



TREATMENT OF AIDS

GUIDELINES FOR THE USE OF ANTIRETROVIRAL THERAPY IN MALAWI

**First Edition:
October 2003**

Ministry of Health and Population, Malawi



National AIDS Commission

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FORWARD

Since 2001, Malawi has been offering triple antiretroviral (ARV) therapy to patients at certain designated hospitals in the country. However, the number of patients who have been able to access ARV therapy has been small compared with the size of the HIV epidemic and the number of patients who could potentially benefit from this intervention.

Malawi's successful bid to the Global Fund for AIDS, Tuberculosis and Malaria in mid-2002 changes the situation. In the next six years the Ministry of Health and Population, with the assistance of the National AIDS Commission, aims to scale up ARV therapy to large numbers of patients in the country, from the North to the South.

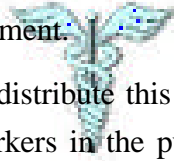
The scaling up of a potentially difficult intervention, such as ARV therapy, will be a considerable challenge to all those involved: - those who plan the framework and the strategy, those who deliver the therapy at the clinics and those who have to take the medication for the rest of their lives.

It is known that the drugs must be provided within a structured framework if the full benefits to the individual are to be realised and drug resistance is to be minimised. Widespread, unregulated use of ARV drugs in the public and private sectors will lead to the rapid development of resistant viral strains, which will spell doom to the individual and will curtail future treatment options. The programme has to, at all costs avoid this

scenario, and do everything possible to protect the value and effectiveness of ARV drugs.

On the basis of this noble goal, the Ministry endorses this first draft of the “Guidelines for Antiretroviral Therapy in Malawi”. The Ministry wishes to note that it has taken 8 months to get to this stage, which is a remarkably short time when one considers how the consultative process was.

The Ministry sincerely appreciates the effort of all the people who have spent many hours in writing committees, consultation groups and dissemination meetings, and who have worked together to ensure the successful completion of an excellent and useful document.



What now remains is to distribute this document, and use it to orient all health care workers in the public and private sector, and insist that health care workers read, understand, and become fully conversant with the protocols so as to adhere to the agreed standardised approach for ARV therapy in Malawi.

If this can be done, then patients with AIDS in Malawi will be offered an excellent standard of care. They deserve no less.

Yusuf Mwawa, MP
Minister of Health and Population

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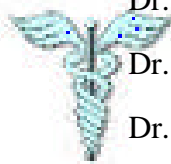
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LIST OF ABBREVIATIONS

AIDS	Acquired Immune-Deficiency Syndrome
ABC	Abacavir (antiretroviral drug)
ARV	Antiretroviral therapy
AZT	(Zidovudine (antiretroviral drug))
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
HIV	Human immunodeficiency virus
HCW	Health care worker
IEC	Information, education and communication
MOHP	Ministry of Health and Population
NFV	Nelfinavir (antiretroviral drug)
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)

3TC	Lamivudine (antiretroviral drug)
TB	Tuberculosis
TLC	Total lymphocyte count
VCT	Voluntary Counselling and Testing
WHO	World Health Organization



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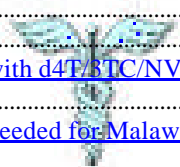
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SUMMARY

Eligibility for ARV therapy:

Adults:

Known to be HIV-seropositive and understand implications of ARV therapy

PLUS any one of the following:

- i. Assessed as being in WHO Clinical Stage 3 or 4
- ii. Have a CD4-lymphocyte count $< 200/\text{mm}^3$
- iii. Assessed as being in WHO Clinical Stage 2 with TLC $< 1200/\text{mm}^3$



Children:

Over the age of 18 months:

Known to be HIV-seropositive and relatives understand implications of ARV therapy

PLUS any one of the following:

- i) Assessed as being in WHO Clinical Stage III
- ii) Assessed as being in WHO Stage I and II with CD4 percentage $< 15\%$

Under the age of 18 months:

Confirmed to be HIV seropositive by a virological test PLUS any one of the following:

- i. Assessed as having a WHO Paediatric Stage III disease.
- ii. Assessed as having WHO Stage I or II disease and a CD4 percentage <20%

Antiretroviral Treatment Regimens:

First Line regimen:

Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP) co-formulation tablets

For adults, formulation depends on body weight cut point

- i) 60Kg or less = d4T/3TC/NVP-30;
- ii) > 60Kg = d4 T/3TC/NVP-40

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

For children, body weight is used to determine size of portion of tablet to give.

Alternative first line regimen substitutions in case of drug reactions:

Severe peripheral neuropathy: which will likely be due to the stavudine component?

- i. Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP)**

Liver disease such as hepatitis: which will likely be due to the nevirapine component?

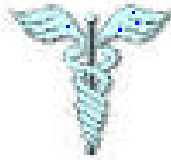
ii. Stavudine (d4T) + Lamivudine (3TC) + Efavirenz (EFZ)

Severe skin reactions: which will likely be due to the nevirapine component?

iii. Stavudine (d4T) + Lamivudine (3TC) + Efavirenz (EFZ)

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

iv. Zidovudine (AZT) + Didanosine (ddI) + Nelfinavir (NFV)



INTRODUCTION

Global Burden of HIV/AIDS

At the end of 2002, 42 million adults and children were estimated to be living with HIV / AIDS in the world. In the year 2002, it was estimated that there were 5 million people newly infected with HIV and there were 3.1 million AIDS deaths. The total number of children orphaned by AIDS and living at the end of 2001 was 14 million.

HIV/AIDS in sub-Saharan Africa and Malawi

Sub-Saharan Africa is the epicentre of this epidemic, with 29.4 million people (or 70%) living with HIV/AIDS by the end of 2002. 85% of all the estimated deaths due to HIV/AIDS since the start of the pandemic have occurred in this region. Approximately 3.5 million new infections occurred in the region in 2002. The estimated number of children orphaned by AIDS living in the region is estimated at more than 11 million.

Malawi has one of the highest HIV/AIDS prevalence rates in the world, with 15% of those aged 15 – 49 years infected, while the national prevalence is estimated at 8.4 percent. By 2000, life expectancy declined to 39 years from a projected 54 years without the HIV/AIDS epidemic.

The National AIDS Commission estimated that in 2001 there were about 1,000,000 adults and children living with HIV/AIDS in the country. HIV/AIDS is now the leading cause

of death in the most productive age group, resulting in 50,000 to 70,000 adult and child deaths annually.

The cumulative number of orphans, directly related to the AIDS epidemic, is approximately 400,000, and more than 60,000 will be added to this pool each year.

AIDS kills young adults in their most productive years, depriving the region of the skills and knowledge base so essential to human and economic development. AIDS leaves countless numbers of grandparents to bring up children. Many orphans cannot attend school; they 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.

So far, sub-Saharan Africa, including Malawi, has offered little challenge to the devastation caused by this virus. With a few exceptions, strategies to prevent the spread of HIV have been unsuccessful. Good quality HIV counselling and testing services are few and far between, clinical care and the resources to treat opportunistic infections are minimal, and for the majority of people with HIV/ AIDS, there is no access to ARV drugs.

Antiretroviral (ARV) therapy in industrialised countries

Combination antiretroviral therapy (ARV) 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. Despite this enormous benefit, the

administration of ARV therapy is not without problems. Treatment of HIV-infection is likely to be life long, because therapy is not curative. Many HIV-infected persons may not tolerate the toxic effects of the drugs, and could have difficulties adhering to treatment which involves large numbers of pills and complicated dosing schedules. Poor adherence to treatment leads to the emergence of drug-resistant viral strains, necessitating new combinations of drugs or new drugs altogether.

Antiretroviral (ARV) therapy in sub-Saharan Africa

In sub-Saharan Africa, as of December 2002, fewer than 30,000 people were estimated to have benefited from ARV drugs. Many of those receiving ARV drugs do so in an unregulated and chaotic manner from within the private sector, with grave consequences for the rapid development of drug resistance.

As a result of strong international pressure, the price of ARV drugs has considerably decreased. The Global Fund to fight AIDS, tuberculosis and malaria (GFATM), established in July 2001, is a source of money, which will enable resource-poor countries to purchase ARV drugs. Agreement has been reached that such countries can purchase generic rather than patented drugs, which again reduces the cost. It is likely then that ARV drugs will become available on a much wider scale than before.

Access to ARVs could be an important component of a strategy to support people living with HIV/AIDS as well as

preventing transmission of infection. People may be more willing to undergo voluntary counselling and testing and disclose their HIV status if there is the possibility of getting effective treatment. By reducing viral load ARV drugs may from a biological viewpoint reduce the risk of sexual transmission. However, the provision of ARV drugs may lead to an increase in unsafe sexual practices, and this may negate the beneficial effects of therapy. 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.

ARV drugs must be provided within a structured framework, “a public health approach”, if the full benefits to the individual are to be realised and drug resistance is to be minimised. Widespread, unregulated access to ARV drugs in sub-Saharan Africa could lead to the rapid emergence of resistant viral strains, spelling doom for the individual, curtailing future treatment options and leading to transmission of resistant virus. A structured framework is therefore essential. There has to be a system to ensure regular procurement and distribution, good patient management, monitoring and evaluation. Such a system is possible within the public health sector as has so far been demonstrated through Tuberculosis Control programmes.

Antiretroviral (ARV) therapy in Malawi

Malawi has been successful in its application to the GFATM, and will receive funds to support a comprehensive national

response to the HIV/AIDS epidemic. Part of this response involves the delivery of ARV therapy.

Patients in certain health facilities in Malawi already receive ARV drugs according to a standardised regimen. In 2002, the number of patients being treated with HAART in the two central hospitals in Lilongwe and Blantyre (904) and the district hospital of Chiradzulu (316) was 1220.

Malawi will build on this existing service, and strengthen it in terms of standardised monitoring, recording and reporting. ARV drugs will first be given to eligible patients in a phased manner in terms of districts to be included.

During this introductory phase, safety, efficacy and the best practical systems of delivery and monitoring of ARV therapy will be determined. Once experience has developed and best practical systems have been worked out, the programme of ARV delivery will be expanded.

Within the four districts, the feasibility of delivering ARV therapy at health centre level will be explored and tested, as this is necessary in order to improve the access of poor people to ARV drugs. At the same time, the ARV delivery programmes will be extended to other districts in the country in a phased manner.

Private practitioners are a valuable part of the health delivery system in Malawi. The government sector will work with private practitioners to ensure that ARV drug regimens,

systems of delivering ARV drugs, monitoring and evaluation are standardised throughout the country.

One of the pre-requisites of being able to prescribe ARV drugs is that the health care worker should have a) undergone a formal training course in ARV therapy and b) be formally certified as competent in managing ARV therapy. Opportunities for training and certification will be available for health care workers in both the public and the private sector.

As ARV therapy is being introduced in Malawi, there will be an information, education and communication (IEC) campaign to sensitise the community, church leaders, traditional healers and other members of civil society about the value and benefits of ARV therapy for a) patients with HIV / AIDS, and b) the development of the country as a whole.

The dangers of unregulated use of ARV drugs, prescription of inappropriate regimens, poor compliance or adherence to drug regimens, and drug pilferage will be emphasised.

