A GUIDE TO
ANTI RETROVIRAL THERAPY

MINISTRY OF HEALTHCARE, NUTRITION AND
UVA-WELLASSA DEVELOPMENT

WORLD BANK

NATIONAL STD/AIDS CONTROL PROGRAMME

JANUARY 2005

A GUIDE TO ANTI RETROVIRAL THERAPY

Prepared by

NATIONAL STD/AIDS CONTROL PROGRAMME

MINISTRY OF HEALTHCARE, NUTRITION AND
UVA-WELLASSA DEVELOPMENT

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Forward

Developing countries are home to 95 per cent of people living with AIDS (PLWA) and in 2002, the World Health Organization conservatively estimated that around 6 million PLWA are in need of antiretroviral treatment (ART). However, only 230,000 were receiving ART.

The Ministry of Healthcare, Nutrition and Uva-Wellassa Development decided that ART has a definite role in the Sri Lanka's healthcare system given the strong health infrastructure, the availability of funds from the National HIV/AIDS Prevention Project supported by the World Bank and the recommendation of the National STD/AIDS Control Programme (NSACP).

The price of antiretroviral drugs has been coming down from a very high level to a level that is still relatively high. There are also the costs of diagnosis, monitoring, managing side effects, and ensuring adequate training for healthcare staff. It is important to note that ART is still generally complicated to take and to adhere to especially for low-income patients. The Ministry of Healthcare, Nutrition and Uva-Wellassa Development recognizes that ensuring access by PLWA to prevention and treatment of opportunistic infections is inexpensive and cost effective.

Therefore, the development of a 'Guide to Antiretroviral Treatment' is very timely and I congratulate the NSACP for undertaking this important task. It is an attempt to inform and enlighten medical professionals in Sri Lanka on antiretroviral drugs, treatment regimens, complications and side effects, and ensuring adherence as well as management of common opportunistic infections.

Dr. H.A.P. Kahanaliyanage
Director General of Health Services

January 2005

Preface

Significant advances in the understanding of HIV/AIDS nave led to the development of a range of drugs to control HIV infection. These drugs are known as antiretroviral drugs (ARVs) and have radically changed the HIV/AIDS landscape within the span of a few years. A combination of three or more ARVs in various regimens forms the staple of HIV treatment today.

The availability of ART has shown to reduce the viral load to undetectable levels as well as to reduce HIV-related morbidity, mortality, incidence of opportunistic infections and hospitalization by 50 to 60 per cent. Therefore, the fatal course of HIV infection can now be altered to a chronic manageable condition that allows an infected person to lead a relatively normal life. However, it must be emphasized that ARVs do not cure HIV infection and prevention is still the most important strategy to control HIV/AIDS.

Although Sri Lanka has relatively few HIV-infected persons, the National STD/AIDS Control Programme (NSACP) has been advocating for ART for the past 2 years and it is deeply satisfying to be able to provide ART to our patients who need it most.

The NSACP undertook to develop the Guide to Antiretroviral Treatment to inform and educate the medical professionals in the use of ARVs. This Guide should enable rational use of standardized ARV regimens. The ARVs currently available in Sri Lanka are limited in number. It is important to note that cross-resistance between specific drugs have been documented. Frequent or unnecessary change of antiretroviral treatment decreases future options.

I thank all the Consultant Venereologists of the NSACP for developing this important document, in particular, Dr. Sujatha Samarakoon and Dr. Lilani Rajapakse for their untiring efforts to review other guidelines and recommendations in order to finalise the Guide.

Since this is a relatively new and rapidly evolving treatment, the Guide would need revision and updating every year or two.

Dr. Iyanthi Abeyewickreme
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National STD/AIDS Control Programme

January 2005

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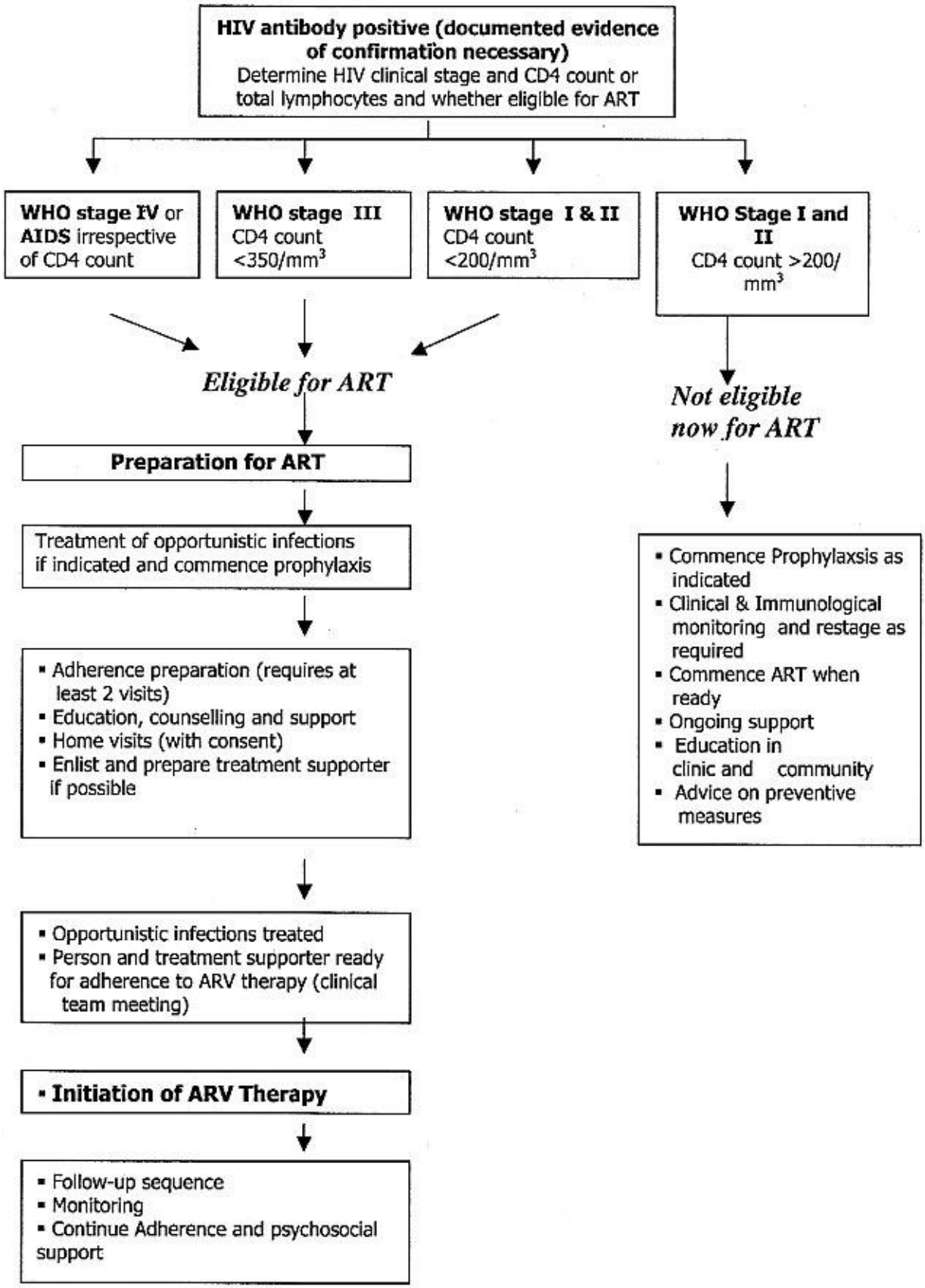

1. ANTIRETROVIRAL TREATMENT (ART)

Prescription of anti retroviral therapy is complex and requires a complete understanding of the rationale, pharmacology, and adverse effects of medication. In addition, the physician needs to be knowledgeable about the treatment of coexisting conditions and the treatment of HIV in special groups such as children and pregnant women.

2. WHEN TO START TREATMENT IN ADOLESCENTS AND ADULTS

Since the CD4 cell count correlates well with the total lymphocyte count in severely symptomatic patients, the individuals with Stage IV of HIV disease have a CD4 cell count equal to or below $200/mm^3$, or a total lymphocyte count equal or below $1200/mm^3$. Therefore, the indication for treatment in stage IV is not dependant on the CD4 determination and based only on a clinical evaluation.

