + 200mg NVP	15 tabs bottle 60 tabs bottle

### Target Doses

Drug	Target dose per 24 hours
<b>d4T</b>	2mg / kg bodyweight
<b>3TC</b>	8mg / kg bodyweight
<b>NVP</b>	120mg / m <sup>2</sup> (Starter phase) 300-400mg / m <sup>2</sup> (Continuation phase)

**2a: Practical dosing table for standard first line ART children under 10kg *if Triomune Baby is available***

Body wt. (kg)	Starter Phase		
	Morning	Evening	Tabs needed 14 days
min	Triomune Baby	Lamivir S Baby	Triomune Baby / Lamivir S Baby
3.00	1	1	14
6.00	1 ½	1 ½	21
10.00	continue with split Triomune 30 / Lamivir S 30		

Continuation Phase		
Morning	Evening	1 month supply
Triomune Baby	Triomune Baby	Max. tabs left for >95% adherence
1	1	60
1 ½	1 ½	90
continue with split Triomune 30		

**Dispensing:**

Triomune Baby should be dispensed in whole bottles of 60 tabs and 30 tabs to make up the required number of tables. Triomune Baby tablets remaining from the starter phase should be used for the continuation phase.

Lamivir S Baby should be dispensed in whole blister packs of 14 tabs or bottles of 60 tabs to make up the required number of tablets.

**2b: Practical dosing table for standard first line ART if Triumune Baby is NOT available**

Body wgt. (kg)	Starter Phase		Continuation Phase							
	Morning Triumune 30	Evening Lamivir S 30	Tabs needed (14 days) Triumune 30	Lamivir S 30	Morning Triumune Baby	Evening Triumune Baby	1 month supply Tabs needed <sup>1</sup> >95% adh.	Max. tabs left for >95% adh.	2 month supply Tabs needed <sup>1</sup> >95% adh.	
3.00	1/4	-	4	-	1/4	-	9	1	16	1
5.00	1/4	1/4	4	4	1/4	1/4	16	2	30	3
8.00	1/4	1/2	4	8	1/2	1/4	24	4	45	5
12.00	1/2	1/2	8	8	1/2	1/2	31	4	59	6
14.00	1/2	3/4	8	11	3/4	1/2	40	6	75	8
19.00	3/4	3/4	11	11	3/4	3/4	47	7	89	9
26.00	3/4	1	11	15	1	3/4	55	8	104	11
30.00	1	1	15	15	1	1	60	9	120	12

Triumune 30 tablets are not scored and should be split using a commercial pill cutter supplied by MOH  
Do not pre-cut tablets as fragments are not firm and may crumble when stored, leading to wrong dosage

<sup>1</sup> Including 6 extra doses safety buffer  
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**Annex 3:** Dosage guidelines for alternative first line and second line ART for children

**3a** Substitution of Nevirapine with Efavirenz for NVP-related skin and hepatic toxicity

Body wgt. (kg)	Prescription		Tablets needed (incl. 4 extra doses safety buffer)	
	Morning	Evening	1 month supply	2 month supply
min max	Lamivir S 30 EFV 600mg	Lamivir S 30 EFV 600mg	Lamivir S 30 EFV 600mg	Lamivir S 30 EFV 600mg
10.00 11.99	1/2 –	1/4 1/3	23 11	44 20
12.00 13.99	1/2 –	1/2 1/3	30 11	58 20
14.00 18.99	3/4 –	1/2 1/3	38 11	73 20
19.00 25.99	3/4 –	3/4 1/2	45 16	87 30
26.00 29.99	1 –	3/4 2/3	53 21	102 40
30.00 39.99	1 –	1 2/3	60 21	116 40
40.00 59.99	1 –	1 1	60 32	116 60

Efavirenz is not licensed for children under 3 years and / or below 10kg

Efavirenz tablets are not scored and can be difficult to split into thirds. Mark the tablets at the split line and cut with a sharp knife.

