Kingdom of Cambodia

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Ministry of Health

National Guidelines for the use of Antiretroviral Therapy in Adults and Adolescents

December 2003

National Center for HIV/AIDS, Dermatology and STD

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Preface

The escalating HIV epidemic in Cambodia is now producing an expanding need for HIV/AIDS care, as people progress to advanced and symptomatic HIV disease. This need for HIV/AIDS care and support will increase considerably over the next decade, as each year approximately 20 000 people will develop AIDS and die unless expanded interventions are available. The limited resources of the Cambodian health care system will be further stretched due to this impact of HIV/AIDS on care needs. The presence of such a large number of HIV infections in the population creates an inescapable increase in demand for health care.

Most health care for PLHA will be delivered within both the private and public health care systems in Cambodia. The majorities of people with HIV infection are presently undiagnosed and initially present with conditions which do not require specific HIV/AIDS management. Unfortunately, the present weakness of the health care services means that many opportunities to provide this first level of care are missed, often with serious health status and economic consequences. At later stages, however, specific HIV/AIDS initiatives and services are often needed; and the availability of antiretroviral drugs now means that this special care can be effective.

In recognition of this, the government strategy for an HIV/AIDS 'continuum of care' is being developed which broadens the focus of HIV/AIDS care beyond hospital-based treatment of AIDS-related conditions. Within this broadened focus, are increased access in rural and urban areas to prompt and effective diagnosis and management of HIV-related infections and conditions (of which TB will be by far the most important), increased access to HIV testing and counselling, strengthening hospital capacities and capabilities for effective diagnosis, improved clinical follow up following HIV diagnosis, provision of prophylaxis against common opportunistic infections, expanded home-based care including referral networks for socio-economic support for children and families, and the provision of antiretroviral drugs.

These Guidelines for the use of antiretrovirals are therefore timely and essential. I trust they will be closely followed by all health care workers involved in the 'continuum of care'; I also trust that they will be regularly reviewed and updated, to keep pace with the rapid development of effective care for PLHA. I would like to congratulate NCHADS, and all its partners, for the hard, professional work that has gone into their development.

Phnom Penh, ...December 2003
Director General for Health

Prof. Eng Huot

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Dr. Mean Chhi Vun
Director of NCHADS

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Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Aquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ARV	Antiretroviral drug(s)
AZT	Zidovudine
CBC	Complete Blood Count
CD4	T-CD4+ Lymphocyte
CMV	Cytomegalovirus
CNS	Central Nervous System
CK	Creatine Kinase
CrCl	Creatinine Clearance
d4T	Stavudine
ddI	Didanosine
DOT	Directly Observed Therapy
EC	Enteric Coated
EFV	Efavirenz
EPTB	Extra-pulmonary Tuberculosis
ESRF	End Stage Renal Failure (Dialysis dependent)
HAART	Highly Active Antiretroviral Therapy
HGC	Hard Gelatin Capsules
HIV	Human Immunodeficiency Virus
IDV	Indinavir
IPT	Isoniazid Preventive Therapy
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LPV	Lopinavir
LPV/r	Lopinavir/Ritonavir
MTCT	Mother to Child Transmission
NFV	Nelfinavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine
OHL	Oral Hairy Leukoplakia

OI	HIV related Opportunistic Infection
PCP	*Pneumocystis carinii* pneumonia
PHA	Person/people living with HIV/AIDS
PI	Protease Inhibitor
PID	Pelvic Inflammatory Disease
PMTCT	Prevention of Mother to Child Transmission
PPD	Purified Protein Derivative (skin test for tuberculosis)
PPE	Papular Pruritic Eruption
PTB	Pulmonary Tuberculosis
r	Ritonavir (when given in association with other PIs for boosting effect)
RTV	Ritonavir
SGC	Soft Gelatin Capsules
STI	Sexually Transmitted Infection
SQV	Saquinavir
TB	Tuberculosis
TFV	Tenofovir
TST	Tuberculin Skin Test
VCT	HIV voluntary counseling and testing
VDRL	Venereal Diseases Reference Laboratory (refers to a test for syphilis)

Introduction

Despite the stabilization of HIV prevalence in Cambodia over recent years there has been a dramatic increase in the number of people living with HIV/AIDS who are ill and in need of health care. This reflects the progression of HIV disease in those infected in the past, particularly the large numbers of people infected during the mid-1990s. It is estimated that the peak incidence of illness and death from HIV/AIDS in Cambodia will occur over the next few years. Each year approximately 20 000 people will develop AIDS and die unless expanded interventions are available.

There is an urgent need to prevent the illness, disability and death of people living with HIV/AIDS in Cambodia. Treatment of HIV itself provides benefit for individuals and families through restoration of function, recovery of hope and prevention of future illness. It mitigates impact by preventing impact. It also strengthens prevention efforts by encouraging testing, reducing stigma and discrimination and potentially reducing transmission.

Since 1996 the lives of people living with HIV/AIDS in the richest countries of the world have changed because of the development of new classes of ARV drugs. HIV is no longer a death sentence, rather a manageable chronic illness. The drugs are not a cure and there are problems associated with treatment, but life expectancy, quality of life, perception of HIV and health care utilization have all been transformed.

The availability of potent ARV drug combinations remains severely restricted in Cambodia. At present less than 5% of PHA who are in need of ARV are able to access these medicines. There are many challenges to addressing this situation. Most importantly, successful ARV therapy does not just involve the purchase of medicines. A system of comprehensive care needs to be established in order to address the complex needs of PHA, particularly for those whose infection is already well advanced. Many operational and logistical issues need to be addressed including design of care services, mobilization and coordination of resources, infrastructure development, drug procurement and distribution, capacity development of health care workers, community mobilization and information management.

This document is designed as a component in the response that is necessary to address the pressing care needs of PHA in Cambodia. It is written primarily for health care workers who are involved in the care of adults and adolescents (>12 years of age) living with HIV/AIDS. It aims to provide a clear explanation of the basics of ARV therapy. It should be used as an introduction and a reference and should not substitute for comprehensive training in the use of ARV. Similarly it does not seek to address the complex operational requirements of comprehensive HIV care in general, nor of ARV provision in particular. These questions are addressed in the recently developed document “Continuum of care for people living with HIV/AIDS – operational framework” and will be further addressed in future publications. The reader is also referred to published national guidelines for detailed recommendations regarding VCT, clinical care of PHA, OI prophylaxis, PMTCT and post-exposure prophylaxis.

What is antiretroviral therapy?

- Antiretroviral (ARV) therapy refers to medicines that are active against the HIV virus. They act by inhibiting two of the enzymes that are needed by HIV in order for it to replicate and infect cells:
  - Reverse transcriptase
  - Protease

- ARV drugs are divided into 4 main classes. Three of the classes inhibit reverse transcriptase and one class inhibits protease:
  - Nucleoside Reverse Transcriptase Inhibitors (NRTI)
  - Nucleotide Reverse Transcriptase Inhibitors (NtRTI)
  - Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
  - Protease Inhibitors (PI)

- The ARV drugs included in these guidelines are those that have sufficient potency and ease of use to be acceptable for use in Cambodia at the present time.
  - NRTI: Zidovudine (AZT or ZDV)
    Stavudine (d4T)
    Lamivudine (3TC)
    Didanoside (ddI)
    Abacavir (ABC)
  - NtRTI Tenofovir (TFV)
  - NNRTI Nevirapine (NVP)
    Efavirenz (EFV)
  - PI Nelfinavir (NFV)
    Indinavir and low dose Ritonavir (IDV/r)
    Lopinavir and low dose Ritonavir (LPV/r)
    Saquinavir and low dose Ritonavir (SQV/r)

- Some PI are used together with Ritonavir (RTV). Although RTV is a potent ARV drug itself, its side effects limit its use in its own right. It can however be used at low dose in order to reduce the metabolism of the other PI, enabling less frequent dosing. Ritonavir must be given as a separate tablet except for LPV/r where a combination capsule is available.

- Other fixed dose combination tablets or capsules are available:
  - Zidovudine + Lamivudine (AZT + 3TC)
  - Stavudine + Lamivudine (d4T + 3TC)
  - Zidovudine + Lamivudine + Nevirapine (AZT + 3TC + NVP)
  - Stavudine + Lamivudine + Nevirapine (d4T + 3TC + NVP)
  - Zidovudine + Lamivudine + Abacavir (AZT + 3TC + ABC)

Principles of antiretroviral therapy

- The aims of ARV therapy are:
  - Maximal and durable suppression of HIV replication
  - Restoration of immune function
  - Improved quality of life
  - Reduction of HIV related morbidity and mortality
  - Prevention of viral resistance and treatment failure

- Prevention of MTCT

- The only ARV treatment regimes able to reliably achieve and maintain the aims listed above are combinations of at least three potent ARV drugs. These combinations are also known as Highly Active Antiretroviral Therapy (HAART).

- Potent ARV combinations can rapidly suppress the replication of HIV. This leads to a rapid fall in the amount of HIV virus in the blood (known as the HIV 'viral load') to below the limit of detection by currently available assays. This reduces the impact of HIV on the immune system and leads to a gradual restoration of immune function, both in terms of *quantity* (as measured by CD4 count) and *quality*.