Since 2004, WHO recommends also to start ARV therapy in patients with symptoms of the stage III of HIV disease irrespective of the CD4 cell count. This new clinical stage III recommendation includes pulmonary TB as a treatment indication irrespective of the level of the CD4 count, as pulmonary TB may occur with any CD4 count level.

Since there is a lack of a good correlation between CD4 count, total lymphocyte count and clinical symptoms in stages I and II this necessitates the evaluation of the level of immunosuppression before starting the treatment. It is indicated in stage II when total lymphocyte count is equal to or below $1200/mm^3$ (measured reliably) or CD4 count is equal to or below $200/mm^3$ and indicated in state I when CD4 count is equal or below $200/mm^3$.

The National STD/AIDS Control Programme (NSACP) has adopted the WHO recommendation that infected adolescents and adults should start ART when they have:

If CD4 Testing Available

- **WHO Stage IV disease, irrespective of CD4 cell count**
- **WHO Stage III disease** (characterised by HIV wasting, chronic diarrhoea, prolonged fever, atypical pulmonary TB, recurrent invasive bacterial infections or recurrent / persistent mucosal candidiasis), **with consideration of using CD4 cell counts below 350/mm^3 to assist decision-making**
- **WHO Stage I or II disease with CD4 cell counts below 200/mm^3**

If CD4 Testing Unavailable

- **WHO Stage IV disease, irrespective of total lymphocyte count**
- **WHO Stage III disease** (characterised by HIV wasting, chronic diarrhoea, prolonged fever, atypical pulmonary TB, recurrent invasive bacterial infections or recurrent / persistent mucosal candidiasis), **irrespective of total lymphocyte count**
- **WHO Stage II disease with a total lymphocyte count < 1200/mm^3**

When CD4 count is unavailable, patients in WHO Stage I will not be considered for ART

WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN ADULTS AND ADOLESCENTS

CLINICAL STAGE 1

1. Asymptomatic
2. Generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

CLINICAL STAGE II

3. Weight loss <10% of body weight
4. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
5. Herpes zoster within the last five 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 leucoplakia
12. Pulmonary tuberculosis
13. Severe bacterial infections (i.e. pneumonia, pyomyositis)

And/or performance scale 3: bedridden <50% of the day during last month

Clinical Stage IV:

14. HIV wasting syndrome*
15. Pneumocystic carinii pneumonia
16. Toxoplasmosis of the brain
17. Cryptosporidiosis with diarrhea > 1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegalovirus disease of an organ other than liver, spleen or lymph node (e.g. retinitis)
20. Herpes simplex virus infection, mucocutaneous (>1month) or visceral
21. Progressive multifocal leucoencephalopathy
22. Any disseminated endemic mycosis
23. Candidiasis of oesophagus, trachea, bronchi
24. Atypical mycobacteriosis, disseminated or pulmonary
25. Non-typhoid salmonella septicaemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma
29. HIV encephalopathy**

And/or performance scale 4: bedridden >50% of the day during last month

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

** 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, which could explain the findings.

3. BASELINE ASSESSMENT

Before any person is started on ART, they should undergo a baseline assessment that addresses the following questions:

- What is the clinical status?
- What is the laboratory status?
- What is the support available to continue treatment?

Having fully explored these questions decide:

- Should OI treatment and/or prophylaxis be provided?
- Should ART be considered? (Determine other medical conditions e.g. TB, pregnancy, major psychiatric illness and other medications being taken including traditional therapies)
- Is the person interested in and motivated to take ART?
- Should other support services be provided? (e.g. counselling, self help groups)

The following table[1] provides a framework for a clinical review of symptoms and signs, medication use, side effects and complications.

4. CLINICAL REVIEW

ASK	LOOK
<u>If this is the first visit:</u> Review history. Check record for special situations like TB/Pregnancy, opportunistic infections, chronic problems medications **<u>For all visits:</u>** ▪ How is the patient? ▪ Any problems developed? ▪ Has the patient had any of the following? ***If yes,*** ask for how long: o Cough? o Night Sweats? o Fever? o STI signs? (use locally adapted screening questions) o Diarrhoea? o Mouth sores? o New skin rash? o Headache? o Fatigue? o Nausea or vomiting? o Poor appetite? o Tingling, numb or painful feet/legs? o Any other pain? ***If yes,*** where? o Sexual problems? ▪ Has the patient needed urgent medical care? ***If yes,*** ask for record/diagnosis ▪ Which medications are being taken and how often? ▪ Assess adherence ▪ Any problems in taking the medicines? how are they taken? ▪ Taking any other drugs (traditional remedies, TB, ARV, illicit drugs, etc.)? ▪ How are things at home? ▪ Is there any thing else they would like to talk about?	**<u>In all persons:</u>** ▪ Look for pallor. ***If pallor*** *is present,* check haemoglobin ▪ Look at whites of the eye. Yellow? ▪ Look for thrush ▪ Weigh the patient and record. Calculate weight gain or loss. If weight loss, ask about food intake ▪ Count pills to estimate adherence ▪ ***<u>If person is sad or has lost interest, assess for depression.</u>*** ***<u>If any new symptoms:</u>*** ▪ Measure temperature ▪ Check for nodes. ▪ Look for rash ▪ Look for evidence of violence ▪ Do further assessment of symptoms. ***<u>If first visit</u>*** **(also check every 6 months; skip if known problem)** Tell the person you want to check his memory: o Name 3 unrelated objects clearly and slowly. Ask person to repeat them: o Can he/she repeat them? (registration problem?) ***If yes:*** wait 5 minutes and ask again: "Can you recall the 3 objects? (recall problem?)

[1] WHO (2004). <u>Chronic HIV Care with ARV Therapy</u>. Integrated Management of Adolescent and Adult Illness: Interim guidelines for first level facility health workers.

5. BASELINE TESTS

In all patients, HIV sero status should have been confirmed at the National Reference Laboratory of the NSACP.

Basic testing should include:

- CD4 count
- Haemoglobin or haematocrit measurement
- Full blood count (to identify a decline in neutrophils and the possibility of the occurrence of neutropenia during ART);
- Liver function tests
- Serum creatinine, blood urea and serum electrolytes to assess baseline renal function;
- Blood sugar;
- Hepatitis B surface antigen
- HCV antibody
- CXR
- Mantoux test
- Pregnancy tests } for women
- PAP smear
- Toxoplasma antibodies
- CMV antibodies
- STI screening

6. ASSESSMENT OF PATIENTS' READINESS FOR THERAPY

- Build up confidence and assess patient's knowledge

- Mention the clinic protocol on ARV treatment including the importance of adherence and explain the objectives of the treatment to patient

- The objectives of the treatment are:
  - to build up immunity
  - to avoid occurrence of OI
  - to increase survival & quality of life

- Repeat discussions may be necessary to prepare patient for therapy

- Ensure the patient has understood that
  - the treatment is a suppressive treatment for viral division
  - the treatment does not kill the virus
  - the treatment has to be taken regularly to avoid resistance and if resistance develops,treatment may fail
  - it is life-long treatment

- Advise and encourage the patient to disclose his diagnosis to his/her partner or a family member and encourage testing of the sexual partner if status is unknown

- Ensure the partner or family has understood their role in supporting therapy

Remember ARV therapy for the individual patient is not an emergency !

The public health emergency is to get large numbers of right patients on treatment with good adherence & good overall HIV chronic care.

For the individual patient, management of life threatening OI can be an emergency

7. COUNSELLING FOR TREATMENT ADHERENCE

When counseling a patient for adherence, the following should be stressed:

- Treatment compliance should be strict and adherence to recommended regimens should be greater than 95% to avoid resistance
- Treatment has to be continued for life
- Timing of drug intake is critical (eg. drugs taken twice daily must be taken every 12 hours +/- one hour)
- Some drugs are taken with food, some drugs are taken on an empty stomach, some require increase intake of water. Those instructions should be given clearly to the patient
- Drug side effects have to be understood
- Financial and social support structures including family members should be assessed.
- Family planning and child bearing issues such as methods of contraception should be addressed
- Patient should understand the need to attend STD clinic regularly for monitoring of efficacy and adherence.

8. STANDARD TREATMENT

The goals of treatment :

- to reduce HIV-related morbidity by controlling immunodeficiency and by reducing the viral load
- to prolong survival and improve quality of life
- to assist the patient to return to normal life

A large number of drugs and drug combinations can be used. The choice of drug-regimen depends on availability of medications, pregnancy, side effects and development of resistance.