FRAMEWORK FOR ANTIRETROVIRAL DRUG DELIVERY

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

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



Goal

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

Objectives and Targets

The objectives and targets of antiretroviral drug delivery are:

- To provide long term ARV therapy to eligible patients
- To monitor and report treatment outcomes on a quarterly basis
- To attain individual drug adherence rates of 95% for patients on ARV therapy

- To increase life span so that 50% of patients on ARV therapy are alive and ambulatory after three years of ARV therapy
- To ensure that 50% of patients on ARV therapy are engaged in their previous employment or any other productive activity within 6 months of starting ARV therapy
- To reduce the number of new orphans registered each year

Strategy

The strategy is to provide standardised combination ARV therapy to HIV-positive persons who present to health facilities and who fulfil the eligibility criteria (see Chapter on Patients Eligible for ARV Therapy); using guardian-supported treatment.

ARV Policy Package

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

- government commitment to ARV delivery
- detection of eligible cases who should have undergone HIV counselling and testing and have a confirmed HIV-seropositive result and who fulfil eligibility criteria
- standardised combination ARV therapy to HIV-seropositive eligible patients under proper case

management conditions with high levels of drug adherence

- regular, secure and uninterrupted supply of ARV drugs to units which are administering ARV treatment
- monitoring system for supervision of ARV therapy, effective patient tracing and follow-up and regular evaluation

Key Operations

- There is an HIV/AIDS Clinical Unit in Ministry of Health and Population, which has overall responsibility for the management of ARV therapy in the country
- The ARV treatment guidelines are available in every treatment unit which administers ARV therapy
- There is a standardised registration, recording and reporting system
- There is a combined training and examination programme covering all aspects of ARV delivery, which all staff involved in ARV delivery must have attended and must have passed
- There is a voluntary counselling and HIV testing service (VCT) linked to every unit providing ARV therapy, which is subject to regular quality assurance and quality control
- ARV treatment units are provided within the general health services, at hospital and also at health centre level

- There is a regular supply of ARV drugs and HIV testing materials
- There is a plan of supervision
- There is a plan of regular reporting and evaluation
- HIV / AIDS research is fully regulated to support patient care and implementation of the ARV treatment guidelines
- There is a development plan with budget details, funding sources and responsibilities

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

Indicators to measure progress with ARV delivery

Input indicators:

- An ARV treatment guideline manual (reflects government commitment)
- Number of HIV Clinics administering ARV therapy
- Number of staff trained and accredited in the use of ARV drugs
- No stock-outs of ARV drugs and HIV test kits, and uninterrupted supplies of ARV drugs to patients

Output indicators:

- The number of patients who start on standardised ARV therapy

- The percentage of patients who show 95% adherence to ARV therapy
- The percentage of patients on ARV therapy alive at a given time
- The percentage of patients alive on ARV therapy who are ambulatory (or in the case of children are engaged in age-related day time activities)
- The percentage of patients alive on ARV therapy who are engaged in previous work or employment
- The number of new orphans registered each year in a district in which ARV therapy is being administered
- In a sample of specimens assessed, the percentage of patients with undetectable viral load 6 months after the introduction of HAART



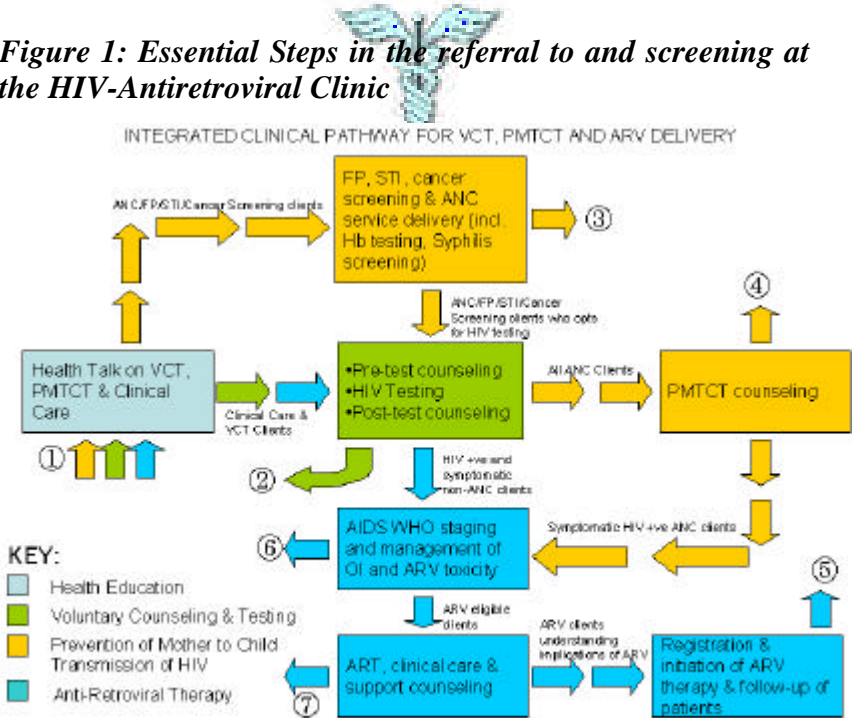
THE HIV ANTIRETROVIRAL CLINIC AND STAFF

Referral to the VCT Unit and to HIV-Antiretroviral Clinic

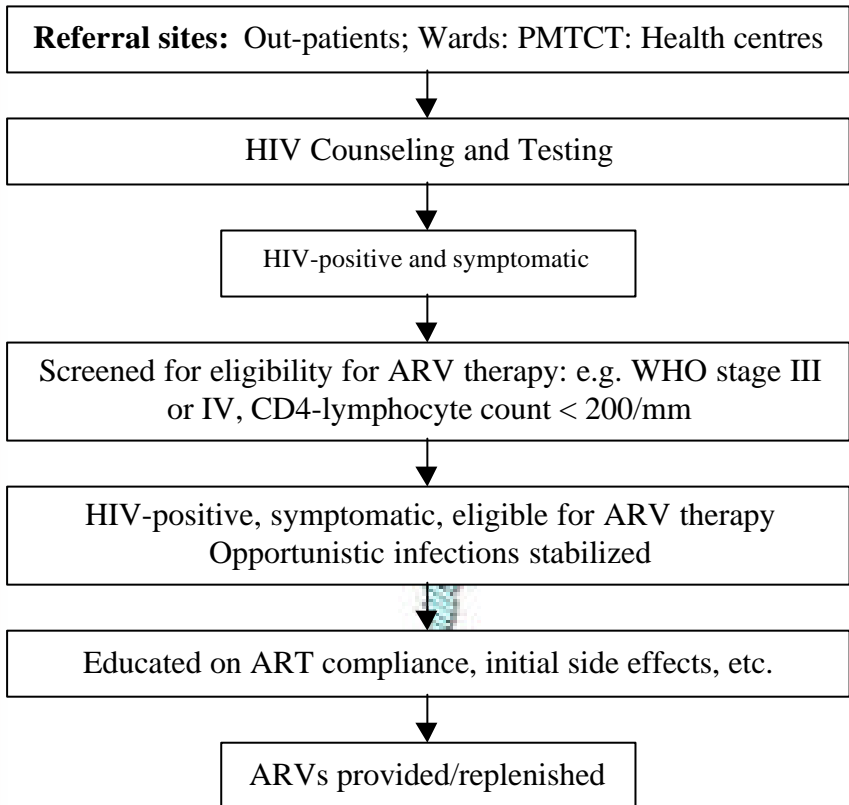
Referral to the VCT Unit can be from several sites such as the general outpatient department, the general wards, the TB wards, the antenatal clinic or the laboratory.

All referrals will undergo voluntary counselling and HIV testing. Persons who test HIV-positive at the VCT unit will need to be classified into a) asymptomatic and b) symptomatic. Those who are symptomatic will be referred to the HIV-Antiretroviral Clinic for further assessment (see Figure 1).

Figure 1: Essential Steps in the referral to and screening at the HIV-Antiretroviral Clinic



Summary on the Antiretroviral Clinic access steps



The HIV-Antiretroviral Clinic

ARV therapy will be provided to eligible patients initially from HIV-ARV Clinics. The clinics will be situated in either central hospitals or the district / mission hospitals. 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 HIV-ARV clinics:-

- The Clinic should be physically integrated with the general out-patient services
- The Clinic must not be too far from the voluntary counselling and testing (VCT) unit, the wards and out-patient departments, and the hospital laboratory service where HIV testing is carried out
- The Clinic is specifically for HIV-positive symptomatic patients, who need skilled care for the management of their opportunistic infections and malignancies and who need ARV therapy
- The Clinic will carry out the WHO Clinical Staging assessment in HIV-positive symptomatic patients, as this staging determines whether or not the patient is eligible for ARV therapy
- The Clinic needs space and possibly separate rooms for:-
 - a. Counselling, support and education of patients on ARV therapy
 - b. Clinical management of opportunistic infections, WHO clinical staging assessments, and clinical assessment of possible ARV toxicity
 - c. Registration and initiation of ARV therapy and follow-up of patients on ARV therapy

- d. The Clinic will dispense ARV drugs, and in this way there will be a more robust accountability of drug usage. In urban areas a contractual arrangement may be set up with private pharmacies to take up the dispensing function. Patient visits will be planned and organised as discussed under Monitoring and Recording Treatment Response.

Once experience has developed in the delivery of ARV therapy from hospital clinics, then consideration will be given to setting up similar-type clinics at health centres to improve patients' access to ARV therapy.

HIV-Antiretroviral Clinic Staff

The number and type of staff needed to run the Clinic will be determined by the hospital's resources. For example, the ARV clinic may run on five days a week or two days a week. Whenever it is being run, the minimum staff requirement is:-

1 clinical officer	(full-time) for the time of the clinic
1 nurse	(full-time) for the time of the clinic
1 counsellor	(full-time) for the time of the clinic
1 ward clerk equivalent	(full-time) for the time of the clinic

Provided certain criteria are met (see below), medical officers and clinical officers can initiate and prescribe ARV drugs within these clinics. Provided certain criteria are met, medical assistants and nurses can also assist medical and clinical officers to administer and deliver ARV drugs within these clinics.

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



Laboratory Back-up: minimum requirements

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

PATIENTS ELIGIBLE FOR ARV THERAPY

ADULTS [persons aged 13 years and above]:

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

Patients are known to be HIV-seropositive

Patients must have undergone HIV counselling and testing, 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 ARV therapy.

Patients understand the implications of ARV therapy

Patients must have undergone more than one counselling session either group and/or individual counselling during which the implications of ARV therapy have been discussed, in particular that ARV therapy requires high adherence and compliance with prescribed regimens and is a life long commitment.

Patients who are moribund and severely ill with an opportunistic infection or HIV-related malignancy should be treated appropriately and stabilised before considering the possible use of ARV therapy. They can then be re-assessed for

counselling and testing on a case by case basis, and a decision made about whether or not to start ARV therapy. ARV therapy is not an emergency treatment.

Patients are assessed as being in WHO Clinical Stage 3 or 4

Patients who fall into WHO Clinical Stage 3:

Patients who just have minor manifestations of a) oral hairy leukoplakia and b) vulvo-vaginal candidiasis without other systemic features are not eligible for ARV therapy.