- As immune function is restored the risk of HIV associated illness decreases. In individuals and populations using ARV therapy the risk of illness and death is dramatically reduced. However, the process of immune restoration is gradual, occurring over many months or even years, and is not perfect. Some risk of opportunistic infection or other HIV related illness persists at least for a time, necessitating the use of OI prophylaxis and ongoing monitoring for new HIV related illness in many people taking ARV.

- ARV therapy is not a cure. It suppresses HIV replication, but does not stop it. If ARV therapy is ceased HIV replication quickly returns to pre-treatment levels and promptly begins to damage the immune system once again.

- HIV develops spontaneous genetic mutations at a very high rate. Effective combination ARV therapy reduces the rate of development of these mutations by continuously suppressing HIV viral load to very low levels. If sub-optimal ARV therapy is used (for example, inappropriate combinations or intermittent dosing) the combination of ongoing viral replication and the presence of ARV drug will lead to the growth of viral populations that carry a genetic mutation which protects against these drugs. Eventually this population will become dominant and the particular ARV combination being used will become ineffective. This resistant virus population may also be transmitted to others.

Starting antiretroviral therapy

Step 1 Confirm HIV infection

- Think of HIV when someone has
  - Risk behavior
  - Pregnancy
  - Sexually transmitted infection
  - Tuberculosis
  - Clinical suggestion of HIV infection (See Table 1 below)

- Refer or provide pre- and post-test counseling and HIV testing to those identified to be at risk of HIV infection and all those who request testing.

Step 2 Initial consultation

- Ask about
  - Diagnosis of HIV: when and where was HIV infection diagnosed and were there any previous negative HIV tests
  - Previous HIV care including CD4 counts and ARV use
  - Past medical history and current symptoms (See Table 2, page 11)
  - Medications
  - Social and financial situation

- Perform a complete physical examination looking especially for signs listed in Table 2 (page 11).

- Determine HIV clinical stage (See Annex 1, page 27)

- Provide initial counseling and education (See Table 1 below)
  - Assess understanding
  - Provide information
  - Provide supportive counseling

Table 1: Basic HIV facts

HIV is a virus that weakens the body's ability to protect itself against other illnesses
AIDS is the illness that occurs when the body's defenses have been weakened by HIV
HIV can be spread by sexual intercourse via blood, semen or vaginal fluids
HIV can also be transmitted by blood transfusion, reusing needles or from mother to child during pregnancy, labor or breast feeding
HIV cannot be transmitted by normal social contact, kissing, sharing food or by insects
Someone can be infected with HIV and be well for many years
Treatment can control HIV infection, but cannot cure it

Table 2: Symptoms and signs suggestive of HIV infection

Stages of HIV infection	Ask about (History)	Look for (Examination)
No symptoms		
No symptoms	None	None
Mild symptoms		
Mild weight loss (less than about 5kg)	Weight loss	Weight loss
Skin, mouth and nail diseases[1]	Skin, mouth and nail problems[1]	Skin, mouth and nail problems[1]
Shingles	Painful blistering rash on one side of the body	Shingles
Repeated upper respiratory tract infections	Colds, sore throats, sinusitis	
Serious symptoms		
Serious weight loss (more than about 5kg)	Weight loss	Weight loss
Diarrhea for more than one month	Diarrhea	
Fever for more than one month	Fever and/or sweats	Fever
Thrush in the mouth[2]	Sores, bad taste or white spots in mouth	White spots in mouth
Chronic vaginal thrush	Chronic vaginal itch and white discharge	White vaginal discharge

Pulmonary tuberculosis	Chronic cough, weight loss, fever, sweats	Weight loss, signs of pneumonia
Pneumonia	Acute cough, fever, shortness of breath	Signs of pneumonia
Very serious symptoms[3]		
Serious weight loss plus either diarrhea or fever for more than a month	Weight loss, diarrhea, fever, sweats	Weight loss and fever
Thrush in the esophagus	Pain when swallowing	
Pneumocystis carinii pneumonia (PCP)	Shortness of breath and fever getting worse over a few weeks	Dyspnea and fever
Extrapulmonary tuberculosis	Abdominal pain, swollen lymph nodes	Abdominal tenderness, swollen lymph nodes
Cryptococcal meningitis	Headache, fever	Fever
Toxoplasmosis	Focal weakness, headache, seizures, fever	Altered mental state, focal neurological signs, fever
HIV encephalopathy[4]	Declining mental function	Decreased mental function
CMV retinitis	"Floaters" Decreased vision	Decreased vision Retinal lesions
Chronic herpes genital ulcer	Genital ulcer	Genital ulcer

[1]seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis
[2]Also oral hairy leukoplakia
[3]Other illnesses not included here include penicilliosis, atypical mycobacteria, non-typhoid salmonella septicemia, lymphoma and Kaposi sarcoma
[4]Also progressive multifocal leukoencephalopathy

Step 3 Decide if ARV should be started

- ARV therapy is appropriate if the criteria in Box 1 are fulfilled.
- HIV viral load is not recommended as a criterion for starting ARV[1].
- The success of ARV therapy is dependent on the understanding and commitment of the individual taking the ARV.
- Most people will be able to adhere well to ARV therapy. It is not easy to predict who will have difficulties.
- The 'National guidelines for selection of PHA for ARV therapy' should be used if the demand for ARV is greater than supply.

Box 1: Criteria for starting ARV

Individual has WHO Stage 4 disease* OR CD4 count less than 200 cells/mm^3
AND
Individual has adequate understanding and commitment to continuous, lifelong therapy
AND
Ongoing supply of appropriate combination ARV can be guaranteed
AND
Adequate human resources and infrastructure for delivery of ARV exists

*See Annex 1 (page 27)

[1]There is currently no consensus on the role of HIV viral load in deciding when to initiate ARV therapy. It is possible that PHA with HIV viral loads above 100 000 copies/ml would benefit from commencement of ARV therapy, but as this investigation is not readily available in Cambodia and ARV supply remains limited, priority should be given to PHA who qualify for ARV therapy on clinical and CD4 criteria.

Step 4 Prepare for ARV therapy

- Exclude active OI that need immediate treatment, especially tuberculosis.

- Discuss the following
  - Basic HIV facts
  - ARV therapy is not a cure and it is lifelong
  - Benefits of ARV therapy
  - Possible side effects of ARV therapy and the importance of reporting possible side effects promptly
  - Success is dependent on 'adherence'
  - The best chance for success is with the first treatment with ARV
  - Drug interactions
  - The duration for which ARV supply can be guaranteed

- Provide opportunities for further counseling regarding
  - Adherence (See page16)
  - Risks and benefits of disclosure of HIV status
  - Social and financial support

- Perform baseline laboratory assessment (See Table 3, page 13). Additional investigations should be performed as clinically indicated.

Table 3: Recommended laboratory assessment before starting ARV therapy

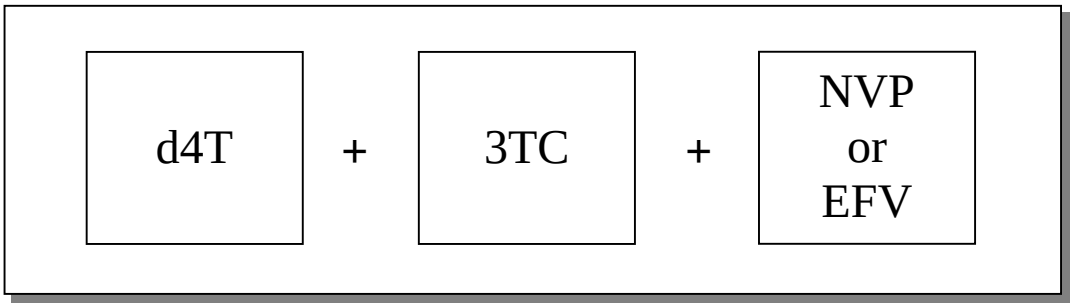
Test	Who?	Reason	Management
Essential			
HIV Antibody	All	To make sure ARV is given to the right people	Do not give ARV if the diagnosis of HIV has not been confirmed
CD4	All	Baseline	Give ARV if CD4 is less than 200
CBC	If using AZT	AZT can cause anemia or low white cell count	Do not give AZT if Hb<100 g/l
ALT or AST	If using NVP	People with increased ALT/AST are at higher risk of liver side effects from NVP	Do not give NVP if ALT/AST > 3xULN. Look for cause if ALT/AST is raised
Recommended			
CBC	All	Can help to exclude OI	Look for cause of anaemia
ALT or AST	All	People with increased ALT/AST are at higher risk of liver side effects from ARV	Do not give EFV or RTV (or NVP) if ALT/AST > 5xULN. Look for cause if ALT/AST is raised
Chest X Ray	All	To screen for pulmonary TB	Check sputums if CXR is abnormal or if cough present. Treat TB if present
Creatinine or urea	If using IDV	IDV can cause renal stones and renal impairment	Avoid IDV if creatinine or urea is raised
Pregnancy test	If using EFV	Teratogenic	Do not use EFV if pregnant
Optional			
Creatinine or urea	All	The dose of ARV may need to be changed if increased	See Table 9 (page 29)
Pregnancy test	Women	Plan appropriate treatment	See 'Pregnancy' (page 22)
Glucose	Especially if using a PI	PIs can cause high blood glucose and diabetes	Avoid PI if pre-existing diabetes. If drug therapy is necessary, use metformin
Amylase	Especially if using ddI	ddI can cause pancreatitis	Avoid ddI if amylase > 2xULN

