Guidelines For The Clinical Management Of HIV Infection In Adults And Adolescents

In Myanmar

THIRD EDITION

National AIDS Programme
Department Of Health, Ministry Of Health, Myanmar
2011

World Health Organization
Country Office for Myanmar

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Contents

List of abbreviations

3TC	lamivudine
ABC	abacavir
AFASS	affordable, feasible, acceptable, safe, sustainable (breastfeeding)
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
AZT	Azidothymidine or zidovudine (ZDV)
BD	twice daily
bPI	boosted protease inhibitor
CD4 count	CD4+ T-lymphocyte count
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
d4T	stavudine
ddI	didanosine
EFV	efavirenz
FTC	emtricitabine
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IDV	indinavir
INH	isoniazid
IPT	isoniazid prophylaxis therapy
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	ritonavir boosted lopinavir
MTCT	mother-to-child transmission (of HIV)
MDR-TB	Multidrug-resistant tuberculosis
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTP	National Tuberculosis Programme
NVP	nevirapine
OD	once a day
PCP	Pneumocystis pneumonia
PEP	Post exposure prophylaxis
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission (of HIV)
PPE	pruritic papular eruption
/r	low-dose ritonavir to boost another PI
RLC	resource limited country
RLS	resource limited situation
RTV	ritonavir
SQV	saquinavir
TST	tuberculin skin test
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
VL	viral load

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Nay Pyi Taw, 2011

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Foreward

Guidelines for the management of HIV/AIDS need to be updated regularly. This is because HIV/AIDS is a relatively new disease and with the passage of years, more experience is gained, new drugs are discovered and new treatment protocols introduced. More and more results of trials involving various aspects of the management of HIV become available and new insights and better understanding of the disease are being obtained. Long term use of ART has also resulted in realization not only of the pros and cons of some drug combinations and treatment regimens but also serious side effects of some of the antiretroviral drugs.

In resource rich countries the latest technology and the newest ART drugs can be employed but in many resource limited situations a balance has to be struck between what resources are available and what is the best possible solution for a PLHIV.

Recommendations would also need to be evidence based. The present guidelines are an update of the Myanmar Guidelines for the Clinical Management of HIV infection in Adults and Adolescents published in 2007 (1) and are also adapted from Antiretroviral Therapy for HIV Infection in Adults and Adolescents – Recommendations for a Public Health Approach, 2010 revision, published by World Health Organization (2), which is a carefully reviewed evidence-based document for resource limited situations.

These guidelines have been written to serve all medical personnel treating patients with HIV in Myanmar. It is meant not only for the National AIDS-STD programme but also for local and international NGOs, hospital doctors and general practitioners in the public and private sectors. With this objective a workshop was held at Nay Pyi Taw on 10th March 2011. The participants included representatives from the National AIDS-STD programme, Department of Health, National Health Laboratory, professors from Universities of Medicine, physicians from Specialist Hospitals Mingaladon and Thaketa, Nay Pyi Taw General Hospital, representatives from WHO, UNAIDS, UNICEF, UNFPA and also representatives from MSF- Holland, MSF-CH, UNION and also included PLHIV. A consensus was reached on what was to be recommended for the new guidelines and a draft was produced. The draft guidelines were further reviewed by a review team and the final draft was written to encompass all the recommendations .

These guidelines are not written for the specialist physician or for the exceptional patient. The physician has to treat according to what is best for the patient and the individual patient has a right to choose. These guidelines are meant to serve as a rational basis to treat HIV for the average medical doctor working anywhere

in Myanmar so that people living with HIV can have access to treatment and care wherever they are. As facilities and resources will vary from place to place, region to region, options are given and health care providers or implementers of ART programmes can choose what is most suitable and appropriate in a given situation.

Summary of key recommendations for ART in the new guidelines

1. When to start ART
i. HIV positive asymptomatic ARV naïve individuals – CD4 ≤ 350 cells/mm3
ii. HIV positive symptomatic ARV naïve individuals- WHO clinical stage 2 if CD4 ≤ 350 cells/mm3 OR WHO clinical stage 3 or 4 irrespective of CD4 cell count
iii. HIV positive pregnant women – CD4 ≤ 350 cells/mm3 irrespective of clinical symptoms OR WHO clinical stage 3 or 4 irrespective of CD4 cell count
iv. HIV/TB coinfection ARV naïve individuals – presence of active TB disease if CD4 ≤ 500 cells /mm3 (if MDR-TB, ART indicated regardless of CD4 count)
v. HIV/HBV coinfection – individuals who require treatment for their HBV infection irrespective of CD4 cell count

2. What antiretroviral therapy to start
i. HIV positive ARV naïve adults and adolescents – AZT or TDF + 3TC (or FTC) + EFV or NVP (d4T not preferred because of side effects, but if it is used initially, should not be for an extended period and should replace d4T with AZT or TDF)
ii. HIV positive pregnant women – same as above. AZT preferred but TDF acceptable. EFV preferred over NVP if CD4 count ≥ 250 cells/mm^3 because of risk of NVP toxicity; do not initiate EFV in first trimester. HIV positive women with prior exposure to MTCT - for details see text.
iii. HIV/TB coinfection – AZT or TDF + 3TC (or FTC) + EFV ; ART to be started 2 to 8 weeks after start of TB treatment ; NVP not recommended
iv. HIV/HBV coinfection – NNRTI regimens that contain both TDF + 3TC (or FTC)

3. Recommended second-line antiretroviral therapy
i. HIV positive adults and adolescents: a. If d4T or AZT used in first line therapy – TDF + 3TC (or FTC) + ATV/r or LPV/r b. If TDF used in first line therapy – AZT + 3TC (or FTC) + ATV/r or LPV/r
ii. HIV positive pregnant women – same as for adults and adolescents
iii. HIV/TB coinfection – substitute rifabutin (150 mg 3 times/week) for rifampicin if available; if not available same NRTI backbone plus LPV/r or SQV/r with adjusted dose of RTV (LPV/r 400mg/400 mg BD or LPV/r 800 mg/200 mg BD or SQV/r 400 mg/400 mg BD
iv. HIV/HBV coinfection – AZT + TDF + 3 TC (or FTC) + ATV/r or LPV/r

* ABC and ddI can be kept as backup options if AZT or TDF cannot be used

4. PMTCT

i. ART for HIV infected pregnant women who need treatment for own health

ART eligibility criteria

a). All women with CD4 ≤ 350 cells/mm3 irrespective of clinical symptoms

b). Clinical stage 3 or 4 regardless of CD4 count

When to start ART - As soon as feasible

Recommended first line regimens-

- AZT (TDF) + 3TC (FTC)+ NVP or EFV (EFV preferred if CD4 ≥ 250 cells/mm3 but not in first trimester)

Prophylaxis for infants born to pregnant women on ART-

- All infants regardless of feeding mode – daily NVP or AZT (BD) for 4-6 weeks

ii. ARV prophylaxis for pregnant women who do not need treatment for their own health

When to start ARV prophylaxis

- As early as 14 weeks of pregnancy

Prophylaxis regimens for the mother-

Option A :

- AZT during pregnancy plus
- sd-NVP at onset of labour plus
- initiation of AZT + 3TC for 7 days postpartum (omit sd-NVP + 3TC if >4 wk AZT)

Option B: (continued until delivery or if breastfeeding continued until 1 week after breastfeeding has stopped)

- AZT + 3TC+ LPV/r (or ABC or EFV)
- TDF + 3TC (or FTC) + EFV

Prophylaxis regimens for exposed infants

Option A:

- Breastfeeding infants –NVP from birth until 1 week after all exposure to breastfeeding has ended
- Non-breastfeeding infants – NVP or sd-NVP + AZT for 4 – 6 weeks

Option B:

- All infants regardless of infant feeding mode – NVP or AZT for 4 – 6 weeks

iii. Infant feeding recommendation for known HIV- infected women – to decide

- Avoid all breastfeeding only if safe formula feeding is possible (will most likely give infant greatest chance of HIV free survival) or if breastfeeding judged to be best option – exclusive breast feeding for first 6 months, introduce complementary food thereafter, continue breastfeeding for 12 months, wean gradually within 1 month.

Conditions needed to safely formula feed-

Avoiding breastfeeding will most likely give the infant the greatest chance of HIV free survival but only if all the following conditions are met. If these conditions cannot be fulfilled breastfeeding would be the best option for the HIV infected mother.

a. safe water and sanitation are assured at the household level and in the community; and
b. the mother, or other caregiver can reliably provide sufficient formula milk to support normal growth and develoment of the infant; *and*
c. the mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition; *and*
d. the mother or caregiver can, in the first six months, exclusively give infant formula milk; *and*
e. the family is supportive of this practice; *and*
f. the mother or caregiver can access health care that offers comprehensive child health services.

1.Introduction

HIV is now a treatable condition and the majority of people who have HIV remain fit and well on treatment. Despite this, a significant number of people are unaware of their HIV infection and remain at risk to their own health and of unknowingly passing their virus on to others. Late diagnosis is the most important factor associated with HIV related morbidity and mortality. Patients should therefore be offered and encouraged to accept HIV testing in a wider range of settings than is currently the case.

Voluntary Counselling and Testing (VCT)

Also known as client –initiated HIV testing and counselling it involves individuals actively seeking HIV testing and counselling at a facility that offers these services. Client initiated HIV testing and counselling usually emphasizes individual risk assessment and management by counsellors, addressing issues such as the desirability and implications of taking a HIV test and the adoption of individual risk reductions strategies. However in practice, VCT rates are not very high and many people at risk of HIV infection remain unaware of their infection and the possible risks that they carry.

Provider-initiated HIV testing and counselling (3)

This refers to HIV testing and counselling which is recommended by health care providers to persons attending health care facilities as a standard component of medical care. The main purpose of such testing and counselling is to enable specific clinical decisions to be made and/or specific medical services to be offered that would not be possible without knowledge of the person's HIV status.

In the case of persons presenting to health facilities with symptoms and signs that could be due to HIV, it is the basic responsibility of health care providers to recommend HIV testing and counselling. Provider initiated HIV testing and counselling also aims to identify unrecognized or unsuspected HIV infections in persons attending health care facilities. Greater knowledge of HIV status is critical to expanding access to HIV treatment, care and support in a timely manner and offers people living with HIV an opportunity to receive information and tools to prevent HIV transmission to others. Many opportunities to diagnose and counsel individuals at health facilities are being missed and provider initiated HIV testing and counselling facilitates diagnosis and access to HIV related services.

The procedure includes a simplified pre-test information and the person is offered an "opt-out" approach to HIV testing which means he has the right to opt-out or refuse to take the HIV test. Individuals must be given sufficient information to make an informed and voluntary decision. Individuals must specifically decline the HIV test if they do not want it to be performed. Verbal communication is normally adequate for the purpose of obtaining informed consent. Coercive or mandatory HIV testing should not be done and compulsory testing of individuals on public health grounds should not be carried out.

Provider initiated HIV testing and counselling should be accompanied by HIV-related prevention, treatment, care and support services.

HIV test is recommended –

1. For all patients whose clinical presentation might result from underlying HIV infection
2. As a standard part of medical care for all patients attending health facilities in generalized HIV epidemics (especially where HIV prevalence is consistently over 1% in pregnant women).
3. More selectively in low HIV prevalence areas.
4. For sexual partners of HIV positive persons.

Efforts must be made to ensure a supportive environment when carrying out provided initiated HIV testing and conditions must be in place to maximize positive outcomes and minimize potential harm to patients.

When recommending HIV testing the aim should be to do what is in the best interest of the patient. This requires giving individuals sufficient information to make an informed and voluntary decision to be tested. Patient confidentiality must be strictly maintained. Post- test counselling is necessary and patients should be referred to appropriate services.

Provider initiated HIV testing and counselling may be also carried out in the following health care facilities –

1. Medical and surgical in-patient and out-patient facilities, including TB clinics
2. Antenatal and postpartum clinics
3. STI clinics
4. Health services for most-at-risk populations.

It should be emphasized that as in the case of VCT, provider initiated HIV testing is voluntary and the “three C’s” – informed consent, counselling and confidentiality – must be observed.

HIV testing

Diagnosis of HIV infection can be carried out by detecting any of the following :

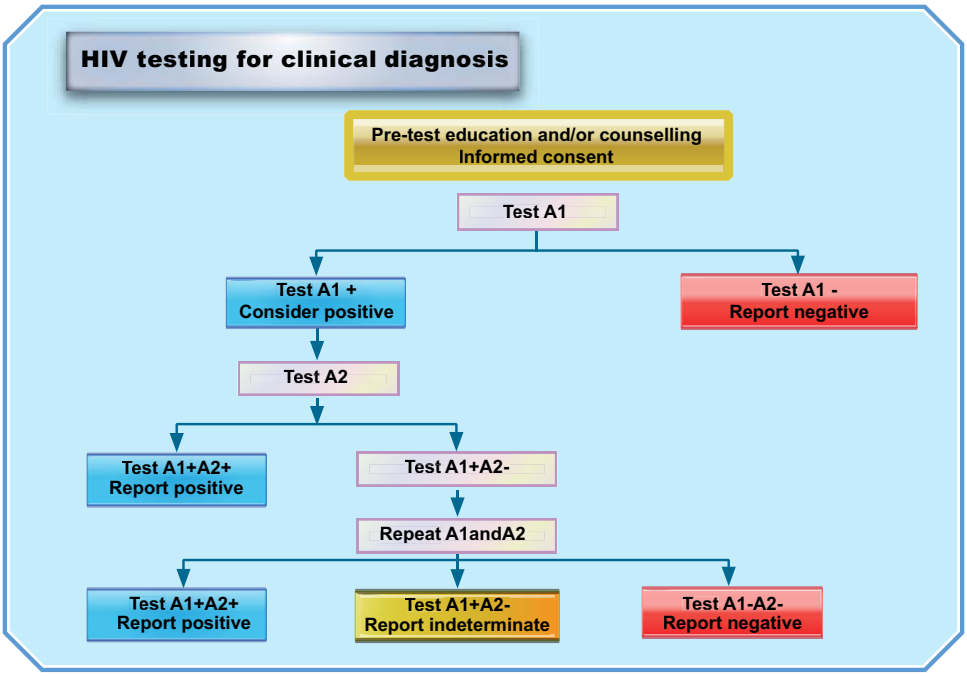
- Antibodies to HIV
- p24 antigen
- HIV nucleic acid (RNA/DNA)

The most commonly used method for the diagnosis of HIV infection is detection of anti-HIV antibodies in serum or plasma. It is economical, rapid and can be performed easily in most laboratories. Although HIV antibody tests nowadays have a high degree of sensitivity and specificity there is no perfect HIV antibody tests and therefore the diagnosis of HIV infection is based on a multi-test algorithm for detecting antibodies to HIV.

The gold standard for HIV testing is screening with ELISA and confirming with Western Blot technique. In developing countries, to minimize cost and maximize accuracy , WHO and UNAIDS have established strategies and algorithms for HIV antibody testing regarding screening, surveillance and diagnostic purposes.

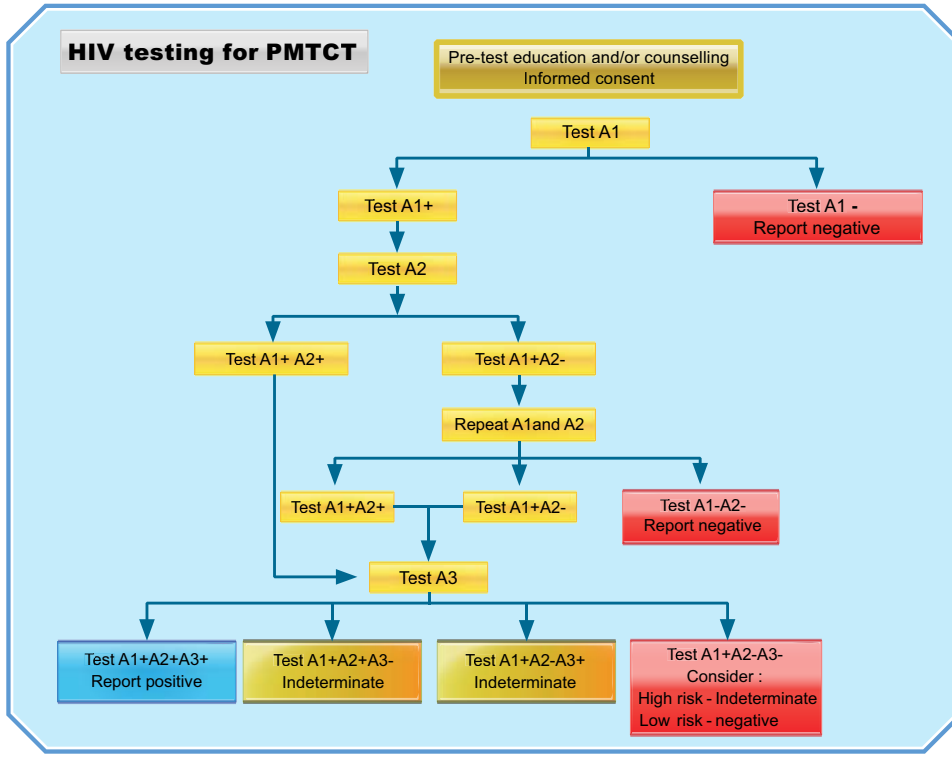
Diagnostic testing involves initial screening with a highly sensitive test and confirmatory testing with a highly specific test. The assays used should be based on different principles and/or different antigens. Two testing strategies are shown here for clinical diagnosis and for PMTCT (5). A1, A2, A3 represent three different assays. Indeterminate results are retested two weeks later on a new specimen and if still negative can be repeated at 4 weeks, 3 months, 6 months and 12 months and if still indeterminate at 12 months it is considered negative. However molecular methods (nucleic acid testing by PCR) can be used to resolve 2 indeterminate test results.

Figure 1.1 HIV testing for clinical diagnosis



N.B.- A1, A2 represent two different assays.