Antiretroviral drugs : general principles

NRTIs	NtRTI	NNRTIs	PIs
Zidovudine (ZDV)	Tenofovir (TDF)*	Nevirapine (NVP)	Saquinavir (SQV)*
Didanosine (DDI)*		Efavirenz (EFV)	Ritonavir (RTV)
Lamivudine (3TC)			Lopinavir (LPV)*
Stavudine (d4T)			Amprenavir (APV)*
Abacavir (ABC)*			Nelfinavir (NFV)*
Zalcitabine (ddC)*			Indinavir (IDV)

* Currently not available in Sri Lanka

NRTI = nucleoside reverse transcriptase inhibitor
NNRTI = non-nucleoside reverse transcriptase inhibitor
NtRTI = nucleotide reverse transcriptase inhibitor
PI = protease inhibitor

All these drugs act by blocking the action of enzymes which are important for the replication and functioning of HIV. The enzyme ***reverse transcriptase*** initiates copying of the viral genetic code (RNA) into the genetic code of the infected host cells (DNA). After this, the HIV genetic material is integrated into the host's DNA. This is followed by multiplication, creating several billion copies

of HIV per day. The enzyme ***protease*** contributes to viral reproduction by enabling the assembly and release of viable particles of HIV from infected cells.

The drugs must be used in combination, usually three drugs together. The term Highly Active Anti Retroviral Treatment (HAART) is used to describe a regimen of three or more antiretroviral drugs.

Antiretroviral dosages and recommendations

Nucleoside RTIs:	
Zidovudine (ZDV)	300mg bd do not use with d4T
Stavudine (d4T)	40mg bd (if weight <60Kg, use 30 mg bd) do not use with ZDV
Lamivudine (3TC)	150 mg bd
Didanosine (ddI)	400mg bd (if weight <60 Kg, use 250 mg od) If Tenofovir (TDF) is associated the ddI dose should be reduced to 250mg (>60Kg) or 125mg (<60Kg) to be taken on empty stomach
Abacavir (ABC)	300 mg bd do not re-start after withdrawal
Non-nucleoside RTIs:	
Efavirenz (EFZ)	600mg od (do not use during pregnancy) Consider increasing dose to 800mg if given with rifampicin Avoid fatty meals
Nevirapine (NVP)	200mg od for 14 days, followed by 200mg bd (warn patient about rash)
Protease inhibitors:	
Nelfinavir (NFV)	1250mg bd to be taken with food
Indinavir/ritonavir	800mg/100mg bd (1.5 litre fluids per day)
Lopinavir/ritonavir	400mg/100mg bd to be taken with food
Saquinavir/ritonavir	1000mg/100mg bd

Note: od – once daily administration
bd - twice daily administration

9. RECOMMENDED FIRST-LINE ARV REGIMENS

In accordance with "WHO scaling up antiretroviral therapy in resource-limited settings" the NSACP has selected suitable regimens of treatment. As in other developing countries, Sri Lanka has opted for a first line regimen composed of two nucleosides and a non nucleoside RT inhibitor. Protease inhibitors containing regimens have been identified for secondary options.

WHO recommended first line regimens:

d4T + 3TC + NVP
ZDV + 3TC + NVP
D4T + 3TC + EFV
ZDV + 3TC + EFV

These regimens include anti-retrovirals in fixed-dose combinations (FDCs) which promote better adherence which would in turn limit the emergence of drug-resistance.

Fixed dose combinations (FDC) of antiretrovirals available

Three-drugs FDC	d4T (40mg) + 3TC (150mg) + NVP (200mg) BID**
	d4T (30mg) + 3TC (150mg) + NVP (200mg) BID**
	ZDV (300mg) + 3TC (150mg) + NVP (200mg) BID**
	ZDV (300mg) + 3TC (150mg) + ABC (150mg) BID *
Two drugs FDC	d4T (40mg) + 3TC (150mg) BID
To be used with a third selected one :	d4T (30mg) + 3TC (150mg) BID
	ZDV (300mg) + 3TC (150mg) BID

WHO encourages the use of fixed dose combinations when formulations of proven quality are assured. The main disadvantage of the FDC is the need to withdraw all three drugs, if a reaction to one of the three component drugs occurs.

** With this FDC there is the requirement for a lead-in dose of nevirapine 200mg od for the first two weeks.

* Not recommended if other alternatives available

10. SPECIFIC INSTRUCTIONS

How to give d4T+3TC+NVP regimen

Note that when initiating the above regimen **NVP** requires an escalating dose starting with once daily for the first 2 weeks, then twice a day.

Adult dose and adolescence dose

- Stavudine (d4T) 30 mg twice a day
- Lamividine (3TC) 150mg twice a day
- Nevirapine (NVP) 200mg once a day for the first 2 weeks followed by 200mg twice a day

FIRST 2 WEEKS

In the morning - 1 tablet of d4T+3TC+NVP (Fixed drug dose tablet)

In the evening - 1 tablet of d4T+ 3TC (Fixed drug dose tablet)

AFTER 2 WEEKS

One tablet of d4T+ 3TC+ NVP twice a day (12 hourly)

That is
In the morning - 1 tablet of d4T+3TC+NVP (Fixed drug dose tablet)

In the evening - 1 tablet of d4T+3TC+NVP (Fixed drug dose tablet)

No diet restrictions

The most common side effect is a **rash.** Patients who develop a rash during the 14 day lead-in period should not increase the dose to twice daily until the rash has resolved. Rash is usually mild to moderate but requires discontinuation only in a few patients.

How to give d4T+3TC+ EFV regimen

Adult dose and adolescence dose

- Stavudine (d4T) 30 mg twice a day
- Lamividine (3TC) 150mg twice a day
- Efavirenz (EFV) 600mg once a day at night

In the morning - 1 tablet of d4T+3TC (Fixed drug dose tablet)

In the night - 1 tablet of d4T+3TC (Fixed drug dose tablet) and one tablet of EFV

EFV may be taken with or without food but do not take with high-fat meals

EFV is teratogenic - **Do not use** EFV in pregnancy and in women in the reproductive age who are not on contraception.

How to give ZDV +3TC+ NVP regimen

Note that when initiating the above regimen **NVP** requires an escalating dose of once daily for the first 2 weeks, then twice a day.

Adult dose and adolescence dose

- Zidovudine (ZDV) 300 mg twice a day
- Lamividine (3TC) 150mg twice a day
- Nevirapine (NVP) 200mg once a day for the first 2 weeks followed by 200mg twice a day

FIRST 2 WEEKS

In the morning - 1 tablet of ZDV +3TC+NVP (Fixed drug dose tablet)

In the evening - 1 tablet of ZDV +3TC (Fixed drug dose tablet)

AFTER 2 WEEKS

One tablet of ZDV +3TC+NVP twice a day (12 hourly)

That is
In the morning - 1 tablet of ZDV +3TC+NVP (Fixed drug dose tablet)
In the evening - 1 tablet of ZDV +3TC+NVP (Fixed drug dose tablet)

No diet restrictions

How to give ZDV +3TC+ EFV regimen

Adult dose and adolescence dose

- Zidovudine (ZDV) 300mg twice a day
- Lamividine (3TC) 150mg twice a day
- Efavirenz (EFV) 600mg daily at night

In the morning - 1 tablet of ZDV + 3TC Fixed drug dose tablet

In the night - 1 tablet of ZDV +3TC Fixed drug dose tablet and one tablet of Efavirenz –EFV

EFV may be taken with or without food but do not take with high-fat meals
EFV is teratogenic - **Do not use** EFV in pregnancy or potential/intended future pregnancy..