Lipids	Especially if using a PI	PIs can cause raised blood lipids	Avoid PIs if raised blood lipids
Hepatitis B and C serology	Especially if using NNRTI or RTV	PHA with hepatitis B or C are at higher risk of liver side effects from ARV	Consider avoiding NVP (and RTV and the combination of d4T+ddI) if hepatitis B and/or C positive
TST	All	To screen for latent TB	Consider IPT for PHA who are TST positive (>5mm induration)
VDRL	All	To screen for latent syphilis	Treat for latent syphilis if positive
HIV viral load	All	Baseline	No specific change to management

Step 5 Decide which ARV to use

- Always start with two NRTIs plus a potent third drug (see Box 2 below).
- Dual therapy (two ARV drugs) is not recommended because of limited efficacy and rapid development of resistance
- d4T has few side effects in the short term, but often causes lipoatrophy and/or peripheral neuropathy in the long term.
- 3TC has very few side effects and is also active against hepatitis B.
- EFV is preferred over NVP as it is taken once per day, has fewer side effects and can be given together with rifampicin, but is teratogenic and more expensive (See Table 10, page 32 and Annex 2, page 28).
- Use EFV except if the lower cost of NVP would increase the number of PHA able to be treated or if the individual is pregnant or at risk of pregnancy.
- d4T+3TC+NVP is available in a single tablet. The risk of NVP side effects (especially rash) can be reduced by starting with a lower dose of NVP. For the first two weeks give d4T+3TC+NVP as one of the daily doses and d4T+3TC alone as the other daily dose, then increase to the full dose of one d4T+3TC+NVP tablet twice a day.

Box 2: Recommended first line ARV therapy



- There are many alternative combinations of two NRTIs and a potent third drug (See Table 4 below). These are not recommended, but are medically acceptable and can be used in exceptional circumstances.

- AZT has more side effects in the short-term (e.g. nausea and anemia) and is more expensive than d4T, but has less long-term toxicity such as lipoatrophy.

- d4T + ZDV should never be used together because of antagonism

- d4T + ddI should not be used together because of possible increased rates of lactic acidosis, particularly in pregnant women, liver side effects, pancreatitis and peripheral neuropathy.

- PI (NFV, IDV/r, LPV/r, SQV/r). These agents have potent anti-HIV activity, but have tended to be associated with relatively higher pill burdens, cost and long term toxicity (See Table 10, page 33 and Annex 2, page 28).

- ABC comes in a fixed dose combination with AZT+3TC and can be given with anti-TB medicines, but may be less effective in advanced disease, is relatively expensive, has not been used extensively in pregnant women and has a 5% risk of hypersensitivity reaction.

- TFV is a newer drug which has potent anti-HIV activity, activity against hepatitis B and seems to have a low rate of side effects

- The triple NRTI combination of AZT/ddI/3TC can be used in situations where access to NNRTIs or PIs is extremely limited.

Table 4: Alternative ARV combinations

NRTI	Third drug
AZT + 3TC or AZT + ddI or ddI + 3TC	IDV/r or LPV/r or SQV/r or NFV or ABC or TFV

Continuing antiretroviral therapy

Support ARV adherence

- 'Adherence' is taking medication continuously; not missing or delaying doses. It is the key factor in successful ARV therapy.

- Poor adherence leads to treatment failure, drug resistant HIV, reduced treatment options and increased cost of ARV regimens.

- Adherence to daily, lifelong medication is hard work. No one can achieve perfect adherence all the time.

- The assessment of an individual's adherence to ARV by health care workers is often inaccurate. Spend more time supporting adherence than trying to assess it.

- The best way to support adherence is to focus on the needs of the person taking ARV.

- Practical ways to support adherence include training someone to be an 'adherence counselor', establishing a support group or MMM, encouraging people to find an 'adherence supporter' or 'buddy'and linking people with health centers or HBC teams.

- Never start ARV at the first visit. Spend time giving information and answering questions about ARV. The quality of inter-personal communication is critical.

- Encourage people taking ARV to become actively involved in their own care. Assist them to understand HIV and its treatment, to identify their own barriers to adherence and to find ways to overcome these barriers.

- Identify and address mental health issues, particularly depression, and harmful substance use.

- Minimize the 'pill burden', the number of tablets required each day.

- ARV side effects reduce adherence. Encourage people taking ARV to report new symptoms whenever they develop. Check for side effects at each visit and deal with them promptly. Particularly important are nausea, vomiting and diarrhea, and, in the longer term, lipodystrophy.

- Directly observed therapy (DOT) is not recommended as it is unlikely to be sustainable in the long term.
- Voluntary interruption of ARV therapy is sometimes used by people taking ARV to take a rest from the daily discipline of ARV or because of side effects. It is associated with risks of seroconversion illness and OIs, particularly in those with low CD4 counts. It is not recommended as part of standard clinical practice.

- Explore the risks and benefits of disclosure of HIV status. Whilst support from friends and family can significantly improve adherence, stigma and discrimination can undermine adherence.

- Adherence is a continuous process. Talk about it at every visit.

Monitor ARV therapy and manage adverse events

Monitor ARV therapy

- Anyone starting ARV should see their doctor:
  - 4 weeks (and 2 weeks if possible) after starting ARV
  - Monthly until they understand ARV and there are no new medical problems
  - Then at least 3 monthly with monthly visits to pick up medication and discuss adherence and any new symptoms with a member of the treatment team.

- People usually start to improve after a few weeks of ARV therapy. Successful ARV therapy will usually result in more energy, improved sense of wellbeing, weight gain, improvement in existing illnesses and less new

illnesses. Overall function can be measured using the Karnofsky performance scale (See page 42).

- Evaluating treatment success is complicated. Opportunistic infections can still develop, particularly if the CD4 count is still below 200, but are much less common. CD4 count is an important measure of treatment success (See page 25).

- Emphasize to people taking ARV the importance of reporting new symptoms as soon as possible. Ask about and examine for new symptoms and signs at each visit. Determine whether they are due to:
  - New illness including a new OI (See Table 2, page 11)
  - Drug side effects
  - Immune reconstitution (See page 17)

- Perform regular laboratory monitoring (See Table 5, page 16). Additional investigations should be performed as clinically indicated.

Table 5: Recommended laboratory monitoring during ARV therapy

Test	Who?	Reason	Frequency	Management
Essential				
CD4	All	To monitor effectiveness of ARV therapy	3-6 monthly	See 'Changing ARV therapy' (page 26)
CBC	If using AZT	AZT can cause anemia or low white cell count	After 2 weeks, 4 weeks and then every 3 months	Hb>80g/l or falls >25%: check for OI and check Hb again in 2-4 weeks. Hb<80g/l: check for OI and change AZT
ALT or AST	If using NVP	NVP can cause liver side effects	After 2 weeks, 4 weeks and then every 3-6 months	ALT/AST raised <5xULN: check ALT/AST again in 2-4 weeks. ALT/AST>5xULN: change NVP
Recommended				
CBC	All	To screen for OI	3-6 monthly	Check for OI and check Hb again in 2-4 weeks.
ALT or AST	All	ARV can cause liver side effects (especially NNRTIs)	After 1 month, then every 3 months	ALT/AST raised <5xULN: check ALT/AST again in 2-4 weeks. ALT/AST>5xULN: change NVP, EFV, RTV
Optional				
Creatinine or urea	All, especially if using IDV	ARV can cause kidney side effects and the dose of ARV may need to be changed if Cr/Ur are increased	After 1 month, then every 3-6 months	See Table 9 (page 29)
Glucose	Especially if using a PI	PIs can cause high blood glucose and diabetes	Yearly	See 'Class side effect: hyperglycaemia and diabetes' (page 40)
Lipids	Especially if using a PI	PIs can cause abnormal blood lipids	Yearly	See 'Class side effect: hyperlipidaemia' (page 41)
HIV viral load	All	To monitor effectiveness of ARV therapy	3-6 monthly	Consider changing therapy if repeatedly detectable HIV virus

Diagnose and manage opportunistic infections

- Despite successful ARV therapy, OIs can still occur. See Table 2 (page 11) for a brief list of symptoms and signs that may be due to OIs and 'Guidelines For The Clinical Management of HIV Infection In Adults' for more detailed guidance on the diagnosis and management of OIs.

Diagnose and manage ARV side effects

- Explain to people taking ARV the most common side effects of their ARV combination. Drug side effects usually occur in the first few weeks and are usually mild and resolve after a month or so. Side effects can, however, occur at any time and can be serious. See Table 6 (page 18), 'Changing ARV therapy (page 24), Annex 2 (page 28) and Table 10 (page 32) for advice on management of side effects.

Diagnose and manage immune reconstitution

- The symptoms and signs of many infections are partly due to the reaction that they provoke from the immune system. When ARV therapy is given it strengthens the immune reaction to infections leading to an increase in various manifestations. This can result in
  - Previously asymptomatic infections becoming symptomatic
  - Apparent worsening of symptomatic infections even if they are being successfully treated.