Patients with other features shown in Table 1 are eligible for ARV therapy, regardless of peripheral lymphocyte counts or CD4 lymphocyte counts. The opportunistic infections listed in Table 1 should receive treatment and be stabilised before ARV therapy commences

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

Table 1: Features of WHO Clinical Stage 3

WHO Clinical Stage 3:

- Oral candidiasis
- Unintentional weight loss > 10% of body weight in the absence of concurrent illness
- Chronic diarrhoea > 1 month

- Prolonged fever (intermittent or constant) > 1 month
- Pulmonary tuberculosis within the past year
- Severe bacterial infections (e.g. pneumonia, pyomyositis)

Patients who fall into WHO Clinical Stage 4:

Patients with features shown in the Table 2 are eligible for ARV therapy, regardless of peripheral lymphocyte counts or CD4 lymphocyte counts. The opportunistic infections listed in Table 2 should receive treatment and be stabilised **before** ARV therapy commences.

Table 2: Features of WHO Clinical Stage 4

WHO Clinical Stage 4:

- HIV wasting syndrome (weight loss > 10% of body weight and either chronic fever or diarrhoea in the absence of concurrent illness)
- Pneumocystis carinii pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea > 1 month
- Isosporiasis with diarrhoea > 1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus of an organ other than liver, spleen or lymph node
- Herpes simplex infection, mucocutaneous for > 1 month or visceral

- Progressive multifocal leucoencephalopathy
- Any disseminated endemic mycosis
- Candidiasis of oesophagus, trachea and bronchus
- Atypical mycobacteriosis, disseminated or lungs
- Non-typhoidal salmonella septicaemia
- Intrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma
- HIV encephalopathy

Patients have a CD4 lymphocyte below 200/mm³

Any patient HIV-seropositive with a CD4 count below 200/mm³ is eligible for ARV therapy regardless of WHO Staging or symptoms.

Patients are assessed as being in WHO Stage II with a total lymphocyte count < 1200/mm³

A total lymphocyte count < 1200/ mm³ in conjunction with clinical staging has useful prognostic significance. Therefore, patients with a low total lymphocyte count and any features shown in Table 3 are eligible for ARV therapy.

Table 3: Features of WHO Clinical Stage 2

WHO Clinical Stage 2:

- Unintentional weight loss < 10% of body weight in the absence of concurrent illness

- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
- Herpes zoster within the last 5 years
- Recurrent upper respiratory tract infections (i.e., bacterial sinusitis)

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

CHILDREN [persons aged 12 years or below]:

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

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 ARV therapy.

Paediatric patients will be eligible for ARV therapy if their care-givers have received appropriate counselling and understand the implications of ARV therapy 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 ARV therapy.

VCT in children will be provided in the presence of a caregiver. However, older children and adolescents will need to be actively involved in counselling and HIV testing decisions. 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 ARV therapy need to be explained to the caregiver and the child in an age-adapted fashion.

The presence of trans-placental maternal antibody means that HIV infection cannot be diagnosed using antibody-based HIV tests in children less than 18 months of age. Furthermore, normal CD4 counts and the proportion of lymphocytes expressing CD4 vary with age, particularly in young children.

Since the proportion of CD4 positive lymphocytes is less age-dependant than the absolute CD4 count, the CD4 percentage is generally preferred as a measure of immune-status in HIV-infected children. However, above the age of 6 years the absolute CD4 lymphocyte count can be used. Calculation of CD4 percentage among children considered for ARV therapy requires measurement of the total lymphocyte count in addition to the CD4 count.

Eligibility

HIV-infected children may be eligible for ARV therapy on the basis of clinical symptoms or a low CD4 percentage. CD4 measurements used for such decision-making should be


obtained when children are stable and have recovered from acute infection.

Children over the age of 18 months

For HIV-seropositive children over the age of 18 months, ARV therapy may be considered for children with WHO Stage III disease (i.e. clinical AIDS), regardless of CD4 percentage. For children with WHO Stage I or II HIV disease, ARV therapy is recommended if the CD4 percentage is less 15%.

The WHO Staging system for HIV infection in children is shown in Table 4.

Table 4: WHO Staging System for HIV Infection and Disease in children



<p>Clinical stage I:</p> <ul style="list-style-type: none"> • Asymptomatic • Generalised lymphadenopathy <p>Clinical stage II:</p> <ul style="list-style-type: none"> • Unexplained chronic diarrhoea • Severe persistent or recurrent candidiasis outside the neonatal period • Weight loss or failure to thrive • Persistent fever • Recurrent severe bacterial infections <p>Clinical stage III:</p>
--

- AIDS-defining opportunistic infections
- Severe failure to thrive
- Progressive encephalopathy
- Malignancy
- Recurrent septicaemia or meningitis

Children under 18 months of age

Where virological confirmation of infection is available (PCR or immune complex - dissociated p24 antigen detection or HIV culture), ARV therapy may be offered to children with proven HIV infection and a WHO Paediatric Stage III disease (i.e. clinical AIDS) or a WHO Stage I / II disease and a CD4 percentage < 20%.

Where virological confirmation is not possible, ARV therapy may be offered to HIV-seropositive children with WHO Stage III disease and a CD4 percentage < 20%.

Many of the clinical symptoms in the WHO classification are not specific for HIV infection and overlap significantly with those seen in children without HIV infection. Thus, in the absence of virological testing and CD4 cell assay availability, HIV-exposed infants < 18 months of age should generally not be considered for ART regardless of symptoms.

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

ANTIRETROVIRAL DRUGS: GENERAL PRINCIPLES

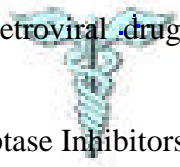
Aims of Treatment

The three main aims of ARV therapy 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

ARV Drug Classes

Currently available antiretroviral drugs belong to two major classes:



- i) Reverse Transcriptase Inhibitors (RTIs)
- ii) Protease Inhibitors (PIs)

Reverse transcriptase Inhibitors are further divided into 3 groups:

- i) Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)
- ii) Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)
- iii) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Examples of antiretroviral drugs in each of these classes are shown in Table 5.

Table 5: Different classes of antiretroviral drugs

NsRTI	NtRTI	NNRTI	PI
Zidovudine (ZDV)	Tenofovir (TDF)	Nevirapine (NVP)	Nelfinavir (NFV)
Didanosine (ddI)		Efavirenz (EFZ)	Saquinavir (SQV)
Lamivudine (3TC)			Ritonavir (RTV)
Stavudine (d4T)			Lopinavir (LPV)
Zalcitabine (ddC)			Indinavir (IDV)
Abacavir (ABC)			Amprenavir (APV)

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

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

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

Class-specific and drug-related side effects:

Class-specific side effects:

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

Drug specific side effects:

NRTIs:	
Zidovudine	Nausea, headache, fatigue, muscle pains, anaemia, agranulocytosis
Didanosine	Nausea, diarrhoea, neuropathy, pancreatitis

Lamivudine	Nausea, headache, fatigue, muscle pains
Stavudine	Neuropathy, pancreatitis, gastrointestinal effects, insomnia
Zalcitabine	Neuropathy, pancreatitis, oral ulcers
Abacavir	Nausea, fatigue, sleep disturbance, hypersensitivity reaction
NNRTIs:	
Nevirapine	Skin rash, hepatitis
Efavirenz	Skin rash, central nervous system disorders, teratogenicity
PIs:	
Nelfinavir	Diarrhoea, nausea, skin rash
Saquinavir	Diarrhoea, nausea, headache
Lopinavir/ ritonavir	Diarrhoea, nausea, headache, abnormal taste, peri-oral numbness, pancreatitis
Indinavir	Nephrolithiasis, diarrhoea, nausea, abdominal pain, headache
Amprenavir	Diarrhoea, nausea, abnormal taste, peri-oral numbness

Standard Adult Antiretroviral Drug Doses

Drug class / drug	Dose
NsRTIs:	
Zidovudine	300 mg twice daily
Didanosine	400 mg once daily (250 mg once daily if < 60Kg)
Lamivudine	150 mg twice daily
Stavudine	40 mg twice daily (30 mg twice daily if < 60Kg)
Zalcitabine	0.75 mg three times daily
Abacavir	300 mg twice daily
NtRTI:	
Tenofovir	300 mg once daily
NNRTIs:	
Nevirapine	200 mg once daily for 14 days, then 200 mg twice daily
Efavirenz	600 mg once daily
PIs:	

Nelfinavir	1250 mg twice daily
Saquinavir / ritonavir	/ 1000 mg / 100 mg twice daily
Lopinavir / ritonavir	400 mg / 100 mg twice daily
Indinavir / ritonavir	800 mg / 100 mg twice daily



STANDARDISED TREATMENT FOR MALAWI

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
- abacavir was not a good choice because of the hypersensitivity reaction which might be difficult to identify in rural areas

NNRTIs:

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

PIs:

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

The choice of the first line regimen:

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

The dosages depend on body weight:

Less than 60 Kg: Use d4T/3TC/NVP-30 (d4T30mg + 3TC150 mg + NVP 200mg)

60 Kg and above: Use d4T/3TC/NVP-40 (d4T40mg + 3TC150 mg + NVP 200mg)

Components of the first line regimen:

Stavudine (d4T)

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

The dose is: 40 mg twice a day for patients 60Kg or above
30 mg twice a day for patients less than 60Kg.

It is recommended that dose reduction occurs for peripheral neuropathy.

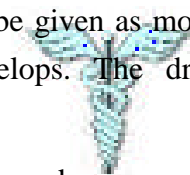
Side effects: the main immediate side effect is peripheral neuropathy: long term side effects include lactic acidosis and other manifestations of mitochondrial dysfunction

- 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.



The dose is 150 mg twice a day

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.

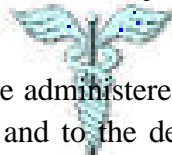
Nevirapine (NVP)

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

The drug may be given as monotherapy for the prevention of mother to child transmission, but otherwise is used in combination for long term ARV therapy.

The dose is 200 mg once daily for the first two weeks, followed by 200 mg twice daily thereafter. This lead in dose is important to reduce the frequency of rash.

There are two major side effects, which occur principally during the initial 8 weeks of treatment. The first major effect is a coetaneous hypersensitivity reaction (fever, rash, arthralgia and myalgia), which can lead to a life-threatening Stevens Johnson syndrome. The second major effect is drug-induced hepatitis.



- Nevirapine may be administered on its own to pregnant women in labour and to the delivered infant within 72 hours of birth for prevention of mother to child transmission
- Nevirapine is also combined with Stavudine and Lamivudine, as triple therapy.

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

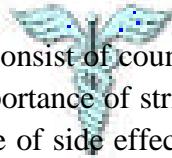
- There is an interaction with rifampicin, a drug which also induces cytochrome p450. Rifampicin decreases the levels of nevirapine by 37% and therefore decreases its effectiveness and increases the risk of inducing NVP resistance.
- There is an interaction with ketoconazole leading to a 30% increase 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.