Do not pre-cut tablets as fragments are not firm and may crumble when stored, leading to wrong dosage

**3b** Substitution of Stavudine with Zidovudine for d4T-related toxicity (e.g. peripheral neuropathy)

Body wgt. (kg)	Prescription		Tablets needed (incl. 4 extra doses safety buffer)	
	Morning	Evening	1 month supply	2 month supply
min	AZT 300mg + NVP 200mg 3TC 150mg	AZT 300mg + NVP 200mg 3TC 150mg	AZT 300mg + NVP 200mg 3TC 150mg	AZT 300mg + NVP 200mg 3TC 150mg
8.00	1/4 1/2	1/4 1/4	15 23	29 44
10.00	1/2 1/2	1/4 1/2	23 30	44 58
15.00	1/2 3/4	1/2 1/2	30 38	58 73
20.00	3/4 3/4	1/2 3/4	38 45	73 87
25.00	3/4 1	3/4 3/4	45 53	87 102
30.00	1 1	3/4 1	53 60	102 116
35.00	1 1	1 1	60 60	116 116

AZT should not be started if Hb is less than 8g/dl

These dosage guidelines also apply for use of AZT / 3TC as post exposure prophylaxis in children.

AZT / 3TC and NVP tablets are not scored into quarters. Split using a commercial pill cutter supplied by MOH.

Do not pre-cut tablets as fragments are not firm and may crumble when stored, leading to wrong dosage.



**3c** Second line ART for children

Body wt. (kg)		Prescription			Tablets needed (incl. 4 extra doses safety buffer)										
		Morning	Evening		1 month supply		2 month supply								
min	max	ABC 300mg	LPV/r 200/50 mg	ABC 300mg	LPV/r 200/50 mg	ABC 300mg	ddl 125mg	LPV/r 200/50 mg	ABC 300mg	ddl 125mg	ddl 200mg	LPV/r 200/50 mg			
10.00	11.99	1/2	125mg	1	1/4	-	1/2	23	32	-	46	44	60	-	88
12.00	14.99	1/2	125mg	1	1/4	-	1/2	23	32	-	46	44	60	-	88
15.00	19.99	1/2	200mg	1	1/2	-	1/2	30	-	32	46	58	-	60	88
20.00	24.99	3/4	200mg	1 1/2	1/2	-	1	38	-	32	76	73	-	60	146
25.00	29.99	3/4	250mg	1 1/2	3/4	-	1 1/2	45	60	-	90	87	120	-	174
30.00	34.99	1	250mg	1 1/2	3/4	-	1 1/2	53	60	-	90	102	120	-	174
35.00	44.99	1	325mg	2	1	-	1 1/2	60	32	32	106	116	60	60	204
45.00	49.99	1	325mg	2	1	-	2	60	32	32	120	116	60	60	232
50.00	54.99	1	400mg	2	1	-	2	60	-	60	120	116	-	120	232

The appropriate Didanosine (ddl) dosage in mg is obtained by combining ddl 125mg and ddl 200mg capsules.

Transfer-In Date

ART no

Year

**Patient / Guardian Details**

Patient Name			
Sex, Birth date	DOB	Patient Phone	
Phys. Address			
Guardian Name		Guardian Phone	
Agrees to FUP			

**Status at ART initiation**

Clin Stage	1	2	3	4	Pres
CD4 / TLC	%				
Cov/Tlc Date					
Height, Wt.	cm	kg			
Age at Init.					

**First positive HIV test**

TB status at initiation	None	Past	Curr
KS	N	Y	Y
Pregnant at initiation	N	Y	Y
Ever taken ARVs	N	Y	Y
Last ARVs (drug, date)	2 <sup>nd</sup> Line		

Date, Place	Rapid PCR	
ART Regimens	Start date	
1 <sup>st</sup> Line	d4T 3TC NVP	
All 1 <sup>st</sup> Line		
2 <sup>nd</sup> Line		