- These manifestations are not a result of an infection alone or the immune system alone, but are due to an interaction between the two. They usually occur a few weeks after commencing ARV, but can occur any time in the first 3-6 months of ARV therapy.

- The most important immune reconstitution syndrome is that due to TB. This is sometimes called 'paradoxical reaction' and can also be seen in non-HIV infected people being treated for TB. Typically it involves fever and increase in TB lesions: lymph nodes, pulmonary infiltrates, ureteric strictures or CNS lesions.
- The usual approach to management is
  - Continue ARV
  - Start/continue treatment for the symptomatic infection
  - Consider a short course of corticosteroids if symptoms become severe (e.g. dyspnoea, CNS symptoms, renal obstruction)

Table 6: ARV side effects*

Drug	Class	Drug specific side effects

and drug class	specific side effects	Skin	Blood	Gastrointestinal	Neuromuscular	Other
Zidovudine (ZDV or AZT)	**Lipoatrophy** **Lactic acidosis** **Hepatic toxicity**		**Anaemia** **Neutropenia**	Nausea (common)	Headache (common) Myopathy Cardiomyopathy	
Stavudine (d4T)				**Pancreatitis** Hepatic toxicity	**Peripheral neuropathy** Guillain-Barre like syndrome	Lactic acidosis Lipoatrophy
Lamivudine (3TC)						No common side effects
Didanosine (ddI)				**Pancreatitis** Diarrhea, Nausea, Vomiting, Abdominal pain	**Peripheral neuropathy**	
Abacavir (ABC)						**Hypersensitivity syndrome**
Tenofovir (TFV or TDF)						No common side effects
Nevirapine (NVP)	**Rash** **Hepatitis**	**Rash**		**Hepatitis**		Hypersensitivity syndrome
Efavirenz (EFV)		Rash		Hepatitis	**Frequent and diverse CNS effects#**	**Teratogenicity**
Nelfinavir (NFV)	**Lipodystrophy** **Insulin resistance and diabetes** **Hyperlipidemia** **Hepatitis** Bone disorders Increased bleeding in hemophiliacs			**Diarrhoea** Abdominal pain		
Indinavir + Ritonivir (IDV/r)		Alopecia, dry skin and lips		Hyperbilirubinaemia Oesophageal reflux	Parasthesia	**Kidney stones**
Lopinavir + Ritonavir (LPV/r)				Diarrhoea	Parasthesia	Hyperlipidaemia
Saquinavir + Ritonavir (SQV/r)				Nausea Diarrhoea	Headache Parasthesia	

*Major side effects are in bold

#Includes dizziness, headache, insomnia, depression, impaired concentration, agitation, nightmares, sleepiness, severe depression, suicidal ideation, mania and delusions.

Minimize the development of resistance

- The development of resistance is an inevitable consequence of treatment of any infectious disease. It is not a sufficient argument for withholding treatment.

- HIV resistance to ARV reduces efficacy of ARV therapy, increases the cost of ARV regimen and can be transmitted to others. Minimize it:

- Support adherence. Imperfect adherence is the most important cause of drug resistant HIV (See page 16)

- Use ARV correctly. Inappropriate use of ARV by untrained practitioners is a very important cause of drug resistant HIV. ARV should only be prescribed by trained doctors who can ensure appropriate arv combinations, dosing, monitoring, supply and switching.

- Never use less than three effective ARV drugs together. If an ARV drug needs to be ceased then all ARV should be ceased until a complete ARV regimen can be restarted.

- Reduction in risk behavior by people taking ARV is an important mechanism to reduce the spread of drug resistant HIV. Adherence is also critical as this reduces the amount of HIV in blood and body fluids and reduces the risk of HIV transmission.

- Testing for HIV resistance is not recommended for routine clinical practice, but should be monitored at a population level.

Provide holistic support

- Provision of drugs alone does not work. Success of ARV therapy depends upon a holistic approach to the needs of PHA. This includes
  - Psychological support. Appropriate psychological support at difficult times can improve long term outcomes.
  - Nutritional support. Many people able to access ARV are not able to access adequate food intake. This should be addressed in all people taking ARV.
  - Social and financial support can help as PHA become stronger. Income generation and training to allow return to economic independence can be particularly important.

- Linkage with other available services is critical for treatment success particularly home care teams and PHA support groups. See 'Continuum of Care for people living with HIV/AIDS – Operational Framework' for ways to link ARV therapy into a comprehensive care approach.

Support behavior change and disclosure

- A good time to explore risk behavior is after a few months of ARV therapy. Ask about sexual behavior, condom use, planned pregnancies and contraception. Support the development of safe sexual practices over time.

- Reinforce that people living with HIV should not donate blood and should make sure that no one uses a needle after they have used it, whether it is for medical treatment, tattooing or injecting drug use.

- Explore the risks and benefits of disclosure of HIV status including to sexual partners. There is a responsibility to ensure that others are not exposed to the risk of HIV infection and greater support can come from disclosure of

HIV status, but this needs to be balanced against the risk of further stigma and discrimination.

Management of specific groups

Early HIV infection

- Acute HIV infection is often associated with mild, non-specific symptoms and is rarely diagnosed. It may present with more marked symptoms of fever, rash, lymphadenopathy, photophobia and occasionally OIs such as oral candidiasis.

- Although there are theoretical reasons for initiating ARV therapy in the rare instances when early HIV infection is diagnosed, there is insufficient evidence to recommend this as standard of care at present.

People who have taken ARV therapy previously

- Management of people who have 'ARV experience' is complicated and should be done in consultation with someone experienced in ARV therapy.

- Taking an appropriate combination of three potent ARV drugs for a period of time and ceasing all drugs at the same time does not carry a high risk of resistance. Evaluate whether ARV therapy is indicated and if so restart an appropriate combination. Use the original combination if this was appropriate, well tolerated and taken correctly.

- People who have taken NRTI monotherapy or bi-therapy for less than 2-3 months should generally be changed to 3 potent ARV drugs.

- People who have taken NRTI monotherapy or bi-therapy for more than 2-3 months have a significant risk of having NRTI resistant HIV strains. Management of this group is complicated. One approach is to continue two or three NRTIs if the individual is not showing any evidence of treatment failure. If treatment failure occurs, the most effective regimen possible should be given including NNRTI and/or PI classes.

- The management of people who have taken other inappropriate ARV combinations should be individualized based on previous treatment history. If this is not known first line ARV therapy can be used (d4T+3TC+NNRTI) with close monitoring for treatment failure.

Pregnant women and women of childbearing potential

- Recommended ARV drugs for pregnant women are AZT, 3TC, NVP, NFV or SQV/r. AZT and 3TC should be included whenever possible.

- NVP or NFV are the most widely used drugs combined with AZT+3TC. Do not use efavirenz because of the risk of teratogenicity.

- SQV/r or IDV/r are alternative drugs to combine with AZT+3TC. IDV should be avoided close to delivery due to risk of neonatal hyperbilirubinemia. PIs may increase the risk of gestational diabetes.

- The risk of lactic acidosis/hepatic steatosis is increased during pregnancy. Do not use d4T+ddI as this combination seems to increase the risk further.

- It is acceptable to use NNRTIs in a treatment combination if a woman has previously received single dose NVP without other ARV for PMTCT.[1]
- Women who are not on ARV at the start of pregnancy should start ARV whenever it is indicated. Some women may want to delay ARV until the end of the 1st trimester to reduce any possible risk of teratogenicity.[2]

- Women on ARV who become pregnant should continue ARV therapy.[3] The ARV regimen should be optimized to ensure the lowest possible maternal HIV viral load at the time of delivery as this is the most important predictor of MTCT. EFV and the combination of ddI+d4T should be changed to other agents.

- Give AZT, 3TC, ddI, d4T and NVP at the usual dose.

- Continue ARV during labor. NVP should still be given to the baby.

- Pay extra attention to adherence during and after pregnancy as adherence to ARV can be particularly difficult during this time.

- Counsel mothers on ARV regarding their infant feeding options as per the National Guidelines on PMTCT.

[1]There is currently no data available to clarify whether women who take single dose NVP without other ARV are at increased risk for failure of NNRTI based regimens due to NVP resistance.
[2]The timing of initiation of ARV in an ARV-naive pregnant woman is directed by an analysis of the risk of adverse effects on the foetus versus the risk to both mother and child of delaying therapy. There is conflicting data regarding the teratogenicity of ARVs. Mitochondrial dysfunction in infants with intrauterine exposure to ARVs has been reported, but if there is an association it is likely to be rare. On the other hand uncontrolled viral replication in early pregnancy may result in transmission of HIV to the foetus, but this is also known to be rare.
[3]Some women may consider temporarily ceasing ARV during the first trimester to reduce the risk of adverse effects on the fetus, but this risk is likely to be low, especially if recommended ARV are used.

- The efficacy of ARV in prevention of MTCT via breast milk is not known. ARV therapy could theoretically reduce the amount of HIV in breast milk and so reduce transmission, but sub-optimal concentrations of ARV may not be sufficient to reduce the HIV viral load and may lead to the development of resistant HIV.

- Women taking ARV who decide to breastfeed should continue taking ARV.

- NNRTIs and PIs lower blood levels of OCP, so additional or alternative methods of contraception should be used. It is not known whether this effect is sufficient to reduce the efficacy of injectable hormonal contraception.