Introduction of the first line regimen for individual patients

- Eligible patients will be seen and assessed in one of the treatment units. This assessment will also be carried out in conjunction with a patient's guardian, with due attention being paid to confidentiality and informed consent.
- Assessment will consist of counselling the patient about the drugs, the importance of strict adherence to therapy, what to do in case of side effects and the importance of continuing to practice safe sex (see Chapter on Education)
- Assessment will also involve determining whether there are any contraindications to d4T/3TC/NVP. The main contraindication is obvious liver disease [jaundice or ascites]; in this situation d4T/3TC/NVP will not be prescribed. Another possible contraindication is severe peripheral neuropathy: if this is felt to be due to HIV infection, the d4T/3TC/NVP may help and under strict supervision the ARV drug can be given (also see Chapter on anti-TB drugs).



- The patient will be weighed, and then prescribed either d4T/3TC/NVP-30 or d4T/3TC/NVP-40 depending on body weight.
- If facilities permit, blood will be taken for Full blood count, Liver Function tests, Serum creatinine and CD4-lymphocyte counts. However, these blood tests are not mandatory.
- Patients will be given drugs for two weeks as follows:

d4T/3TC/NVP 1 tablet mane plus d4T/3TC 1 tablet nocte

The introduction of d4T/3TC/NVP in this fashion is because of the need to reduce the frequency of rash caused by Nevirapine. If a rash occurs during this first two weeks, the dose of d4T/3TC/NVP is not to be increased (see section on skin rash on page 98).

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

d4T/3TC/NVP 1 tablet mane plus 1 tablet nocte

- Patients will be seen every four weeks, and provided there are no problems will be prescribed drugs again for 30 days. If any side effects are experienced between clinic visits, patients will be educated about the need to report to a health facility.

- The review at 2 weeks and monthly can be delegated to a trained Nurse or Medical Assistant with a provision that he/she will refer the patient for clinical assessment by trained doctor or Clinical Officer if any side effects or problems are enlisted.

Table 6: Summary table on the Introduction of First line ARV therapy

First two weeks	D4T/3TC/NVP 1 tablet in the morning Plus D4T / 3TC 1 tablet in the evening
Thereafter	D4T/3TC/NVP 1 tablet in the morning Plus D4T/3TC/NVP 1 tablet in the evening

Table 7: Contraindication to d4T/3TC/NVP

Obvious liver disease (e.g., jaundice or ascites)

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 page 94), and some of these may be serious enough to require stopping the first line regimen.

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

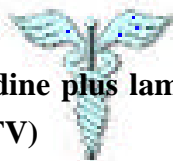
i) Severe peripheral neuropathy: due to the stavudine component

Change to: **zidovudine plus lamivudine plus nevirapine (AZT + 3TC + NVP)**

The patient will need regular monitoring every 6 months with measurements of haemoglobin

ii) Liver disease such as jaundice: due to the nevirapine component

Change to: **stavudine plus lamivudine plus efavirenz (d4T + 3TC + EFV)**



Note: Women of child-bearing age will need to take additional or alternative precautions to avoid pregnancy because of the risk of teratogenicity of EFV.

iii) Severe skin reaction: due to the nevirapine component

Change to: **stavudine plus lamivudine plus efavirenz (d4T + 3TC + EFV).**

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

It is expected that all HIV-Antiretroviral clinics will be able to manage adverse drug reactions to the first line regimen and implement a change to an alternative first line regimen when indicated. In addition to having triple therapy (d4T/3TC/NVP-30 and d4T/3TC/NVP-40) and dual therapy (d4T/3TC-30 and d4T/3TC-40), all clinics should have available sufficient supplies of: - triple therapy (AZT/3TC/NVP); and monotherapy (EFV).

The Second line Regimen:

The second line regimen is used when patients have failed the first line regimen. Failure is defined as either the development of a new WHO Clinical Stage 4 feature or a CD4 count of <30% of peak value or of < 200/mm³, which is confirmed one month later in a patient who has been on ARV therapy for 6 months or more and has been adhering to therapy.

The decision to change to the second line regimen should not be made lightly, because the regimen is more difficult for patients to take and requires more management. Patient should be referred to treatment centres that can best assess for failure and institute second line regimen.

Replacement of d4T/3TC:

A reasonable dual nucleoside component alternative to d4T / 3TC is Zidovudine and didanosine (AZT / ddi), although there is nucleoside analogue cross-resistance. Nucleoside cross-resistance may compromise the potency of AZT / ddi,

particularly in the presence of long-standing virological treatment failure.

The use of AZT would require the need for regular Haemoglobin measurements. The side effect profile of ddI is similar to that of d4T. Didanosine (ddI) is a difficult drug to take, and needs to be taken on an empty stomach.

Replacement of NVP:

Because of cross-resistance with other members of the NNRTI class, nevirapine has to be replaced with a protease inhibitor. Nelfinavir is the first choice, and if unavailable then this could be replaced with indinavir. The main side effects are gastrointestinal.

The following drug regimen is therefore the chosen second line option: **Zidovudine (ZDV) + Didanosine (ddI) + Nelfinavir (NFV)**

EDUCATION FOR THE PATIENT AND GENERAL PUBLIC

Education for the patient

Before patients start on ARV therapy they must understand the implications of therapy and be prepared to accept therapy as a life long commitment. It is recommended that wherever possible group counselling sessions are conducted on HIV /AIDS with due reference to the benefits and dangers of ARV therapy followed by individual counselling sessions.

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

Patient education must occur at the start of ARV therapy and during therapy. It is recommended that every 6 months, patients receive education about the importance of strict adherence to therapy.

IEC materials on ARV therapy will be distributed to health facilities and public places, and radio broadcasts will be a regular feature, so that patients and the general public are made aware of the benefits and dangers of ARV therapy. These

materials will be field tested and regularly evaluated to ensure that the messages given are appropriate and clear.

The key messages about ARV drugs 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 where appropriate
- Only drugs prescribed from certified practitioners should be taken
- All the drugs have to be taken according to the prescription advice, otherwise they will become ineffective because of resistance
- Drugs must not be shared with relatives or friends
- If 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
- If there is evidence that drugs are being sold in market places this must be reported to the health authorities in order for action to be taken - such practices will lead to the development of widespread resistance to ARV therapy
- ARV drugs in the first line regimen and alternative first line regimens can be taken independently of food. However, ARV drugs in the second line regimen need to be taken in relation to food. For example, ddI has to

be taken on an empty stomach while protease inhibitors in general have to be taken with food.

- It is important that patients on ARVs try and get a balanced diet rich in proteins, carbohydrates, vitamins and essential trace elements as possible (see Nutrition guidelines).
- If the patient dies, the remaining ARV drugs must be returned to the ARV Clinic even in such cases where these were paid for, or where the household or neighbourhood has another client on similar ARV drug regimen.

Education for the general public

Key messages for the general public are:-

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

- In general alcohol must be avoided due to its causative association to liver disease.



ARV THERAPY IN SPECIAL SITUATIONS

Women of Childbearing Potential and who are Pregnant

Nevirapine, one of the components of d4T/3TC/NVP, i.e. first line regimen can lower the blood concentration of oral contraceptives, hence an additional or alternative contraceptive method (such as medroxyprogesterone for women or condoms for men) should be considered to avoid pregnancy in women using an oestrogen containing oral contraceptive method. If efavirenz is used as proposed in one of the alternative first line drug regimens, it is important to note that efavirenz is teratogenic. For this reason, women who are taking efavirenz must also 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. On general principles if a woman is known to be pregnant and is starting ARV therapy, this should be delayed until after the first trimester unless benefits outweigh the disadvantages.

Any pregnant woman who is taking triple ARV therapy 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 nevirapine as a single oral dose of 2mg/kg within 72 hours of birth.

d4T/3TC/NVP can therefore be safely given to lactating mothers. However, an attempt should be made to explain to the expectant mother that having more pregnancies may be detrimental to the woman's health status.

Patients with Liver Disease

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

Patients with Renal Failure

Prior to treatment patients should be assessed for advanced renal failure. If, from the history and/or clinical symptoms and signs, renal impairment is suspected patients should be referred to a centre where a) urine analysis, creatinine and blood urea nitrogen testing as well as abdominal ultrasonography can be performed and b) specialist advice is available. Renal failure will not automatically exclude patients from treatment, because patients with HIV nephropathy can directly benefit from ARV therapy.

Nevirapine does not require dose adjustment in renal failure. Both stavudine and lamivudine are eliminated by the renal route, and need dose adjustments as renal failure progresses. Specialist advice is needed for the administration of ARV therapy 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 should be started at central hospital level.

Down to a clearance of 50 ml/min standard doses can be taken; any lower clearance rate requires half dose of stavudine (d4T). In the case of lamivudine the standard dose can be given down to a clearance of 50 ml/min, then below that the suitable reductions have to be made according to the schedule provided below in Table 10:-

Figure 2: Lamivudine dosages in relation to creatinine clearance

Creatinine Clearance	Lamivudine Dosages
50 - 30 ml/min	150 mg daily
29 - 15 ml/min	150 mg start dose; 100 mg daily
14 - 5 ml/min	150 mg start dose; 50 mg daily
Less than 5 ml/min	50 mg start dose; 25 mg daily

CHILDREN

ARV therapy 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 working in clinics providing treatment for children must have received appropriate training in the use of ARV therapy.

Choice of the first line ARV-regimen

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

There is considerable advantages if the treatment guidelines for adults and children on antiretroviral therapy in Malawi recommended the **same** drugs and formulations. Health worker, patient, guardian and community education are easier with recommendations common to adults and children, as are issues of drug availability and transition from paediatric to adult care.

It is recommended, therefore, that children receive **d4T + 3TC + NVP given as divided tablets according to weight as set out in Annex 1**. It should be pointed out that the use of this triple therapy combination in children has no conclusive evidence base, although on general principles it is reasonable to believe that it will be as effective as in adults.

As outlined elsewhere, 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 should the child develop a rash or become unwell. Guardians should be instructed not to stop therapy without authorisation from clinic staff. Where possible the initial phase of anti-TB treatment should be completed prior to commencement of ARV therapy to minimise problems with drug interactions and adherence.

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

Children, like adults, may experience adverse reactions to the first-line regimen, and some of these may be serious enough to require stopping the first line regimen. The same recommendations, as for adults, apply to children:-

Severe peripheral neuropathy: due to the stavudine component

- i) Change to **zidovudine plus lamivudine plus nevirapine (AZT + 3TC + NVP)**

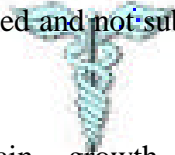
Liver disease such as jaundice: due to the nevirapine component

- ii) Change to **stavudine plus lamivudine plus efavirenz (d4T + 3TC + EFV)**

Severe skin reaction: due to the nevirapine component

- iii) Change to **stavudine plus lamivudine plus efavirenz (d4T + 3TC + EFV)**.

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 and not substituted.



Monitoring

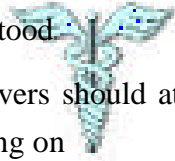
In children, weight gain, growth and development are important clinical monitoring indicators. Weight and height (if possible) should be assessed using growth charts; these measures are particularly important for monitoring response to therapy in the absence of CD4 counts and percentages.

Drug Adherence in Children

To promote drug adherence the following steps are recommended:

- i. At HIV-ARV clinics ARV-drugs must always be available
- ii. Before initiating ARV treatment in children

- a. A person responsible for drug administration should be clearly identified
- b. Caregivers should be provided with a written medication-schedule emphasising the need for a modified dosing scheme during the first two weeks of therapy, together with the need to report promptly the appearance of rash or other new symptoms
- c. Caregivers should repeat the dosing schedule to make sure that the schedule is understood
- d. Caregivers should attend education sessions focusing on
 - 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.)