Figure 1.2 HIV testing for PMTCT



N.B A1, A2, A3 represent three different assays.

HIV Counselling (3,4,6)

Pre test counselling

All clients who request/receive HIV testing should be given information on the following:

- The risks for transmission and how HIV can be prevented.
- The reason why HIV testing is being recommended. The benefits and consequences of HIV testing; in the case of pregnant women the risks of transmitting HIV to infants and possibility of preventing this
- The testing process
- Assurance about confidentiality and the right to decline the HIV test
- The meaning of the test results in understandable language

Post test counselling

- Clients should be counselled for a positive or a negative result and have the result explained
- Clients should be assured of confidentiality

In case of positive results, the counsellor needs to:

- Provide emotional support
- Assess the individual's ability to cope
- Assess the social support available
- Explain how to prevent HIV transmission to uninfected or untested partners
- Encourage individuals to share their HIV status with their sexual partners
- Refer the individual for clinical monitoring and follow up and to evaluate the need for ART

In case of negative results, the counsellor needs to:

- Encourage the HIV negative individual to adopt safe practices (condom use)
- Explain that the individual has to be tested again in 6 to 8 weeks in case the first test was performed during the "window period".
- Explain that a negative test performed during the "window period" may not mean that the individual is definitively uninfected.

The WHO clinical clinical staging of HIV disease

The revised WHO clinical staging of HIV disease is designed to be used in patients with confirmed HIV infection. Along with CD4 count testing, where available, the staging system is used to guide decisions on when to start opportunistic infection (OI) prophylaxis and when to start and switch ART.

WHO clinical staging of HIV disease in adults and adolescents (7)

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (<10% of body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulcerations Pruritic papular eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical stage 3
Unexplained weight loss (>10% of body weight) Unexplained chronic diarrhea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g.pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (< 8 g/dl), neutropenia (< 0.5 x 10^9 /l)and/or chronic thrombocytopenia (< 50 x 10^9 /l)

Clinical stage 4
HIV wasting syndrome
Pneumocystis jiroveci pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal >1 month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococossis including meningitis
Disseminated nontuberculous mycobacteria infection
Progressive multifocal encephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis* (histoplasmosis, coccidiomycosis)
Recurrent septicaemia (including nontyphoidal Salmonella)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

* Disseminated penicilliosis in south-east Asia

Source: Revised WHO clinical staging and immunologic classification of HIV and case definition of HIV for surveillance, 2006.

2.Antiretroviral Therapy

Goals of antiretroviral therapy

1. Improvement in quality of life and prolongation of life
2. Reduction of HIV related morbidity and mortality
3. Greatest possible reduction in viral load (<50 copies/ml) for as long as possible to stop or delay disease progression
4. Restoration and preservation of immune function
5. Minimize side effects of drugs
6. Reduce HIV transmission

When to start Antiretroviral Therapy

- All patients with CD4 counts of ≤ 350/mm3 irrespective of the WHO clinical stage
- All patients with WHO clinical stage 1 and 2 should be tested for CD4 counts to decide when to start ART
- All patients with WHO clinical stage 3 or 4 irrespective of CD4 count

Current evidence indicates that starting ART at CD4 counts of ≤ 350/mm3 reduces absolute risk of death, disease progression (including TB) and the occurrence of serious adverse effects in ART naïve HIV infected people compared to starting ART at CD4 counts of ≤ 200/mm3 (8,9,10). Therefore the current recommendation is to start ART at CD4 count ≤ 350/mm3.

Most people at CD4 count of 200 - 350/mm3 will be asymptomatic. Therefore to start ART in asymptomatic people, measuring CD4 counts becomes necessary. Even in WHO clinical stage 3 or 4 when ART is started, it is best to measure baseline CD4 counts and check periodic CD4 counts to determine the response to ART.

People with WHO clinical stage 1 and 2 will be usually in the asymptomatic stage or will only have signs or symptoms not severe enough to seek medical advice. However it is now recognized that some of them will have low CD4 counts of ≤ 350/mm3. Therefore CD4 counts become very important in the new guidelines and attempts should be made to measure CD4 counts in all cases for success of ART.

Starting ART earlier also results in reduction of sexual transmission as well as MTCT of HIV. There is also reduction in TB as well as invasive bacterial infections when ART is started earlier rather than later.
However the consensus at the present is that in resource limited countries it may not be necessary to start ART at CD4 counts of > 350/mm3 except in special situations.

In practical terms however most patients with HIV will still be presenting at WHO clinical stage 3 or 4 when they will be quite ill and the CD4 count will be usually <200/mm3. Priority should be given to these patients for access to ART. In the long run however providing ART at CD4 counts of ≤ 350/mm3 will be beneficial not only for the individual patient but also more cost effective since there will no longer be any need to hospitalize patients or to treat opportunistic infections and because of reduction in morbidity and mortality.

For these reasons wider access to HIV testing and CD4 count measurements become important and provider initiated testing and counselling should be carried out on a wider scale.

While increased access to CD4 testing is a priority, the lack of a CD4 count should not be a barrier to the initiation of ART . (Start ART - WHO clinical stage 3 and 4; among the stage 2 conditions pruritic papular eruption (PPE) typically occurs when the CD4 count is <200/mm3 and ART may be started even if CD4 counts are not available.)

N.B. When starting ART in WHO clinical stage 3 and 4, opportunistic infections should be diagnosed and treatment started before starting ART. ART is not started without diagnosing and treating OIs in majority of cases.

Criteria for starting ART in specific populations

1. Pregnant women-
   - Start ART in all pregnant women with HIV and CD4 ≤ 350/mm3 irrespective of clinical symptoms.
   - Start ART in all pregnant women with HIV and WHO clinical stage 3 or 4 irrespective of CD4 count
   - Pregnant women in WHO stage I or 2 should have CD4 testing to start ART or ARV prophylaxis.
2. HIV/TB coinfection –
   - All patients with HIV and active TB should be started on ART if CD4 count is ≤ 500/mm3. If MDR-TB is present ART is indicated regardless of CD4 count.
3. HIV and hepatitis B co-infection (irrespective of CD4 count) if treatment for HBV is indicated.

Pregnant women

– see Prevention of Mother to Child Transmission of HIV.

HIV/TB coinfection

Tuberculosis is one of the most common health problems even before the HIV era and with the HIV epidemic, the prevalence of TB has increased worldwide. It is the most common opportunistic infection in HIV infected persons in resource limited countries. Immunosuppression predisposes to acquisition of new infection as well as reactivation of latent TB. Active TB is also known to hasten further immune deterioration. ART has

been reported to reduce TB rates at the individual level and to reduce TB recurrence rates. TB transmission rates and mortality rates at the population level can be also reduced if there is a high coverage of ART in patients with TB. The risks for TB infection starts to increase within one or two years after HIV infection begins and it has been shown that it becomes significantly high when the HIV positive patient remains below a CD4 count of < 500/mm3. The longer a person stays at CD4 count of < 500/mm3 the greater the risk of reactivation or new TB infection, active TB, recurrence and reinfection and death from tuberculosis (referred as "TB death zone") (11- 14). If the appearance of an OI is caused by immunosuppression,` the immunosuppression has to be corrected (with ART) and it has been proposed to initiate ART in people with active TB at whatever the CD4 count in people with HIV. However taking into account operational considerations the recommendation in this guideline is to start ART in the presence of active TB when the CD4 count is $\leq$ 500/mm3, when the risk of immunosuppression becomes quite high for effects from tuberculosis activity and not wait till the CD4 count is $\leq$ 350/mm3. However if MDR-TB is present ART is indicated at whatever the CD4 count.

In fact the greatest reduction in incidence of HIV-related TB can be seen when ART is started as soon as people test HIV positive. This has not yet been adopted as a public health strategy.

Earlier initiation of ART could be the most powerful strategy to reduce both HIV and TB incidence.

ART recommendations for HIV/TB coinfection

- It is recommended to start ART in HIV infected individuals with active TB with CD4 counts of $\leq$ 500/mm3 when the effects of immunosuppression become significantly high for tuberculosis.
- If MDR-TB is present ART is indicated at whatever the CD4 count
- Start TB treatment first followed by ART as early as 2 weeks and usually not later than 8 weeks.
- Use EFV as the preferred NNRTI in patients started on ART while on TB treatment.
- Those HIV positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells cells/mm^3) should receive ART immediately within the first 2 weeks of initating TB treatment. (76)

HIV and hepatitis B coinfection

Individuals with HIV/HBV coinfection have a increased risk of developing chronic HBV infection, an increased risk of fibrosis and increased risk of death compared to HBV

infected individuals without HIV infection. Therefore it would be beneficial to start ART in all HIV/HBV coinfected individuals who require treatment for their HBV infection (i.e. chronic active hepatitis) irrespective of the CD4 count or the WHO clinical stage. In such situations TDF and 3TC (or FTC) containing ART combinations should be used since both these agents have activity against HBV.

While this recommendation is important (HBsAg carrier rates in resource limited countries can be 10% or higher) liver biopsy and HBV viral loads are usually not available and implementation of this recommendation can be generally difficult; this will have to await development of simple guidelines to diagnose chronic active hepatitis.

HIV and hepatitis C conifection

Hepatitis C (HCV) coinfection is associated with accelerated progression of liver disease and increased risk of death in HIV positive persons. The effect of HCV on HIV disease progression however is uncertain. HCV infection is difficult to treat in a public health setting as interferon injections and ribavirin have to be used. Ribavirin causes drug interactions with AZT, ABC, d4T, ddI and ATV. There are no clear cut guidelines for treatment of HIV/HCV coinfection in a public health setting; meanwhile the initiation of ART in HIV/HCV coinfected people should follow the same principles and guidelines as for ART treatment of HIV infections without HCV coinfection. (2). Patients should be closely monitored for increased risk of drug toxicities. All HIV positive patients with HBV or HCV coinfection should avoid alcohol and other hepatotoxic drugs.

The CD4 count (15)

CD4+ T lymphocytes or T helper cells are subsets of lymphocytes (CD stands for clusters of differentiation; numbers represent specific subsets) that play a vital role as co-ordinators of the body's immune response. CD4 cells are the primary target of HIV. Loss of CD4 cells results in weakening of the immune response and the ability of the host to respond to foreign antigens, rendering the host susceptible to infections and ultimately leading to the acquired immune deficiency syndrome.

CD4 counts are monitored to assess immune suppression and disease progression in HIV infected persons and decisions to start prophylaxis of opportunistic infections. Changes in CD4 cell counts are an important indicator of the response to ART. The CD4 count is the most important key marker for initiation and monitoring of ART and is an indicator of the effectiveness of ART.

Other factors that affect the CD4 count besides the HIV disease process are – diurnal changes (higher in the evening), modest decrease during acute infections and major surgery and decrease during corticosteroid administration. Deceptively high CD4 counts are seen in HTLV-1 coinfection and after splenectomy.

CD4 counts may vary with the method used. Using the Cyflow Partec counter (which is commonly used) the normal CD4 count ranges from 430 to 1600/mm3. When interpreting CD4 counts it is important to follow the trend rather than specific values since there may be some degree of physiological and analytical fluactuations. In adults the absolute number of CD4 cells are counted but in infants and young children the CD4 percentage (of total lymphocytes) is more informative. The CD4 count can be repeated every 3 to 6 months according to the situation. Result of a CD4 count that is not consistent with prior trends should be repeated before making any clinical decisions.

Classification of Antiretroviral Drugs

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) :
Zidovudine (ZDV) (also known as azidothymidine or AZT)*
Stavudine (d4T)*
Lamivudine (3TC)*
Emtricitabine (FTC)*
Didanosine (ddI)*
Abacavir (ABC)*
Nucleotide Reverse Transcriptase Inhibitor -
Tenofovir (TDF)*

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) :
Nevirapine (NVP)*
Efavirenz (EFV)*
Etravirine (ETR)
Delavirdine (DLV)

Protease Inhibitors (PIs) :
Lopinavir (LPV)
Ritonavir (used to boost other PIs only)*
Ritonavir boosted lopinavir (LPV/r)*
Atazanavir (ATZ)
Darunavir (DRV)
Fosamprenavir (FPV)
Indinavir (IDV)*
Nelfinavir (NFV)
Saquinavir (SQV)
Tipranavir (TPV)

Integrase Inhibitor :
Raltigravir (RAL)

Fusion Inhibitor :
Enfuvirtide (T20) *s.c.only*

CCR5 Antagonist :
Maraviroc (MVC)

**available in Myanmar*

What ART combination to start

3 drug combinations should always be used for antiretroviral therapy.
In ART naïve individuals one of the following regimens can be started –

- AZT + 3TC + EFV
- AZT + 3TC + NVP
- TDF + 3TC (or FTC) + EFV
- TDF + 3TC (or FTC) + NVP

AZT + 3TC + EFV

This is a preferred first line regimen especially when there is HIV/TB coinfection where NVP is to be avoided since rifampicin reduces NVP drug levels which could cause NVP resistance. Where NVP cannot be used because of the risk of hepatotoxicity in hepatitis viruses associated liver disease or alcoholic liver disease this regimen is also preferred.
There is a chance of the development of AZT associated anaemia which is most common in the first 6 months of treatment but which can occur any time, sometimes abruptly to dangerous Hb levels. Patients are warned to report immediately when severe pallor or shortness of breath develops. In advanced disease when there is anaemia (Hb < 10 g/dl) it may be advisable to avoid AZT. It has been reported that baseline anaemia predicts development of ZDV anaemia which supports baseline haemoglobin testing and avoidance of ZDV if patient is anaemic (16).

[N.B. In advanced disease with very low CD4 counts and low BMI, anaemia is present in most patients (17,18). This anaemia is usually due to anaemia of chronic disease due to opportunistic infections or HIV itself, made worse by nutritional deficiencies (especially iron and folate deficiency) due to loss of appetite or chronic diarrhea. Treatment of OIs and ART usually improves the anaemia but AZT itself is capable of causing bone marrow suppression and some patients may have a severe fall in Hb levels. With preexisting anaemia of Hb < 10g/dl there is a risk of a further fall in Hb to dangerous level. Hb level is monitored at 4, 8 and 12 weeks of AZT therapy and the patient is advised to report if shortness of breath or severe pallor develops while on AZT therapy].

EFV is sometimes associated with giddiness , insomnia and nightmares which usually disappear after a few days.
EFV is potentially teratogenic and should be avoided in women who can become pregnant and is also avoided in the first trimester of pregnancy when it should be substituted with NVP. EFV may be less likely than NVP to be associated with the development of drug resistance.
3TC and FTC are interchangeable.

AZT + 3TC + NVP

This is widely available in a fixed dose combination , there is extensive experience with its use and the cost is lower than EFV containing regimen. This combination is also an option in pregnancy in the first trimester, when EFV may have teratogenic effects.

In terms of efficacy there is no difference between NVP and EFV based regimens. AZT has the same potential for anaemia (17,18).

NVP sometimes causes serous side effects. It is not advisable to use NVP together with rifampicin since rifampicin causes reduced NVP levels. NVP is associated with the occurrence of skin rash, Stevens-Johnson syndrome and hepatotoxicity . If severe side effects occur NVP should be discontinued permanently and not restarted (19-27).
In women with CD4 count >250/mm^3 (or in men with CD4 >400/mm^3) NVP is not advised; it should be used with caution, if other choices are not available, since there may be an increased risk of hypersensitivity and hepatotxicity. Close monitoring is advised in the first 12 weeks of therapy with NVP. Patient taking NVP should be advised to report immediately if nausea, fever, rash or jaundice develops.

NVP is started with 200 mg OD dose for 2 weeks (lead-in dose) after which it is increased to the usual dose of 200 mg BD. This will allow NVP to induce its own metabolism (enzyme auto-induction); if NVP is started 200 mg BD straight away there may be very high drug levels with toxicity. NVP containing regimens are contraindicated for prophylaxis in HIV negative persons.

TDF + 3TC (or FTC) + EFV

This is also a preferred first line combination.
The advantage is that the 3 drugs are available as one pill once daily combination which is very simple to use. It is the preferred regimen when there is HIV/HBV coinfection where both TDF and 3TC have activity against HBV. It also avoids the potential hepatotoxicity of NVP. TDF has been reported to have a potential for nephrotoxiciy (proximal tubular damage, acute and chronic renal failure) but the incidence is quite low (1- 2%); predisposing factors include advanced age, low body weight, higher initial serum creatinine levels, comorbidities (diabetes, hypertension),other nephrotoxic medicines, concomitant PI use and advanced HIV infection (28). Creatinine measurements may be needed, or more simply proteinuria or glycosuria (due to tubular dysfunction without diabetes) can be checked every 6 months in those at risk. Creatinine clearance is more sensitive than serum creatinine and can be calculated (Cockcroft-Gault formula). This combination is also preferred if there is HIV/TB coinfection and also in late stage disease when AZT had to be avoided because of anaemia (17, 18).

TDF + 3TC (or FTC) + NVP

This combination is less costly than the above combination and can be also used when there is HIV/HBV coinfection. The potential problem with NVP has been discussed.

Triple NRTI combination

- AZT + 3TC + ABC
- AZT + 3TC + TDF

The above triple nucleoside regimens ("triple nukes") can be used for individuals who are unable to tolerate or have contraindications to NNRTI- based regimens, particularly in the following situations, but are inferior to the afore-mentioned regimens of 2 NRTIs+NNRTI –

- HIV/TB coinfection
- Pregnant women
- Chronic viral hepatis B
- HIV-2 infection (HIV-2 infection is rare except in west Africa. NNRTIs are not effective in HIV-2 infection)

The combinations – ABC+3TC+TDF and TDF+ ddI+ 3TC are not advised since they have shown higher rates of virological failure.