Table 1 - First-line ARV regimen in adults and adolescents and characteristics

ARV Regimen	Major potential toxicities	Usage in women in child-bearing age or who are pregnant	Usage in TB co-infection	Availability in three drug fixed dose combination	Laboratory monitoring requirements
d4T/3TC/NVP	d4T-related neuropathy, pancreatitis and lipoatrophy; NVP-related hepatotoxicity and severe rash	Yes	Yes in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin based regimen	Yes	Basic
ZDV/3TC/NVP	ZDV-related GI intolerance, anemia, and neutropenia; NVP related hepatotoxicity and severe rash	Yes	Yes in rifampicine-free continuation phase of TB treatment. Use with caution in rifampicin-based regimen	Yes	Basic
d4T/3TC/EFV	d4T-related neuropathy, pancreatitis and lipoatrophy; EFV-related CNS toxicity teratogenicity	No	Yes, but EFV should not be given to pregnant women or women of childbearing potential	No. EFV not available as part of FDC. However partial FDC available for d4T/3TC	Basic
AZT/3TC/EFV	ZDV-related GI intolerance, anemia, and neutropenia; EFV-related CNS toxicity teratogenicity	No	Yes, but EFV should not be given to pregnant women or childbearing women	No. EFV not available as part of FDC. However partial FDC available for ZDV/3TC	Basic

The four selected first regimens are considered to be approximately equally potent. Therefore, other factors have to be taken into account in making the choice

The choice between stavudine (d4T) and Zidovudine (ZDV) :

- d4T does not require hemoglobin monitoring
- It is associated with lipodystrophy, neuropathy (particularly when combined
- with DDI)
- d4T causes metabolic abnormalities like lactic acidosis

- ZDV is less implicated in metabolic complications, but is more likely to cause nausea, headache, anemia and neutropenia.

- ZDV should not be used in case of anaemia or when there is no laboratory facility to monitor the haemoglobin level. One should be very cautious on using ZDV in late disease stages because of coexistence of severe anaemia.

- d4T can be substituted for ZDV in the event of intolerance to the latter and vice versa (except in the case of suspected lactic acidosis, in which instance neither drug should be prescribed).

The choice between nevirapine (NVP) and efavirenz (EFV)

- NVP and EFV : are both potent NNRTIs

- The major toxiticities associated with EFV are central nervous system (CNS) related, and teratogenicity.. The CNS symptoms typically abate after 10 to 14 days.

- NVP has a higher incidence of rash, which may be severe and life threatening. NVP has also a higher risk of hepatotoxicity.

- EFV should not be used during pregnancy

- NVP is currently recommended to be used with rifampicin but with caution when other preferential options are not available (because of a decline in the plasma level of NVP which reduces its efficacy and potentially accumulates hepatotoxocity). Studies are ongoing which may change the recommendation.

ZDV and d4T should never be used together because of proven antagonism between (page 13)

11. MEDICAL CONTRAINDICATIONS TO FIRST-LINE ARV REGIMEN

Contraindication	Definition	Comments	Recommendation
Pregnancy or possible pregnancy		Contraindication to efavirenz (EFV) (teratogen)	EFV should not be used during pregnancy or if access to effective contraception cannot be assured
Severe Anemia	Hb<7.0 g/dL	Contraindication to use of zidovudine	Use alternate first-line regimen, d4T + 3TC + NVP
Severe neutropenia	Neutrophil count <750/mm3		
Severe renal insufficiency	Creatinine >3 times normal	Contraindication to ARV use	Patient not currently eligible for ART. Conduct diagnostic evaluation and reassess for ART eligibility if renal or hepatic function improves
Severe hepatic insufficiency	Liver function tests > 5 times normal		
History of prior ARV intolerance	If intolerant of zidovudine, use lamivudine + stavudine + nevirapine. If intolerant of nevirapine, consider zidovudine + lamivudine + efavirenz. Other substitutions may require expert advice.		
History of prior ARV use (other than PMTCT)	Use of any ARV for more than four weeks	Potential for ARV resistance	Expert management required. Consult expert for case-by-case advice.
Current use of anti-TB medications	Use of rifampin	Drug-drug Interactions with nevirapine	If CD4 count high, consider deferring ARVs until TB therapy is completed. If not, use alternate first-line regimen, simultaneously/concommitently eg. ZDV + 3TC + EFV or ZDV + 3TC + ABC

12. ADVERSE EFFECTS

All drugs have class specific adverse effects

*	NRTIs	mitochondrial toxicity (eg. fatty changes in the liver, myopathy, pancreatitis, lactic acidosis)
		lipodystrophy syndrome with prolonged use
*	NtRTI	renal toxicity, possible mitochondrial toxicity.
*	NNRTIs	skin rash
		abnormal liver enzymes/hepatitis

* PIs lipodystrophy syndrome

elevated serum cholesterol and triglycerides

elevated blood glucose

Other specific drug side effects include :

Nucleoside RTIs:	
Zidovudine (ZDV)	Nausea, headache, anaemia, fatigue, muscle pains
Stavudine (d4T)	Peripheral neuropathy, pancreatitis
Lamivudine (3TC)	Nausea, headache, anaemia, fatigue, muscle pains (rare)
Didanosine (DDI)	Nausea, diarrhoea, peripheral neuropathy, pancreatitis
Abacavir (ABC)	Nausea, fatigue, sleep disorder, hypersensitivity (5%)
Non nucleoside RTIs:	
Efavirenz (EFZ)	Neuropsychiatric disorders, rash, teratogenic
Nevirapine (NVP)	Skin rash, hepatitis
Protease inhibitors:	
Nelfinavir (NFV)	Diarrhoea, nausea, skin rash
Indinavir/ritonavir	Nausea, abdominal pain, kidney stones, diabetes
Lopinavir/ritonavir	Diarrhoea, skin rash, headache, weakness Metabolic disorders (diabetes, hyperlipemia)
Saquinavir/ritonavir	Diarrhoea, headache, confusion

13. MONITORING EFFICACY OF ARV TREATMENT

Efficacy of ART has to be monitored by regular evaluation of clinical improvement and immunologic response assessed by the CD4 count (CD4 lymphocyte level).

Clinical Evaluation

- feeling of well being
- body weight
- resolution of symptoms, worsening of symptoms, new symptoms
- clinical performance status
- occurrence or recurrence of HIV related events (after at least 3 months of being on an ARV regimen)

Immunological evaluation

Regular CD4 counts must be performed to assess immunological function.

- Treatment failure is suggested by persistently declining levels of the CD4 count when measured on two occasions 3 to 6 months apart.
- 25-50 cells/mm^3 above baseline CD4 count over the 1st year of therapy indicates treatment success

Monitoring of ART

Monitoring	Laboratory marker
Virological	Viral load Resistance to anti retroviral drugs
Immunological	CD4 count. Total lymphocyte count
Opportunistic infections	Occurrence of new infections Recurrence of treated infections Anti-microbial susceptibility
Adverse drug reaction	Liver and kidney function tests

SUGGESTED CLINICAL EVALUATION AND MONITORING

Investigation	At Baseline	Time interval from start of ART							
		2 Weeks	4 Weeks	8 Weeks	12 Weeks	Monthly	3-4 Monthly	6 Monthly	Annually
Clinical review	√	Monitor tolerability and adherence				Until stable	Once stable		
STI Screen, Pap in women	√							Higher risk	Lower risk
Mantoux test (PPD)	√								Previous negative
CXR	√		When required						
CD4 (or TLC)	√				√		√		
Viral load*	√				√		√		
FBC (Hb & WBC/DC)	√		√		√		√		
Lipid Profile			When required					On PI/NNRTI +risk	On PI/NNRTI
Fasting Blood sugar									
Liver function tests (ALT & AST)	√	On NVP	On NVP		√		√		
Serum creatinine	√		when required						
Blood urea	√		When required						
Serum electrolytes			When required						
Hepatitis B S Ag	√								
HCV antibody	√								
Pregnancy test for women	X								
Toxoplasma antibodies*	√								
CMV antibodies*	√								

* Not essential, desirable if available

14. REASONS FOR CHANGING ARV TREATMENT

The treatment may need to be changed if there has been treatment failure or if the patient is unable to tolerate the drugs due to toxicity. Change of regimen should only be undertaken if poor adherence is not the cause of failure, in which case treatment should be withheld until all adherence issues have been addressed.

14.1 Treatment failure

The patient must have been on ARV therapy for 6 months or more and have been adhering to treatment before recorded "as failed".

Treatment failure can be defined as clinical failure, immunologic failure and/or virologic failure.

Clinical failure can be defined as assessed by disease progression : recurrence of prior OI or occurrence of new OI or malignancy.

Clinical and/or CD4+ cell count definitions of treatment failure in HIV+

Clinical signs of treatment failure	CD4 cell criteria for treatment failure
• Occurrence of new opportunistic infection or malignancy signifying clinical disease progression. This must be differentiated from the immune reconstitution syndrome which can occur in the first three months following the initiation of ART. The latter does not signify treatment failure and the opportunistic infection should be treated as usual, without changes in the antiretroviral regimen. • Recurrence of prior opportunistic infection • Onset or recurrence of WHO Stage III conditions (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis)	• Return of CD4 cell to pre-therapy baseline or below without other concomitant infection to explain transient CD4 cell decrease. • >50% fall from on therapy CD4 peak level without other concomitant infection to explain transient CD4 cell decrease. • Interpretation of CD4 count should be made carefully within the frequent variations.