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

Second line Regimen for use in children in Malawi

The same recommendations, as for adults, apply to children:-

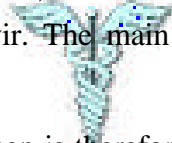
Replacement of d4T/3TC:

A reasonable dual nucleoside component alternative to d4T / 3TC is Zidovudine and didanosine (AZT / ddi), although there

is nucleoside analogue cross-resistance. Nucleoside cross-resistance may compromise the potency of AZT / ddI, particularly in the presence of long-standing virological treatment failure. The use of AZT would require the need for regular Haemoglobin measurements. The side effect profile of ddI is similar to that of d4T. Didanosine (ddI) is a difficult drug to take, and needs to be taken on an empty stomach.

Replacement of NVP:

Because of cross-resistance with other members of the NNRTI class, nevirapine has to be replaced with a protease inhibitor. Nelfinavir is the first choice, and if unavailable then this could be replaced with indinavir. The main side effects are gastrointestinal.

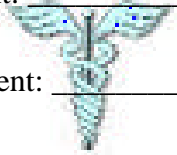


The following drug regimen is therefore the chosen second line option: **Zidovudine (ZDV) + Didanosine (ddI) + Nelfinavir (NFV)**

Treatment Card

A treatment card should be given to the caregiver at the initiation of ARV therapy. The card should give details of the treatment prescribed including dose and frequency. This card (see Figure 3) should normally be carried inside the child's health record (Health Passport) and should accompany the child at each clinic visit.

Figure 3: ARV Treatment card for children:

ARV Treatment Card	
Name of patient:	_____
ARV Registration Number:	_____
Name of Guardian:	_____
Date of Birth:	_____ Sex: _____
Date of starting treatment:	_____
Weight at start of treatment:	_____
	
Treatment:	(d4T/3TC/NVP)
Date: __ / __ / __	Weight: ____Kg Dose: _____
Date: __ / __ / __	Weight: ____Kg Dose: _____
Date: __ / __ / __	Weight: ____Kg Dose: _____
Date: __ / __ / __	Weight: ____Kg Dose: _____

TREATMENT OF HIV-POSITIVE PATIENTS WITH TUBERCULOSIS

Background:

Patients with tuberculosis are treated with standardised regimens in Malawi. All regimens include an Initial Phase of Treatment with 3 to 5 drugs, and a continuation phase usually with two drugs (see TB Treatment Manual, 2002, Edition 5).

In the initial phase of treatment, all drug combinations include rifampicin, which interacts with nevirapine. In the continuation phase of treatment for new patients with smear-positive pulmonary TB (PTB), smear-negative PTB and extrapulmonary TB, the treatment is daily ethambutol and isoniazid for 6 months. In new patients with TB meningitis and patients being treated for recurrent TB, the continuation phase includes rifampicin.

As a matter of principle while Malawi gathers experience with using ARV therapy in TB patients, d4T/3TC/NVP will not be used in conjunction with rifampicin.

Eligibility for treatment and when to start ARV therapy:

All patients with tuberculosis are potentially eligible for ARV therapy, because they are either categorised as WHO Clinical Stage III or IV. In the initial phase of anti-TB treatment, ARV therapy will not be given because of the interaction between rifampicin and nevirapine. Once the patient has completed the initial phase of treatment and started on the continuation phase

of anti-TB treatment with isoniazid and ethambutol (EH), the patient will then be eligible for ARV therapy. Because rifampicin has a long half-life, it is advised that ARV therapy with d4T/3TC/NVP is started after the patient has been on EH for two weeks.

Steps in the treatment of TB patients with ARV therapy

The following steps are recommended:-

- HIV-positive TB patients can receive anti-TB drugs and ARV drugs at a) the same HIV-ARV clinic, b) the same TB office or c) the TB office and the ARV Clinic. Every attempt should be made to make these visits user friendly and convenient for the patient
- Patients will be registered for ARV therapy in the usual way. Their TB treatment cards will also be kept at the HIV-ARV clinic, for completion by the health personnel; TB treatment cards will be marked with the unique ARV registration number. Anti-TB drugs (EH) will also be stocked and dispensed at the clinic
- TB patients will receive EH, pyridoxine 10mg daily, and ARV therapy in accordance with the introduction steps for d4T/3TC/NVP. If TB patients are taking cotrimoxazole (CTX) prophylaxis, CTX will be continued along with ARV therapy: [it is not known definitely whether CTX should be continued or stopped in these circumstances, and relevant operational research will need to be carried out to answer this question]

- For the first two weeks of ARV therapy the patient will take d4T/3TC/NVP 1 tablet daily plus d4T/3TC 1 tablet daily. The patient will be reviewed after two weeks, but will be asked to report earlier if there are any side effects, which may result from anti-TB treatment and ARV therapy.
- After two weeks, the patient will be started on d4T/3TC/NVP 1 tablet twice a day, and will be discharged on 30 days supply of d4T/3TC/NVP, EH, CTX and pyridoxone 10 mg daily. The patient will be asked to return to the clinic every 4 weeks. At this time, the ARV patient master card will be completed, the TB Treatment card will be completed and the patient re-issued with drugs for 30 days.
- At the end of anti-TB treatment, the TB treatment card will be returned to the District TB Officer. Details will be entered in the TB register, including the ARV unique registration number. The patient will continue to receive d4T/3TC/NVP at the HIV-ARV Clinic.

Table 8: A Summary table on ARV therapy with anti-tuberculosis treatment

Phase of Anti-TB Treatment	ARV therapy
Initial Phase [RHZ(E)]	No ARV therapy
Continuation Phase (EH)	<ul style="list-style-type: none"> • Wait for 2 weeks before ARV therapy to allow rifampicin levels to disappear

- | | |
|--|---|
| | <ul style="list-style-type: none">• Then start therapy with d4T/3TC/NVP |
|--|---|

- Any patient starting anti-TB treatment while already on d4T/3TC/NVP will have the ARV drugs changed to d4T/ 3TC/ EFV until the initial phase with rifampicin is completed. Women must be given appropriate contraceptive advice. When continuation phase is started the patient is changed back to d4T/3TC/NVP.
- Patients on the re-treatment regimen, which contains rifampicin throughout, should also be considered for an alternative first line ARV treatment regimen; e.g.
- d4T/3TC/EFV. Women must be given appropriate contraceptive advice.



TREATMENT OF HIV-POSITIVE PATIENTS WITH MALIGNANCY

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

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

One of the core elements of treatment for HIV-related malignancy is the provision of ARV therapy. In fact, in patients with benign, non-aggressive cutaneous forms of Kaposi sarcoma ARV therapy on its own is sufficient enough treatment. However, for most patients treatment of HIV-related malignancies should also include the use of cytotoxic drugs, if these are available.

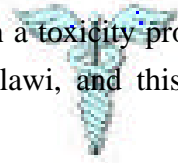
This strategy applies to patients with **aggressive Kaposi's Sarcoma** (in which lesions are associated with a significant impact on functional and/or vital prognosis) **or lymphoma**. Even though not curative, the addition of cytotoxic therapy can significantly increase the patients' quality of life and length of survival, although these drugs in their own right are immunosuppressant.

Bleomycine, Vincristine, Etoposide, Cyclophosphamide, Methotrexate (to name only those available in Malawi) figure

among the drugs ordinarily used in various protocols of mono or preferably poly-chemotherapy. These drugs are usually only available at central hospitals in Malawi. Radiotherapy, which is not currently available in Malawi, is also frequently recommended.

Whenever possible, cytotoxic therapy should be combined with ARV therapy, and patients referred to central hospitals for administration of intermittent cycles of cytotoxic chemotherapy.

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



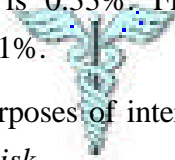
The common principal toxicities caused by the available cytotoxic and ARV drugs are shown below:-

- Vincristine and Etoposide may induce neurological toxicity, and particularly peripheral neuropathy, like Stavudine (D4T) and Didanosine (DDI)
- Bleomycine may cause muco-cutaneous reactions, like Nevirapine (NVP)
- Cyclophosphamide, Methotrexate, Etoposide are all myelotoxic, like Zidovudine (AZT). This association requires more frequent measurements of the full blood count

MANAGEMENT OF 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 also 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 0.33%. From mucous membrane exposure it is less than 0.1%.



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

High risk:

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

Low risk:

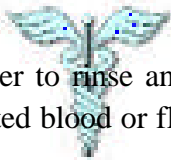
All other exposures, including percutaneous injuries with solid needles, exposures to fluids other than blood, and exposures to the non-intact skin, are considered *low risk exposures*.

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

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

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

Immediate measures:

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

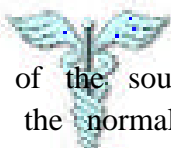
Post-exposure prophylaxis (PEP): low risk and high risk

“**PEP**” refers to the treatment of occupational exposures using antiretroviral (ARV) therapy. ARV therapy started immediately after exposure to HIV may prevent HIV infection, although this protection is not 100%. Treatment should be

initiated within 1-2 hours of injury or exposure. Where this is not possible, it is still reasonable to start PEP up to 48 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.
- The HIV status of the source patient should be determined using the normal counselling protocol. However if the patient or guardians decline testing, a senior management member will have to negotiate and authorise testing.
- The HCW must also undergo counselling and testing, preferably using rapid tests, immediately or within 72 hours of exposure. The HCW must be advised to practice safe sex and use condoms until either a) the source patient has been found to be HIV-negative or b) until 6-months have elapsed and the HCW is then found to be HIV-negative. If the HCW is HIV-positive, then PEP is not necessary and can be stopped: the HCW should be referred for primary care. Likewise if the source patient is HIV negative PEP can be stopped



- A senior clinician must evaluate the HCW after 72 hours and document the event (e.g., on a PEP record), then give a prescription for the rest of the 30 days
- 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 9: The PEP Regimen

DRUG	DOSE	FREQUEN CY	DURATIO N
Zidovudine (AZT) 300mg/ Lamivudine (3TC) 150mg (Duovir)	One tablet	Twice a day (BD)	30 days

Dual therapy should be available at every health facility and at central medical stores. In cases of high risk exposure or when the source patient is already on ARV therapy, nelfinavir 1250 mg twice daily (to be taken together with meals) can be added to the dual NRTI therapy.

Table 10: Recommended HIV serology after exposure

Baseline (Day zero)	Follow-up 1	Follow-up 2	Follow-up 3
Within 72 hours of exposure	Six weeks	Three months	Six months

Health workers 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.



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 or defiled. 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-sero-negative and who have been raped should be offered post -exposure prophylaxis. The only exception is when the assailant is known to be HIV-sero-negative as well.

Persons who present with a history of rape within the previous 48 hours, with a history of penetration, should be offered PEP. The same procedures 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 and should be stopped if already started, 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. Follow-up HIV testing is done at 72 hours (baseline), 6 weeks, 3 months and 6 months.