3TC + d4T+ NVP combination

This combination has been extensively used in the initial years of ART programmes. It is an effective regimen but stavudine (d4T) has been found to have high rates of unwanted side effects. The lipodystrophy that it causes is very disfiguring. There is also hyperlipidaemia, peripheral neuropathy and risk of lactic acidosis. For this reason it is no longer recommended to be used in first line regimens. However in advanced HIV disease when there is anaemia and AZT has to be avoided and where an alternative is not available or cost is a factor in resource limited situations (this d4T based combination is the least costly ART combination) it may still be used initially and it can be substituted with AZT when the patient's condition and anaemia improves (29) usually before 6 to 12 months. Stavudine should not be used for an extended period of time and the dose should not be more than 30 mg BD. Stavudine may be used as a reserve drug when AZT or TDF cannot be used. On the basis of an assessment of cost and feasibility it is advisable to phase out stavudine gradually. AZT or TDF can be substituted for those already taking stavudine when it is safe to do so.

NRTIs not to be used together

- AZT + d4T (antagonism)
- d4T + ddI (overlapping toxicities)
- 3TC + FTC (interchangeable)
- TDF + ddI + any NNRTI (early rate of virological failure)

Important side effects and switching in first line ART

AZT - severe anaemia can develop and sometimes very suddenly any time but especially during the first 6 months; warn patients about pallor and severe shortness of breath; stop AZT; can recover if mild but may need erythropoietin or blood transfusions; substitute with TDF.

d4T – the side effects of lipodystrophy, hyperlipidaemia, peripheral neuropathy and lactic acidosis develop over time; not advisable in first line regimens; if used initially, switch with AZT or TDF; should not use d4T for extended periods of time.

TDF – potential for renal toxicity; check creatinine (creatinine clearance), proteinuria, glucosuria.

NVP – always use lead-in dose (200 mg OD x 2 weeks and continue 200 mg BD); watch out for rash, Stevens-Johnson syndrome, hepatotoxicity especially during first 3 months; stop NVP immediately and if reactions severe, can be fatal; may require special care. Do not use NVP again. Change regimen. NVP toxicity may occur at all stages of immune suppression but is more common in women with CD4 > 250/mm3 and in men with CD4 > 400/mm3.

EFV – can have insomnia, nightmares, severe giddiness at start of treatment but usually goes away after one or 2 weeks. Night time dose ; do not take with food to minimize side effects; substitute with NVP in first trimester of pregnancy because of potential teratogenecity **.**

N.B. – When stopping NVP or EFV continue NRTI backbone (2 drugs) for at least 7 days to cover the long half-life of NNRTI decay and reduce the risk of NNRTI resistance.

Table 2.1 Monitoring ART in those at higher risk of adverse effects

ARV drug	Major toxicity	High-risk situations
d4T	Lipodystrophy, neuropathy, lactic acidosis	Age > 40 yr, CD4 < 200/mm3, BW > 75 kg, INH or ddI use
AZT	Anaemia, neutropenia	Anaemia at baseline, CD4 < 200/mm3, BW < 50 kg
TDF	Renal dysfunction	Underlying renal disease, age > 40 yr, BW < 50 kg, diabetes, hypertension, PI or nephrotoxic drugs
EFV	Teratogenicity Psychiatric illness	First trimester of pregnancy Depression or psychiatric illness
NVP	Hepatotoxicity	HCV and HBV cointection

Table 2.2 Dosage and important side effects of first line ARV drugs

ARV drug	Dosage	Side effects
NRTIs -		
AZT	300 mg BD	Bone marrow suppression, severe anaemia (any time), gastrointestinal intolerance, Skin and nail pigmentation
3TC	150 mg BD 300 mg OD	Generally well tolerated Acute exacerbation of hepatitis may occur if it is withdrawn in HBV coinfected patients who stop 3TC
FTC	200 mg OD	Generally well tolerated, cutaneous hyperpigmentaiton Acute exacerbation of hepatitis may occur if it is withdrawn in HBV coinfected patients who stop FTC
d4T	30 mg BD	Lipodystrophy can be severe; hyperlipidaemia especially hypertriglyceridaemia Peripheral neuropathy Lactic acidosis
ddI	400 mg OD (>60 kg) 250 mg OD (<60 kg)	Pancreatitis, lactic acidosis, peripheral neuropathy, hepatitis, hepatic steatosis
ABC	300 mg BD	Hypersensitivity reactions
TDF (NtRTI)	300 mg OD	Renal toxicity, decrease in bone density Acute exacerbation of hepatitis may occur if it is withdrawn in HBV coinfected patients who stop TDF
NNRTIs-		
NVP	200 mg BD, initially 200 mg OD x 2 wk	Hypersensitivity reaction Rash Stevens-Johnson syndrome Hepatic toxicity hyperlipidaemia
EFV	600 mg OD	Similar to NVP but milder and less frequent Giddiness in first few days, can be severe Potentially teratogenic in first trimester of pregnancy

Important messages when starting ART (30)

- Patients should understand
  - that ART is suppressive therapy
  - that ART is life-long
  - that near perfect adherence is necessary to prevent ART resistance
  - that there are possibilities of side effects
- Assessment of patient readiness should be carried out before starting ART (ART should never be prescribed casually at the first visit).

Ensuring treatment adherence counselling

- Establish trusting relationship
- Provide necessary information and advice
- Identify and encourage peer/family/friends/support groups participation
- Try to fit in ART into patients lifestyle and daily events
- Discuss cost if patient/family/friends have to pay
- Discuss need for regular follow up; patient's address, how he will attend clinic, who will help, cost of travel
- Assess readiness and commitment of patients for ART
  - past ability to attend clinic regularly
  - past ability to take drugs regularly, e.g. co-trimoxazole prophylaxis
  - past ability to complete full course of TB treatment if relevant
  - adequate understanding of what is involved
- Treatment adherence should be very strict. The oft quoted 95% adherence (31) to recommended regimens should be emphasized to prevent ART resistance. This means that missing more than 3 doses per month with BD dose is associated with risk of developing drug resistance. (This is difficult but should still be emphasized even though recent evidence suggests that lesser degree of adherence is possible with highly potent modern regimens (32) since the purpose is to emphasize the importance of adherence).
- If regular doses are missed or late, reinforce adherence counselling. May need to enlist help from peers, family etc.
- Timing of drug intake is crucial. E.g. BD drugs are taken every 12 hours +/- one hour. Missed doses can be taken up to 6 hours in a BD regimen. If > 6 hours late, skip dose and take next normal dose.
- Drug side effects have to be understood and explained in advance
- Do not acquire drugs only when the supply runs out. Always keep some spare pills for emergencies.
- People on ART still need to use condoms
- Herbal products may interact with ART
- Regular clinic attendance for monitoring of efficacy and adherence is essential.
- Patients should not take prescription and go away.

Treatment regimen should be simplified by reducing the number of pills, reducing the number of dosing and minimizing side effects. Fixed dose combinations are very useful. Only officially approved drugs should be used.

Adherence may be measured by patient self-report, pill count and report of primary care provider.

At every visit check -

- Number of doses missed in last 3 days
- Number of doses missed since last visit
- If doses taken at correct time
- If dose is correct
- Reason for failure of adherence
- Reinforce adherence

Use fixed dose combination (FDC) pills if possible. Use of FDCs reduces pill burden and improves adherence. The following ARV drugs are available as fixed dose combination pills (combined into one pill):

AZT + 3TC

AZT + 3TC + ABC

3TC + d4T + NVP (usually not advised as first line ART)

AZT + 3TC + NVP

3TC + TDF + EFV (single daily dose, triple drug combination)

FTC + TDF + EFV (single daily dose, triple drug combination)

When to switch to second line ART

When the first line ART regimen fails it becomes necessary to switch to second line ART.

Second line regimens are expensive – about 5 to 10 times more than the standard first line ART regimen. Therefore utmost attempt must be made to optimize adherence and prevent resistance to first line regimens.

ART switching-

- Where available , use viral load (VL) to confirm treatment failure
- Where routinely available , use VL every 6 months to detect viral replication
- A persistent VL of > 5000 copies/ml confirms treatment failure
- Where VL is not available, use immunological criteria (CD4 count) to confirm clinical failure.

Table 2.3 ART switching criteria

Failure	Definition	Comments
Clinical failure	New or recurrent WHO stage 4 condition	Condition must be differentiated from immune reconstitution inflammatory syndrome (IRIS) Certain WHO clinical stage 3 conditions e.g. pulmonary TB, severe bacterial infections may be an indication of treatment failure
Immunological failure	Fall of CD4 count to baseline or below *OR* 50% fall from on treatment peak value *OR* Persistent CD4 count < 100/ mm^3	Without concomitant infection to cause transient CD4 cell decrease
Virological failure	Plasma viral load > 5000 copies/ml	The optimal VL threshold is not determined but values > 5000 copies/ml are associated with clinical progression and fall in CD4 count

Virological failure (incease in HIV viral load) usually occurs before immunological failure (fall in CD4 count) and clinical failure (new or recurrent opportunistic infections). Clinical monitoring alone results in increases in mortality and disease progression. Clinical monitoring may result in late switches to second line ART so that more drug resistant HIV clones have developed.

Immunological criteria (CD4 count) is not a good predictor of virological failure. Some individuals with immunological failure still have virological suppression and risk being unnecessarily switched to second line.
When early switching is done when virological failure occurs some of the first line ARV drugs will still be effective thus maximizing the effect of second line ART regimens which are expensive and not universally available (some first line ARVs are still employed together with a new class in second line ART). Late switching, after a protracted period following clinical failure will render the second line ART regimen to be less effective as the viral load gets higher and more drug resistant clones to remaining NRTIs develop.

The cost of a single viral load test is less than the cost of one month's supply of a second line regimen. However expensive equipment is required and the test requires expertise to perform. Efforts should be made to make viral load measurements as much as possible to maximize ART.
ART can be started without doing VL but its use is actually necessary to diagnose ART failure, in a timely manner. While expensive, VL has the potential to save the cost of expensive second line drugs by confirming they are needed.

Routine viral load strategy for failure and switching

The objective of the routine VL strategy is to detect virological failure early, leading to adherence interventions or changes in therapy that will limit ongoing viral replications, reduce the risk of accumulation of resistance mutations and protect the drug susceptibility of second line and subsequent ART regimens.

Routine viral load testing, every 6 months -

- If VL > 5000 copies/ml, take adherence interventions.
- Then repeat VL.
- If VL < 5000 copies/ml, do not switch to second line.
- If VL > 5000 copies/ ml, switch to second line.

Targeted viral load testing

Targeted VL testing can limit unnecessary switching to expensive second line ART.

To save costs, it can be carried at 6 months of ART and/or only when there is suspected clinical or immunological failure. In such a case –

- If VL > 5000 copies/ml, take adherence interventions
- Repeat VL
- If VL < 5000 copies/ml, do not switch to second line
- If VL > 5000 copies/ml, switch to second line.

N.B. In cases where ART is started very late with very low CD4 counts, the CD4 count may not rise back to normal. In such cases VL determination will indicate that the ART regimen is effectively working if the VL remains suppressed.

Plasma HIV Viral Load (33)

Plasma HIV viral load is measured using PCR (polymerase chain reaction) technology. The result is expressed as copies/ml. In HIV symptomatic or in late cases VL may be as high as 100,000- 1,000,000 copies/ml or more. The lowest level of detection is < 50 copies/ml or 400-500 copies/ml depending on the sensitivity of the test. Plasma viral load can be used to monitor therapeutic success of ART. It is the most important indicator of response to ART. The ideal aim of ART is to reach sustained undetectable plasma VL (< 50 c/ml). For most individuals who do not have resistant HIV and have good adherence to ART viral suppression is generally obtained in 12 – 24 weeks. In patients with a suboptimal response to ART other causes should be excluded which include adherence, drug interactions or malabsorption. The probability of HIV transmission is directly correlated with VL (34) . Effective ART with sustained VL below 50 c/ml almost eliminates or substantially reduces HIV transmission with nearly any type. There is little likelihood of developing resistance or disease progression at this VL level. Thus effective ART resulting in undetectable VL is very important not only in preventing sexual transmission and mother-to- child transmission, but also in reducing HIV transmission in the community when a wide ART coverage can be obtained. The cost of a single HIV viral load test is less than the cost of a month's supply of second line ART but requires expensive equipment and expertise to perform. However its importance in monitoring ART cannot be overemphasized and attempts are needed to make this test widely available. However lack of VL facilities does not preclude effective ART.

Second-line ART Regimens (2,35, 36)

A boosted protease inhibitor (bPI) plus two NRTIs are used for second line ART.
ATV/r and LPV/r are the preferred PIs for second-line ART
A simplified second line ART is recommended –

- If d4T or AZT has been used in first line therapy, use TDF + 3TC (or FTC) plus a boosted PI
- If TDF has been used in first line therapy, use AZT + 3TC plus a boosted PI should be used as second line therapy.

Use of PIs (Protease inhibitors)

Boosted PIs (bPI) provide most of the antiviral activity in second line regimens. Only boosted PIs are recommended for use. Ritonavir is a PI which acts as an inhibitor of cytochrome enzymes involved in metabolism of protease inhibitors. Thus it can reduce the dose (reduce side effects) and increase interval between doses of PIs (improve compliance) with which it is combined (PI/r). Ritonavir is not used by itself as a PI.

Among the PIs, use of indinavir is no longer recommended as this causes serious problems with renal stones especially in tropical climates.
ATV/r has the advantage of once daily dosing, and it does not cause PI cross resistance.

NRTIs in second-line ART-

- Residual activity of first-line NRTIs (with the possible exception of 3TC or FTC) is more likely the earlier ART failure is detected and switching is started. (Thus the importance of viral loads). Any new NRTI may be compromised in the second line regimen if there is late switching after ART failure because of the development of cross resistance among NRTIs. (Cross resistance of ARV drugs may develop within the same class).
- 3TC may remain useful in second line regimens even if there is resistance as such strains may protect potential NRTI options and avoid PI monotherapy.
- ABC and ddI are not recommended as preferred options in second line regimens.

Table 2.3 Protease inhibitors, dose and side effects

Protease Inhibitor	Dose	Important side effects
Indinavir (IDV)	800 mg 8 hrly	High incidence of renalstones; no longer recommended
Saquinavir (SQV) SQV/r	SQV/r 1000/100 mg BD	GI and metabolic side effects; many drug interactions
Ritonavir (RTV)	Only used to boost other PIs in doses of 100 – 400 mg a day	GI intolerance mainly, dyslipidaemia
Lopinavir/r (LPV/r)	400/100 mg BD 800/200 mg OD (OD for treatment-naïve patients)	GI intolerance; dyslipidaemia
Atazanavir/r(ATZ/r)	300/100 mg OD	jaundice
Darunavir/r(DRV/r)	600/100 mg BD	Hepatotoxicity, rash, dyslipidaemia

Third-line ART regimens

- Plans should be made for third-line therapy that consider costs, sustainability and equitable access to ART
- Third line regimens should include new drugs likely to have anti-HIV activity such as second-generation NNRTIs, PIs and integrase inhibitors.
- Patients on a failing second-line regimen with no new options should continue with a tolerated regimen.

While there is need to plan for third-line ART, because of financial constraints in resource limited countries, priority should be on expanding access to first line ART and failing that access to second line ART. Boosted darunavir (DRV/r) has potent anti-HIV activity and has excellent activity against HIV strains that are resistant to other PIs.

Etravirine (ETR) is a second generation NNRTI which is active against most but not all EFV or NVP resistant virus.

Raltegravir (RAL) is an integrase inhibitor, a new drug with potent antiretroviral actions, but the cost is high.

In trials combination of these agents have been used effectively. In resource limited countries the availability is uncertain.

For these reasons it is of utmost importance to make the first-line and second ART regimens work by all means (adherence, viral loads).The first chance is the best chance.

Table 2.4 Laboratory monitoring

Laboratory monitoring of ART	
Hb	Hb initially and at 4, 8, 12 weeks and every 3 months if AZT used ; every 6 months desirable
CD4 count	Initially and every 6 months
Plasma viral load (if possible): routine Plasma viral load : targeted	Every 6 months At 6 months and as needed only to confirm virological failure
Fasting blood sugar	Every 6 months desirable
ALT	Every 6 months (if NVP used at 4,8 12 weeks) desirable but not compulsory
Creatinine (for Cr clearance calculation)	Every 6 months if TDF used especially in high risk patients
Lipid profile (at least cholesterol and triglyceride)	Every 6 months (desirable)
Urinalysis (proteinuria, glucosuria)	Every 6 months if TDF used
Chest X- ray	Initially and when indicated

N.B. In resource limited settings, laboratory monitoring is not a prerequisite for starting ART (37). Routine monitoring is best but symptomatic laboratory monitoring is recommended for safety and to check for toxicity and to limit costs on those on ART. If resources are available it is best to use viral load testing to detect early ART failure. It is also advisable to test for HBsAg, HCV antibodies and VDRL if available before starting ART.

ARV associated adverse drug reactions

Common adverse effects of ARV drugs include fat maldistribution, hyperlipidaemia, lactic acidosis, hepatotoxicity, impaired glucose tolerance, pancreatitis and peripheral neuropathy and these are due to mitochondrial toxicity.

Lipodystrophy consists of two components viz. fat accumulation and lipoatrophy. Fat accumulation is seen in the upper back (buffalo hump), the breasts, within the abdominal cavity and in subcutaneous tissue. Metabolic syndrome may also develop. Lipoatrophy causes loss of subcutaneous fat in the face, extremities and buttocks. Lipodystrophy can be disfiguring and may not be reversible. Lipodystrophy is seen with ART ; stavudine is the commonest cause of lipoatrophy and it may be caused to a lesser extent by AZT and ddI .Fat accumulation is seen more commonly with PIs.

Lactic acidosis/Hepatic steatosis – can complicate NRTIs usually due to d4T. Severe lactic acidosis is less common but can be lethal.

Insulin resistance is common with PIs but diabetes is less common except in those with a family history.

Hyperlipidaemia especially hypertriglyceridaemia can be due to HIV infection with or without ART but more often with ART; this can increase the risk of cardiovascular disease. AZT, d4T and PIs are especially responsible. Lovastatin and simvastatin should not be used with PIs because of drug interaction.