Patients who fail to respond to the first treatment regimen that they have received, should be treated with a different regimen. The treatment should include at least three new drugs, with one from at least one new class to minimize the risk of cross-resistances.

Treatment failure needs to be differentiated from an ***Immune Reconstitution Syndrome (IRS)*** which can be seen within the first several weeks after the institution of therapy if a subclinical infection is present at baseline. IRS is characterized by the appearance of signs and symptoms of an opportunistic disease a few weeks after the start of potent antiretroviral therapy in the setting of advanced immunodeficiency, as an inflammatory response to previously sub-clinical opportunistic infection.

IRS does not signify treatment failure and the OI should be treated as usual without changing the ARV regimen.

- Never add a single ARV drug to a failing regimen
- Never replace a single (or more) drug(s) in a failing regimen
- If ARV drugs are to be discontinued due to failure, replace the entire regimen.

14.2 Treatment toxicity

If the patient has drug toxicity, therapy may be altered as follows:

Change of a single drug in a multi-drug regimen is permitted, ie. the offending drug may be replaced with an alternative drug of the same class that does not have similar effect (substitution of ZDV for d4T in case of anaemia, or EFV for NVP in case of CNS toxicity or pregnancy).

It is preferable to pursue drug substitution where feasible, so that premature switching to completely new alternative regimens is minimized.

14.3 Major potential toxicities of first-line ARV regimens and recommended drug substitutions

Regimen	Toxicity	Drug substitution
d4T/3TC/NVP	* d4T-related neuropathy or pancreatitis * d4T-related lipoatrophy * NVP-related severe hepatotoxicity	* Switch d4T → ZDV * Switch d4T → TDF or ABC * Switch NVP → EFV
d4T/3TC/NVP	* NVP-related severe rash (but not life threatening) * NVP-related life threatening rash (Stevens-Johnson syndrome)	* Switch NVP → EFV * Switch NVP → PI
ZDV/3TC/NVP	* ZDV-related persistent GI intolerance or severe hematological toxicity * NVP-related severe hepatotoxicity * NVP-related severe rash (but not life threatening) * NVP-related life threatening rash (Stevens-Johnson syndrome)	* Switch ZDV → d4T * Switch NVP → EFV (except in pregnancy. In this situation switch to NFV, LPR/r or ABC) * Switch NVP → EFV * Switch NVP → PI
d4T/3TC/EFV	* d4T-related neuropathy or pancreatitis * d4T-related lipoatrophy * EFV-related persistent CNS Toxicity	* Switch d4T → ZDV * Switch d4T → TDF or ABC * Switch EFV → NVP
ZDV/3TC/EFV	* ZDV-related persistent GI intolerance or severe hematological toxicity * EFV-related persistent CNS toxicity	* Switch ZDV → d4T * Switch EFV → NVP

14.4 Laboratory indications to change ARVs due to toxicity		
Haematology	Haemoglobin	Less than 7.0 g/dL
	Neutrophil count	Less than 750/mm^3
	Platelets	Less than 50,000 mm^3
Chemistries	Creatinine	More than 3 x upper limit of normal
	Glucose (fasting non diabetics)	Less than 39 mg/dL or more than 251 mg/dL
Liver Function tests	AST(SGOT)	More than 5 x upper limit of normal
	ALT (GPT)	More than 5 x upper limit of normal
	Alkaline phosphatase	More than 5 x upper limit of normal
	Bilrubin	More than 2.5 x upper limit of normal
Pancreatic enzymes	Amylase, lipase	More than 2 x upper limit of normal

15. NEW TREATMENT REGIMENS - SWITCH AND SECOND LINES

1) Protease inhibitors-based regimens:

PIs were not considered as the first line due to the following:

- High pill burden, metabolic abnormalities
- Food and water requirements in some case
- Significant interactions with rifampicin that complicate their use during TB treatment
- Metabolic abnormalities
- The need for a functioning cold chain for ritonavir boosted regimens
- The unavailability of co-formulation with NRTI
- High cost

However, they should be considered as first line in case of intolerance to NNRTI class of drugs.

Ritonavir-boosted PIs are preferred because of their high potency and relatively lower pill burden but the requirement for a cold chain and frequent laboratory monitoring support will present problems in many settings.

Indinavir boosted with Ritonavir is recommended as 2nd line treatment in Sri Lanka.

(Other PIs are Lopiniavir/Ritonavir (LPV/r) which is administered only twice a day but causes frequent elevations in plasma lipids levels.

Saquinavir/Ritonavir (SQV/r) is compatible with rifampicin administration and is also a safe option in pregnancy.*

* (PIs are presently not available in Sri Lanka)

16. TREATMENT ADHERENCE AND DRUG RESISTANCE SURVEILLANCE

- Poor adherence is associated with viral mutations due to persistence of viral division
- Viral mutations are associated with drug resistance
- Drug resistance is associated with treatment failure
- Drug resistance does not occur with an optimal treatment that inhibits viral replication
- Drug resistance does not occur without any treatment
- Drug resistant virus may be transmitted to partners if safe sex is not practiced.

Drug resistance occurs when a suboptimal treatment does not fully prevent virus from replicating (detectable viral load). Since viral load testing will not be introduced in a broad fashion in the developing world in the near future due to cost and technical considerations, focusing on maximizing adherence is even more crucial to try to avoid drug resistance and ensure durability of ARV regimen effect.

Studies of drug adherence in the developed world have suggested that rates > 95% are desirable to maximize the benefits of ARV treatment and avoid treatment failure.

The increase in antiretroviral drug resistance may lead to increase transmission of resistant viral strains. Currently approximately 10% of new HIV 1 infections in the United States and Europe are with viral strains exhibiting resistance to at least one drug.

Genotyping is not routinely performed in resource limited settings for patient management.

At the national level, a drug resistance sentinel surveillance system should be implemented to regularly modify recommended treatment regimens, according to the prevalence rate of drug resistance in the infected populations.

17. MANAGEMENT OF OPPORTUNISTIC INFECTIONS (OIs)

17.1 OPPORTUNISTIC INFECTIONS FREQUENTLY CAUSING RESPIRATORY SYMPTOMS

17.1.1. PNEMOCYSTIS PNEUMONIA (PCP)

Common etiological agent: ***Pneumocystis carinii (jiroveci)***

Clinical presentation:

Typical symptoms are subacute onset and progression of fever, exertional dyspnea, chest tightness and dry cough. Auscultation of the chest may reveal no signs aside crackles. The patient becomes increasingly ill as disease progresses, with worsening of dyspnoea, tachypnoea, hypoxia, and maybe even confusion and delirium. Symptoms may be present for 2-6 weeks or more before the diagnosis is made. PCP is not commonly seen with CD4 count more than 200 cells/μl

Diagnosis

Initial diagnostic approach to PCP is the consideration of the clinical likelihood of disease. The initial recommended investigation is a chest X-ray.

Chest X-ray

Classically the radiograph is abnormal with symmetrical, bi-lateral perihilar infiltrates which spreads to the perply and may progress to diffuse confluent alveolar shadowing. In about 20% atypical presentations are seen, e.g. lobar consolidation. In some chest ragiograph may be normal. Pleural effusion is rare. If present consider an alternative diagnosis.

CT Scan

High resolution Computed Tomograph (CT) of the chest may reveal typical "Ground Glass" changes.

Arterial Blood Gases

Blood gas analysis should be undertaken to assess the disease severity. Arterial blood gases may demonstrate hypoxaemia (while breathing room air), with a Pa O2 <70mm Hg, increased A- a oxygen gradient of > 30 mm Hg or oxygen saturation of <94% which indicates moderately severe or severe disease. Arterial oxygen tension or saturation falls commensurately with pulmonary involvement.

Definitive diagnosis

Definitive diagnosis is by demostrating the organism in broncho-alveolar lavage fluid or induced sputum.

Management and treatment:

Treatment

TMP 15-20 mg/kg/day + sulfamethoxazole 75-100 mg/kg/day PO
(2 double-strength tablets or 4 single strength tablets every 8 hours for 21 days)
(for an average built Sri Lankan person, 3 single strength tablets three times a day may be adequate)
OR IV in 4 divided doses if patient cannot take or tolerate oral cotrimoxazole.