MONITORING ARV THERAPY

Registration of Patients on ARV Therapy

Each patient who starts ARV therapy will be given a unique treatment unit ARV Registration Number. This number can reflect the district in which the patient is registered, the year of registration and the number during that year. This will be stamped on the patient case file, the patient master card and the patient identity card.

There are various ways of keeping the registration system:-

- iv. Patient case files and master cards will be kept in a hanging file within a cabinet. these hanging files will be hung consecutively according to ARV registration numbers in cabinet drawers. Hanging files will be separated according to quarters of the year: e.g. quarter-1: [Jan – Mar]; quarter-2: [Apr – Jun]; quarter-3: [Jul – Sep]; quarter-4: [Oct – Dec].
- v. Patient case files will be kept separately, and the patient master cards kept consecutively in a hard back lever arch file: the master cards will be separated according to quarters of the year as described above

Patient master cards (**Annex 2**) should have all registration data entered at the time when the patient starts ARV therapy. This will include:- ARV registration number, name, address, age, sex, weight, whether the patient is a “transfer in” from another treatment unit, name of identifiable guardian, the

reason for starting ARV therapy, the date of starting first line ARV therapy, the dose of d4T/3TC/NVP, the date of starting second line ARV therapy and the reason. Patient master cards will either be kept in the patient files or be kept separately in a hardback lever arch file.

Patient identity cards (**Annex 3**) will be smaller and will contain the same basic information as the patient master card. This will include:- ARV registration number, name, address, age, sex, weight, whether the patient is a “transfer in” from another treatment unit, name of identifiable guardian, the reason for starting ARV therapy, the date of starting first line ARV therapy, the dose of d4T/3TC/NVP, the date of starting second line ARV therapy and the reason.

Patients can either have ARV identity cards which shall be kept along with their health passports. An alternative is for patients to have their health passports stamped with the identity card form, and the relevant information written in.

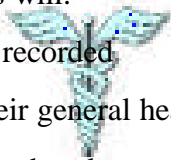
MONITORING AND RECORDING TREATMENT RESPONSE

Patient visits:

Patients will be seen two weeks after starting ARV therapy, and then 4-weekly for routine assessment and drug refills.

Patients will be seen by ARV Clinic staff or delegated health centre staff or dispensing pharmacy staff for the routine monthly follow-up and drug refill visits. For the 2-week and six monthly visits, clinician at ARV clinic will see the patient.

At monthly visits, patients will:

- 
- Have their weight recorded
 - Be asked about their general health
 - Be asked about whether they are ambulant or in bed
 - Be asked about whether they are working
 - Be asked about side effects and symptoms (see Table 11)
 - Have their returned pill bottles inspected to count the remaining drugs
 - Collect another 30 day supply of drugs or have ARV therapy stopped
 - Be reminded about the importance of strict adherence to therapy

At these monthly visits, if the patient is well then there is no need to see a clinician. However, it is recommended that all

patients, regardless of symptoms, see a clinician at least once every six months.

Table 11: Check List of Symptoms for patient attending the Clinic

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

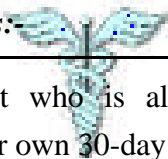
The information about weight and the answers to questions will be recorded in the patient master cards (**Annex 2**). In order

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 consecutive months: after this the patient must be seen at the clinic and must collect his/her own supply of drugs.

Recording Standardised monthly outcomes:

Standardised outcomes will be monitored monthly. Table 12, Table 13, Table 14, Table 15 **and** Table 17 show and explain the standardised outcomes.

Table 12: Outcome status:



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

Note 1:

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

Start (Start): i.e. the patient has started ARV therapy and continues to take the first line regimen

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

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

- i. Where no CD4 count is possible, the development of a new WHO Clinical Stage 4 feature
- ii. Where CD4 count is possible, a CD4 count is $< 30\%$ of the peak value and $< 200/\text{mm}^3$ obtained on ARV therapy and this low CD4 count confirmed one month later. The first CD4 count should be carried out 6 months after starting ARV therapy and every 6 months thereafter.

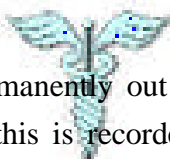
In the case of Failure, the patient can a) either change from the first line regimen to the second line regimen or b) if there is no

established second line regimen, a decision is made by a senior clinician whether or not to stop therapy.

Note 2:

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

Note 3:



If a patient transfers permanently out of a district to another ARV treatment facility, this is recorded in the patient master card. The patient takes that master card to the new district, where it is indicated that he/she is a transfer-in. The patient and master card is placed in the cohort of the new district which corresponds to the cohort in which the patient was first registered in the original district. The patient is added to the cohort of the new district and deleted from the cohort of the original district, so that there is no duplicate counting of patients.

Table 13: Ambulatory status:-

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

	activities
Bed (Bed)	Unable to walk to the treatment unit and spends most of the time in bed at home

Table 14: Work status:-

Yes (Yes)	Engaged in previous work or employment
No (No)	Not engaged in previous work or employment

Table 15: Side effects:-

Yes (Yes) : specify side effects E.g. (Yes-PN) (Yes-HP) (Yes-SK)	Side effects stated by patient after questioning from health worker:- PN = peripheral neuropathy HP = jaundice, liver failure SK = cutaneous hypersensitivity
No	No side effects stated by patient

Pills left in ARV container: _____

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

The number of ARV pills, which are left in the container at the next visit, are counted: if the patient comes at 4 weeks, there should be 4 pills left. The number of pills left should be

counted and indicated in the column box. If pill counts are 8 or less, this is equivalent of 95% drug adherence. If the patient comes early, the number of days on ARV therapy is calculated, multiplied by two and used to determine the number of tablets which should have been taken to be measured against pills left.

If the container is not returned to clinic or the patient comes late to clinic and has finished the pills, self-reporting of drug adherence will be carried out: in these circumstances the registration officer will decide whether or not there is 95% adherence. At every visit, health personnel must talk to the patient about the importance of drug adherence.

The ARV pills remaining in the container can both be recycled and given back to the same patient or be placed in a box and used to administer to other patients starting ARV therapy.

ADHERENCE TO ARV THERAPY

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

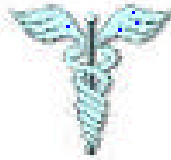
Every patient should identify a guardian to remind, facilitate and support the patient in taking medications on a regular and timely basis. This form of treatment is termed “ERT”, **Empowered Reinforced Therapy**, or “GST”, **Guardian Supported Therapy**, and both may include an element directly observed treatment. At each clinic visit, the returned bottle must be counted for “pills”, and a record made of the number of pills left in the container. If pills are not counted because the patient is late or has left the pill container behind, self-reporting of adherence is carried out.

At the same time, the patient must be counselled about the importance of strict adherence to treatment. Treatment units should have an ample supply of IEC (Information, Education and Communication) patient leaflets, explaining the importance of good drug adherence and the dangers of poor adherence.

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

restarted at least after 2 weeks, if there is cause to imply that patient will now be adherent.

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



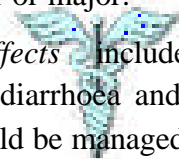
MONITORING AND MANAGING DRUG TOXICITY

Adverse effects of ARV therapy

Clinical monitoring of side effects will be carried out during treatment. Routine laboratory monitoring is not required.

Health personnel can monitor adverse effects in the following two ways. First, they can teach patients how to recognise symptoms of common adverse effects and to report if they develop such symptoms. Second, they can specifically ask about symptoms when patients report to collect drugs.

Side effects can be minor or major:

- 
- *Minor side effects* include headaches, nausea, abdominal pain, diarrhoea and difficult in sleeping at night. These should be managed symptomatically.
 - Major side effects are divided into immediate and long term.
 - Immediate side effects include peripheral neuropathy, hepatitis, pancreatitis and cutaneous hypersensitivity.
 - *Long term side effects* include lactic acidosis and lipodystrophy syndrome

Management of major side effects is discussed below.

Table 16: Major side effects with d4T/3TC/NVP

<p><i>Immediate Side Effects</i></p> <p>Peripheral Neuropathy</p>

Hepatitis
Pancreatitis
Cutaneous hypersensitivity
<i>Long Term Side Effects</i>
Lactic acidosis
Lipodystrophy syndrome

Management of peripheral neuropathy

This is often due to the stavudine (d4T) component and should be diagnosed if the patient complains of pain, paraesthesiae, numbness or weakness of the lower limbs.

Wherever possible, risk factors for peripheral neuropathy should be minimised. For example, TB patients on isoniazid should be given pyridoxine 10 mg daily before starting ARV therapy, and those experiencing symptoms should be given 25 mg daily.

Patients should always be advised not to take alcohol when on ARV drugs..

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

- First, treat the patient with multi-vitamins and amitriptyline 25 mg nocte

- If this combination is unsuccessful after a minimum of 2 weeks, 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 after a month, then the dose of d4T/3TC/NVP should be reduced from d4T/3TC/NVP-40 to d4T/3TC/NVP-30 if the patient is on the higher dose
- If peripheral neuropathy continues to be severe and progressing, the ARV regimen may have to be stopped and replaced with an alternative first line regimen: Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP).



Management of hepatitis

This is often due to the nevirapine component and 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 aspartate transaminase is higher than 5 times the upper limit of normal, this is an indication to stop the ARV therapy.

In some well resourced facilities, liver function tests may be performed on a regular basis. In these circumstances, the

finding of an aspartate transaminase higher than 5 times the upper limit of normal is an indication to stop the ARV therapy.

If the hepatitis is thought to be due to the ARV therapy or the cause of hepatitis cannot reliably be determined, then d4T/3TC/NVP should **not** be restarted and must **not** be given again. Once the hepatitis has resolved, treatment can re-start with an alternative first line regimen:

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

If the hepatitis is thought to be due to another cause, e.g. infectious hepatitis, the ARV drugs can be started again **under very careful observation as an in-patient**. The management in such cases is as follows. Once the liver function tests have returned to normal or 4 weeks after the jaundice has resolved in treatment units where LFTs are not possible, d4T/3TC/NVP can be re-started; first at 1 tablet daily PLUS d4T/3TC 1 tablet daily for two weeks; and then d4T/3TC/NVP 1 tablet twice a day.

Management of pancreatitis

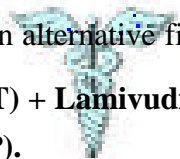
This is often due to the stavudine or, more rarely, the lamivudine component. Pancreatitis should be suspected if the patient develops severe upper abdominal pain, nausea and vomiting. In such cases, patients should be referred to a central hospital for specialist investigation. The diagnosis depends on 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 is difficult to make.

A diagnosis of pancreatitis requires that the d4T/3TC/NVP regimen be **stopped**. The same drugs must not be re-introduced, and continuation with ARV therapy once the disease has resolved means starting with an alternative first line regimen, preferably using a NRTI without pancreatic toxicity such as AZT.

If the diagnosis is likely, but it is not possible to confirm, then the ARV therapy with d4T/3TC/NVP regimen should be **stopped**. Once the pancreatitis has settled completely, ARV therapy can restart with an alternative first line regimen:

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



Management of cutaneous hypersensitivity

This is often due to the nevirapine component.