Osteoporosis and avascular necrosis of the femoral head may be seen in patients on long term ART.

Important drug interactions

Drug interactions should be checked when prescribing ARVs.

Many drugs are metabolized in the liver by cytochrome enzymes. A drug which induces the cytochrome liver enzyme that metabolizes another drug reduces the therapeutic concentrations of the second drug. A drug which inhibits the cytochrome enzyme used by another drug increases the concentration of the second drug.

Rifampicin is a potent enzyme inducer and it reduces the drug levels of NNRTIs (NVP > EFV), PIs, ethinyl oestradiol, clarithromycin among others. Rifampicin should not be used with NVP. Rifabutin causes less enzyme induction.

All PIs are enzyme inhibitors and ritonavir is the most potent. Ritonavir increases the drug levels of benzodiazapines, opiate analgesics, carbamezapine, clarithromycin , cisprapride and quinine, sometimes to toxic levels. However RTV increases the activity of glucoronyl transferase enzyme and therefore reduces the levels of ethinyl oestradiol. Other PIs also cause increase levels of sidenafil, tricyclic antidepressants, statins, diltiazem and clarithromycin.

The enzyme inhibitor action of RTV is made use of by combining with other PIs so that the dose of PIs can be reduced and the interval of dosing increased. This reduces the toxicity of PIs and also improves compliance (e.g. LPV/r, ATV/r)

RTV as well as azole antifungals (especially ketoconazole) and clarithromycin by causing enzyme inhibition increases the drug levels of antihistamines terfenadine and astemizole which can result in cardiotoxic side effects and these should not be used together.

Anticonvulsants (phenobarbitone, phenytoin, carbmezapine) as enzyme inducers decrease the levels of many PIs, and PIs acting as enzyme inhibitors may increase the drug levels of some anticonvulsants (carbamezapine)– drug interaction acting both ways.

Azole antifungals and PIs may also interact both ways increasing the drug levels of each other.

NNRTIs decrease the drug levels of anticonvulsants, clarithromycin and ethynil oestradiol.

Drug interactions can be sometimes complex. Warfarin levels can be decreased or increased by NNRTIs or PIs.NRTIs do not use the cytochrome P450 enzyme and do not cause drug interactions through this enzyme system but may affect GI absorption or renal elimination.

(For details refer to www.aidsinfo.nih.gov;www.hivinsite.com;
www.hiv-druginteractions.org)

3.Opportunistic Infections in HIV/AIDS

Most people with HIV die of opportunistic infections. Prevention, diagnosis and treatment of OIs is an important part of the management of HIV, since most people still present with OIs in resource limited countries. Major OIs need to be diagnosed and treatment started before starting ART. Giving ART without diagnosing and treating major OIs in late disease will lead to disaster. However in advanced states of immunosuppression typical signs and symptoms of infections will be absent or masked. It is important to be vigilant in treating late HIV. Unusual infections that do not occur in immunocompetent persons will also occur.
Specific HIV associated OIs occur at specific levels of immunosuppression (38) according to their degree of pathogenecity. Knowledge of CD4 count helps in the differential diagnosis of OIs. Other HIV associated conditions also relate to the CD4 count (Table 3.1).

Cotrimoxazole prophylaxis (39)

Cotrimoxazole prophylaxis is a very important part of the management of a patient with HIV. It is recommended for all symptomatic individuals (WHO clinical stages 2, 3 or 4) including pregnant women. Where CD4 count is available, cotrimoxazole prophylaxis is recommended for individuals with CD4 count of $\leq$ 350/mm3, particularly in resource-limited settings where bacterial infection and malaria are prevalent among PLHIV. If the main target is for prophylaxis against *Pneumocystis jiroveci* pneumonia and toxoplasmosis infection cotrimoxazole can be started at a threshold of CD4 $\leq$ 200/mm3.

One double-strength tablet daily of cotrimoxazole daily is recommended (960 mg = 800 mg sulfamethaxazole + 160 mg trimethoprim).
Since the most common initial side effect of cotrimoxazole and antiretroviral therapy especially NVP and EFV is rash, it is recommended to start cotrimoxazole prophylaxis first and to initiate ART two weeks later if the individual does not develop rash with cotrimoxazole.

Skin reaction is the commonest side effect with cotrimoxazole. Other side effects are bone marrow toxicity and hepatotoxicity. Side effects can be monitored clinically. Patients starting cotrimoxazole are advised to stop the drug if an adverse effect is suspected and to report to the nearest clinic. Erythema and a mild macupapular rash may be observed and antihistamines given but if there is vesiculation, mucosal ulceration and exfoliative dermatitis, cotrimoxazole should be stopped immediately and discontinued permanently. However drug related adverse effects are not common and typically occur within the first few weeks of starting prophylaxis. Clinical monitoring is usually sufficient. The safety of cotrimoxazole in long-term use has been established.

Cotrimoxazole can be discontinued as prophylaxis against PCP and toxoplasmosis when the CD4 count rises above 200 cells/ mm3 with ART for at least six months.

Dapsone 100 mg a day may be used if there is hypersensitivity to cotrimoxazole, but dapsone is less effective than cotrimoxazole. If there is hypersensitivity to both cotrimoxazole and dapsone there is no other alternative in a resource limited setting. It may be possible to carry out cotrimoxazole desensitization under careful supervision.

Both cotrimoxazole and dapsone can cause intravascular haemolysis in patients with G6PD deficiency and should not be prescribed if the patient is known to be enzyme deficient. Routine screening for G6PD is usually not carried out in a resource limited setting.

Major opportunistic infections (40)

While many opportunistic infections may occur the following are the major opportunistic infections seen in this country and physicians treating HIV patients should be familiar with the diagnosis and treatment of these conditions since they can be associated with significant morbidity and mortality.

1. *Mycobacterium tuberculosis*
2. *Pneumocystis jeroveci pneumonia*
3. *Cerebral toxoplasmosis*
4. *Cryptococcosis*
5. *Systemic penicilliosis*

Table 3.1 Correlation between CD4 count and HIV associated OIs and conditions

CD4 > 500/mm^3	
• Acute primary infection • Persistant generalized lymphadenopathy	• Recurrent vaginal candidiasis
CD4 <500/mm^3	
• Pulmonary tuberculosis • Pneumococcal pneumonia • Herpes zoster • Oropharyngeal candidiasis • Oral hairy leukoplakia • Extra-intestinal salmonellosis	• HIV associated ITP (Immune thrombocytopenia) • Cervical intra-epithelial neoplasia II-III • Kaposi's sarcoma (rare in Myanmar)

CD4 <200/mm^3	
• Extrapulmonary/military tuberculosis • *Pneumocystis carinii (jeroveci)* pneumonia • Oesophageal candidiasis • Mucocutaneous herpes simplx • *Cryptosporidium* (diarrhea) • *Microsporidium* (diarrhea)	• HIV associated wasting • Peripheral neuropathy
CD4 <100/mm^3	
• Cerebral toxoplasmosis • Cryptococcal meningitis • Penicilliosis (*Penicillium marneffei)* • Non-Hodgkin lymphoma • Primary CNS lymphoma	• HIV associated dementia • Progressive multifocal leukoencephalopathy
CD4 <50/mm^3	
• CMV retinitis/gastrointestinal disease	• Disseminated *Mycobacterium avium intracellulare* disease

HIV/TB coinfection

Tuberculosis is the most common major opportunistic infection in HIV patients in developing countries and is the foremost cause of death in such patients. Immunosuppression due to HIV not only causes TB reactivation but also contributes to new infection (41).

The CD4 T-lymphocyte that is activated due to infection from M. tuberculosis produces more HIV than a quiescent cell so that there is a higher viral load which in turn increases the rate of disease progression and also increases HIV infectiousness. HIV drives the TB epidemic . More TB infection in the population in turn predisposes more HIV positive people to develop tuberculosis as a major opportunistic infection (41).

TB in HIV can be found at all levels of CD4 counts in HIV patients. The clinical and pathological picture of tuberculosis depends on the level of immunosuppresion i.e. the CD4 count. Before there is profound immunosuppresion (usually CD4 count > 200/mm3) the usual picture of pulmonary tuberculosis with apical infiltrations, cavitation and fibrosis is found. With advancing degrees of immunosuppresion i.e. with falling CD4 count , pulmonary TB changes in clinical pattern. There is less apical infiltrations or cavitation. There can be infiltrations in the middle or lower lobes, the

chest X-ray appearance may become atypical or non-specific. Sputum smears are less likely to be AFB positive as immunosuppresion advances. In the chest X-ray the hilar and mediastinal glands become enlarged.

In advanced immunosuppression there is extrapulmonary spread of tuberculosis. Pleural effusions and pericardial effusions, military TB, TB menintitis, TB of bone especially vertebra with psoas abscess may occur.

Widespread lymphadenopathy due to TB is a common presentation in HIV late stages. The cervical, axillary, hilar and mediastinal glands are involved. Intra-abdominal lymph notes become enlarged which may occur in isolation or occur together with lymphadenopathy elsewhere. Ultrasound examination of the abdomen is a very useful investigation in patients with HIV to diagnose intrabdominal lymphadenopathy due to tuberculosis (42,43,44). Ultrasound examination is easily available in many places in the country and is relatively inexpensive.

Whereas without immunosuppression, the typical histological features of tuberculosis with caseous necrosis, epithelioid cells, Langhan's giant cells can be found on biopsy, with very low CD4 counts the histological examination will not reveal these classical appearances – this is non-reactive tuberculosis. On the other hand the tissue can be stained with acid-fast stain which will demonstrate the acid-fast bacilli without granuloma formation.

When lymphadenopathy in a patient with HIV who has the clinical features of fever, night sweats and weight loss is seen tuberculosis should be suspected.

PGL (progressive generalized lymphadenopathy) may develop in 30-50% of patients with HIV. PGL involves more than 2 extra-inguinal lymph node areas, usually in the posterior triangle of the neck and epitrochlear regions, more than 1 cm in diameter. The nodes are not tender and are symmetrical. PGL does not involve the mediastinal or intra-abdominal lymph nodes and is not associated with fever or systemic symptoms. PGL is due to reactive hyperplasia in lymph nodes and regresses slowly as immunosuppression advances. The diagnosis is clinical. PGL has no prognostic significance. PGL should not be confused with tuberculous lymphadenopathy in HIV.

Diagnosis of tuberculosis will depend on the clinical symptoms, and sputum smears for AFB should always be performed; sometimes a biopsy may be necessary e.g. in a lymph node. However, many a time in very ill cases diagnosis will have to depend mainly on clinical features and treatment (full treatment) may have to be started on an empirical basis after excluding other differential diagnosis (45).

Tuberculosis in HIV patients is treated just like TB in immunocompetent persons –

standard 4 drugs (HRZE) for 2 months followed by 2 drugs (HR) for another 4 months. The continuation phase with HR is extended to 7 months in case of tuberculous meningitis, military TB and spinal TB with neurological involvement. The response to treatment is usually very good ; in most cases, fever subsides and there is some clinical improvement usually in two weeks time.

However there are some problems associated with the use of anti-TB drugs in HIV patients. Rifampicin will induce the enzymes that metabolize NVP as well as PIs so that the drug levels of these agents decrease with the potential to develop drug resistance by HIV. Adverse effects of anti-TB drugs are also seen more frequently in patients who have HIV. In advanced immunosuppression starting ART before giving TB treatment or starting ART very soon after TB treatment will lead to exacerbation of the signs and symptoms of tuberculosis due to effects of the recovering immune system which had failed to react to the tubercle bacilli. This is known as immune reactivation inflammatory syndrome (IRIS). Starting ART very soon will lead to severe reactions whereas delaying ART will predispose to further immune deterioration.
(For more detailed discussion on this important topic of TB HIV see references 46,47)

ART recommendations for HIV/TB coinfection

- It is recommended to start ART in HIV infected individuals with active TB with CD4 counts of $\leq$ 500/mm3 when the effects of immunosuppression become significantly high for tuberculosis.
- If MDR-TB is present ART is indicated at whatever the CD4 count
- Start TB treatment first followed by ART as early as 2 weeks and usually not later than 8 weeks.
- Use EFV as the preferred NNRTI in patients started on ART while on TB treatment.
- Those HIV positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells cells/mm^3) should receive ART immediately within the first 2 weeks of initating TB treatment. (76)

Optimal Timing of ART during TB Therapy: Findings of the SAPiT Trial (48, 49)

Initiation of ART during TB treatment reduced mortality by 55% compared to ART initiation upon TB treatment completion. However, optimal time to initiate ART during TB treatment remains unclear. In patients with pulmonary TB/HIV co-infection with $CD4^+$ counts <50 cells/mm^3, early ART initiation within 2 weeks of TB treatment initiation was associated with better AIDS-free survival, albeit with increased risk of IRIS. However, in patients with CD4 ≥50 cells/mm^3, delaying initiation of ART to the first 4 weeks of continuation phase of TB reduced the risk of IRIS and drug switches without compromising AIDS-free survival.

ART drug interaction with rifampicin

Rifampicin induces the metabolism of NVP lowering drug levels which can lead to NVP resistance. Therefore EFV is advised instead of NVP in patients taking TB treatment with rifampicin who are given ART. The alternative is to use ABC instead of a NNRTI ("triple nukes" – AZT + 3TC + ABC) but this is less preferable than EFV.

Similarly rifampicin induces the metabolism of protease inhibitors, so that boosted protease inhibitors in standard doses are not to be used together with rifampicin.

The other alternative is to substitute streptomycin for rifampicin but this involves giving daily injections and this may not always be possible.

A superboosted dose of ritonavir to increase level of PIs (ritonivir 400 mg instead of the usual dose of 100 mg to boost the PI) or doubling the usual PI/r dose can be employed if an alternative to rifampicin is not available, but these measures are associated with greater toxicity and require more frequent and close monitoring.

Rifabutin can be used as an alternative to rifampicin for those on ART especially if second line ART with boosted PIs is used. Rifabutin has minimal effect on bPI unlike rifampicin. The suggested dose of rifabutin with a bPI is 150 mg 3 times/ week. Rifabutin is not yet generally available.

MDR-TB in HIV

There is a risk of MDR-TB in patients with HIV and ideally all TB/HIV coinfected patients should have drug sensitivity tests for anti-TB drugs ; this is not yet possible on a wide scale at the present. All HIV patients with suspected MDR-TB should be referred to NTP. ART is indicated in all MDR-TB/HIV coinfected patients regardless of CD4 counts. MDR-TB in HIV patients carries a poor prognosis. Treatment is difficult and costly. History of inadequate treatment for tuberculosis is the strongest risk factor for MDR-TB.

Isoniazid prophylaxis in HIV (50,51,52)

HIV is the strongest risk factor for developing tuberculosis disease in those with latent or new *Mycobacterium tuberculosis* infection. The risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have HIV infection. TB is responsible for more than 25% of deaths in people living with HIV. A high rate of previously undiagnosed TB is common among people living with HIV (53). WHO has recommended at least 6 months of isoniazid prophylaxis therapy (IPT) for children and adults living with HIV and those receiving ART and those who have successfully completed TB treatment regardless of the degree of immunosuppression if active tuberculosis can be excluded. Active TB can be excluded by the use of a simplified screening algorithm that relies on four clinical symptoms.

Adults and adolescents with HIV who do not have any one of the symptoms of current cough, fever, weight loss or night sweats have a very low probability of active TB and should be offered IPT. Those who report any one of these symptoms should be evaluated for TB and other diseases. Chest X-ray may supplement the usefulness of symptom based screening but is not a requirement for IPT which can also be carried out without tuberculin skin test even though the greatest benefit will be seen in those with a positive skin test. IPT is effective in reducing the overall risk of developing TB in HIV positive persons by 33% up to 64%, the higher rate of effectiveness being seen in those who are TST positive. INH is given at a dose of 300 mg/day for 6 months. Contraindications to IPT include active hepatitis (acute or chronic), alcoholism, and peripheral neuropathy.

It has been shown that INH resistance is not significantly associated with providing IPT (54).

At the present in Myanmar, isoniazid prophylaxis therapy as primary prevention is being evaluated by the National Tuberculosis Programme in a pilot project in 9 townships for introducing it on a wider scale.

Pneumocystis jeroveci pneumonia (55,56)

Pneumocystis jeroveci (previously known as *Pneumocystis carinii)* is a fungus that causes pneumonia in patients with CD4 count <200/mm3. There is subacute onset and progression of exertional dyspnoea, non productive cough and fever over days or weeks. The dry cough and the exertional dyspnoea are progressive and in advanced cases cyanosis is seen with the slightest exertion. Chest X-ray shows bilateral symmetrical interstitial shadows fanning out from the hilum and sparing the apices (differential diagnosis is acute pulmonary oedema) but in spite of the marked radiological appearance, auscultation of the lungs is remarkably free of physical signs except for the tachypnoea.

Definitive diagnosis requires staining the sputum (the best specimen is induced sputum) with Giemsa stain or cresyl violet or Wright stains for the presence of cysts and trophozoites. The cysts are better stained with silver methanamine nitrate stain. Immunoflourescent stains or PCR can be also used. These would not usually be available and a presumptive diagnosis is made from the clinical and radiological picture. Treatment should be started immediately with cotrimoxazole double strength 2 tables TDS for 3 weeks. Alternative is pentamidine iv infusion which is not usually available or with primaquine 15-30 mg base/day plus clindamycin 600 mg 8 hourly iv or oral for 21 days. Severe cases require prednisolone 40 – 60 mg per day for 5 days which is gradually tapered until day 21. Prompt treatment is essential as the diagnosis is often late in RLS and mortality can be high. Cotrimoxazole prophylaxis is continued until the CD4 count rises to >200/mm3 with ART. Cotrimoxazole prophylaxis is given to all patients in WHO stage 3 or 4 or in those with CD4 < 200 cells/mm3 to prevent PCP.