In mild cases treatment for 14 days may be adequate.

Patients with moderately severe or severe disease (PO2 <70mm Hg or A-a gradient >35 mmHg) should receive corticosteroids

Prednisone 40 mg BD for 5 days
40 mg daily for 5 days
20 mg daily for 11 days

Alternative treatment

TMP 15mg/kg/day PO + Dapsone 100mg/day for 21 days
Pentamidine 4mg/kg/day IV for 21 days
Clindamycin 600mg IV q8h or 300-450 mg PO 6h + primaquine 15-30mg base/day for 21 days

Preventative Therapy (Primary Prophylaxis)

WHO Stage II, III and IV condition regardless of CD4 count, Stage I with CD4 < 200 (if available)

Preferred regimen:

Trimethoprim-sulfamethoxazole (TMP-SMX) one DS tablet per day or two single strength tablets per day). If the patient cannot tolerate 960mg, one single strength (480mg) tablet per day may be given.

Alternative regimens

TMP-SMX 1 DS tablet, 3 times a week

If intolerant to Trimethoprim-sulfamethoxazole:

Dapsone 100mg once a day or 50 mg bd

In patients with CD4 <100 and positive toxoplasma antibodies, add pyrimethamine 50 mg weekly + folinic acid 25mg weekly to this regimen.

Patients who have increased CD4 > 200 cells/mm^3 for 3 months may safely discontinue

(1) Primary prophylaxis, and (2) Secondary prophylaxis.

Secondary Prophylaxis

Everyone who has had PCP must continue with maintenance therapy with two tablets SS or 1 DS tablet of cotrimoxazole per day for life if not on ARV.

17.1.2 BACTERIAL PNEUMONIA

Symptoms

Productive cough, purulent sputum and fever for 1-2 weeks. Differentiate from PCP which presents more slowly and there is normally no sputum. Typical CXR finding is lobar consolidation. Gram-positive pyogenic bacteria will be the most probable cause of bacterial pneumonia

Diagnosis

- Chest X-ray (lobar consolidation)
- Sputum examination including: Gram stain- Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Acid Fast stain –Tuberculosis, Wright stain - Histoplasmosis, Cryptococcus, Penicillium marnefei
- Sputum culture and sensitivity

Treatment

Selection of antibiotics should be based on sputum examination

Primary Prophylaxis

Cotrimoxazole one single-strength tablet once a day. Cotrimoxazole (given for PCP prophylaxis) may reduce the incidence of bacterial pneumonia

17.2 OPPORTUNISTIC INFECTIONS FREQUENTLY CAUSING HEADACHE/NEUROLOGICAL SYMPTOMS

17.2.1 CRYPTOCOCCAL INFECTION

Common etiological agent: *Cryptococcus neoformans*

Clinical presentation

The usual presentation is subacute meningitis with fever, headache, vomiting and neck rigidity in a patient with a CD4 <100/mm^3

Diagnosis

Lumbar puncture, India Ink stain of CSF and/or serum for cryptococcal antigen. CSF-Cryptococcal Antigen (CRAG) is positive in over 90 percent of cases.

Management and Treatment

Treatment

Preferred: Amphotericin B 0.7mg/kg IV daily + 5 flucytosine 100mg/kg/day PO in four divided doses for 14 days (induction phase) followed by fluconazole 400mg daily for 8-10 weeks or until CSF is sterile(consolidation phase).
Maintenance therapy with fluconazole 200mg daily for life or until immune system recovery (suppressive phase).

Alternative regimens:

1. Amphotericin B 0.7mg/kg IV daily for 2 weeks + 5 flucytosine 100mg/kg/day po for 14 days **followed by** itraconazole 200mg bid for 8 weeks
2. Ampotericin B 0.7mg/kg/day IV for 2 weeks **followed by** fluconazole 400mg/day PO for 8 – 10 weeks
3. Fluconazole 400-800 mg/day PO + 5 flucytosine 100 mg/kg/day PO for 6 - 10 weeks followed by fluconazole 200mg once daily

Notes on the use of amphotericin B
Amphotericin B is given by slow IV infusion over 45 minutes 4 times per day. Patient needs careful observation, especially with initial doses as fever and chills can occur. The other main side effects of Amphotericin B are electrolyte disturbances (especially hypokalaemia) and hypoglycaemia. Frequent monitoring of electrolytes and blood sugar are required, with 5% dextrose co- infusion and potassium supplements to maintain normal levels

Secondary Prophylaxis

Preferred: Fluconazole (200mg daily).
Pregnant women should not take fluconazole

Comments

Discontinue secondary prophylaxis when CD4 count is 100-200 cells/mm^3 for 6 months after initiating ART.

Primary Prophylaxis

Not indicated.

17.3 OPPORTUNISTIC INFECTIONS FREQUENTLY CAUSING SKIN AND MUCOSAL SYMPTOMS

17.3.1 ORAL CANDIDIASIS

Common etiological agent *: Candida albicans* is the predominant species, but ***C. tropicalis, C. glabrata and C. krusei,*** occur occasionally.

Clinical presentation
Changes in taste and burning sensation in the mouth. May be associated with dysphagia. The presence of odynophagia is indicative of oesophageal involvement.

Pseudomembranous candidiasis is characterised by removable white or creamy plaques consisting of a mixture of fungal hyphae, desquamated epithelium and inflammatory cells. These plaques can appear anywhere on the oral and pharyngeal mucosa.

Erythematous candidiasis is less obvious, manifesting as red patches on the palate and dorsal surface of the tongue and buccal mucosa.

Angular cheilitis is another form which manifests as cracking, fissuring, and redness at the commissures; these may be unilateral or bilateral and may be found in the absence of intraoral candidiasis.

Hyperplastic candidiasis, which presents as non-removable white patches, is rare.

Diagnosis:

- KOH preparation of a smear from lesion,
- Culture / ABST provides information about the antifungal susceptibility, and
- Salivary candidal count.

Treatment Schedule

Nystatin oral lozenges	500,000 units for immuno suppressed patients, one or two lozenges dissolved slowly in the mouth, 4-5 times a day. Continued for 48 hours after lesions have resolved
Nystatin Vaginal Tablets (in the absence of oral preparations)	100,000 units, to be dissolved in the mouth three times a day
Miconazole Oral Gel	*10 mg* One tablet dissolved slowly in the mouth three times a day
Ketoconazole	*200 mg*, One or two tablets, once a day with food, for 7 - 14 days
Flucanazole	*100 mg* Once daily for 7 - 14 days
Itraconazole	*200 mg* Once daily for 7 - 14 days

Prophylaxis with systemic antifungals must be considered, as relapses are common.

17.3.2 CANDIDA OESOPHAGITIS

Empiric diagnosis - based on presence of oral candida (80%), odynophagia & CD4 <100 cells/mm3 and response to treatment.
Endoscopy recommended with atypical presentations or failure to respond to empirical treatment.

Preferred regimen

Fluconazole 200mg /day oral up to 800mg /day for 14-21 days

(Flucanazole is clinically superior to ketoconazole and Itraconazole due to more predictable absorption)

Alternative regimen

Amphotericin B 0.3-0.7 mg/kg/day IV for 14-21 days
Itraconazole: 200mg / day oral for 14-21 days
Ketoconazole 200-400mg /day oral for 14-21 days

Secondary prophylaxis

(Only with relapsing disease)

Fluconazole 100-200mg /day

Primary prophylaxis

Not recommended

17.3.3 VAGINAL CANDIDIASIS

Preferred regimen

Nystatin vaginal cream PV at night for 14 days
Clotrimozole 1% cream PV at night for 7 days
Or 100mg tablet per vaginal at night for 3 days or 7 days
Miconazole 2% cream PV at night for 7 days
Or 200mg vaginal tablet at night for 3days or 7 days

If persistent or refractory

Fluconazole 100-200mg oral for 1-7 days
Itraconazole 200mg twice a day for 1 day

17.3.4 HERPES SIMPLEX VIRUS INFECTION (HSV)

Clinical presentations

Typical blisters usually in oral, genital or peri rectal area when CD4 <100 cells /mm^3.

Diagnosis

Diagnosis based on history, examination and laboratory investigations (HSV culture)

Treatment of Genital and Oro labial herpes

Normal saline washes, analgesics for pain
Aciclovir 200mg 5 times/day for 7 days (14 days if disseminated mucocutaneous HSV is present), OR
Aciclovir 400mg tid/day for 7 days

For severe cases, Aciclovir IV 5 mg/kg/8 hourly until lesions regress.

In HSV encephalitis, Aciclovir 10 mg/kg/IV 8 hourly x 14-21 days

Secondary Prophylaxis

In cases of frequent recurrences (> 6 recurrences/year), long-term suppressive therapy with Acyclovir 400 mg twice daily may be necessary.

Primary Prophylaxis –

Not recommended

17.3.5 HERPES ZOSTER

Clinical presentations

Typical painful blisters in clusters along dermatomes. Can involve the eye.

Diagnosis

Clinical diagnosis based on history and examination
No laboratory tests required

Treatment

Aspirin or paracetamol 500mg qid and local lesion care with antiseptics
Local application of lidocaine gel 2 percent may help improve pain relief in some patients.

Calamine lotion is cheap, soothes the skin, reduces intense pruritus and accelerates drying up process.

Aciclovir 800mg 5times a day for 7 days

Severe cutaneous or visceral disease or acute retinal necrosis – Aciclovir IV 30 mg/kg/day.

Antibiotics for secondary infection

Post-herpetic neuralgia is uncommon, but if present, should be treated with pain modifying agents: phenytoin 100mg slowly increasing to 250-300mg daily or carbamazapine 100mg daily increasing to 400mg daily in 10 days.

Primary Prophylaxis

Not recommended

Secondary Prophylaxis

Not recommended

17.4 OPPORTUNISTIC INFECTIONS FREQUENTLY CAUSING DIARRHOEA

17.4.1 DIARRHOEA

Gastro intestinal pathogens in HIV infected patients

Stomach:

Cytomegalovirus
Mycobacterium avium complex (MAC)

Small Intestine:

Cryptosporidium
Microsporidium
Isospora belli
MAC
Salmonella Spp
Campylobacter jejuni
Mycobacterium Tuberculosis

Colon:

Cytomegalovirus
Cryptosporidium
MAC
Shigella flexneri
Clostridium defficile
Campylobacter jejuni
Herpes simplex virus

Diagnosis

Identification of the organism by multiple stool examinations. Stool culture is most valuable for salmonella, shigella and campylobacter infection.
Stain for AFBs (TB and MAC) & modified AFB stain (cryptosporidium, isospora)
Culture for bacterial pathogens (salmonella, shigella, Mycobacterium Avium Complex in HIV infected patients are frequently bacteraemic).

Preventive Therapy

Cotrimoxazole (given for PCP prophylaxis) may reduce the incidence of some bacterial diarrhoeas

Treatment

Initial treatment should be with rehydration fluids (oral and/or IV fluids and electrolytes) and
Cotrimoxazole, 960mg bid po for 5 days + metronidazole 400 mg tid po for 7 days.

If no response and/or fever and bloody stools: Ciprofloxacin 500 mg bid PO for 5 days. If no response, mebendazole 100 mg tid PO for 7 days.

Constipating agents Loperamide 4mg initially, followed by a further 2mg after unformed stools (maximum daily dosage 16 mg),diphenoxylate 5 mg, 4 times/day or codeine10mg/3times/day.

Constipating agents should not be used in patients with bloody diarrhoea.

Treatment Schedule – Gastrointestinal disorders in HIV/AIDS

Salmonella and Shigella	Cotrimoxazole 5-10mg/kg/day + or 1 double strength bid or 2 simple strength tablets bid for more than 2 weeks. Ciprofloxacin 500 mg-700 mg oral bid or 400 mg IV bd for 7-14 days in mild cases and 4-6 weeks in advanced AIDS. Ceftriaxone 1-2 G/day IV for more than 2 weeks.
Campylobacter jejuni	Erythromycin 500 mg, 6 hourly, for 7 days
Entamoeba histolytica	Metronidazole 400 mg tid for 7 days, followed by diloxanide 500 mg tid for 10 days
Giardia	Metronidazole 400 mg tid for 7 days
Strongyloides	Thiabendazole 25 mg/kg, 3 times a day for 3 days
Cryptosporidium	No proven effective treatment. Resolve when on HAART.
Microsporidium	Albendazole 400 mg bd for 14 days
Isospora belli	Thiabendazole 1 DS bd for 10 days
Herpes simplex virus	Aciclovir 200 mg, 5 times a day for 5 days

17.5 OTHER OPPORTUNISTIC INFECTIONS AND HIV-RELATED ILLNESSES

17.5.1 CYTOMEGALOVIRUS (CMV)

(Cytomegalovirus is a virus that infects the entire body)

Clinical presentations

Retinitis (in eye, retina): blurry vision or loss of central vision that can lead to blindness.
Colitis (colon): fevers, diarrhoea and stomach pain.
Esophagitis (throat): ulcerations, pain and difficulty in swallowing.
Pneumonitis (lungs): pneumonia-like symptoms.
Encephalitis (brain): confusion, fever and tiredness.

Diagnosis

Retinitis: refer to Ophthalmologist
Esophagitis and colitis: endoscopy and/or biopsy.
Pneumonitis: Check for PCP and tuberculosis first (**EPSA**). Diagnosis of CMV needs referral to specialized hospital
Encephalitis: CT scan, etc.

Treatment

If specific therapy is unavailable, commence ART

17.5.2 CERVICAL CANCER

Clinical presentations

Often asymptomatic. Can cause vaginal discharge, vaginal bleeding and pelvic pain

Diagnosis

Annual PAP smear is recommended for all HIV positive women as they are at increased risk of cervical dysplasia and cancer.

Treatment

Patients with Pap smear reports of dysplasia or intraepithelial neoplasia require colposcopy and may require cone biopsy or surgery. Adjuvant therapy (chemotherapy/radiotherapy) may be required. Therefore refer to a gynaecologist.

17.5.3 TOXOPLASMOSIS

Clinical presentations

Altered mental state (confusion, delusional behavior), severe headaches, focal signs such as hemi-paresis, fever, seizures and coma. Can also affect the eye causing eye pain and reduced vision.

Diagnosis

Clinical diagnosis based on the symptoms
Cerebral CT scan will confirm the diagnosis

Preferred Treatment

Pyrimethamine 200mg oral loading dose then 50-75mg once a day + sulfadiazine 1g every 6 hours IV for 3-6 weeks depending on response to treatment followed by long-term secondary prophylaxis.

Sulphadiazine may cause anaemia, thrombocytopenia, and leucopenia. Careful hematological monitoring with complete blood count is recommended. Rash can be associated with the use of pyramethamine and sulphadiazine. Patients who do not show response to therapy within 1-2 weeks or who develop complications of therapy should be referred to specialist facility.

Alternative Treatment

Clindamycin 600mg every 6 hours

Secondary Prophylaxis

Pyrimethamine 50 mg once a day + Sulfadiazine 500 mg four times per day

ANNEXURE 1

MANAGEMENT OF SYMPTOMS RELATED TO OPPORTUNISTIC INFECTIONS, OPPORTUNISTIC INFECTION PROPHYLAXIS, ART AND IRS

Symptom	Managing symptoms of OIs and HIV-related illness	Side effects of ARV and OI prophylaxis and their management	Immune reconstitution syndrome (IRS) Consider during first 3 months on ART
Nausea Vomiting	Metoclopramide 10mg TID Prochlorperazine 5-10 mg TID Chlorpromazine 25-50mg every 6-12 hours	**ART**: Take ART with food (except ddI and indinavir). If on AZT, usually self-limiting after 2 weeks. Treat symptomatically. Stop ART if lactic acidosis suspected **Cotrimoxazole:** Take with food **INH:** Take at bedtime, if vomiting, stop INH	Hepatitis B and C can occur with IRS. Suspect if nausea, vomiting plus jaundice
Diarrhoea	Drink extra fluid. At least 200-300 ml in addition to usual fluid intake after each loose stool. Oral rehydration solution (ORS) 2-4 litres per day If persists or worsens, investigate and treat cause or give empirical therapy	**ART:** NFV commonly causes diarrhoea **(less common with saquinavir)** Loperamide 10-20 mg BID if no fever/no blood in stool If no response after 2-4 weeks, change ART	Temporary flare ups of MAC or CMV may cause diarrhoea. Continue ART and treat symptomatically
Indigestion	Aluminium or magnesium sulphate tablets 1-2 tabs every 6 hours If persists or worsens, treat for esophageal candidiasis. If no response, refer to next level	**ART:** Take ART with food except ddI and IDV	Oesophageal candida may require treatment
Anxiety, bizarre dreams, psychosis, depression	Care counselling and referral to specialist as needed.	**ART:** This may be due to EFV. Give at night; counsel and support (usually lasts < 3 weeks). Amitriptyline 25 mg (increasing to 100mg) once daily before bed. Call for advice or refer if severe depression or suicidal or psychosis	These CNS effects are not associated with IRS