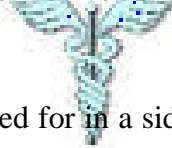
In the first two weeks: If a rash occurs in the first two weeks, then the patient must be closely observed either in or out of hospital. There should be no escalation of the dose of nevirapine, which remains at 200 mg once a day. If the rash improves or remains stable, then the dose of nevirapine can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

After the first two weeks: Any new skin manifestation requires that the patient be assessed at hospital. 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. If the rash becomes worse, and particularly if there is mucosal membrane involvement, the ARV therapy must be stopped.

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

- i. exfoliative dermatitis or toxic epidermal necrolysis
- ii. mucous membrane involvement
- iii. hypotension



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

Once the rash has resolved, d4T/3TC/ NVP must **not** be re-started and must **not** be given again. An alternative first line regimen should be given:

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

Long term side effects:

d4T/3TC/NVP may be associated with long term side effects, such as lactic acidosis and lipodystrophy syndrome.

Lactic acidosis is a rare, but potentially fatal, side effect and will be difficult to diagnose under resource-poor conditions. The pathogenesis is believed to be due to the mitochondrial toxicity of NRTIs, in this case d4T and 3TC. Patients typically present with fatigue, nausea, vomiting, abdominal pain, muscle pains, weight loss and shortness of breath.

The diagnosis should be considered if the above symptoms develop fairly rapidly over a few days in a previously stable patient. Confirmation of the diagnosis is by a low serum bicarbonate, lactic acidosis and high creatinine phosphokinase, all of which are difficult to measure in Malawi. If the diagnosis is suspected clinically, the patient should be referred to one of the central hospitals for specialist advice. The most important therapeutic intervention is to stop the ARV therapy.

The incidence of lactic acidosis is increased in pregnancy, so the above mentioned symptoms occurring in a pregnant woman should be a cause for concern. Other risk factors include a)

concomitant use of metformin with ARV therapy, b) heavy alcohol consumption and c) alcohol binge drinking.

Lipodystrophy syndrome is usually seen in patients taking protease inhibitors, although they can occur with any antiretroviral drug. Clinical features include central obesity and peripheral fat wasting. There is often associated hyperglycaemia and hyperlipidaemia. If the diagnosis is suspected clinically, the patient should be referred to one of the central hospitals for specialist advice



MONITORING AND MANAGING IMMUNE RECONSTITUTION

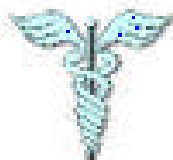
In patients who are severely immunocompromised, the initiation of ARV therapy may be associated in the first one to two months with an increase in the inflammatory response as a result of immune restoration or reconstitution. The clinical illness resulting from immune restoration or reconstitution is termed a paradoxical response.

The clinical spectrum of paradoxical responses includes fever, lymphadenopathy, lung and central nervous system involvement. Patients who have a latent infection with *Mycobacterium tuberculosis* may develop overt tuberculosis.

Paradoxical reactions should be managed according to the presenting illness, and may require anti-pyretics such as aspirin and anti-inflammatory drugs, antibiotics and even consideration of corticosteroids.

One special example of immune reconstitution is a patient developing overt tuberculosis soon after starting ARV therapy. In this situation, the first line ARV therapy with d4T/3TC/NVP must be changed to an alternative first line regimen such as d4T/3TC/EFV. The TB must be treated with anti-TB drugs, and once the patient is on the continuation phase of anti-TB treatment with ethambutol and isoniazid, then the first line ARV therapy with d4T/3TC/NVP can be restarted.

If the patient develops a disease, which is not TB, then the first line ARV therapy should be continued.



COHORT ANALYSIS OF TREATMENT OUTCOME

Monitoring may be done manually and/or electronically. It is strongly recommended that all treatment units administering ARV therapy have a standardised system of manual or electronic monitoring.

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

For ARV treatment, there are two monitoring forms:-

- 1) Quarterly ARV Cohort Analysis Form. The updated quarterly information for each specified cohort will be entered into a new form (**Annex 4**), and filed in a special hard back arch lever file or in a cabinet drawer. The health care worker in charge of the ARV clinic treatment unit will be responsible for completion of this form. Details will be checked during supervisory visits.

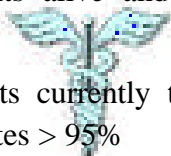
For a particular quarterly cohort, the number of patients registered during that quarter remains constant. The treatment outcome, the ambulatory status, the work status and the drug adherence rates are recorded.

- 2) Cumulative ARV Quarterly Analysis Form. This form is completed every quarter, and represents a cumulative account of the previous updated quarterly ARV cohort

analysis forms (**Annex 5**). The supervisors will be responsible for the completion of this form.

A copy of the quarterly ARV Cohort Analysis Form and the Cumulative ARV Quarterly Analysis Form will be kept by a) the treatment unit, b) the District Health officer, c) the supervisor and d) the HIV/AIDS Unit in the Ministry of Health and Population (MOHP). The cumulative Analysis Form will enable the HIV/AIDS Unit in MOHP to have regular up to date information on:-

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



- number of patients on ARV therapy who are back in their previous employment

This information will be used for 6-monthly and annual reports. It will enable the MOHP to assess the effectiveness of the ARV treatment in Malawi, and will allow the MOHP to identify problems and institute appropriate measures to overcome them.



SURVEILLANCE FOR ARV DRUG RESISTANCE

Resistance testing is either done by genotype testing or phenotype testing. Genotype testing looks for mutations on the reverse transcriptase or protease gene that impart partial or complete resistance to HIV. 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.

In Malawi, it will not be possible to monitor for drug resistance on an individual level. A central reference laboratory will be set up with links to an external supranational laboratory to monitor ARV drug resistance. This will be done periodically by annual sentinel surveillance of patients who have been on ARV therapy for over one year. Details of how patients will be sampled, how these surveys will be carried out and the level of drug resistance at which a decision is made about changing nation-wide to a new ARV regimen are not provided in these guidelines: expert assistance will therefore be sought to design the system.

SUPERVISION

Supervision is best done by a team outside of the treatment unit. This will be coordinated by the HIV/AIDS Clinical Unit of the Ministry of Health and Population.

Supervision should be done quarterly. The purpose of the supervision is:-

- To manually check on the ARV data and complete the cumulative ARV quarterly cohort analysis form
- To Ensure that manual data base tallies with the electronic data base
- To collect information from the district social welfare office about newly registered orphans (number entered in Form in **Annex 6**)
- To perform with the local pharmacist drug security check lists (see below)
- To complete a quarterly continuum of care form which includes other HIV-related activities such as a) VCT services update, b) use of isoniazid preventive therapy, c) PMTCT activities, d) presence of ARV drugs outside of the treatment unit in the private sector or market (**Annex 6**).
- To ensure that the ARV treatment guidelines are being adhered to

ANTIRETROVIRAL DRUG SUPPLY AND USE

All ARV drugs for use in Malawi must have appropriate WHO certification.

The regular supply of ARV drugs, their appropriate storage and use and the monitoring of drug security are three essential prerequisites for success of ARV treatment units.

The details of how the ARV drugs will be purchased and distributed within Malawi have yet to be worked out. Procurement of ARV drugs will need to be linked with some form of quality assurance, both at international level (i.e., using WHO systems of pre-testing) and at national level.

However, 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. Otherwise, there may be leakage of ARV drugs out of the hospital which compromises the success of the programme.

Table 17: Drug security

Drug consumption by patients = drug usage from the
treatment unit

Drug security is checked every quarter during the routine supervisory visits, using the drug security check form shown in **Annex 7**. Details are described below.

Patient consumption:*d4T/3TC/NVP:*

The cumulative number of patients alive and taking first line regimen ARV drugs (d4T/3TC/NVP) is obtained from the data entered into the ARV cumulative quarterly analysis form. This data provides the number of patients taking d4T/3TC/NVP during the quarter. From this information it is possible to calculate the amount of d4T/3TC/NVP consumed during the quarter being evaluated. Each patient will consume 180 tablets in the quarter.

Note: this calculation provides an overestimation of ARV drug consumption for the following two reasons:-

- i. Patients take one tablet of d4T/3TC/NVP for the first two weeks, instead of two tablets of d4T/3TC/NVP. Thus, in the last two weeks of the quarter being evaluated, the above formula overestimates the amount of d4T/3TC/NVP consumed
- ii. In the last quarter, patients registered in the second month will consume 120 tablets and those registered in the third month will consume 60 tablets. Again, the above formula will overestimate the amount of d4T/3TC/NVP consumed

As the number of patients coming on to ARV drugs increases, this over-estimation as a percentage of the total drug consumption will decrease. Nevertheless, performing this

calculation of drug consumption is useful **because if drug usage exceeds the calculated drug consumption there has to be leakage of drugs out of the system.**

D4T / 3TC:

Patients take one tablet of d4T / 3TC in the first two weeks of introduction to ARV. Thus, the consumption of this combination during the quarter is the number of patients registered for ARV in the quarter multiplied by 14. This again overestimated the number of drugs consumed. Nevertheless, performing this calculation of drug consumption is useful **because if drug usage exceeds the calculated drug consumption there has to be leakage of drugs out of the system.**



Drug usage:

Drug usage during the quarter is calculated from a) drug stocks at the end of the quarter preceding the evaluation, b) new drugs received during the quarter being evaluated and c) drugs stocks at the end of the quarter being evaluated. These calculations will have to be worked out for d4T/3TC/NVP and for d4T/3TC.

Comparison of patient consumption and drug usage: action taken in miss-matches

Comparisons are made between patient consumption and drug usage. **If drug usage exceeds patient consumption, then leakage has occurred.** Leakage occurs either at the pharmacy

level or in the HIV-ARV Clinic where the drugs are dispensed. In the case of a mismatch between consumption and usage, then the matter is reported to the District Health Officer and District Health Management Team. The HIV/AIDS Unit in MOHP is also contacted. If the internal enquiry fails to identify the source of the problem, then legal proceedings must be undertaken. While these are going on, it is essential that the service delivery of ARV continues.

Drug formulations needed for Malawi

Table 18 provides the necessary drug formulations needed for Malawi:



Table 18: Drug formulations needed for Malawi:

D4T/3TC/NVP (both -30 and -40 formulations)
D4T/3TC (both -30 and -40 formulations)
AZT/3TC/NVP (triple combination)
AZT/ddI (dual combination, with ddI ~enteric coated)
AZT/3TC (dual combination)
EFV
NVP
Nelfinavir

TRAINING IN USE OF ARV THERAPY

Background

It is essential that staff who are to manage patients with ARV therapy be well trained in their usage. A training package will be developed. This training package will include a 3 – 5 day module on management of ARV drugs and opportunistic infections. The core material for the module will be the “ARV Treatment Guidelines” and “the Guidelines for the Management of HIV/AIDS related conditions”. The details of the training module have yet to be worked out, but the training will have to run in Malawi, with appropriate practical exposure of the trainees to ARV delivery centres implementing this ARV Treatment Guidelines manual.

Training:

There will be two types of training:-

i. Pre-service training.

Medical students, paramedical students and nursing students will all undergo a modular training in use of ARV therapy and management of opportunistic infections. These modules will need to be integrated into the curricula of the various training institutions.

ii. In-service training.