Toxoplasmosis (57,58)

Toxoplasma gondii is a protozoan; primary infection is from eating undercooked meat which contain tissue cysts or ingestion of oocysts excreted in cats' feces. This commonly causes asymptomatic infection in immunocompetent hosts. In HIV patients with CD4 count < 100/mm3 it usually causes cerebral abscesses due to reactivation of latent cysts in the brain. The usual clinical presentation is with fever, headache, confusion and/or focal neurological deficits. Toxoplasma IgG, IgM antibodies are not of help in diagnosis. Toxoplasma IgG antibodies are present in >50% of the population without any symptoms. The presumptive diagnosis is based on CNS imaging – CT or MRI. Typical features are 2 or more ring enhancing lesions with intravenous contrast. Most patients respond very well to treatment with clinical and radiological improvement in 2 weeks or less which is diagnostic. Failure to respond should prompt the consideration of alternative diagnosis especially tuberculoma, brain abscess or primary CNS lymphoma. In resource limited situations, CNS imaging is unavailable and in such situations treatment can be tried on clinical suspicion especially with the onset of focal neurological signs and look for clinical response to treatment.

Initial treatment is with pyrimethamine 200 mg oral for one day then 50-75 mg per day plus sulphadiazine 1000-1500 mg 6 hourly per day plus leucovorin 10-25 mg oral/day for 6 weeks. Maintainenance is with pyrimethamine 25-50 mg po/day plus sulphadiazine 500 mg 6 hourly / day plus leucovorin 10-25 mg/day. The higher dose is for those weighing >60kg; leucovorin (folinic acid, not folic acid) is necessary to prevent bone marrow suppression due to pyrimethamine. Maintenance treatment is necessary until the CD4 reaches 200/mm3 with ART.

The alternatives are pyrimethamine plus clindamycin 600 mg every 6 hours or atovaquone 1500 mg BD with food .

Cryptococcosis in HIV (59-61)

Cryptococcus neoformans , which is a yeast usually present in soil ,bird droppings and moldy air, usually enters the body through inhalation. There may be fungal pneumonitis but it is usually subclinical. The usual diagnosis is subacute meningitis with fever and headache. The headache becomes more and more severe and relentless and unresponsive to analgesics if the condition is not diagnosed. The headache is described as splitting and excruciating and is a very prominent symptom unlike any other headache. Features of increased intracranial pressure then develop. Cryptococcal meningitis usually occurs at CD4 count < 100/mm3, usually at CD4 < 50/mm3. Signs of meningeal irritation may be absent because of severe immunosuppression. Serum cryptococcal antigen is positive in >95% of cases, fungal blood culture may be positive but the diagnosis can be easily made from CSF stained with India ink which will show yeast cells with characteristic thick walls. There may be very little CSF pleocytosis; the protein is raised; CSF opening pressure is typically very

high. Initiation of treatment is with i.v. amphotericin 0.7 mg/kg plus fluconazole 400 mg i.v./oral /day for at least 2 weeks followed by consolidation with fluconazole 400 mg po OD for 8 weeks followed by maintenance of fluconazole 200 mg OD until CD4 count rises to 200/mm3 with ART. However in resource limited situations fluconazole 800 mg/day (or more - 1200 mg per day) provides the only practical regimen for the first 2 weeks since it is more convenient, less toxic, less expensive and more easily available than amphotericin. Itraconazole 200 mg BD in the consolidation and 200 mg OD in the maintenance phase may be used.

Cryptococcal meningitis in HIV is associated with a high mortality and failure to manage elevated ICP is the most common cause. Intravenous mannitol may be used initially but removing the CSF until the pressure decreases 50% is more effective.
Immune reconstitution syndrome (IRIS) is sometimes seen following initiation of ART in cryptococcal meningitis. ART may also unmask cryptococcal meningitis.

Penicillium marneffei infection in HIV (62)

Systemic infection with *Penicillium marneffei* is one of the common OIs in south-east Asia including Myanmar. Patients can present with fever, lymphadenopathy, hepatosplenomegaly and anaemia but the most prominent feature is the skin lesion. Skin lesions usually start on the face and upper body and become generalized throughout the body. It is seen usually when the CD4 count is <100/mm3. The lesions are papules with central umbilication. Diagnosis can be established by taking a smear by scraping the skin lesions which is then stained with Giemsa's stain. The fungus is dimorphic but exists in the yeast form in the human body. It is seen as oval yeast cells with a characteristic central septation. Untreated systemic penicilliosis can lead to death. Severe infections have to be treated with intravenous amphotericin infusion 0.7 mg/kg/day for 14 days followed by itraconazole 400 mg for 10 weeks followed by secondary prophylaxis of 100 mg until ART increases the CD4 count to >100/mm3. Relaspe is common without secondary prophylaxis. Less severe cases can be treated with oral itraconazole alone which is preferred to fluconazole. Voriconazole can be also used.

The differential diagnosis is disseminated histoplasmosis and disseminated cryptococcosis which can also present with similar skin lesions and which are also treated similarly with antifungal agents. Skin lesions may resemble molluscum contagiosum (pox virus) but this causes skin lesions only without systemic involvement.

Other conditions and opportunistic infections in HIV

Seroconversion illness or Acute HIV syndrome

This usually occurs 3 to 6 weeks after infection with HIV and about half of all patients may experience this syndrome. It causes a 'flu like illness with fever, skin rash, lymphadenopathy, pharyngitis and myalgia and resolves spontaneously in most cases. In some patients it may be more severe with meningitis or encephalitis. It represents a burst of viraemia. This is followed by a prolonged period of clinical latency.

Clinical latency.

The length of time from infection to the development of clinical disease varies but in most patients it is from 6 to 10 years. However during this period HIV disease with active virus replication is ongoing. The rate of disease progression is directly related with HIV viral load or RNA levels, those with high VL progressing more rapidly. A small proportion of patients known as *slow progressors* show a very slow decline of CD4 counts even longer and a tiny subset know as *elite controllers* show VL <50 copies/ml with very little signs of disease progression.

PGL (progressive generalized lymphadenopathy)

This may develop in 30-50% of patients with HIV. PGL involves more than two extra-inguinal lymph node areas, usually in the posterior triangle of neck and epitrochlear regions, measuring more than 1 cm in diameter. The nodes are not tender and are symmetrical. PGL does not involve the mediastinal or intra-abdominal lymph nodes and is not associated with fever or systemic symptoms. PGL is due to reactive hyperplasia in lymph nodes and regresses slowly as immunosuppression advances. The diagnosis is clinical. PGL has no prognostic significance. PGL should not be confused with tuberculous lymphadenopathy associated with HIV.

Differential diagnosis of lymphadenopathy in a patient with HIV

- PGL - seen in early stages, disappears as immunosuppression advances
- Tuberculosis – most commonly in late HIV with symptoms of fever, weight loss etc
- Lymphomas – especially high grade B-cell lymphoma, rapidly progressive and less common as cause of lymphadenopathy
- Bacterial infections – localized usually
- Fungal infections
- Kaposi's sarcoma – very uncommon in Myanmar

Herpes zoster

It is one of the early manifestations of immunosuppression; even though there is a risk at all strata of CD4 count it is usually seen when the CD4 count falls to ≤ 350/mm3. Sometimes it can be multidermatomal. Diagnosis is clinical from the appearance of painful vesicular eruptions along the distribution of a dermatomal nerve. Herpes zoster involving the cornea can cause blindness and when the nasociliary branch of the 1st division of the Vth cranial nerve is involved, treatment should be prompt since there is a risk of corneal involvement. Early treatment with acyclovir 800 mg 5 times a day for 7 – 10 days is given. Analgesics may be required both for the acute pain and post-herpetic neuralgia. Herpes zoster may be seen as IRIS. Since zoster occurs before other opportunistic infections, a scar caused by herpes zoster should alert one to the diagnosis of HIV if another OI is suspected e.g. tuberculosis.

Seborrhoeic dermatitis

This presents as an erythematous scaly rash on the face especially on the eyebrows and along the sides of the nose, but is also present on the scalp, presternal and occasionally pubic areas. The yeast *Pityrosporum* can be recovered from the lesions. Ketoconazole 2% cream plus hydrocortisone 2% cream can be applied twice a day. Ketoconazole or selenium sulphide shampoos can be also used.

Pruritic papular eruptions

PPE is a very common condition seen when the CD4 count is < 200/mm3. It is a cutaneous marker for immunosuppression (63) and is very common in developing countries. It is a very intensely pruritic papular eruption in the exposed parts of the extremities and is thought to be due to an intense allergic reaction to insect bites (mosquitoes, bugs) (64). Scratching produces hyperpigmentation and hyperkeratosis. Treatment is with anti-pruritic drugs. Local application of calamine lotion can be applied but in severe cases, steroid creams may be used to interrupt the vicious cycle of pruritis and scratching. Local steroids should not be use for prolonged periods since they may be absorbed. PPE can be a tell-tale sign in patients with HIV.

Scabies

Caused by the mite *Sarcoptes scabiei*, it is not a sign of HIV infection but may be seen since it is a very common condition and should not be mistaken with PPE. There are intensely pruritic small red papules with burrow tracts, where the skin is thin so that they are characteristically found in the webs of the fingers and toes and in the genitalia region, axillae and breasts. They can also spread to other parts of the body if the infestation persists. The pruritis is characteristically more severe at night when the mite comes out and burrows under the skin to lay more eggs.

Scabies is not a sign of immunosuppression but scabies crostosus (crusted scabies or Norwegian scabies) is. In this condition because of severe immunosuppression, there is absent or minimal inflammatory response and hundreds of thousands of mites cause infestation of the skin with exudation of serum which becomes crusted.

Scabies is treated with permethrin 5% cream, lindane 1% or benzyl benzoate 25% emulsion. Repeated applications are necessary and household members should also be treated as it is infectious. Norwegian scabies is highly infectious and strict barrier precautions are necessary. In addition to the mentioned medications, keratolytic agents e.g. salicylic acid gel or urea creams are sometimes required.

Candidiasis

Thrush or oral candidiasis is most commonly seen as white painless plaques on the buccal or pharyngeal mucosa that can be easily scraped off. In HIV patients it usually occurs when CD4 is < 250/mm3 but it is also seen in non-HIV patients with the use of antibiotics, oral steroids, and in diabetes, malnutrition and cancer. Candidiasis can extend into the oesophagus usually as CD4 count further falls, causing painful dysphagia but candida oesohagitis can also occur in the absence of oral candidiasis. In the less common erythematous or atrophic form, the tongue and oral mucosa becomes very red. Treatment is with nystatin 500,000 units solution gargled 4 times a day. Fluconazole orally 100 mg/day for 1 – 2 weeks is also quickly effective. Oral ketoconazole or itraconazole are alternatives. With repeated use azole resistance may develop.

Oral leukoplakia

This is seen on the lateral surface of the tongue as vertical striations, believed to be due to EB virus infection. It usually requires no treatment but oral acyclovir 400 mg 5 times daily may be used for florid cases.

Aphthous ulcers

Aphthous ulcers in the tongue or oral mucosa are commonly seen in HIV infection but may be also caused by HSV or CMV; sometimes they are drug induced. Minor ulcers < 1 cm usually heal by themselves but a large ulcer > 1 cm can be deep, painful, prolonged and interferes with eating. Triamcinalone paste can be used to relieve the pain; a tapering dose of prednisolone may be tried. Response to ART is very good (65).

Bacterial infections

Bacterial infections are common in people with HIV . Bacterial pneumonias may occur. Maxillary sinusitis is a known complication of HIV disease. Antibiotics are required.

Diarrhoea

Diarrhoea, intermittent or prolonged is a common complication. It is caused by common bacteria such as shigella, salmonella, *E.coli* and responds to antibiotics. It is also caused by protozoa like amoeba or giardia and responds very well to metronidazole.

TB intestine is one of the causes of chronic diarrhea. It is chronic, does not respond to antibiotics usually used for diarrhea, stool amount is not copious and there may be associated abdominal pain. Presumptive diagnosis may be made from barium

follow-through examination – there is coarsening of villi, flocculation of barium with strictures and dilatation of the small bowel, most noticeable in the ileum. Biopsy may be obtained by colonoscopy from the ileoceacal junction but usually this will not be possible. The condition responds very well to anti-TB treatment.

Late in the course of disease prolonged watery diarrhea not responsive to antibiotics is usually caused by *Cryptosporidium parvum*, a coccidian parasite, which is commonly present in the water and does not cause disease in normal persons. It can be diagnosed by the demonstration of oocysts in the stool stained with modified acid fast stain. Cryptosporidiosis can be treated with nitazoxamide 1 gm BD for 60 days which can be tried but the diarrhea responds best to ART.

Cytomegalovirus (CMV)

CMV can cause pneumonitis, oesophagitis, enteritis, cholecystis and encephalitis in patients with HIV but an important complication is CMV retinitis which is usually seen in patients with CD4 count < 50/mm3. It may be asymptomatic when the periphery of the retina is involved but it is an important cause of blindness when it spreads to the macula area. Diagnosis is mainly clinical with ophthalmoscopy which shows perivascular yellow-white retinal infiltrates with intra-retinal haemorrhages (“scrambled eggs and tomato ketchup” appearance). In resource limited settings treatment is difficult and very expensive. Ganciclovir or foscarnet iv is required to stop visual loss and intravitreous injections of ganciclovir or foscarnet may be effective as secondary prophylaxis. CMV antibodies are present in > 90% of the population.

Thrombocytopenic purpura

Thrombocytopenic purpura is one of the complications seen in HIV. It has been ascribed to immune complexes on platelets as well as to the effect of HIV on megakaryocytes. In cases with very low counts, IVIG as well as steroids have been tried ; the condition responds to ART (66).

HIV and malaria (67)

In malaria endemic areas it has been observed that HIV increases the risk of malaria infection especially in patients with advanced HIV disease. It has been also observed that cotrimoxazole prophylaxis of HIV infected with CD4 count $\leq$ 350/mm3 can reduce the prevalence of malaria in the population. There is no evidence however that malaria has a significant effect on clinical progression of HIV.

HIV associated dementia or AIDS Dementia Complex

Dementia is a complication due to chronic encephalitis due to HIV. Cognitive, motor and behavioral dysfunctions are seen. Its incidence has fallen due to the early introduction of ART.

Wasting syndrome

In HIV wasting syndrome there is unintended loss of weight for >10% associated with fever and chronic diarrhea lasting more than 30 days *in the absence of* an underlying cause other than HIV. It is an indication to start ART. Androgenic steroids and nutritional supplements can be used. Other more common causes of marked weight loss in HIV disease are due to OIs especially tuberculosis.

HIV related tumours or opportunistic tumours in HIV (68)

Kaposi's sarcoma was one of the common AIDS defining conditions in western countries as well as in Africa but is very rare in south-east Asia (69). It is due to human herpes 8 virus (Kaposi sarcoma herpes virus) which causes vascular proliferation and tumour growth mainly in the skin causing coppery papular or nodular lesions but which also spreads to the lymph nodes and viscera. It has been treated with cytotoxic drugs but responds also to ART.

Lymphomas (70) occur with an increased frequency of more than 100 times in people with HIV than in the general population, but overall it is found in less than 10% of cases of HIV disease. It is usually a manifestation of late disease but it is also related to increasing duration of HIV infection. Typical cases are high grade B-cell non-Hodgkin lymphomas. Lymph nodes that are more than 2 cm or progressively enlarging should be biopsied to get the diagnosis. It is difficult to manage especially because of the overlapping toxicities of chemotherapy and ART but improvements in prognosis have been seen. Lymphomas are best treated in a specialized centre.

Primary brain lymphoma is seen particularly in advanced HIV disease and carries a poor prognosis. Presentation is with focal or non-focal signs or with signs of increased intracranial pressure. CD4 count is usually < 50/mm3. Diagnosis requires neuroimaging.

Cancer cervix - Infection with the human papilloma virus (HPV) causing intraepithelial dysplasia of the cervix is more common in women infected with HIV and can lead to cervical intraepithelial neoplasia, eventually causing invasive cancer of the cervix. (71).

For a more comprehensive discussion on diagnosis and management of opportunistic infections please refer to " Clinical case profiles of HIV infection – A colour atlas for HIV clinical care in Myamar", Department of Health, Ministry of Health, Yangon,2010.