Symptom	Managing symptoms of OIs and HIV-related illness	Side effects of ARV and OI prophylaxis and their management	Immune reconstitution syndrome (IRS)
Headache	Paracetamol 1 gm 4-6 hourly Ibuprofen 400 mg 4-6 hourly Aspirin 600mg 4-6 hourly If persists or worsens, the most common causes are cryptococcal meningitis and toxoplasmosis	**ART:** If on AZT or EFV, reassure that this is common and usually self-limiting but can last 4-8 weeks. If persists more than 2 weeks or worsens, call for advice or refer	Assess for toxoplasmosis and cryptococcal meningitis
Neuropathy	Amitriptyline 25 mg (increasing to 100mg) once daily before bed. Plus analgesics as above (It takes 3 weeks before amitriptyline takes effect) If persists or worsens, commencing ART may help	**ART:** Commonly caused by d4T, ddI and ddC Reduce dosage of d4T if possible Add amitriptyline 25 mg (increasing to 100 mg) once daily before bed. Change ART if possible **INH:** Give pyridoxine 100 mg daily	Not an IRS symptom
Abdominal or flank pain, and/or Jaundice (yellow eyes)	(Pancreatitis due to CMV Intestinal perforation due to CMV Hepatobiliary disease due to MAC and Cryptosporidiosis)	**ART:** d4T or ddI may cause pancreatitis which requires stopping these drugs NVP (and EFV less commonly) may cause liver dysfunctions which require stopping these drugs Stop ART if lactic acidosis suspected **Cotrimoxazole**: if jaundice, stop cotrimoxazole **INH:** if jaundice, stop INH	Hepatitis B and C can occur with IRS. Suspect if nausea, vomiting plus jaundice

Symptom	Managing symptoms of OIs and HIV-related illness	Side effects of ARV and OI prophylaxis and their management	Immune reconstitution syndrome (IRS)
Skin rash, itch	Emollient lotion Calamine lotion Mild steroid creams (1% hydrocortisone. 0,01% triamcinolone) Oral antihistamines If persists or worsens, investigate cause and treat or refer to next level	**ART:** If on EFV, give oral antihistamines and review daily. Rash is often self limiting **If on NVP or ABC, assess carefully.** **Stop drug if rash is moderate or severe (generalized, peeling, mucosal involvement).** NFV and IDV also can cause rash **Cotrimoxazole:** Stop if rash is moderate or severe **INH:** Stop if rash is moderate or severe	Skin conditions which can flare up due to IRS in the first 3 months of ART: - Herpes simplex and zoster - Papilloma virus (warts) - Fungal infections - Atopic dermatitis Treat as necessary
Fever	Paracetamol 1 gm 4-6 hourly Ibuprofen 400 mg 4-6 hourly Aspirin 600mg 4-6 hourly If persists or worsens, investigate cause and treat or refer to next level	**ART:** Stop all drugs when hypersensitive reaction of ABC is suspected	Fever soon after commencing ART could be IRS (MAC, TB, CMV HCV, HBV, cryptococcus, herpes zoster)
Cough, difficulty breathing	For wheezing: Salbutamol 2 puff s every 20 minutes x 3 times, then 2 puff s every 3 to 6 hours. If persists or worsens, common causes are PCP, TB, Bacterial or fungal pneumonia	**ART:** Stop ART if lactic acidosis suspected	IRS can be associated with PCP, TB, fungal or bacterial pneumonia
Fatigue, pallor	If persists or worsens, check Hemoglobin for anemia caused by HIV or by MAC Transfuse as necessary (Hb<8)	**ART:** Common for 4 to 6 weeks after starting AZT Stop AZT if severe pallor or symptoms of anaemia or low haemoglobin (<8). **Cotrimoxazole:** Stop the drug if Hb<8	Suspect MAC if fever, fatigue and anemia. Continue ART Once CD4 >50, should resolve without treatment

Annexure 2: ARV Therapy: Adherence Preparation, Support and Monitoring

Guide for Preparing for ARV Therapy

Assess	▪ Person's goals for today's visit ▪ Understanding of ARV therapy ▪ Interest in receiving therapy
Advise on	▪ HIV illness, expected progression ▪ ARV therapy o Benefits-lifesaving drugs. Your life depends on taking them every day at the right time o Very strong medicines o The pills do not cure HIV o The pills do not prevent HIV transmission to others – you must still use condoms and practice safer sex ▪ Need for complete adherence to daily treatment (more than other drugs you may be familiar with – essential to maintain drugs levels in the blood for ARV therapy to work). ▪ Must be taken twice daily without interruption ▪ If you forget a dose, do not take a double dose ▪ Must be taken at right time, every 12 hours (adjust this if on different regime) ▪ If you stop, you will become ill (not immediately – after weeks, months or years) ▪ Possibility of side effects and drug interactions ▪ Importance of disclosure of HIV+ status (partner, family etc) ▪ Importance of testing partner and children ▪ Drugs must not be shared with family or friends
Agree	▪ Establish that the person is willing and motivated and agrees to treatment, before initiating ARV therapy o Has the person demonstrated ability to keep appointments, to adhere to other medications? o Has the person disclosed his or her HIV status? If not, encourage him / her to do so. Disclosure to at least one person who can be the supporter is important o Does the person want treatment and understand what treatment is? o Is the person willing to come for the required clinic follow-up?
Assist	▪ Help the person develop the resources / support / arrangements needed for adherence: o Ability to come for required schedule of follow-up. Discuss how the person will do this o Home and work situation that permits taking medications every 12 hours without stigma o Regular supply of free or affordable medication o Supportive family or friends o ARV adherence support group o Treatment supporter
Arrange	▪ When the person is ready for ARV therapy, discuss at the clinical team meeting then make a plan

Guide for Monitoring and Supporting Adherence

Assess	**Do clinical review and respond to any problems or changes in status. To assess adherence:** ▪ Review the medications with the person and their treatment supporter. Determine whether there is an adherence problem. ▪ Ask questions in a respectful and non-judgmental way: o "Many people have trouble taking their medications, what troubles are you having?"

	○ "Can you tell me when and how you take each pill?" ○ "When is it most difficult for you to take the pills?" ▪ Ask about the common and locally important factors that may interfere with adherence. ▪ Ask about stigma related to taking the pills. ▪ Count pills. ▪ How many pills forgotten yesterday, last 3 days, last month? **If poor adherence: Determine what the problem is:** Side effect?; Simply forgot?; Ran out of pills?; Which dose missed morning or evening? Why?; Cost?; Reminds you of HIV?; Misunderstood?; Changed work situation?; Not comfortable taking medications around others?; Stigma?; Different timing when away from home or holiday, travel, weekend?; Seldom at home and disorganised?; Problems with diet?; Another medical problem?; Screen for excess alcohol use and depression and treat, if present.
Advise on	▪ Reinforce the information given before ▪ Give additional information that may help with adherence problem ▪ Advise on any suggested changes in the regimen.
Agree	▪ Agree on any changes in Treatment Plan and solutions to adherence problems (if present). ▪ Discuss the agreements you have reached and check for their commitment.
Assist	▪ Provide adherence support ▪ Reinforce interventions which match the person's needs and adherence problems, if present. ▪ Make sure that the person has: ○ Plan to link taking medications with daily events such as meals ○ .Any device or skills that he or she needs (e.g. how to use a diary) ▪ Make sure person has the support he or she needs ○ Get help from supporter, other family and friends or peers ○ Help person and supporter to find solutions ▪ If adherence problem: ○ Get help – call for advice ○ Link with home based care or home visits
Arrange	▪ Record adherence estimate on persons card. ▪ Arrange for refills ▪ Arrange for next follow-up visits: ○ In clinic ○ Home visits ▪ Make sure that the person and supporter understand the follow-up plan and how to contact the clinic team if there is a problem.