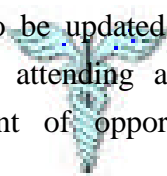
All qualified staff that are to be involved in the provision of ARV therapy must have completed a recognised training

course in ARV therapy. Following a recognised course of training, there will be an examination based on that course. Qualified staff, who have attended the training course will also be expected to attend one of the clinical centres to see first hand the clinical management of ARV therapy

Certification in the use of ARV therapy:

Qualified staff who have undergone a course in ARV therapy and have passed the examination will be certified to use ARV drugs. This certification will be recognised with the Malawi Medical Council.

Certification will need to be updated every three years. Re-certification depends on attending another course in ARV therapy and management of opportunistic infections and passing the examination.



ARV THERAPY AND PRIVATE PRACTITIONERS

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

One of the pre-requisites of being able to prescribe ARV drugs is that the health care worker should have a) undergone a formal training course in ARV therapy and b) be formally certified as competent in managing ARV therapy. This opportunity for training and certification will be available for health care workers in the private sector. In addition, private practitioners will be encouraged to attend a clinical centre with experience in the use of ARV therapy.

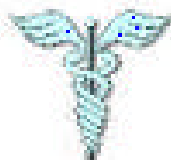
Private practitioners who have undergone a course in ARV therapy and have passed the examination will be certified to use ARV drugs. This certification will be registered with the Malawi Medical Council. Certification will need to be updated every three years. Re-certification depends on attending another course in ARV therapy and management of opportunistic infections and passing the examination.

SUGGESTIONS FOR FURTHER READING

World Health Organization. Scaling Up antiretroviral therapy in resource-limited settings: Guidelines for a public health approach. World Health Organization, June 2002.

Bartlett JG, Gallant JE. Medical Management of HIV Infection. 2003 Edition. Johns Hopkins School of Medicine, Baltimore, USA. ISB Number 0-9716241-1-9

Wilson D, Naidoo S, Bekker L-G, Cotton M, Maartens G. Handbook of HIV Medicine, Oxford / Southern Africa 2002.



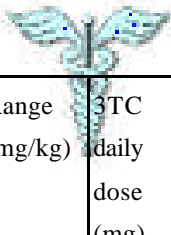
ANNEXES:

ANNEXE 1. DOSAGE GUIDELINES FOR ARV THERAPY IN CHILDREN IN MALAWI

Dose recommendations:

Stavudine (d4T)	2 mg/kg/day
Lamivudine (3TC)	8 mg/kg/day
Nevirapine (NVP)	8 mg/kg/day
i.e. target dose ratio	= 1: 4: 4 (d4T:3TC:NVP)
d4T/3TC/NVP dose ratio	= 1: 3. ⁷⁵ : 5

For d4T/3TC/NVP:



Weight (kg)	Dose Am	Dose Pm	D4T daily dose (mg)	Range (mg/kg)	3TC daily dose (mg)	Range (mg/kg)	NVP daily dose (mg)	Range (mg/kg)
< 8	¼	-	10	1.2 –	37.5	4.7 –	50	6.2 –
8-<12	¼	¼	20	1.7 – 2.5	75	6.2 – 9.4	100	8.3 – 12.5
12-<18	½	¼	30	1.7 – 2.5	112.5	6.2 – 9.4	150	8.3 – 12.5
18-<22	½	½	40	1.8 – 2.2	150	6.8 – 8.3	200	9.1 – 11.1
22-<28	¾	½	50	1.8 – 2.3	187.5	6.7 – 8.5	250	8.9 – 11.4
28-<32	¾	¾	60	1.9 – 2.1	225	7.0 – 8.0	300	9.4 – 10.7
32-<38	1	¾	70	1.8 – 2.2	262.5	6.9 – 8.2	350	9.2 – 10.9
> 38	1	1	80	– 2.1	300	– 7.9	400	– 10.5

ANNEXE 2. PATIENT MASTER RECORD CARD FOR ARV

Unique ARV Number _____ Year _____

Name _____ Age _____

Sex _____ Initial Wt (Kg) _____ Transfer-In (Y/N) _____

Address (physical / PO Box) _____

Name of identifiable guardian _____

Date of starting 1st line ARV regimen: _____

Specify d4t/3TC/NVP formulation: _____

Reason for ARV: _____

Date of starting alternative 1st line ARV regimen: _____

Specify regimen: _____

Reason for alternative 1st line regimen: _____

Month	Date	Wt Kg	Outcome status					Of those alive			Ambulatory		Work / School		Side effects		No. Pills in Bottle	ARV Given	ARV not given
			A	D	DF	Stop	TO	Start	Sbs	Switch	Amb	Bed	Yes	No	Y	N			
Jan																			
Feb																			
Mar																			
Apr																			
May																			
Jun																			
Jul																			
Aug																			
Sep																			
Oct																			
Nov																			
Dec																			

Specify reason for ARV therapy -i.e. inclusion criteria used for adults and for children (e.g. WHO stage [TB or not TB], CD4count, CD4 percentage)

Legend:

Outcome status: A=alive; D=dead; DF=defaulted and not seen for 3 months; Stop=stopped medication; TO=transferred out to another unit

Of those alive: Start=alive and on first line regimen; Sbs=alive and substituted to alternative first line regimen; Switch=alive and switched to a second line regimen because of failure of first line regimen

Ambulatory: Amb=able to walk to/at treatment unit and walks at home unaided; Bed=most of time in bed at home

Work/school: Yes=engaged in previous work /employment or at school; No=not engaged in previous work /employment or not at school

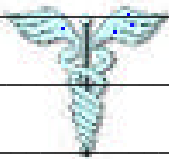
Side effects: If Yes, specify – YES-PN= peripheral neuropathy; YES-HP=hepatitis; YES-SK=skin rash

No. Pills in bottle: if patient comes at 4 weeks count number of pills in bottle

ARV given / not given: tick whether ARV therapy given and indicate how many tablets; if no ARV, then indicate why



ANNEXE 3. PATIENT ARV IDENTITY CARD

IDENTITY CARD	
Name of Patient _____	
Unique ARV Registration Number _____	
Age _____	Sex _____
Address _____	
	
Name of Guardian _____	
Initial Weight (Kg) _____	
Date of starting 1 st line ARV therapy _____	
D4T/3TC/NVP formulation (specify) _____	
Reason for ARV therapy (adults: Stage III, Stage IV, CD4 count < 200, other) (children: Stage III, CD4 percentage <15%)	

Date of starting alternative 1 st line regimen _____	
Reason for starting alternative 1 st line regimen _____	
Date of starting 2 nd line ARV therapy _____	
Reason for 2 nd line ARV therapy _____	

Current Treatment Unit _____

[on back of the Identity card will be written lines for the ARV clinic staff to indicate the date of the next visit]



ANNEXE 4. ARV QUARTERLY COHORT ANALYSIS FORM

NAME OF TREATMENT UNIT _____

COHORT [specify the year and the quarter] _____

Total # of patients initially registered for ARV in the cohort _____

Amended # of patients depending on transfers _____

Year in which evaluation is taking place: _____

Quarter in which evaluation is taking place (Q1,2,3,4) _____

Of total # registered in the cohort:

No. Alive & on ARV therapy _____

No. Alive & on 1st line regimen (Start) _____

No. Alive & on Alternative 1st Line Regimen (Substituted) _____

No. Alive & on 2nd Line regimen (Switched) _____

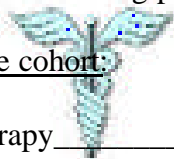
No. Dead _____

No. Defaulted _____

No. Stopped _____

No. Transferred out to another treatment unit _____

Of those Alive:



No. Ambulatory_____

No. At work / school (=Yes)_____

No. With side effects (=No)_____

No. where Pill counts measured in adults and on first line regimen_____

No. With Pill count in bottle of 8 or less tablets_____

Note: Pill count in bottle 8 or less is equivalent to 95% adherence [this is measured for adults and for those on first line regimen only]



ANNEXE 5. ARV CUMULATIVE QUARTERLY COHORT ANALYSIS

NAME OF TREATMENT UNIT _____

Year of evaluation _____

Quarter in which evaluation takes place _____

Number of ARV Quarterly Cohort Analysis forms _____

Total number of patients registered for ARV since programme started _____



Of total number registered for ARV since ARV therapy started:

Total No. Alive and on ARV therapy _____

No. Alive & on 1st Line Regimen (Start) _____

No. Alive & on Alternative 1st Line Regimen (Substituted) _____

No. Alive & on 2nd Line Regimen (Switched) _____

No. Dead _____

No. Defaulted _____

No. Stopped _____

No. Transferred out to another treatment unit _____

Of those Alive:

No. Ambulatory_____

No. At work / school (=Yes)_____

No. With side effects (= No)_____

No. with Pill counts measured in adults and on first line regimen_____

No. With Pill count in bottle 8 or less tablets_____

Note: Pill count in bottle 8 or less is equivalent to 95% adherence [this is measured for adults and for those on first line regimen only]



ANNEXE 6. QUARTERLY CONTINUUM OF CARE FORM

NAME OF TREATMENT UNIT _____

Year _____ Quarter _____

Orphans:

Number of new orphans registered in the quarter (at the District Social Welfare Office) _____

VCT services:



Number of operating VCT sites in the district _____

Number of clients (incl. TB patients) who have been HIV tested in the quarter _____

Number of clients found HIV+ve in the quarter _____

Isoniazid Preventive Therapy (Primary):

Number of HIV+ve clients started on IPT in the quarter _____

To be completed one year later from INH registers:

Number clients who completed IPT in the quarter _____

VCT and NVP to pregnant women:

Number of pregnant women HIV tested in the quarter _____

Number of women found HIV+ve in the quarter _____

Number of women given NVP in the quarter _____

Number of children given NVP in the quarter _____

ARV drugs in market or private shops: (done by quarterly survey)

Comments: _____



ANNEXE 7. DRUG SECURITY CHECK FORM**NAME OF TREATMENT UNIT** _____

Year _____ Quarter evaluated _____

Patient consumption:*D4T/3TC/NVP 2 tablets daily:*Cumulative # of patients on d4T/3TC/NVP (A) _____
(take number from cumulative cohort analysis)D4T/3TC/NVP consumed: $(A \times 180) =$ _____*D4T / 3TC 1 tablet daily for first two weeks:*Number of patients registered for ARV therapy in quarter
evaluated (B) _____
(take number from the quarter just evaluated)D4T/ 3TC consumed: $(B \times 14) =$ _____**Drug Stocks and Drug Usage:****Drug stocks from previous quarter [X]:** _____

New drugs received in quarter being evaluated [Y]: _____

Drug stocks at end of quarter being evaluated [Z]: _____***Drugs used (X + Y - Z):*** _____

Perform the calculations for d4T/3TC/NVP and for
d4T/3TC

Drugs used: d4T/3TC/NVP _____ D4t/3TC _____

Comparison of patient consumption and drug usage:

Drug	Patient consumption	Drug use	Imbalance
D4T/3TC/NVP			
D4T/3TC			



Action taken as a result of drug-overuse _____

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

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

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

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

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

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

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

For any inconsistencies or clarification, users are encouraged to consult Secretary for Health and Population, Ministry of Health and Population, P. O. Box 30377, Lilongwe 3; Tel. 01 789 400; Attention: Director of Clinical and Population Services.