People co infected with TB

- TB is a major cause of illness and death for PHA. It is estimated to occur in approximately 50% of PHA. A recent national survey found that 10% of new TB patients have HIV.

- Start TB therapy immediately after diagnosis of TB. The optimal time to start ARV is not known. If ARV therapy is started early there is a high rate of medication side effects and immune reconstitution disease ('paradoxical reactions'). If ARV therapy is started late there is a high risk of other HIV related illnesses, particularly for people with low CD4 counts. See Table 7 below.

- If giving ARV during the Rifampicin phase of therapy use AZT (or d4T) combined with 3TC and one of the following:
  - EFV is the preferred third drug. The dose of EFV should be increased to 800mg/day unless the individual weighs less than 40kg.1
  - SQV+RTV can be used at a dose of SQV 400mg twice a day plus RTV 400mg twice a day.
  - ABC at usual dose. Note that ABC hypersensitivity may be confused with immune reconstitution disease.
  - NVP is an option of last resort as correct dosing has not been established and it has overlapping hepatotoxicity with TB therapy.

- If the continuation phase of the TB regimen does not contain rifampicin, standard ARV combinations can be used from two weeks after rifampicin is completed. Selection of ARV should consider overlapping toxicities with TB medications, e.g. peripheral neuropathy with d4T or ddI.

- PHA who develop TB whilst on ARV should have their ARV combination adjusted in the same way. After completion of TB treatment the new ARV combination can be continued or changed back to the original.

Table 7: Starting ARV for people being treated for TB

Diagnosis and CD4 Count	Start ARV
PTB and CD4 < 50 OR EPTB	Start ARV as soon as TB medications are tolerated. Usually after 2-4 weeks of TB treatment.
PTB and CD4 50 – 200	Start ARV after two months of TB treatment.*
PTB and CD4 > 200	No ARV. Monitor CD4

* If continuation phase does not contain rifampicin, any ARV combination can be started two weeks after rifampicin is completed.

[1]EFV 600mg/d combined with rifampicin is currently being investigated.

People coinfected with hepatitis B and/or hepatitis C

- The prevalence of hepatitis coinfection in PHA in Cambodia may be approximately 12% for hepatitis B and 15% for hepatitis C.

- Hepatotoxicity of ARV is increased approximately 3-fold in people coinfected with hepatitis B or C, but symptomatic hepatitis remains uncommon (1-2%).

- NVP and the combination of d4T + ddI should be avoided in PHA with abnormal LFTs (raised ALT, AST or bilirubin). If possible, NVP should be avoided in PHA known to be hepatitis co-infected.

- 3TC and/or TFV have anti-hepatitis B activity, but the optimal use of these agents in hepatitis coinfected people has not been established and is difficult in the absence of specialized tests. If it is thought that HIV resistance has diminished the possible anti-HIV effect of these agents, they can be continued for their anti-hepatitis B effect together with 3 effective anti-HIV ARV agents.

- There is a risk of "hepatitis flare" in patients with hepatitis B if 3TC, and presumably TFV, are ceased.

People with other opportunistic infections

- Simultaneous use of ARV with treatment of OI other than TB is not limited by difficult drug interactions and should be feasible in most situations.

- Delay the start of ARV therapy for a few days to a week if the risk of ARV intolerance is high. For example, do not start cotrimoxazole and NVP at the same time as the cause of any rash that developed would be difficult to determine.

- For OI for which effective treatment is not available give ARV early as immune recovery is likely to provide benefit.

- OI prophylaxis should be given according to the National Guidelines on Prophylaxis of Opportunistic Infections.

Changing antiretroviral therapy

Changes because of side effects

- Change one drug if the cause is obvious, otherwise change all.
- Preferably change to drug(s) that do not cause the same side effect.
- If needing to temporarily cease one drug, cease all drugs.
- See 'Diagnose and manage ARV side effects' (page 18), Table 6 (page 18), Annex 2 (page 28) and Table 10 (page 32).

Table 8: Changing ARV because of side effects (see p18 for side effect management)

Drug	Side effect	Suggested immediate action	Suggested future action
NRTI	Lipoatrophy	Consider changing NRTI (d4T or ddI or AZT) to ABC	Can use these drugs again, but will make lipoatrophy worse
	Lactic acidosis	Change NRTI to ABC or TFV	Try to avoid using AZT, d4T or ddI again
AZT	Anaemia (Hb<80 g/l or fall > 25%)	Change AZT to d4T	Avoid AZT
	Neutropenia (neutrophils < $1.0x10^6$/l)	Change AZT to d4T	Avoid AZT
d4T	Peripheral neuropathy (moderate or severe)	Change d4T to AZT	Avoid d4T
ddI	Pancreatitis and peripheral neuropathy	Change ddI to another NRTI (not d4T)	Avoid ddI
ABC	Hypersensitivity Syndrome	Change ABC to another drug depending on previous experience	Never use ABC again as reuse can be fatal
NVP	Rash – moderate to severe (eg bullae, "wet")	Change NVP to EFV	Never use NVP again

	Rash – complicated (mucosal involvement or fever)	Change NVP to PI or ABC	Never use NVP or EFV again
	Hepatitis	Change NVP to EFV	Never use NVP again
	Hepatitis – severe or life threatening	Change NVP to PI or ABC	Never use NVP or EFV again
EFV	CNS effects - severe	Change EFV to NVP	Avoid EFV
	Pregnancy (teratogenicity)	Change EFV to NVP	Can use EFV again when not pregnant
PI	Metabolic complications (hyperglycaemia, hyperlipidaemia) – uncontrolled	Change PI to non-PI if unable to be controlled	Avoid using PI again if possible
NFV	Diarrhoea – severe or persistent	Change NFV to non-PI if possible (or PI/r)	Avoid using NFV again if possible
IDV	Kidney stones – repeated	Change IDV to another PI or other drug	Never use IDV again if possible

Changes because of treatment failure

- Treatment failure can be detected clinically, immunologically or virologically.

- OIs can still occur during ARV therapy, particularly if the CD4 count has not yet increased above 200 cells/mm3, but worsening or failure of overall condition to improve (e.g. progression to more advanced clinical stage) should be seen as evidence of treatment failure.

- Immunological failure is a fall in CD4 count of more than 30% of the peak value or a fall to or below the baseline value. Always repeat CD4 before deciding that treatment has failed.

- Virological failure is repeated detectable HIV in blood.

- The cause of treatment failure is often sub-optimal adherence. This should be identified and addressed.

- Other causes of treatment failure may be difficult to diagnose. These include HIV resistance to one or more of the ARV drugs, poor drug absorption and drug interactions decreasing the blood levels of one or more of the ARV drugs.

- When and how to change an ARV combination is a complex decision that should always be made in consultation with someone experienced in the use of ARV.

- If treatment failure occurs always change to three new ARV drugs. Never add or change a single drug because of treatment failure.

- Always take account of all the previous ARV drugs that have been used as drug resistance will usually persist after an ARV drug is stopped.

- Change the NRTIs to two new NRTIs1 and change the 3rd drug to a new 3rd drug. If the first regimen was d4T + 3TC + NVP/EFV, then AZT + ddI + PI can be used if this regimen fails.

- ❖ Never change NVP to EFV or EFV to NVP because of treatment failure as cross-resistance develops easily. Change a NNRTI to either a PI or ABC if they have not been used previously.[2] Change a PI to either a NNRTI or ABC if they have not been used previously.[2] If the first PI used was NFV then it is possible to change to a PI/r.

[1]ABC can be used with 3TC or ddI if they were not used previously. TFV can be used with a new NRTI.
[2]TFV can substituted as the new 3rd drug, in combination with two new NRTIs, except for ABC + 3TC.

References

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6. Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach: World Health Organisation, 2002.

7. Guidelines for antiretroviral therapy in Zimbabwe: National Drug and Therapeutics Policy Advisory Committee, 2003.

8. Yeni P, Hammer S, Carpenter C, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society - USA Panel. JAMA 2002; 288:222-235.

Annex 1: WHO staging system for HIV infection and disease in adults and adolescents

Clinical Stage I:

1. Asymptomatic
2. Persistent generalized lymphadenopathy (PGL).

Performance scale 1: Asymptomatic, normal activity.

Clinical Stage II:

3. Weight loss, < 10 % of body weight.
4. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis).
5. Herpes Zoster, within the last 5 years.
6. Recurrent upper respiratory tract infections (i.e., bacterial sinusitis).

And/or Performance scale 2: symptomatic, normal activity.

Clinical Stage III:

7. Weight loss, > 10 % of body weight.
8. Unexplained chronic diarrhoea, > 1 month.
9. Unexplained prolonged fever (intermittent or constant), > 1 month.
10. Oral candidiasis (thrush).
11. Oral hairy leukoplakia.
12. Pulmonary tuberculosis, within the past year.
13. Severe bacterial infections (i.e., pneumonia, pyomyositis).

And/or Performance scale 3: bed-ridden, < 50% of the day during the last month.