Atlas of HIV related conditions and Opportunistic Infections

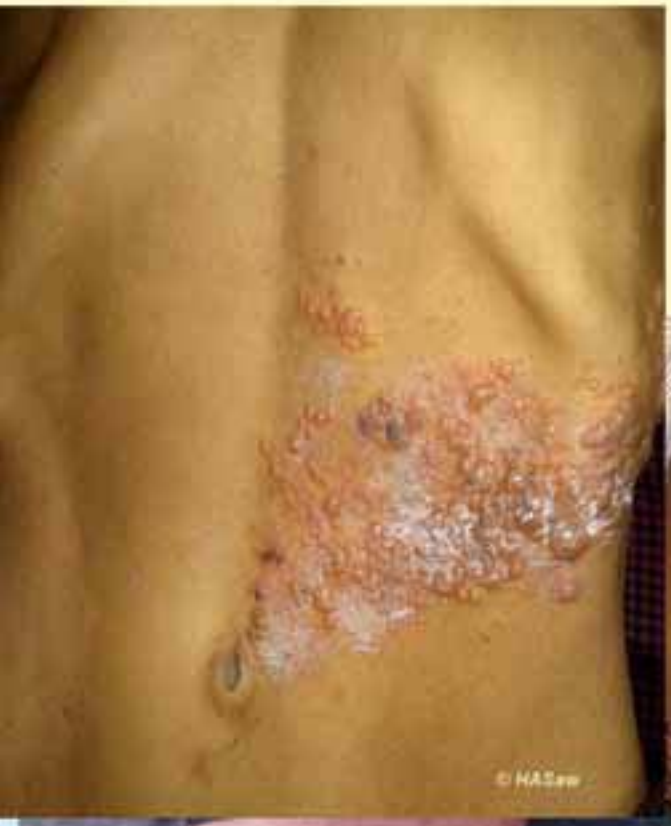
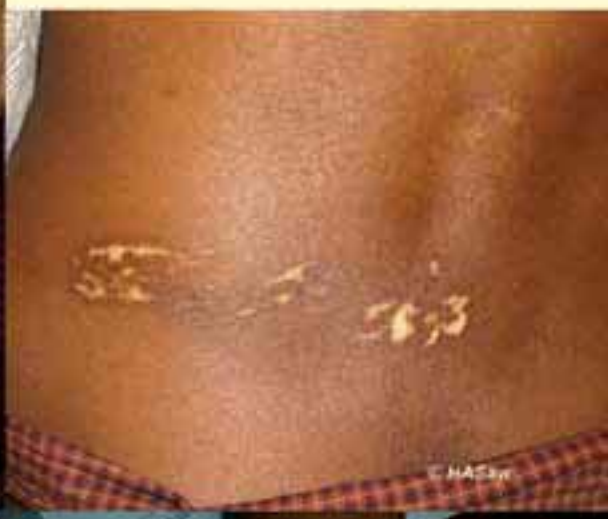
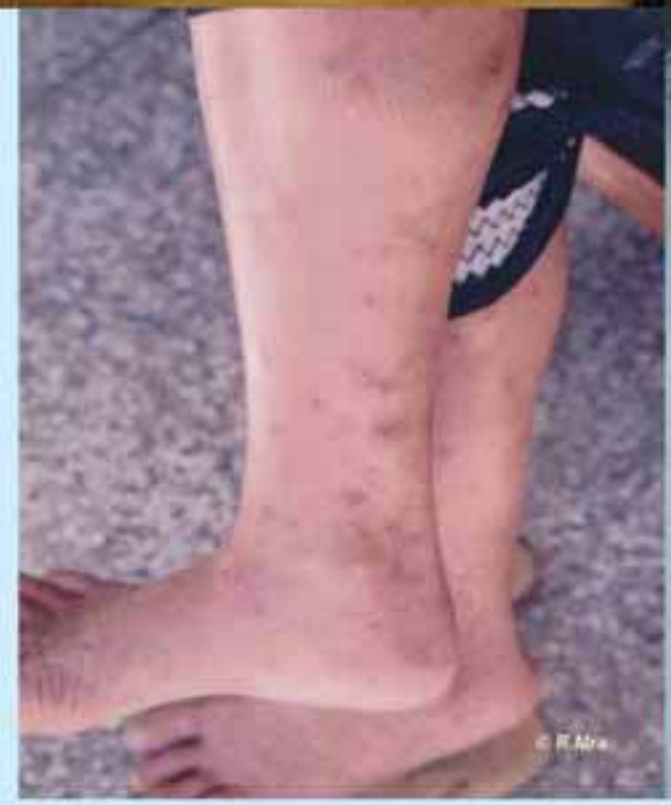


Fig. (3.1- left) Herpes zoster is usually an early manifestation of immunosuppression and usually occurs at around CD4 300/mm3. It is seen as a painful vesicular eruption along a dermatone. It may be recurrent and is sometimes multidermatomal.

Fig. (3.2- below) A herpes zoster scar is sometimes a clue to the presence of HIV infection.





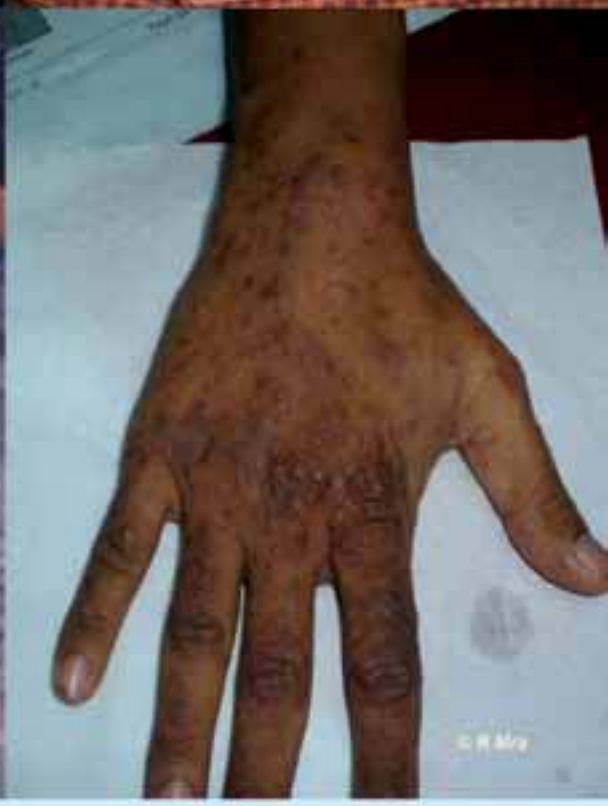


Fig (3.3-above left) & Fig.(3.4 –above right) Pruritic papular eruptions are seen in the exposed parts of the limbs. Scratching produces infection and scarring. Pruritic papular eruption is thought to be due to allergic reaction to insect bites. PPE is not scabies.

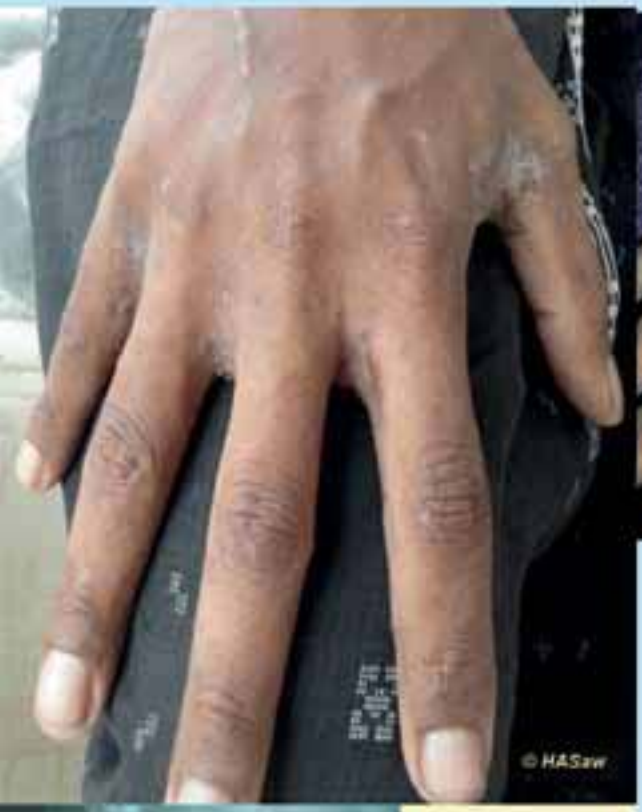


Fig.(3.5 - left)Scabies is cause by *Sarcoptes scabei* mites which burrow into the skin and is usually first seen in areas where the skin is thin e.g. webs of fingers and toes, genitalia and axillae. Scabies is intensely pruritic and the pruritis is worse at night. Scabies is not a sign of immunosuppression and is usually due to poor personal hygiene.

Fig.(3.6 - above right). When there is advanced immunosuppression there is hyperinfestation with the mites which do not cause an inflammatory reaction and pruritis and there is serum exudation causing encrustation. This is known as "crusted scabies" or Norwegian scabies. The condition indicates immunosuppression.

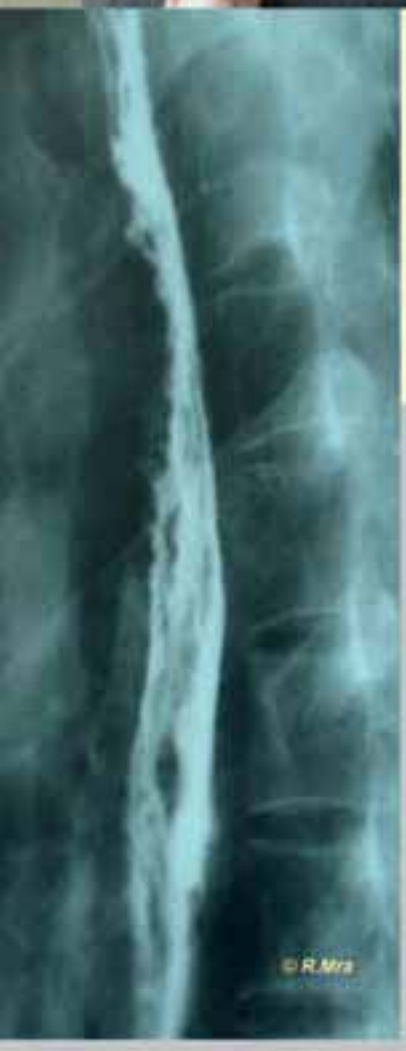


Fig. (3.7 - left) Barium swallow showing oesophageal thrush with mucosal ulcerations.

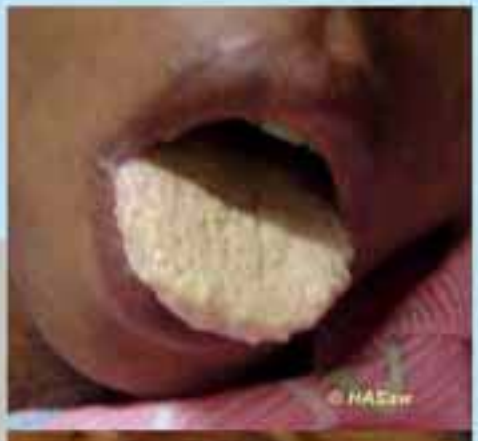
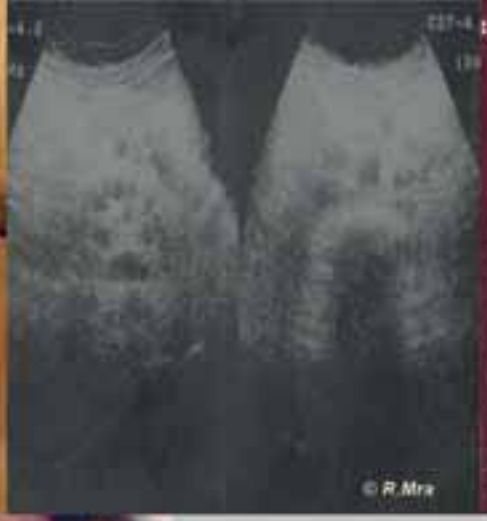


Fig.(3.8 & 3.9 - right) Oral thrush is due to *Candida albicans* in most cases and is usually seen as white plaques which can be easily scaped off (right) and sometimes as erythematous raw red areas (below right). There is soreness of the tongue and mouth. With advanced immunosuppression candidiasis extends into the oesophagus causing ulcerations and dysphagia. (left)



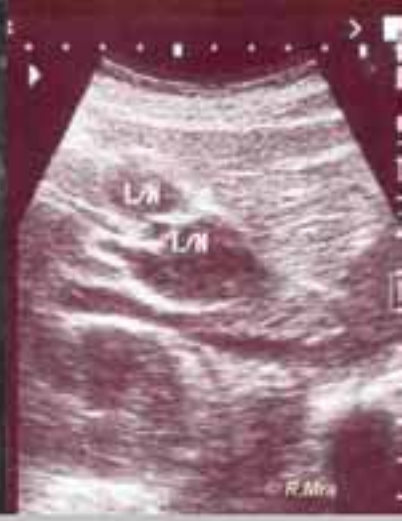


Fig.(3.12 & 3.13 - above). Intra-abdominal lymphadenopathy seen as hypoechoic areas on abdominal ultrasound examination. This is most commonly due to tuberculosis with advanced immunosuppression.

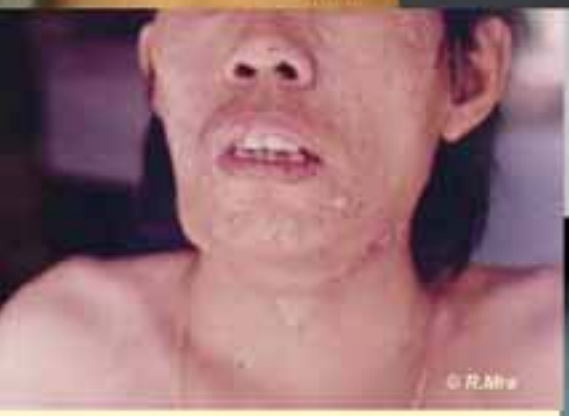
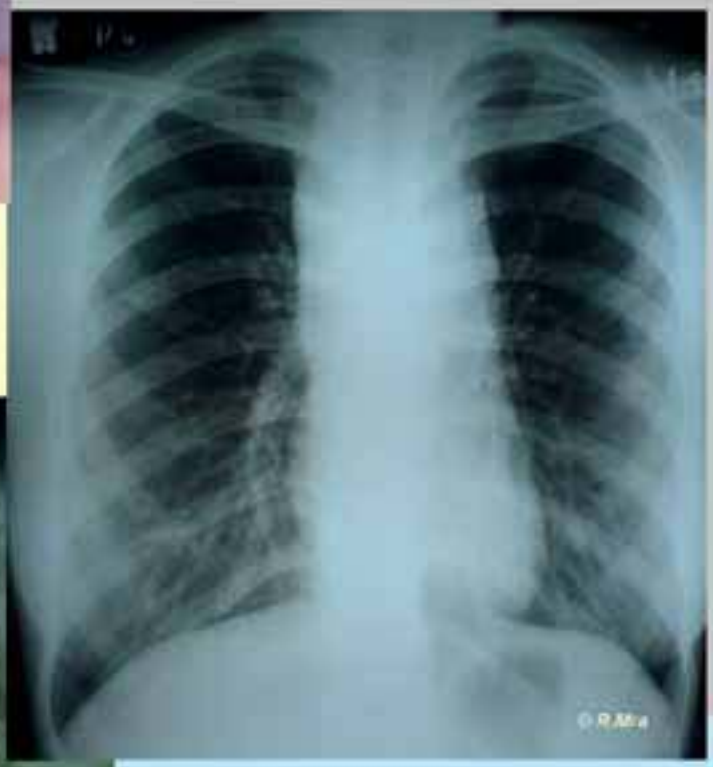


Fig.(3.10 & 3.11 - above) Tuberculosis commonly manifests as lymphadenopathy in HIV/AIDS.



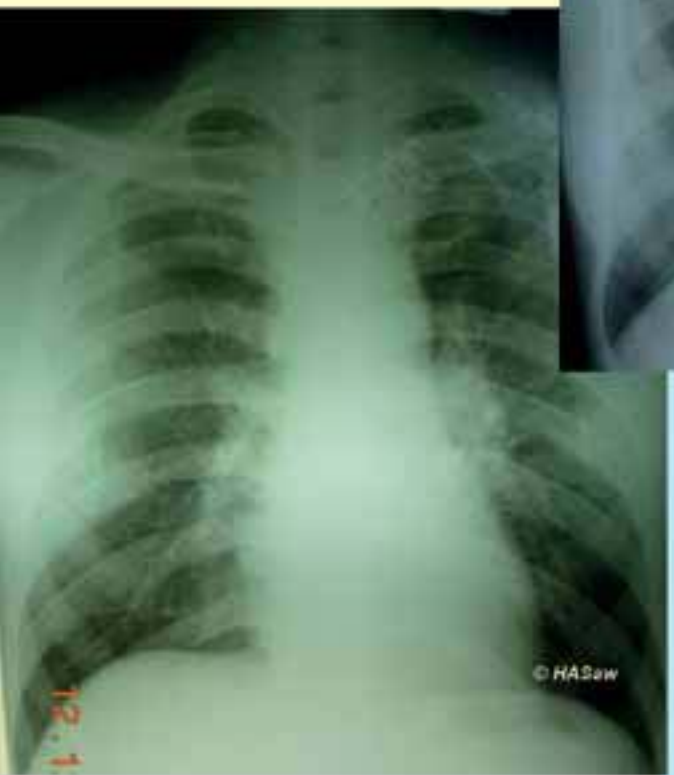


Fig.(3.14- above) & Fig. (3.15– left)Chest x-ray showing mediastinal lymphadenopathy (above) and hilar lymphadenopathy (left). This is most commonly due to tuberculosis in HIV/AIDS especially if associated with prolonged fever, weight loss and night sweats. Lymphoma is a differential diagnosis but is less common than TB.

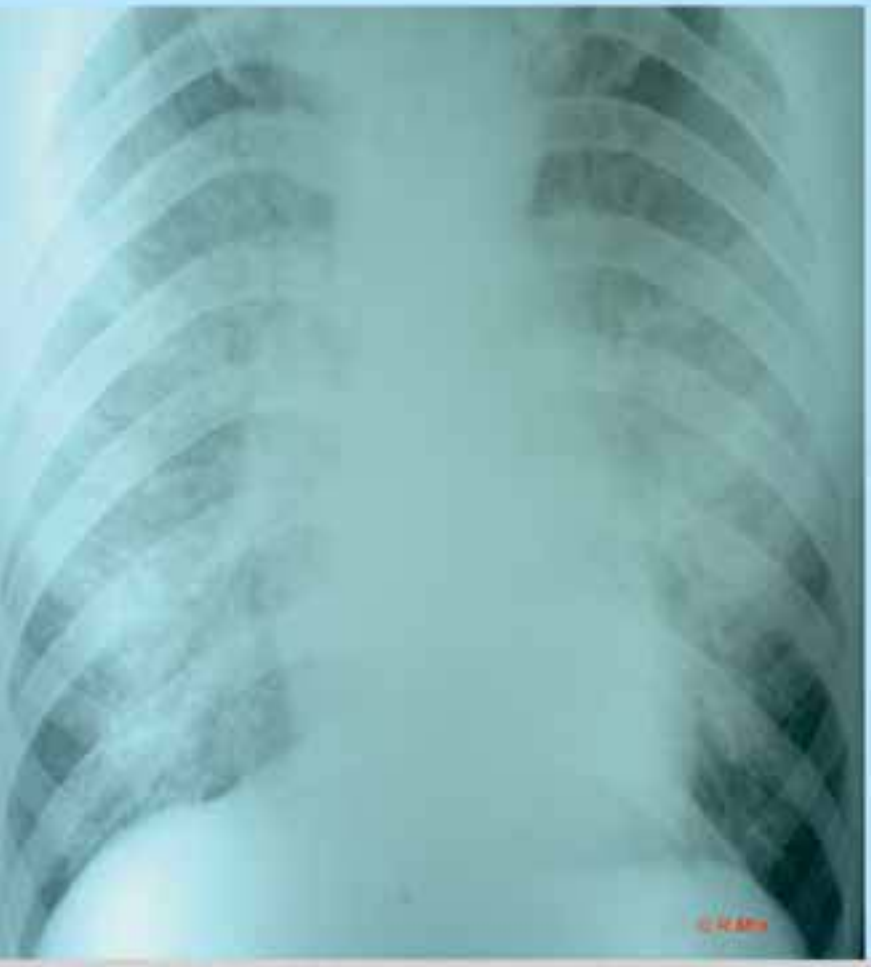
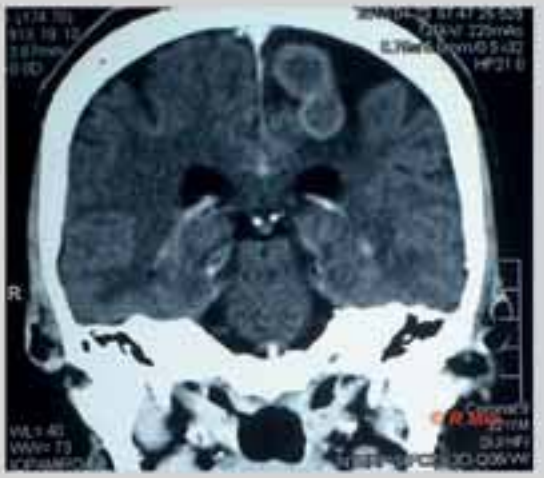
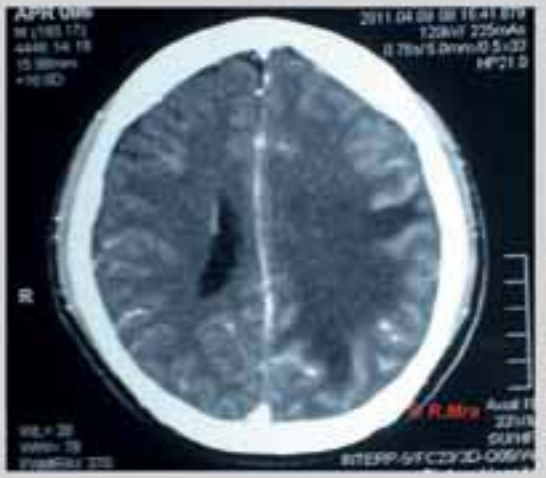


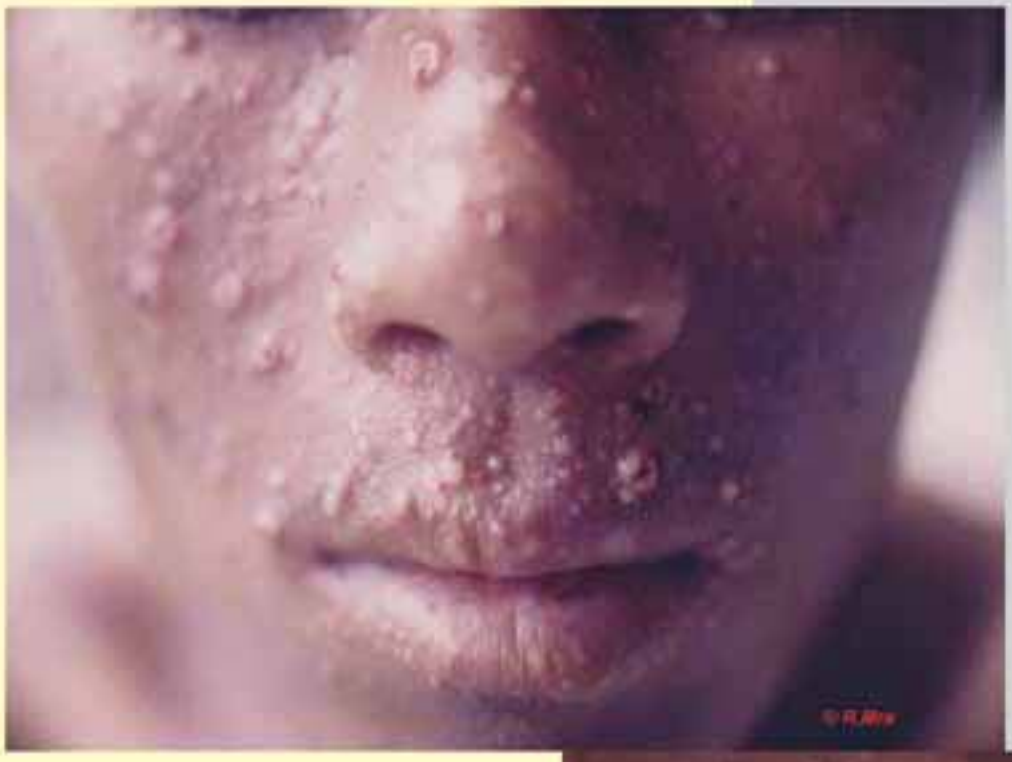
Fig. (3.16) The patient presented with a low grade fever, dry cough and shortness of breath which had become progressively more severe over the past 3 weeks. The dyspnoea became worse after the slightest movement and cyanosis developed on exertion. There were very few lung signs. An urgent chest X-ray showed diffuse pulmonary infiltraties fanning out from the hilar region and sparing the apices and lower regions. The clinical and radiological picture are typical of pneumocystis pneumonia (due to *Pneumocystis jeroveci).* This is a late case. The patient responded to prompt treatment with high dose co-trimoxazole (steroids were also given initially and tailed off).

Fig. (3.17-below left) CT brain - cerebral toxoplasmosis with multiple abscesses with ring enhancement after contrast injection. The patient presented with right-sided hemiplegia and fits. Differential diagnoses included other causes of brain abscesses—pyogenic, tuberculous, fungal or secondaries. In cerebral toxoplasmosis there is a good clinical and radiological response in about 2 weeks with sulphadiazine and pyrimethamine therapy. This patient made a complete recovery and is now well on ART.

Fig. (3.18-below right) CT brain of cerebral toxoplasmosis case. In this picture massive cerebral oedema is seen in the left side of the brain. A small abscess can produce marked cerebral oedema and the small abscess can be missed if the CT slice interval is not small enough. MRI or high resolution CT is the imaging technique of choice. In resource limited settings treatment for cerebral toxoplasmosis is started on clinical grounds alone; one should look for a response to treatment for the clinical diagnosis.







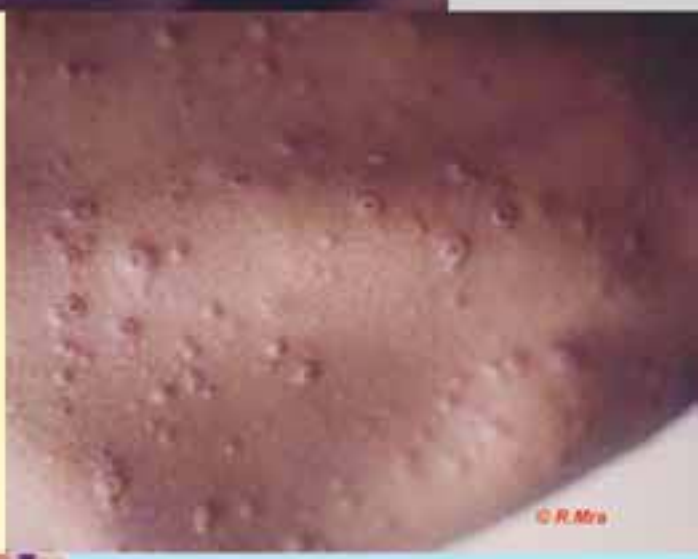


Fig. (3.19) Penicilliosis seen on the face (above)and skin (right).
Umbilicated papular eruptions first appear on the face and spreads to the limbs and trunk. The skin lesions are prominent but this is a systemic fungal infection involving the organs and bone marrow.

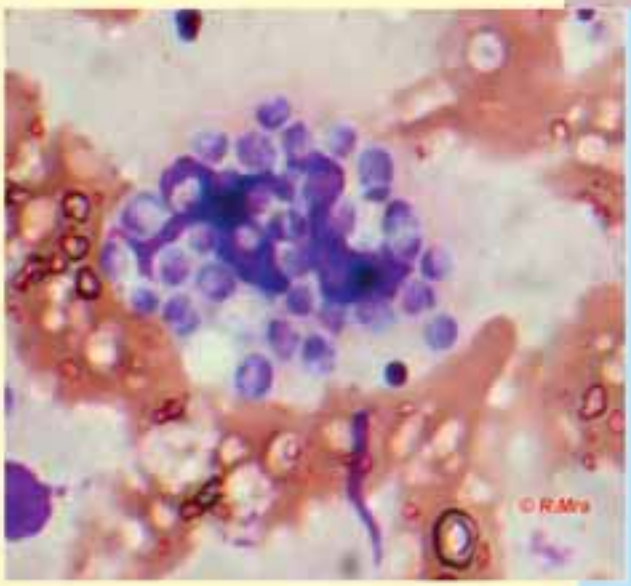


Fig. (3.20 right) Diagnosis is easily made by puncturing and scraping the papules and staining the smear on a glass slide with Leishman's or Giemsa's stain. Fungal bodies are seen inside macrophages with a characteristic central septation. (Oil immersion lens).

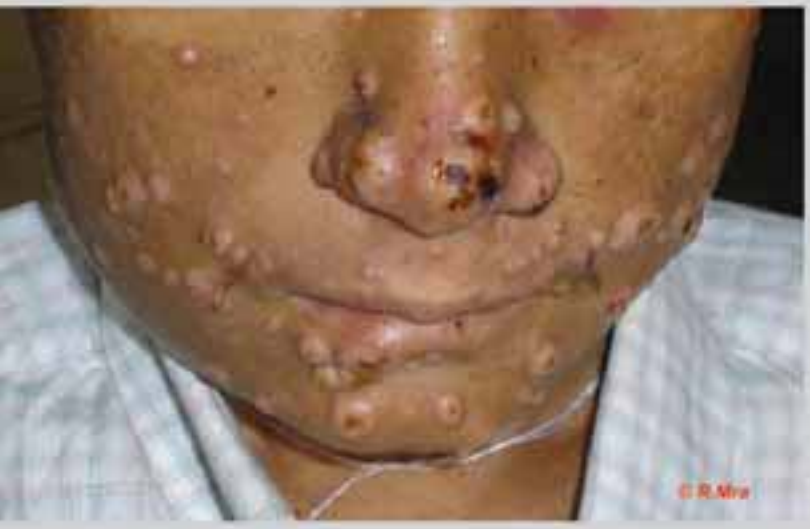


Fig. (3.21 - left) The skin lesions of histoplasmosis appear similar to those of penicilliosis (umbilicated papulo-nodular eruption) as part of systemic infection.

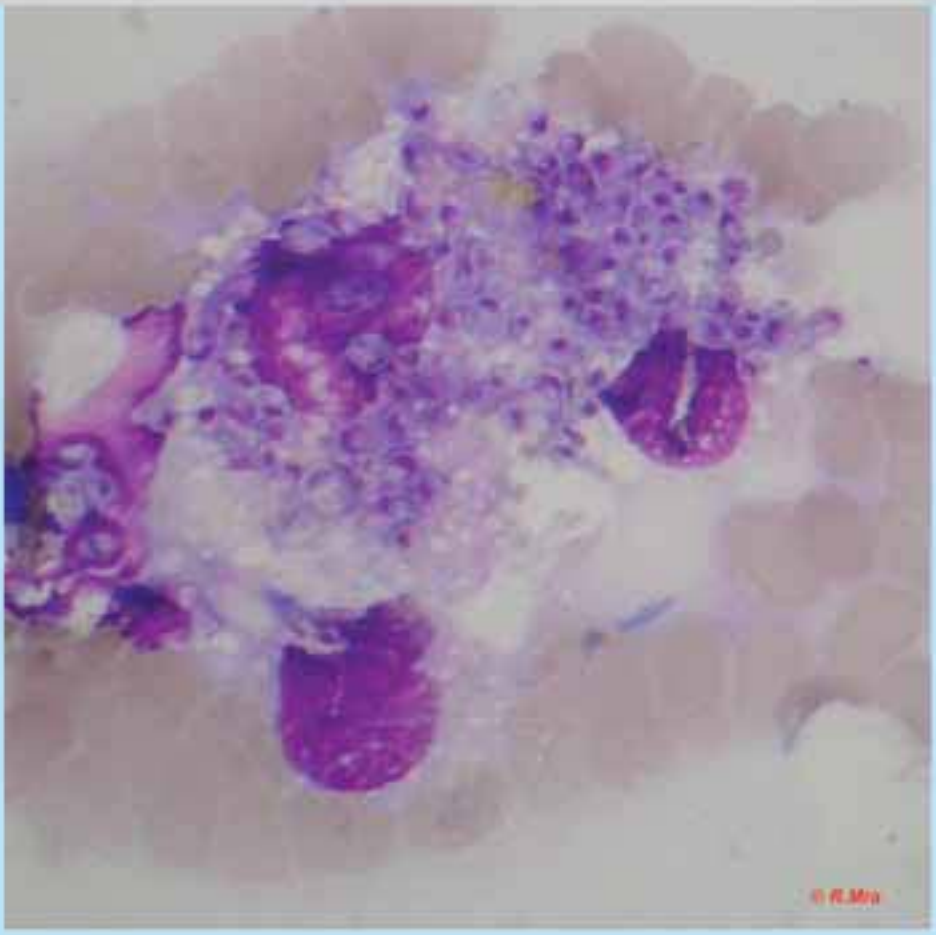


Fig. (3.22- above)The diagnosis of histoplasmosis is made from a skin scraping smear (or sometimes from a bone marrow aspiration smear) Fungal bodies are seen inside macrophages with the chromatin placed eccentrically like a signet ring. (Oil immersion lens, Leishman's stain).

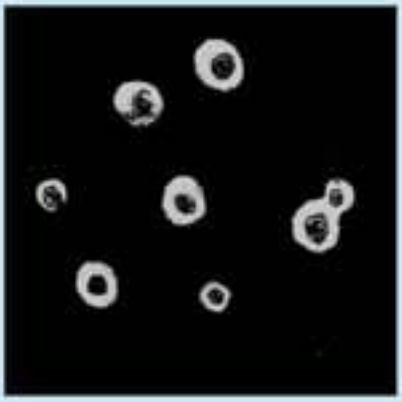


Fig. (3.23-above) India ink preparation of CSF showing yeast cells of *Cryptococcus neoformans* with unstained thick capsules and budding (sketch).

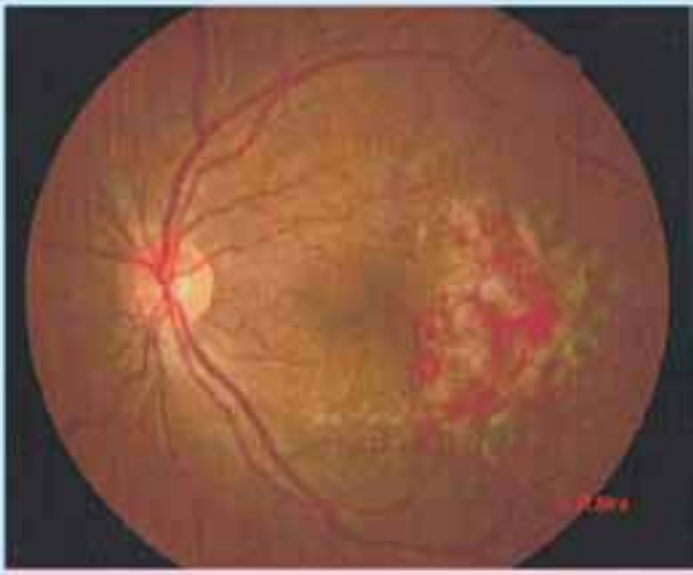
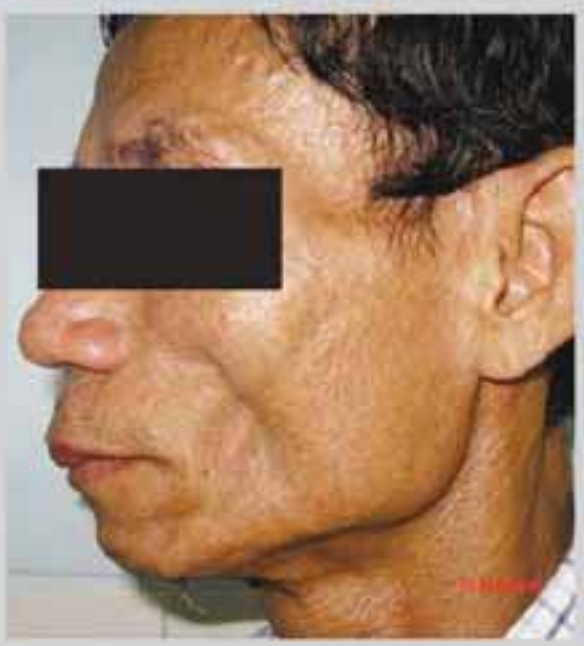


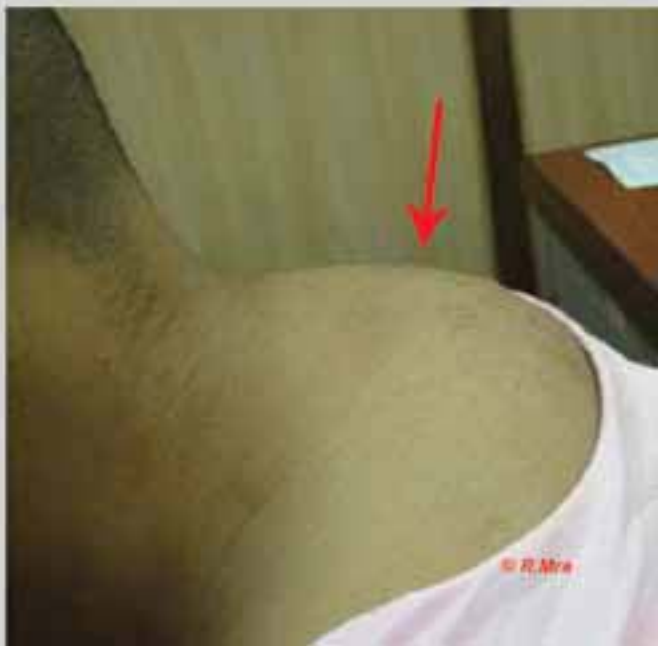
Fig. (3.24 - above) CMV retinitis showing haemorrhagic necrosis of the retina with exudates ("scrambled eggs and tomato ketchup appearance"). Involvement of the macula area causes blindness.

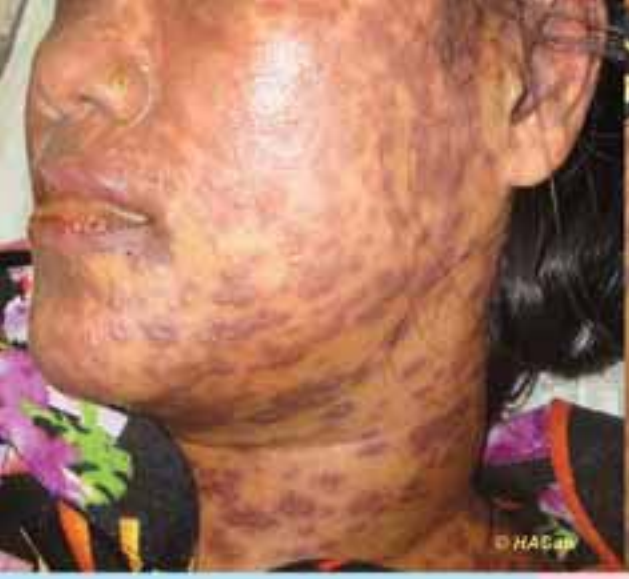
Fig. (3.25 - left) HIV associated lymphoma is a high-grade B cell non-Hodgkin lymphoma.

Fig. (3.26 - below left). Lipoatrophy of face caused by long-term stavudine therapy. Lipoatrophy is also seen in arms, legs and buttocks.

Fig. (3.27 - below right). Lipo-hypertrophy seen in the dorso-cervical region causing a "buffalo hump" appearance. Lipo-hypertrophy is also seen in the breast and abdomen. Lipodystrophy is a common complication seen with long term stavudine therapy.







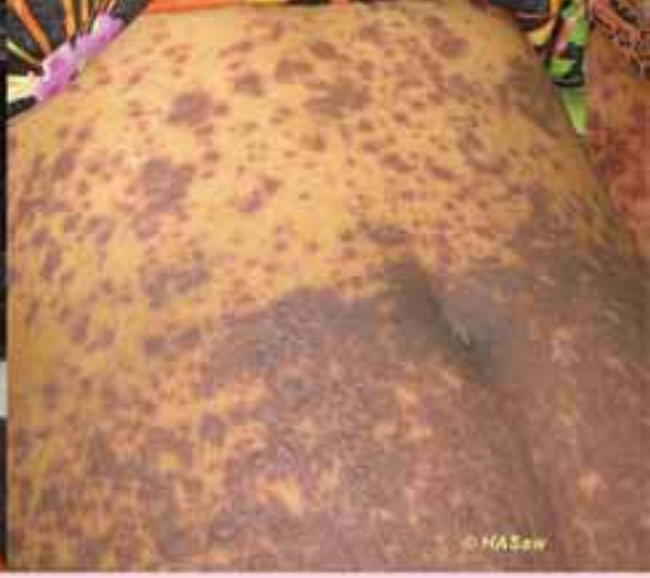


Fig. (3.28 - above left) & Fig.(3.29 - above right).
Stevens-Johnson syndrome due to nevirapine involving the whole body as well as mucous membrane. This is a recognized complication of NVP and can occur at all levels of immunosuppression but particularly in women with CD4 count > 250/mm3(see text).Stevens-Johnson syndrome can be also a rare complication of other drugs e.g. rifampicin, co-trimoxazole

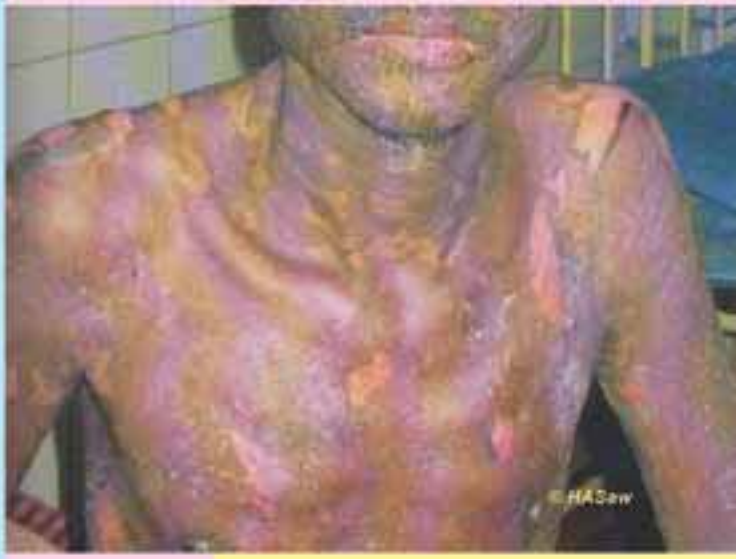


Fig. (3.30 - right). Toxic epidermal necrolysis due to nevirapine.

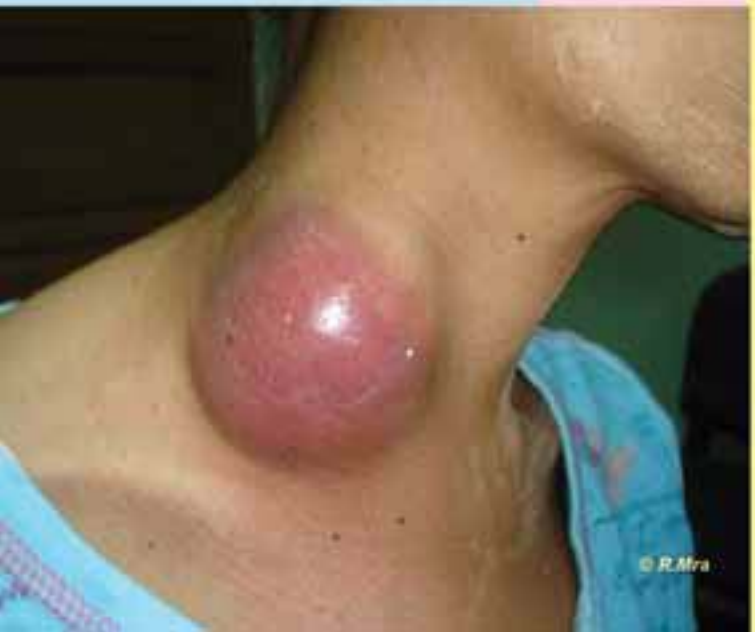


Fig. (3.31 - left) Immune reconstitution inflammatory syndrome or IRIS. This patient had a CD4 count of 50/mm3. There was a small lymph node at the root of the neck. TB treatment was started for pulmonary tuberculosis and ART started 2 weeks later. After one month symptoms worsened and the cervical lymph node had become enlarged, painful and then gradually became fluactuant. It was aspirated (should not be incised) and the pus showed the presence of many AFB. With continued TB treatment and ART the patient gradually improved. It took many weeks for the lymph node to regress and heal. This is an example of the immune reconstitution inflammatory syndrome.

4.Treating late HIV disease

Majority of patients with HIV in resource limited countries will still present with late HIV disease with CD4 counts < 100/mm3 or <50/mm3. They will usually have fever > 1month, diarrhea off and on >1 month, weight loss > 10%, oral thrush, anaemia with or without lymphadenopathy.

There are many causes of fever. Common conditions like pneumonia, typhoid, malaria, urinary tract infections and sepsis have to be excluded. Empirical antibiotics (not quinolones which are active in TB) can be tried. Then, other organisms like *Mycobacterium tuberculosis, Cryptococcus neoformans, Pneumocystis jirovecii, Toxoplasma gondii* and salmonella bacteraemia will have to be considered (72). The most common cause is usually tuberculosis. Lymphadenopathy in the neck, axilla, mediastinum and intra-abdominal region associated with fever, weight loss and systemic symptoms is most commonly due to TB. The chest X-ray appearance may or may not be suggestive of TB. All attempts for a microbiologic diagnosis should be made including sputum smears for AFB, sputum culture, lymph node aspirate smears and the diagnosis may or may not be confirmed but in very ill cases, treatment for tuberculosis will have to be started presumptively if there is a strong clinical suspicion and this may very well be life saving (45). The response to anti-TB treatment is usually good.

Dirrhoea usually responds to the measures already mentioned.

For weight loss, nutritional supplements are given but with response to treatment of OIs followed by ART, weight gain is usually obtained and sometimes this is several kgs. Weight gain is a good indicator of response to treatment.

Anaemia is present in most cases of advanced HIV disease. While it may be contributed by nutritional deficiencies or results from oral candidiasis, diarrhea or poor appetite it is also due to anaemia of chronic disease. With response to treatment of OIs and ART, the anaemia also improves most of the time. Severe anaemia excludes the use of AZT which itself could also cause significant lowering of haemoglobin (16-18).

In late HIV disease, OIs have to be diagnosed and treated first before starting ART. Starting ART without diagnosing and treating OIs can be disastrous.

ART will have to be started soon after treating OIs and in tuberculosis this will be at 2 weeks or not later than 8 weeks. This is because of the risk of immune reconstitution inflammatory syndrome (IRIS) if ART is started at the same time as the treatment of OI. The exact time to start ART in OIs is not exactly established but *vigilance and close observation* is necessary in managing late cases. In patients with pulmonary TB/ HIV co-infection with $CD4^+$ counts <50 cells/mm^3, early ART initiation within 4 weeks of TB treatment initiation was associated with better AIDS-free survival, albeit with increased risk of IRIS. However, in patients with CD4 ≥50 cells/mm^3, delaying initiation of ART to the first 4 weeks of continuation phase of TB reduced the risk of IRIS and drug switches without compromising AIDS-free survival (48,49).

Exacerbation of symptoms and signs can be due to IRIS or to the simultaneous occurrence of another OI. Multiple OIs may occur at the same time and IRIS can also unmask more OIs. Drug reactions or drug resistance are also a possibility.

Close monitoring is the key to successful management of late HIV disease.

Immune Reconstitution Inflammatory Syndrome (IRIS) (73)

After starting ART especially in late HIV disease, some patients experience clinical deterioration. This is because the body's immune system has recovered and starts to react to infections or antigens to which it was not reacting before. The reaction can be sometimes very severe and can cause significant morbidity and mortality if it is not recognized. The reaction is towards viable or dead microbial antigens and sometimes host antigens. The antigenic load of the OI is also important.

IRIS may be associated with paradoxical exacerbation of the OI that is being diagnosed and treated after starting ART.

IRIS may also unmask an OI which was not recognized because it remained silent with advanced immunosuppression.

Autoimmune diseases sometimes appear after starting ART and this is known as autoimmune IRIS (thyrotoxicosis, SLE, other autoimmune disorders have been described after starting ART).

IRIS usually starts within 2 to 3 months of starting ART but it may also be delayed for many months.

Risk factors for IRIS include –

- very low CD4 count at start of ART
- very high VL and very rapid fall in VL after ART
- treatment naïve at start of OI treatment
- short interval between OI treatment and ART

For this reason a brief delay is advisable in starting ART after the treatment of OI is started to control the OI. This delay may be 2 to 8 weeks in tuberculosis depending on the situation. In late disease with very low CD4 counts usually < 50/mm3 delaying ART too long could be dangerous because of the risk of disease progression and this has to be balanced against the risk of IRIS.

When the underlying condition has no specific treatment however ART can be started immediately. Cryptosporidiosis, HIV associated dementia and progressive multifocal leukoencephalopathy are examples where ART is indicated immediately.

IRIS is most commonly seen with TB, cryptococcal meningitis, CMV (which could cause blindness after starting ART), hepatitis B, hepatitis C, herpes zoster and other

conditions. In developing countries, IRIS is most commonly associated with TB. IRIS has been described in one fifth of cases after starting ART in late cases. This underscores the importance of diagnosing and treating HIV earlier.

TB IRIS is associated with fever, enlargement of lymph nodes sometimes with liquefective necrosis, worsening pulmonary infiltrates, pleural or pericardial effusion, expanding CNS tuberculomas or appearance of TB meningitis.

In managing IRIS, treatment for OI as well as ART is continued. The excessive inflammatory response is controlled with NSAIDs or steroids if necessary which are gradually tapered according to symptoms. It may be necessary to stop ART only very rarely in life-threatening IRIS. Differential diagnosis of IRIS includes –

- Treatment failure of the OI (e.g. MDR TB)
- Adverse drug reaction
- A new OI

5. Post-Exposure Prophylaxis (74)

Occupational exposure to HIV can occur because of percutaneous injury with HIV contaminated blood through injuries with needle-sticks and sharps, or exposure of non-intact skin or mucous membrane to blood or body fluids contaminated with HIV. Body fluids that may transmit HIV include not only blood but also genital secretions, CSF, amniotic, peritoneal and pleural fluids.

The risk of transmission of HIV through needle stick injury from HIV infected source is reported as 0.33% and through mucosal surface exposure 0.09%. No transmission of HIV through intact skin has been reported nor has there been any report of HIV infection through solid suture needles. The risks for infections through needle stick injury include deep injury with a hollow needle or sharp instrument with blood on the instrument, needle in a vein or artery and the source having late HIV disease (indicating a high viral load). Even though the risk is small it is definite and post-exposure prophylaxis should be offered which can substantially reduce but not completely eliminate the risk of accidental HIV transmission. PEP can also be applied in cases of unintentional sexual exposure like in rape. PEP is not appropriate in chronic sexual exposure to HIV.

Individuals are eligible for HIV PEP if -

- The exposure occurred within the past 72 hours and
- The exposed individual is not infected with HIV and
- Non-intact skin or mucous membrane was significantly exposed to a potentially infectious body fluid
- And the source is HIV infective or the HIV status is unknown.

People who have been exposed should receive counselling about aspects of PEP as soon as they present following exposure. The information should include the importance of adherence and the side effects and the risk of transmission as part of the counselling. Condom use and other protective preventive measures should be encouraged until a HIV test after 6 months is negative.
Baseline HIV testing is done in the exposed person and repeated at 3 months and 6 months. Rapid HIV test of the source person is done if feasible and this is done after informed consent.

PEP is not indicated –

- If the exposed person is HIV positive already from a previous exposure
- In chronic exposure
- If the exposure does not pose a risk of transmission, i.e. after –
    - Exposure of intact skin to potentially infectious body fluids
    - Sexual exposure using a condom that remains intact
    - Any exposure to non-infectious body fluids (such as faeces, saliva, urine and sweat)
    - Exposure to body fluids from a person known to be HIV negative unless that person is a high risk person suspected to be in the window period.

PEP may never be considered to be 100% effective. Therefore the practice of universal precautions is important in the workplace and primary prevention and risk prevention counselling are also very important in all settings where HIV transmission can occur.

Measures to prevent other blood-borne disease such as hepatitis B and C should also be emphasized.

PEP treatment with 2 NRTIs –

A regimen with 2 NRTIs is recommended if

- HIV status of the source person is unknown

and

- The background prevalence of resistance to ART is <15%

and

- the source person has never used ART

or

- the source person is unlikely to have ART resistance based on ART therapy and adherence history.

Recommended two-drug combination therapy for HIV PEP (given for 28 days)

- AZT + 3 TC
- Alternative is TDF + 3TC
- NVP, ABC and ddI are not used due to their relatively higher risk of potentially serious side effects.

PEP with 3 drugs – 2 NRTIs + PI/r

A regimen consisting of 2 NRTIs + PI/r is considered if –

- The source person is HIV positive, taking ART and is known to have signs of, personal history of, or proven ART resistance

or

The source person's HIV status is unknown

and

- The background prevalence of resistance to ART exceeds 15% (where this is known)

[Available evidence suggests that primary HIV drug resistance rate is low in south-east Asia 5.2% (75); this may rise with more widespread use of ART].

Recommended 3 drug combination (given for 28 days)

- AZT + 3TC + LPV/r
- Alternative is
    - AZT + 3TC + ATZ/r
    - TDF + 3TC + ATZ/r

Clinical management of HIV PEP

Table 5.1 Post exposure prophylaxis of HIV management

Item	Recommended action and notes
Eligilibity	Exposure within 72 hours Exposed individual not infected with HIV Significant exposure Source is HIV infected or unknown HIV status
Informed consent for post exposure prophylaxis	Information about risks and benefits Consent may be given verbally
Medicine	2 NRTIs (part of 1st line ART) Add PI/r if drug resistance likely
Time to initiation	As soon as possible not later than 72 hours
Duration of therapy	28 days
HIV testing with informed consent and pre- and post-test counselling	Baseline HIV test in exposed person Follow up HIV testing 3-6 months after exposure
Additional laboratory tests	Pregnancy test Haemoglobin for AZT containing PEP Hepatitis B and C screening
Counselling	For adherence, side effects, risk reduction, trauma or mental health problems, social support and safety
Referral	Refer as appropriate
Record keeping	Maintain accurate, confidential records
Follow-up – clinical	Assess and manage side effects Assess and support adherence

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