Visit Date <i>day month year</i>	Hgt <i>cm</i>	Wt <i>kg</i>	Adverse Outcome	Outcome Date	Guardian Relation	Guardian Phone	ART Regimen 1 <sup>st</sup> 2 <sup>nd</sup> 3 <sup>rd</sup> 4 <sup>th</sup> Line	Non-Adherence 2 <sup>nd</sup> L start	Side Effects specify / Other in Comments	TB Status Suspected / Confirmed No / Yes	Pill count	Doses missed	ARVs given No. of tablets	To	Comments / Lab Side effect / BMI/TF new OI's	Next appointment																			
																	1	2	3	4	Pres	%	cm	kg	Yes	No	Yes	No	Yes	No	Yes	No			
Jan			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Feb			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Mar			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Apr			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
May			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Jun			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Jul			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Aug			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Sep			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Oct			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Nov			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
Dec			D Def Stop TO				AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		

Extra row for 2-week visit after ART initiation or for any second visit falling in the same month as a previous visit

D Def Stop TO							AZT Erv	2Ad 2Ch NS	No	PN	HP	SK	Oth	N	Y	C	R <sub>x</sub>																		
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Notes

## WHO Clinical Staging

### Adults and Children

- 1 Asymptomatic
  - Persistent generalized lymphadenopathy
- 2 Respiratory tract infections, recurrent (sinusitis, tonsillitis, otitis media, pharyngitis)
  - Herpes zoster
  - Angular cheilitis
  - Oral ulcerations, recurrent
  - Papular pruritic eruptions / Fungal nail infections

- 3 Fever, persistent unexplained, intermittent or constant, >1 month
  - Oral hairy leukoplakia
  - Pulmonary tuberculosis (current)
  - Pulmonary tuberculosis within the last 2 years < 8 g/dl
  - Anaemia, unexplained < 500 /mm<sup>3</sup>
  - Neutropoenia, unexplained < 50,000 /mm<sup>3</sup>
  - Thrombocytopaenia, chronic < 50,000 /mm<sup>3</sup>

- 4 Pneumocystis pneumonia
  - Candidiasis of oesophagus, trachea, bronchi or lungs
  - Extrapulmonary tuberculosis
  - Kaposi's sarcoma
  - HIV encephalopathy
  - Cryptococcal meningitis or other Extrapulmonary cryptococcosis
  - Disseminated non-tuberculous mycobacterial infection
  - Cryptosporidiosis, chronic with diarrhoea
  - Isosporiasis >1 month
  - Disseminated mycosis (coccidiomycosis or histoplasmosis)
  - Symptomatic HIV-associated nephropathy or cardiomyopathy
  - Progressive multifocal leukoencephalopathy
  - Cerebral or B-cell non-Hodgkin lymphoma

### Circle all conditions found in the patient

### Adults only (15 years or older)

- Moderate weight loss <10%, unexplained
- Seborrhoeic dermatitis

- Severe weight loss >10% and/or BMI <18.5kg/m<sup>2</sup>, unexplained
- Diarrhoea, chronic (>1 month) unexplained
- Oral candidiasis
- Severe bacterial infections (pneumonia, empyema, pyomyositis, bone/joint, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- HIV wasting syndrome (severe weight loss + persistent fever or severe weight loss + chronic diarrhoea)
- Bacterial pneumonia, recurrent severe
- Chronic herpes simplex infection (orolabial, genital / anorectal >1 month or visceral at any site)
- Cytomegalovirus infection (retinitis or infection of other organs)
- Toxoplasmosis of the brain
- Non-lymphoid Salmonella bacteraemia, recurrent
- Invasive cancer of cervix
- Leishmaniasis, atypical disseminated

### Children only (below 15 years)

- Hepatosplenomegaly, persistent unexplained
- Lineal gingival erythema
- Wart virus infection, extensive
- Molluscum contagiosum, extensive
- Parotid enlargement, persistent unexplained

- Moderate unexplained wasting / malnutrition not responding to treatment (weight-for-height/ -age 70-79% or MUAC 11-12cm)
- Diarrhoea, persistent unexplained (14 days or more)
- Oral candidiasis (from age 2 months)
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Bacterial pneumonia, severe recurrent
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Severe unexplained wasting / malnutrition not responding to treatment (weight-for-height/ -age <70% or MUAC <11cm or oedema)
- Bacterial infections, severe recurrent (empyema, pyomyositis, bone/joint, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous >1 month or visceral at any site)
- Cytomegalovirus infection: retinitis or other organ (from age 1 month)
- Toxoplasmosis of the brain (from age 1 month)
- Recto-vaginal fistula, HIV-associated

### Presumed severe HIV in infants 0-17 months

Positive antibody (rapid) test **PLUS**  
 one or several of the highlighted clinical conditions in the WHO staging list  
 OR combination of at least 2 of the following:

- Oral thrush
- Sepsis, severe
- Pneumonia, severe

**Ever taken ARVs** Has the patient ever taken any ARVs? (e.g. single dose nevirapine for PMTCT, or triple therapy) If yes, specify drug and approximate date when last taken  
**Outcome** (circle only one option, leave blank if patient alive on ART)  
 D Died  
 Def Defaulted: More than 2 months overdue after expected to have run out of tablets, unknown survival and ART status  
 Stop Patient stopped taking ARVs (clinician's or patient's own decision)  
 TO Transferred to other ART clinic (including 'unofficial' transfers)  
**TB status at initiation**  
 Past PTB within the last 2 years Curr Current episode of TB NS Non-Standard regimen (specify in comments)

**ART Regimen** (circle only one option)  
 1L standard 1<sup>st</sup> line: d4T 3TC NVP  
 AZT AZT 3TC NVP  
 EFV d4T 3TC EFV  
 AZT/EV AZT 3TC EFV  
 2Ad 2<sup>nd</sup> line Adult: AZT 3TC TDF LPV/r  
 2Ch 2<sup>nd</sup> line Child: ddI ABC LPV/r  
 NS Non-Standard regimen (specify in comments)

**Side Effects** (circle at least one option)  
 No No side effects  
 PN Peripheral neuropathy  
 HP Hepatitis  
 SK Skin rash  
 Oth Other ARV drug side effect  
**CPT** Number of CPT tablets given

**ARVs given**  
 P ARVs given to patient  
 TB ARVs given to guardian  
**TB Status current (any form of TB, smear pos or neg)**  
 N TB Not suspected  
 Y TB Suspected  
 C TB Confirmed not (yet) on TB treatment  
 R<sub>c</sub> TB Confirmed & currently taking TB treatment

Patient / Guardian Details				Status at ART initiation				First positive HIV test					
Patient Name		DOB		Clin Stage		TB status at initiation		None		Date, Place		Rapid PCR	
Sex, Birth date		Patient Phone		CD4 / TLC		KS		Past		ART Regimens		Start date	
Phys. Address				Cvd/Tlc Date		%		Y		1 <sup>st</sup> Line		d4T 3TC NVP	
Guardian Name		Guardian Relation		Height, Wt.		kg		Y		All 1 <sup>st</sup> Line			
Agrees to FUP		Guardian Phone		Age at init.				Y		2 <sup>nd</sup> Line			

Visit Date day month year	Wt kg	Hgt cm	ART Regimen 1 <sup>st</sup> Line	ART Regimen 2 <sup>nd</sup> Line	Non-Standard 1 <sup>st</sup> Line	Side Effects specify other in Comments	TB Status current Suspected	Pill count	Doses missed	ARVs given No. of tablets	CPT No. of tablets	Comments / Lab. Side effect / BMRIF new OI's	Next appointment	
														No
Jan			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Feb			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Mar			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Apr			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
May			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Jun			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Jul			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Aug			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Sep			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Oct			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Nov			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
Dec			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	

Extra row for 2-week visit after ART initiation or for any second visit falling in the same month as a previous visit

			1L AZT EFV AZT ERV	2Ad 2Ch NS	No	PN HP SK Oth	N	Y	C	R <sub>t</sub>			P G	
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**ART Patient Master Card – Continuation** Version 3

Transfer-In Date

ART no

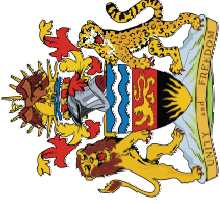
Year

Visit Date day month year	Hgt cm	Wt kg	Adverse Outcome	Outcome Date	ART Regimen 1st Line 2nd Line All 1st Line 2nd Line	Side Effects specify Other in Comments	TB status current Suspected Confirmed No Yes noRx Rx	Pill count	Doses missed	ARVs given No. of tablets To	CPT No. of tablets	Comments / Lab Side effect / BMV/TF new OI's	Next appointment
Jan			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Feb			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Mar			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Apr			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
May			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Jun			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Jul			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Aug			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Sep			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Oct			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Nov			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			
Dec			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G			

Extra row for 2-week visit after ART initiation or for any second visit falling in the same month as a previous visit

			D Def Stop TO		1L AZT EFV AZT ERV 2Ad 2Ch NS	No PN HP SK Oh	N Y C R <sub>e</sub>			P G		
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Notes



**Ministry of Health**  
**ART Clinic Register**  
*Version 3 (February 2009)*

Register No

Clinic Name

District

Date Register Started

Date Register Closed


### Registration Details

### Status at ART initiation

ARV Number	Year	Quarter	Registration Date	Name	Physical Address	Occupation	Sex / Pregnancy	Age	Age Group
							Male	at ART initiation	below 18 months
							Female Non Pregnant		18 mths–below 15 yrs
							Female Pregnant		15 yrs or older
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	
							M FNP FP	A B C	





## ANNEX 6: ART PATIENT IDENTITY CARD

### ART IDENTITY CARD

Treatment Unit:                   ... ..

Patient Name:                   ... ..

ART Number:                   ... ..

Age: ... ..                   Sex: ... ..

Current ARV Regimen:

... ..

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## ARV CLINIC QUARTERLY SUPERVISION FORM – PART 2

Version 5

1. Clinic name		
2. Supervisors names		
3.		
4.		
5. Year and quarter evaluated	Year	Quarter

	Patients registration details	Newly registered in quarter		Cumulative ever registered	
		Clinic own data*	Checked data	Clinic own data*	Checked data
6.	Total registered				
7.	Patients transferred in on ART				
8.	Patients newly initiated on ART				
9.	Males (all ages)				
10.	Non-pregnant Females (all ages)				
11.	Pregnant Females (all ages)				
12.	Adults (15 years or older at ART initiation)				
13.	Children (18 mths - 14 yrs at ART initiation)				
14.	Infants (0-17 months at ART initiation)				
Reason for starting ART					
15.	Presumed severe HIV disease in infants				
16.	Confirmed HIV infection in infants (PCR)				
17.	WHO stage 1 or 2, CD4 below threshold				
18.	WHO stage 2, total lymphocytes <1,200/mm <sup>3</sup>				
19.	WHO stage 3				
20.	WHO stage 4				
21.	Unknown / other reason outside guidelines				
Stage defining conditions at ART initiation					
22.	TB (any form, history of TB or current TB)				
23.	Kaposi's Sarcoma				

\* Supervisors: no need to copy the 'Clinic own data' on this page.

**Primary outcomes as of the end of the quarter evaluated (only cumulative)**

**Cumulative ever registered**

Clinic own data<sup>†</sup>      Checked data

24.	Total alive and on ART		
25.	Died within the 1 <sup>st</sup> month after ART initiation		
26.	Died within the 2 <sup>nd</sup> month after ART initiation		
27.	Died within the 3 <sup>rd</sup> month after ART initiation		
28.	Died after the end of the 3 <sup>rd</sup> month after ART initiation		
29.	Died total		
30.	Defaulted (more than 2 months overdue after expected to have run out of ARVs)		
31.	Stopped taking ARVs (clinician or patient own decision, last known alive)		
32.	Transferred out		

Check completeness of 'Clinic own data'



33.	<i>Total adverse outcomes = Died total + Defaulted + Stopped + TO</i>	A	B
34.	<i>Calculate completeness %      100 - ((B - A) / B) x 100</i>		%

**Secondary outcomes of those alive on ART as of last visit before end of quarter**

35.	ARV regimens	1 <sup>st</sup> Line (Start)	d4T 3TC NVP		
36.		1 <sup>st</sup> Line alternatives	<b>AZT</b> 3TC NVP		
37.			d4T 3TC <b>EFV</b>		
38.			<b>AZT</b> 3TC <b>EFV</b>		
39.		2 <sup>nd</sup> Line adult	AZT 3TC TDF LPV/r		
40.		2 <sup>nd</sup> Line child	ddl ABC LPV/r		
41.		Non-standard	(Patients on any other regimens)		
42.	Total patients with side effects				
43.	Number adults on 1 <sup>st</sup> line regimen with pill count done in last month of quarter				
44.	Number with the pill count in the last month of the quarter at 8 or less				

Current TB status, any form of TB (*only from ARV Patient Master Card, version 3*)

45.	TB not suspected		
46.	TB suspected		
47.	TB confirmed, not yet / currently not on TB treatment		
48.	TB confirmed, on TB treatment		

<sup>†</sup> Supervisors: 'Clinic own data' must be copied on this page for calculation of data completeness.

## Quality check list

49.	<b>General</b>	Clinic orderly and tidy	N	Y
50.		Pharmacy well organized and stock cards up to date	N	Y
51.		Standard M&E tools implemented and maintained (paper or EDS)	N	Y
52.		ARV drug register in use	N	Y

*Correct for more than 98% of cases*

53.	<b>Master cards</b>	Card header details complete	N	Y
54.		TB status, KS and pregnancy (at time of ART initiation) recorded	N	Y
55.		WHO stage defining conditions circled on back of card	N	Y
56.		Details of 2-week initiation visit recorded at bottom of card	N	Y
57.		Weight recorded at each visit	N	Y
58.		ART regimen and side effects recorded at each visit	N	Y
59.		Pill counts recorded at all ARV refill visits	N	Y

60.	<b>Clinic register</b>	Registration numbers assigned correctly and match cards	N	Y
61.		Transfer-ins recorded	N	Y
62.		All case finding columns complete (age, sex, reason,...)	N	Y
63.		Case finding data match cards	N	Y
64.		Outcomes complete and updated every quarter	N	Y
65.		Outcome dates specified	N	Y

66.	<b>Analysis</b>	Patient registration analysis done for quarter	N	Y
67.		Cumulative cohort analysis done for all patients ever registered	N	Y
68.		Cumulative cohort outcomes complete and accurate (>98% from Q 34.)	N	Y

69.	<b>Certificate of excellence</b>	awarded	N	Y
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All answers in the quality check list must be **Yes** and no other major problems noted

70.	<b>Clinic logistics</b>	Total ARV clinic days per week ( <i>specify 0.5 if only half days</i> )			
71.		Days between group counselling and ART initiation			
72.		Average number of staff per clinic day	COs	nurses	clerks

73.	<b>CPT</b>	CPT register in use (including improvised registers)	<b>N</b>		<b>Y</b>
74.		Cumulative total of patients in CPT register			
75.		Approx. % of patients alive on ART who are currently on CPT			%

76.	<b>HTC</b>	HTC register correctly filled	<b>N</b>		<b>Y</b>
77.		Page and month summaries accurately done	<b>N</b>		<b>Y</b>
78.		Totals from last quarter	Total tested	M	FNP
79.		Total positive, referred for ART, PMTCT		Pos	PMTCT

80.	<b>PEP</b>	Total persons given PEP in last quarter			
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81.	<b>CD4 counts</b>	CD4 count machine installed <u>at this facility</u>	<b>N</b>		<b>Y</b>
82.		Total CD4 counts done at this facility in last quarter			

**New patients with HIV-related diseases registered in last quarter**

83.		Is this facility a TB treatment <u>registration</u> site? If no, skip TB section.	<b>N</b>		<b>Y</b>
84.		TB register correctly filled. Page summaries accurately done	<b>N</b>		<b>Y</b>
85.		Totals from last quarter	Total TB cases registered		
86.			Known status		Pos
87.			Total with known HIV status, Total Positive		
			Total already on ART at TB treatment start		

88.	<b>Diflucan register</b>	New cases cryptococcal meningitis			
89.		New cases oesophageal candidiasis			

ANNEX 8: Post-exposure Prophylaxis Drug Register: to be kept in the Pharmacy

Date of Drug Issue	Name of Person given PEP	Age	Sex	Reason for PEP: indicate one reason only			Number of Tins of PEP in Stock	Balance of AZT/3TC	Name and signature of clinician/nurse authorising PEP
				Needle Stick	Mucosal Splash	Rape			