Clinical Stage IV:

14. HIV wasting syndrome, as defined by CDC[1].
15. Pneumocystis carinii pneumonia.
16. Toxoplasmosis of the brain.
17. Cryptosporidiosis with diarrhoea, > 1 month.
18. Cryptococcosis, extrapulmonary.
19. Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes.
20. Herpes simplex virus (HSV) infection, mucocutaneous > 1 month, or visceral any duration.
21. Progressive multifocal leukoencephalopathy (PML).
22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis).
23. Candidiasis of the oesophagus, trachea, bronchi or lungs.
24. Atypical mycobacteriosis, disseminated.
25. Non-typhoid Salmonella septicaemia.
26. Extrapulmonary tuberculosis.
27. Lymphoma.
28. Kaposi's sarcoma (KS).
29. HIV encephalopathy, as defined by CDC2.

And/or Performance scale 4: bed-ridden, > 50 % of the day during the last month.

(Note: both definitive and presumptive diagnoses are acceptable.)

[1]HIV wasting syndrome: Weight loss of > 10 % of body weight, plus either unexplained chronic diarrhoea (> 1 month), or chronic weakness and unexplained prolonged fever (> 1 month).

[2]HIV encephalopathy: Clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.

Annex 2: Antiretroviral agents and side effects

- Get to know the drugs. Spend time becoming familiar with each ARV drug, particularly the side effects it can cause and the management of these side effects.

- This section begins with two tables: the first (Table 9, page 29) provides a summary of some features of each ARV drug. The second table (Table 10, page 32) gives an overview of ARV side effects. Following the tables each ARV drug is listed with discussion of its side effects.

- ❖ See also ‘Principles of ARV therapy’ (page 8), ‘Diagnose and manage ARV side effects’ (page 18), Table 6 (page 19), ‘Management of specific groups’ (page 22) and ‘Changing ARV therapy’ (page 26).

Table 9: ARV dosage, formulation, requirements and use in specific groups

Drug and drug class	Dose	Formulations	Cold storage needed for long term storage	Food effects	Renal and hepatic impairment*	Pregnancy (See page 22)	TB/HIV co-infection (See page 24)
NRTI							
Zidovudine (ZDV or AZT)	300mg (one tablet) twice per day	Capsule 100 mg, 250 mg; Tablet 300mg; Injection 10 mg/ml in 20 ml vial; Oral solution 10 mg/ml	No	None	No change necessary	Preferred	Preferred
Stavudine (d4T)	40mg (one capsule) twice per day OR 30mg (one capsule) twice per day if <60 kg	Capsule 15 mg, 20 mg, 30 mg, 40 mg; Oral solution 1 mg/ml	Only for reconstituted oral solution	None	CrCl 10-50ml/min: halve each dose	Yes (not combined with ddI)	Acceptable, but increased risk of neuropathy
Lamivudine (3TC)	150mg (one tablet) twice per day	Tablet 150mg; Oral solution 10mg/ml	No	None	CrCl 10-50ml/min: 150mg daily	Preferred	Preferred
Didanosine (ddI)	>60kg: 200mg (one tablet) or 250mg (powder) once or twice per day or 400mg (one EC capsule) once per day <60kg: 125mg (two tablet) or 167mg (powder) twice per day or 250mg (two tablet or one EC capsule) once per day	Tablet 25 mg, 50mg, 100 mg, 150 mg, 200 mg; Powder 100mg, 167mg, 250mg; EC Capsule 125mg, 200mg, 250mg, 400mg	Only for powder	Take at least 30 minutes before or 2 hours after meal	CrCl 10-50ml/min: Normal dose, but only once per day	Yes (not combined with d4T)	Acceptable, but increased risk of neuropathy
Abacavir (ABC)	300mg (one tablet) twice per day	Tablet 300mg; Oral solution 20mg/ml	No	None	No change necessary	No	Yes, but may be difficult to diagnose ABC hypersensitivity in this setting
NtRTI							

Tenofovir (TFV or TDF)	300mg (one tablet) once per day	Tablet 300mg	No	Take with meal	Do not give to patients with renal impairment (CrCl < 50ml/min)	No	No
NNRTI							
Nevirapine (NVP)	200mg (one tablet) once per day for two weeks, then 200mg (one tablet) twice per day	Tablet 200 mg; Oral suspension 10mg/ml	No	None	Renal: No change necessary Hepatic: avoid	Preferred	Avoid if possible as overlapping toxicity and dosing is not clear
Efavirenz (EFV)	600mg (one capsule) once per day	Capsule 50 mg, 100 mg, 200 mg, 600mg; Syrup 30mg/ml	No	Avoid taking with high fat meal	Renal: no change necessary Hepatic: consider alternative drug	No	Preferred
PI							
Nelfinavir (NFV)	1250mg (five tablets) twice per day	Tablet 250 mg; Powder 50 mg/g	No	Take with food; at least a light meal	No data	Preferred	No
Indinavir + ritonivir (IDV/r)	400mg/100mg (two capsules) twice per day	IDV Capsule 100 mg, 200 mg, 333 mg, 400 mg; RTV Capsule 100mg; oral solution 80mg/ml	Only for RTV capsules: stable for 30 days at room temperature	None	Renal: avoid if possible. No change necessary in dose. Hepatic: avoid	Yes	No
Lopinavir + ritonavir (LPV/r)	400mg/100mg (three capsules) twice per day (co-formulated)	Capsule 133.3 mg + 33.3 mg; Oral solution, 80mg/ml + 20mg/ml	Yes; stable for 2 months at room temperature	Take with food	Renal : no data Hepatic : Avoid	No	No
Saquinavir + ritonavir (SQV/r)	1000mg/100mg (six capsules) twice per day	SQV Capsule (hard gel (HGC) or soft gel (SGC) filled) 200 mg ; RTV Capsule	Only for SQV SGC (stable for 3 months) and	None	Renal : no data Hepatic : avoid	Yes	Yes

		100mg; Oral solution 80mg/ml	RTV capsules (stable for 30 days) at room temperature				
Combination							
Zidovudine + lamivudine (AZT + 3TC)	300mg/150mg (one tablet) twice per day		No	None	Use individual formulations if CrCl < 50ml/min	Preferred	Preferred
Stavudine + lamivudine (d4T + 3TC)	40mg/150mg (one tablet) twice per day OR 30mg/150mg (one tablet) twice per day if <60 kg		No	None	Use individual formulations if CrCl < 50ml/min	Yes	Acceptable, but increased risk of neuropathy
Stavudine + lamivudine + nevirapine (d4T + 3TC + NVP)	After two week induction, 40mg/150mg/200mg (one tablet) twice per day OR 30mg/150mg/200mg (one tablet) twice per day if <60 kg		No	None	Renal : Use individual formulations if CrCl < 50ml/min Hepatic : Avoid	Yes	Avoid if possible as overlapping toxicity, increased risk of neuropathy and dosing is not clear
Zidovudine + lamivudine + nevirapine (AZT + 3TC + NVP)	After two week induction, 300mg/150mg//200mg (one tablet) twice per day		No	None	Renal : Use individual formulations if CrCl < 50ml/min Hepatic : Avoid	Preferred	Avoid if possible as overlapping toxicity and dosing is not clear
Zidovudine + lamivudine + abacavir	300mg/150mg//300mg (one tablet) twice per day		No	None	Use individual formulations if CrCl < 50ml/min	No	Yes, but may be difficult to diagnose ABC hypersensitivity in this setting

(AZT + 3TC + ABC)							

*ESRF is not considered in these recommendations. For specific information on patients with CrCl<10ml/min or on dialysis refer to reference texts.

Table 10: Management of major side effects of ARV

Side effect	Major ARV causes	Presentation	Prevention	Management
Abdominal pain	Hepatitis: d4T, NVP, EFV, RTV Pancreatitis: ddI, d4T	Abdominal pain	Check ALT (and hepatitis serology) at baseline. Avoid these agents if risks for hepatitis or pancreatitis	Check amylase and ALT. Consider abdominal ultrasound. See 'Hepatitis' or 'Pancreatitis' or 'Lactic Acidosis'
Anaemia	AZT	Weakness, lethargy, dizziness	Check CBC at baseline. Avoid AZT if Hb<100g/l.	Hb>80g/l: check for OI. Check Hb again in 2-4 weeks Hb<80g/l: cease AZT
Central Nervous System effects*	EFV	Central Nervous System symptoms*	Consider using other ARV if any mental illness or harmful substance use	Mild symptoms: continue EFV, monitor, give EFV at night Severe symptoms: cease EFV
Diarrhoea	ddI, NFV, RTV	Diarrhoea	Nil	Check for other causes. Give symptomatic treatment. Cease drug if severe or persistent
Headache	AZT, EFV	Headache	Nil	Check for other causes. Cease drug if severe or persistent
Hepatitis	d4T, NVP, EFV, full dose RTV	Lethargy, nausea, vomiting, abdominal pain, jaundice	Check ALT (+/- hepatitis serology) at baseline. Avoid these drugs if risks for hepatitis	ALT/AST<5xULN: check ALT/AST again in 2-4 weeks. ALT/AST>5xULN: cease drug
Hyperbilirubinaemia	IDV	Nil	Nil	Usually nil required
Hyperglycaemia/ diabetes	All PIs	Lethargy, thirst, polyuria, polydipsia	Avoid PIs if risks for diabetes	If diabetes develops, start metformin. Increase medications as needed. If unable to be controlled cease PI
Hyperlipidaemia	All PIs, especially RTV	Nil	Avoid PIs if risks for hyperlipidaemia	Continue PI and add anti-lipid therapy. If unable to be controlled cease PI (see page 41)
Hypersensitivity syndrome	ABC, NVP	Rash (esp.NVP), fever, hepatitis, eosinophilia	Nil	Cease drug and never restart as restarting may be fatal.
Kidney stones	IDV	Loin pain, haematuria	Maintain hydration. Drink >1.5l/day	Cease IDV. Hydration and analgesia. Restart IDV unless repeated episodes
Lactic acidosis	AZT, d4T, ddI	Lethargy, nausea, vomiting, diarrhoea and dyspnoea.	Avoid d4T +ddI (especially during pregnancy)	See Table 11 (page 34)
Lipodystrophy	All (especially AZT, d4T and ddI for lipoatrophy and PIs for central fat accumulation)	Peripheral fat wasting, central obesity, visceral fat accumulation, 'buffalo hump' and breast enlargement	Consider using drugs other than d4T and PIs	Cease d4T or AZT
Myopathy	AZT	Proximal muscle wasting and	Nil	Cease AZT

		weakness		
Nausea/vomiting	AZT, ddI, RTV, LPV/r	Nausea/vomiting	Nil	Check for other cause. Give symptomatic treatment. Cease drug if severe or persistent
Neutropenia	AZT	Nil	Check CBC at baseline. Avoid AZT if neutrophil count<$1x10^6$/l. Check CBC at 4 weeks.	Neutrophil count>$1x10^6$/l: check CBC again in 2-4 weeks. Neutrophil count<$1x10^6$/l: cease AZT
Pancreatitis	ddI, d4T	Nausea, vomiting, abdominal pain	Avoid ddI, d4T if risks for pancreatitis	Check amylase. Cease drug if amylase > 500 or severe or persistent symptoms.
Peripheral neuropathy	d4T, ddI	Peripheral numbness, tingling, pain or weakness	Consider using drugs other than d4T, ddI	Cease drug unless mild and stable
Rash	NVP (also ABC)	Erythema, bullae, mucosal ulceration	Two week low dose initiation of NVP	ABC: cease drug and never restart as restarting may be fatal NVP: cease drug if severe, bullae, mucosal involvement or fever
Teratogenicity	EFV	Congenital defects	Avoid EFV if risk of pregnancy	Cease EFV

*Includes dizziness, headache, insomnia, depression, impaired concentration, agitation, nightmares, sleepiness, severe depression, suicidal ideation, mania and delusions.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Class side effect: Lactic acidosis/hepatic toxicity

- Asymptomatic elevations in blood lactate level are common in people taking NRTIs. They are not predictive of lactic acidosis.

- Symptomatic elevations in blood lactate are less common and true lactic acidosis is rare, but often fatal (See Table 11 below).

- Risk factors for lactic acidosis are the use of NRTIs, in particular d4T and/or ddI. Other possible risk factors are female sex, high body mass index, pregnancy and acquired riboflavin and thiamine deficiency.

- Symptoms include weakness, lethargy, nausea, vomiting, diarrhoea and dyspnoea.

- Laboratory features are acidosis with an increased anion gap and raised lactate, AST/ALT, creatinine kinase, lactate dehydrogenase and amylase. If

measurement of lactate is not available a constellation of the above symptoms with increased anion gap acidosis and raised AST/ALT is suggestive of lactic acidosis.

- Cease all NRTIs as soon as suspected. Treatment is supportive (fluid replacement, bicarbonate and respiratory support if available).

- Restart ARV without d4T or ddI and preferably without AZT or 3TC, particularly if the episode was life threatening. For example, combine ABC or TFV with a NNRTI and a PI.

- Raised ALT or AST occurs in 5-15% of people taking NRTIs, but is symptomatic in less than 1%.

Table 11: Features and management of hyperlactataemia

Grade	Lactate (mmol/l)	Frequency (%)	Management		Mortality (%)
			No symptoms	Symptoms	
Severe	>10	0.1	Cease ARV	Cease ARV	80
Moderate	5-10	1	Observe	Exclude other causes and cease ARV	0
Mild	2-5	5	Observe and look for other metabolic complications	Exclude other causes and consider ceasing ARV	0

Class side effect: Lipoatrophy

- Lipoatrophy is part of the lipodystrophy syndrome. It seems to be more closely associated with the use of NRTIs, particularly d4T and AZT. It results in reduction in peripheral fat, particularly of the face, arms, legs and buttocks, resulting in a characteristic appearance with prominent cheek bones and prominent veins on the limbs.

- Lipoatrophy is common and generally becomes apparent after one to two years of therapy. Studies investigating the role of switching drugs in the management of lipoatrophy have generally had disappointing results. Switching d4T or AZT to ABC has shown very slow reversal of peripheral lipoatrophy. Drug treatment is currently being studied.

Zidovudine (AZT)

- Anaemia and neutropenia are the major side effects. The overall rate of these side effects is 5-10%, but is much higher in people with advanced HIV disease. Management is either by dose reduction (if not severe), transfusion and/or discontinuation.

- Headache, nausea and fatigue occur in approximately 5-10% of people, but usually resolve over a few weeks.

- Myopathy with myalgia, proximal weakness and wasting can occur and is usually reversible with cessation of AZT.

Stavudine (d4T)

- The major side effect of d4T is peripheral neuropathy. It is more common and more severe with higher dose, longer duration of use, more advanced HIV disease and with the use of other neurotoxic drugs, particularly ddI. Symptoms usually gradually resolve over a few weeks after cessation of d4T, but can persist and cause wasting.

- d4T is more likely to cause the NRTI class-specific side effects than other NRTIs: lactic acidosis, hepatic toxicity and lipoatrophy.

- d4T can also cause pancreatitis. Again, this is more common when d4T is given together with ddI.

- A Guillain-Barre like syndrome has occurred with d4T. If there are any signs consistent with this syndrome, for example motor weakness, then d4T should be ceased.

Lamivudine (3TC)

- 3TC is well tolerated with very few side effects.

- Uncommon, but reported side effects are headache, fatigue, nausea, vomiting, diarrhoea, pancreatitis, peripheral neuropathy, neutropenia and hepatic toxicity.

Didanosine (ddI)

- The major side effects of ddI are peripheral neuropathy and pancreatitis. Peripheral neuropathy occurs in approximately 6-15% of users. The risk is probably increased if d4T is given at the same time. Symptoms usually resolve over a few weeks after cessation, but can persist and cause wasting.

- Pancreatitis occurs in approximately 1-7% of users and is fatal in 1%. Risk factors are use of higher doses, high alcohol consumption, severe obesity, hypertriglyceridaemia, gallstones and the use of other drugs that can cause pancreatitis such as d4T. ddI must be ceased if pancreatitis occurs.

- ddI can also cause diarrhoea, nausea, vomiting or abdominal pain in about 5-18% of users.

Abacavir (ABC)

- The major side effect of ABC is hypersensitivity syndrome. It occurs in 3-5% of users and can be fatal. The average time to onset is one week after ABC is started and over 90% of cases will occur in the first six weeks, but it can occur at any time.

- Typical symptoms are constitutional and include:
  - Fever is the most common feature.

- Rash is common, but not prominent.
- Gastrointestinal: nausea, vomiting, diarrhoea, abdominal pain
- Respiratory: pharyngitis, cough, dyspnoea
- Generalised arthralgia, myalgia, headache, malaise

- Examination may show fever, rash, lymphadenopathy and mucosal ulceration. Investigation may reveal elevated liver enzymes, creatinine kinase, creatinine and thrombocytopenia.

- Differentiation from other illnesses can be extremely difficult. Most characteristic of ABC hypersensitivity are:
  - Involvement of multiple organ systems, for example gastrointestinal and respiratory symptoms
  - Acute onset of symptoms
  - Worsening of symptoms as further doses of ABC are taken

- People taking ABC should be intensively counselled regarding hypersensitivity syndrome and advised to report any symptoms promptly. If hypersensitivity is suspected by a health care provider, ABC should be ceased and never restarted, because re-challenge can result in rapidly fatal reactions. Management is supportive. There is no evidence that steroids are of benefit.

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

Tenofovir (TFV)

- TFV is very well tolerated with few side effects. Nausea, vomiting and diarrhoea can occur and are usually mild. Increases in liver functions tests

have been reported. There have also been case reports of Fanconi syndrome and renal impairment, but definite causation has not been established.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Class side effect: Rash and hepatitis

- Rash can occur with both NVP and EFV, but severe rash including Stevens-Johnson syndrome has only been described for NVP.

- There does not seem to be cross-reactivity for rash between NVP and EFV, so EFV can be used if rash has occurred with NVP and vice versa. However, if the NVP rash is severe or associated with mucosal involvement, EFV should not be used.

- Hepatitis can occur with both NVP and EFV, but is more common with NVP (See Table 11). It is probably safe to use the other agent if hepatitis occurred with NVP or EFV, except if the hepatitis was severe or life threatening.

Table 12: NNRTI side effects (Grade 3/4) in the 2NN study

Percentages	NVP 400mg once/d	NVP 200mg twice/d	EFV 600mg once/d
Clinical hepatotoxicity	1.4	2.1	0.3
Laboratory hepatotoxicity	13.2	7.8	4.5
Central nervous system toxicity	1.8	4.9	6.5
Discontinuation due to toxicity	24.1	21.2	15.5

Nevirapine (NVP)

- The major side effects of NVP are rash and hepatitis.

- Rash occurs in about 17% of users, is serious enough to result in discontinuation in 6-8% and develops into Stevens Johnson syndrome or toxic epidermal necrolysis in 0.3%.

- The most common time for development of rash is in the first two to four weeks. It is usually erythematous, maculopapular, confluent and most prominent on the body and arms. Fever, myalgia, hepatitis and eosinophilia can also occur.

- If mild to moderate rash without other symptoms or mucosal involvement occurs, NVP can be continued with careful observation. During the two-week low dose NVP initiation, it is preferable to cease all ARV if rash occurs. Restart ARV including NVP once the rash has settled. Do not increase the dose of NVP until the rash has resolved. Steroids are not useful.

- If any of the following are present, NVP should be permanently ceased and neither NVP or EFV given in the future:
  - Severe rash
  - Rash with bullae or target lesions
  - Mucosal involvement
  - Hypersensitivity syndrome: fever, myalgia, hepatitis and eosinophilia.

- Hepatitis can occur alone or with rash and/or hypersensitivity syndrome. Abnormal liver function tests occur in about 15% and clinical hepatitis in about 1-5%. Rarely, hepatic failure and death can occur. About two thirds of cases occur in the first 3 months of use, but can occur at any time.

- Risk factors for NVP associated hepatitis are abnormal liver function tests at baseline, excess consumption of alcohol, older age, female sex, co-infection with hepatitis B or C and a higher CD4 count.

- Symptoms are generally non-specific: malaise, anorexia, nausea, vomiting. It should be noted that abdominal pain and jaundice do not always occur. As detailed above, hepatitis may occur as part of a hypersensitivity syndrome with rash, fever, myalgia and eosinophilia.

- NVP should be permanently discontinued if NVP associated hepatitis is diagnosed. EFV can be used if the hepatitis was not severe or life threatening.

Efavirenz (EFV)

- The major side effects of EFV affect the central nervous system.

- These side effects occur in 30-50% of users and include dizziness, headache, insomnia, depression, impaired concentration, agitation, vivid dreams, nightmares and sleepiness. These symptoms usually settle after a couple of weeks. Less than 2% of users develop major psychiatric symptoms such as severe depression, suicidal ideation, mania and delusions. These usually occur in those with a previous history of mental illness or substance use disorders.

- If symptoms are mild, EFV can usually be continued and may be given at nighttime to reduce their effect. If severe, EFV should be permanently ceased.

- Other side effects of EFV are rash and hepatitis (See ‘Class-specific side effect: rash and hepatitis’, page 37). It is also teratogenic and should not be given during pregnancy, particularly during the first trimester.

Protease Inhibitors (PIs)

Class side effect: metabolic complications

- All PIs can cause a group of metabolic complications that include lipodystrophy, insulin resistance and diabetes, hyperlipidaemia.

Class side effect: lipodystrophy

- This syndrome includes peripheral lipoatrophy, which is more closely associated with the use of NRTIs particularly d4T, and central fat accumulation (central obesity, visceral fat accumulation, 'buffalo hump' and breast enlargement), which is more closely associated with the use of PIs. This complication of PI therapy often coexists with other metabolic complications.

- Lipodystrophy occurs in the majority of people taking a combination of NRTIs and and a PI. It generally becomes apparent after one to two years of therapy. Studies investigating the role of switching drugs in the management of lipodystrophy have generally had disappointing results. Switching the PI to a non-PI drug has not been shown to provide substantial benefit. Switching d4T or AZT to ABC has shown very slow reversal of peripheral lipoatrophy. Drug treatment of lipodystrophy is currently being studied.

Class side effect: insulin resistance and diabetes

- Insulin resistance occurs in up to 40% of PI users, hyperglycaemia in 3-17% and clinical diabetes in 1%. Onset is usually a few months after starting therapy.

- When symptoms occur they are those of diabetes: lethargy, thirst, polyuria and polydipsia.

- PIs can usually be continued together with drug management of hyperglycaemia/diabetes. Studies are ongoing, but metformin is probably the best first line treatment. If severe or difficult to control, PIs should be ceased. Hyperglycaemia usually, but not always, resolves after cessation.

Class side effect: hyperlipidaemia

- All PI drugs can cause elevation of triglycerides and cholesterol, but RTV seems to cause the most marked elevations. Whether these elevations increase the risk of cardiovascular disease is not yet clear.

- Drug therapy for hyperlipidaemia should be initiated at standard thresholds. Isolated increase in LDL-cholesterol should be treated with a statin, preferably pravastatin because this drug has less interactions with PIs. Start at low doses and watch carefully for the development of myopathy. Isolated increase in triglycerides should be treated with a fibrate, for example gemfibrozil or fenofibrate. Combined increases in LDL-cholesterol and triglycerides can be treated with either a statin or a fibrate. Data available to date suggests that drug therapy is not effective at lowering either LDL-cholesterol or triglycerides to generally accepted targets. Combined therapy with a statin and a fibrate may be more effective, but may also increase the risk of myopathy. Severe elevations in lipids are best managed by switching the PI to a drug from another class, although the lipid abnormalities may persist despite this.

Class side effect: hepatitis

- PIs, particularly RTV, can cause elevation of liver enzymes and clinical hepatitis at any time during treatment by an unknown mechanism.

- Risk factors include elevated liver function tests at baseline, excess alcohol intake, hepatitis B and/or C coinfection and the use of other hepatotoxic drugs including d4T.

- Minor elevations in liver enzymes can be observed and the PI continued. If more marked elevations or clinical hepatitis occur the PI should be permanently discontinued.

Class side effect: bone disorders

- Regimens containing PIs seem to be associated with an increased risk for osteopenia, osteoporosis and avascular necrosis.

Nelfinavir (NFV)

- NFV is relatively well tolerated with the only significant side effect being gastrointestinal upset. Diarrhoea commonly occurs soon after starting NFV and usually, but not always, resolves over a few weeks. Abdominal pain and flatulence also occur.

Indinavir/ritonavir (IDV/r)

- The major side effect of IDV is kidney stones (nephrolithiasis), which occurs in about 10% of users. It presents with typical flank pain and haematuria. Management is supportive with hydration and analgesia. IDV (and therefore all ARV) should be ceased for a few days until symptoms settle. Unless repeated episodes have occurred, IDV can be restarted with close attention to ongoing hydration. All people taking IDV should be advised to drink at least 1.5 liters of fluid per day.

- Asymptomatic indirect hyperbilirubinaemia is seen in about 10% of users, usually in the first few weeks of treatment. Clinical jaundice or elevations in transaminases are rare and so usually no specific management is required.

- IDV can also cause retinoid-like side effects: alopecia, dry skin, dry lips and ingrown nails.

- About 3% of people taking IDV develop oesophageal reflux.

- The ritonavir component can cause peri-oral and peripheral paraesthesia. This is not dangerous, but can be severe enough to require change of drug.

Lopinivir/ritonavir (LPV/r)

- The major side effects of this combination are probably due to the RTV component: diarrhoea and hyperlipidaemia. Pancreatitis has also occurred, possibly secondary to hypertriglyceridaemia. Paraethesia can occur.

Saquinavir/ritonavir (SQV/r)

- The major side effects of this combination are likely to be more associated with the RTV component: nausea, diarrhoea, abdominal pain, headache, paraesthesia and liver toxicity.

Annex 3: Important ARV drug interactions

- There are many complicated interactions between ARV and with other drugs.

- Table 14 gives an overview of major drug interactions. There are many more interactions. Always check reference texts for interactions before prescribing new drugs.

Table 13: Important ARV drug interactions

Interacting drug	NVP	EFV	NFV	IDV/r	LPV/r	SQV/r
Ketoconazole	X	?	OK			
Rifampicin	Use with caution	EFV 800mg/d	X	X	X	Give both drugs at full dose
Rifabutin	OK	RBT 450-600 mg/d	RBT 150mg/d NFV 1000mg tds			RBT 250mg 2-3/week
Clarithromycin	OK	X	?		?	
Oral contraceptive[1]	X	X	X	X	X	X
Methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone
'Statins'[2]	?	?	X		X	X
Other drugs that should not be co-administered	Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine	Astemizole Terfenadine Cisapride Midazolam Ergotamine	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-	Astemizole Terfenadine Cisapride Midazolam Ergotamine

		Dihydro-ergotamine Garlic supplements	Dihydro-ergotamine Garlic supplements	Dihydro-ergotamine Garlic supplements Flecanide Pimozide	ergotamine Garlic supplements Flecanide Pimozide	Dihydro-ergotamine Garlic supplements Flecanide Pimozide
Miscellaneous	Can lower steroid levels	Monitor warfarin if co-administered				

[1]Additional or alternative methods of contraception should be used.
[2]Pravastatin can be used.

Annex 4: Karnofsky Performance Scale

Table 14: Karnofsky performance scale

Level of function	Score	Description
Able to carry on normal activity and to work; no special care needed.	**100**	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	**70**	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead