Orientation program for Doctors.

Management of Opportunistic Infections and Anti retroviral therapy.

Date:
June 17th & 18th; 2005

Venue:
Frontier Management center,
Hoysala Nagar, Ramurthy Nagar,
Bangalore.

Conducted by:
SAMRAKSHA
NO.17/1,Harris Road,
Benson Town,
Bangalore-560046.

Schedule for the doctors training programme from June 17th & 18th; 2005.

DAY-1	
Topic details	**Resource person**
Registration	
Introduction to HIV/AIDS	Dr.B.Satish HIV consultant & doctor in-charge Seva clinic; Samraksha
PPTCT, universal precautions & PEP	Dr. B. Satish HIV consultant & doctor In-charge Seva clinic; Samraksha
Work experience in people living with HIV/AIDS	Dr.Lal; Delhi
Common OI's in HIV and treatment. Introduction to Anti-retroviral therapy	Dr.B.Satish HIV consultant & doctor In-charge Seva clinic; Samraksha
Day-2	
ARV's, challenges, difficulties with anti-retroviral therapy, Interactions and side effects of ARV's and secrets of successful ART adherence	Dr.K.Satish, Chest physician, Workhardt hospital &honorary consultant Samraksha
Management of ART in govt.set-up.challenges, difficulities, with anti-retroviral therapy	Dr.Mahesh Sr.Research officer, ART Unit, Bowring & lady curzon hospital
Common OI's in HIV/AIDS	Dr.Rao, Consultant-chest & maternity clinic, Bangalore
Syndromic case management of STI's Management of PLHAs in private clinics	Dr.Anna rao, In-charge doctor, Samraksha, Asha Jyothi, Kushtagi.

FOR FREE ARV TREATMENT

1. **ART UNIT,**
   OPD BLOCK,
   KIMS HOSPITAL
   HUBLI

2. **BOWRING HOSPITAL**
   ART UNIT, SHIVAJINAGAR,
   BANGALORE.

3. **ART UNIT,**
   K.R NAGAR, MYSORE.

CARE CENTRES FOR IN-PATIENT SERVICES

1. **SAMRAKSHA**
   ASHA KIRAN RESPITE HOME
   # 37,ST JOHNS ROAD,
   NEAR LAXMI THEATRE,
   BANGALORE.

SERVICES OFFERED

- Admissions
- Medical consultation for opportunistic infections
- Nursing care
- Palliative care
- Counseling
- Monitoring of anti retroviral therapy
- Out –patient service.

-SAMRAKSHA, ASHA JYOTHI
NH-13, TENGUNTA ROAD,
KUSTAGI, KOPPAL DISTRICT

SERVICES OFFERED-
(SAME AS ABOVE)

2.**SNEHADAAN**
AMBEDKAR NAGAR, SARJAPUR ROAD, BANGALORE-35

SHEHADAAN,
MANGALORE.

3. **FREEDOM FOUNDATION,**
#180,HENNUR CROSS,
ST.THOMAS TOWN, MANGALORE.

PH.# 25440135.

- FREEDOM FOUNDATION,
BELLARY.

REFERRALS

HIV TESTING:

1. All districts & talukas VCTC/PPTCT Centers from Monday to Saturday
2. Samraksha-Asha jyothi, Kustagi, NH-13, Koppal district on all Saturdays.
3. Samraksha-seva clinic, # 37, st. Johns road, near old Laxmi theatre, Bangalore.ph. # 25512375 on all weekdays.

CD4 COUNT

NIMHANS, DEPT.OF VIROLOGY, ADMINISTRATIVE BLOCK, BANGALORE.
(Blood to be collected before 11 am.
Testing is done only on Tuesdays / Fridays.
If you're sending the sample, Rs.500 will be charged.)

ANAND DIAGNOSTICS LAB

#11,blue cross-chambers, infantry road, Bangalore.
(On all days-Monday to Saturday, Rs.1000/- will be charged.)

CHAPTER – 2

Natural History and Clinical Manifestations of HIV/AIDS

Eighteen years ago, the terms HIV/AIDS were not known to the medical fraternity. But now it is the second leading cause of death among young adults in United States and has had a profound impact on the health of people worldwide. A family physician has got a very important role in continuum of care of an HIV/AIDS patient while a specialist is involved only in critical care. So the basic objectives of this chapter revolve around the following:

1. To familarise the physician with the course HIV will follow once it enters the human body.
2. The various clinical sign and symptoms that indicate clinical diagnosis of AIDS.
3. When to subject the patient to various laboratory tests.
4. When to refer the patient to a specialist.

But one must be very clear that as per government policy, there are no special AIDS clinics, or AIDS hospitals or AIDS specialists. All doctors are expected to treat AIDS patients without any bias and discrimination.

With a high case fatality rate, significant impact on health and society, lack of definite curative treatment or vaccine, HIV/AIDS pandemic is one of the most serious health problems of this century. The current AIDS cases reveal the transmission dynamics of past years and burden of illness in near future. Similarly, the prevelance and incidence of HIV infection today may be fully revealed only in future years. The mean time from initial infection to diagnosis of AIDS is around 9 years but now various epidemiological studies have been shown that the rate of disease progression varies substantially depending on various viral, host and environmental co-factors, mode of transmission, age at infection, treatment interventions and prophylaxis strategies. Hence it is very pertinent to look into natural history of HIV infection.

NATURAL HISTORY OF HIV

A. HIV Transmission

The primary modes of HIV transmission are sexual contact, receipt of infected blood and its products, organs and tissue donations and pregnancy and breast feeding, percutaneous exposures (accidental or I/V drug users). A clear understanding of HIV

transmission is integral to providing effective counselling about the risk and prevention of HIV transmission.

B. Clinical Stages of HIV Disease

Infection with HIV leads to a progressive impairment of cellular immune function, characterized by a gradual decline in peripheral blood CD4+T – lymphocyte levels which results in an increasing susceptibility to wide variety of opportunistic viral, bacterial, protozoal and fungal infections and to certain malignancies also. The course of the disease is marked by increasing levels of viral replication, emergence of more virulent viral strains and progressive destruction of immune system. However, the natural history of HIV infection is changing with better diagnosis, anti-retro-viral (ARV) therapy, and early treatment and prophylaxis of various opportunistic infections.

Early, patients with HIV infection were categorized as having either, AIDS-Related Complex (ARC) or asymptomatic disease. As more information has been gathered on HIV, these terms have been outdated. Various classifications have been proposed over years based on various clinical and laboratory parameters but the one proposed by Centre for Disease Control and prevention (CDC), Atlanta, USA using CD4 count as marker for relative risk of developing HIV related opportunistic infection is given below.

Stage I: Acute (Primary) Infection (SERO CONVERSION)

Initial primary- infection with HIV is usually asymptomatic. However, after an incubation period of 2-6 weeks. (longest upto 36 weeks), there is a phase of viraemia and upto 50% of individuals experience an acute infections mononucleosis like illness or a viral syndrome. There may be high fever, lymphadenopathy, pharyngitis, arthralagia, *amorbillifom* rash and myalgia. The illness usually lasts 2 weeks or less and may even go uninvestigated as possibility of HIV infection is frequently not explored at this stage. Around 10-20% patients may present with headache, meningo-encephalitis, peripheral neuropathies, myelopathy, Bell's Palsy or G.B. Syndrome. One may occasionally also get oropharyngeal candidiasis.

There is severe CD4 lymphopaenia and this may drop to levels indicative of advanced HIV disease but typically it rebounds to near normal in 2-3 weeks in most of cases. In some case CD4 count may remain suppressed and this may be *harbinger* of a more accelerated course of disease.

HIV antibody tests are often negative in early stages of HIV seroconversion illness: The diagnosis depends on tests to detect viral antigen (e.g. p24 antigen and PCR tests).

2. Tuberculosis: disseminated, miliary, extra-pulmonary and extensive pulmonary tuberculosis.

3. Neurological impairment preventing independent daily activities, not known to be due to the conditions unrelated to HIV infection (e.g. trauma).

4. Candidiasis of the oesophagus (dagnosable by odynophagia with oral candidiasis).

5. Clinically diagnosed life threatening or recurrent episodes of pneumonia, with or without etiological confirmation.

6 Other conditions:

- Crytococcal meningitis
- Neuro-toxoplasmosis
- Cytomegalovirus retinitis
- Penicillium marneffei infection
- Recurrent Herpes zoster and multi-dermatomal, and
- Disseminated molluscum

7. Kaposis sarcoma

For children (upto 12 years of age)

A. Two positive tests for HIV infection (by ERS test) among children 18 months or older, or confirmed maternal HIV infection for children less than 18 months; and

B. Presence of at least two major and one minor signs in the absence of known causes of immuno-suppression

Major Signs

1. Loss of body weight or failure to thrive that is known to be due to medical causes other than HIV infection.
2. Chronic diarrhoea (intermittent or continuous)
3. Prolonged fever (intermittent or continuous)

Minor Signs

1. Repeated common infections (e.g. pneumonitis, ottitis, phayngitis)
2. Generalised lymphadenopathy
3. Oropharyngeal candidiasis
4. Persistent cough for more than one month
5. Disseminated maculo-papular dematitis

SYMPTOMATIC HIV INFECTION

Various systemic manifestations in patients with HIV include weight loss (more than 10% of body weight), fever (more than one month duration), aesthenia, diarrhoea, cough, pruritis, dysphagia, headache, dyspnoea, amenorrhoea (females). The various common manifestations in different organ systems are listed below:

Cutaneous and Oral Manifestation of AIDS

Infections:	Herpes Zoster and simplex Fungal infection (Candidiasis) Cryptococcosis Histoplasmosis Molluscum Contagiosum Folliculitis Polymyositis Hairy leukoplakia Pencillium marneffei infections
Neoplastic	Kaposi's Sarcoma Lymphoma Basal cell carcinoma
Others	Pruritic papular dermatitis Seborrhoeic dermatitis Drug eruptions Vasculitis/Gingivitis Pencillium marneffei infections

Gastrointestinal Manifestation

Persistent Diarrhoea	Crytosporidiosis Isopora Shigella Salmonella E. Histolytica Giardia, Microspora
Colitis	Cytomegalovirus Kaposi's sarcoma
Dysphagia	Oral & Oesophageal Candidiasis CMV Oesophagitis Oral hairy leukoplakia Gingivitis/Ulcer

Stage II: Early (Asymptomatic) Disease (CD4 Count>500/mm³)

This is the longest period in course of HIV disease in which patient is asymptomatic and remains apparently healthy for a few years or more. This period may be, on an average, 8-10 years in Western countries but in India it has been found to be 5-7 years. But there are still no large epidemiological studies to confirm this. The relatively symptom free period may be punctuated by various dermatological conditions like seborrhoeic dermatitis, pruritis, cellulitis, reactivation of latent Herpes Zoster infection, worsening of psoriasis. Sometimes oral hairy leukoplakia may be identified at this stage of disease. There may be symptoms and signs suggestive of polyclonal activation of immune system manifesting as idiopathic thrombocytopenic purpura (ITP), G-B Syndrome, auto-immune demyelination of peripheral nerves, polymyositis and mononeuritis multiplex. The manifestation of HIV infection during this period correlates poorly with risk of disease progression.

Another feature seen frequently is symptomless Persistent Generalised Lymphadenopathy (PGL). This is seen 3-5 years after HIV infection and usually involves one or more extra inguinal lymph nodes (cervical or axillary) with nodes being more than 1 cm in diameter, not matted and persisting for more than three months duration.

Laboratory data shows leukopenia, thrombocytopenia, polyclonal activation of immune cell and altered serum transaminase levels. Even without ARV therapy chances of patients in this stage progressing to AIDS within 2 years is less than 5%. The CD4 count continues to decline progressively and though difficult to predict, on an average there is decrease of 40-80 cells/mm³/year without ARV therapy.

David Ho, in his studies, has shown a definite benefit in sense of delay in progression when ARV therapy is started in this phase. But if antiretroviral therapy is not economincally feasible, one must always be on look out for various opportunistic infections which can be effectively cured with locally available drugs.

Stage III: Intermediate HIV infection (CD4 count 200-500/mm³)

As CD4 count falls, the complications of HIV infection begin to occur more frequently or worsen in severity. The person gets other disorders (earlier referred to as ARC) like recurrent HSV & HZV infection (shingles), mild oropharyngeal or vaginal candidiasis, oral hairy leukoplakia indicates a higher risk of progression to AIDS. Mycobacterium tuberculosis is seen commonly with a CD4 count around 250/mm³. Atypical and extrapulmonary tuberculosis (affecting lymph nodes or causing tubercular meningitis) are also common.

When left untreated, patients with intermediate HIV disease have 30-50% chance of developing an AIDS defining conditions or dying within next 18-28 months; With ARV therapy, however, the risk is reduced two to three folds.

Stage II - CD4 > 500/mm³.
C/M - Skin manifestations
Polyclonal Immune Activation - ITP GBS. Neuropathies.
PGL

Stage III - CD4 200 - 500/mm³.

Stage IV: Late Stage HIV Disease (CD4 count 50-200/mm^3)

According to revised CDC definition of AIDS, all patients in this group are now defined as having AIDS. The most commonly noted opportunistic infections during this stage include cerebral toxoplasmosis, PCP, cryptococcal meningitis, cytomegato virus retinitis etc.

Combination ARV therapy does halt the rapid progress to some extent and aggressive nutritional counselling is warranted to maintain immune system function as well as delay development of AIDS wasting syndrome.

Stage V: Advanced HIV Disease (CD4 count <50/mm^3)

Even with therapy, the patients with advanced HIV disease have a likelihood of dying within a 2 year period due to any of opportunistic infections.

As the CD4+ count gets depleted further, the spectrum of infections widens and frequent relapses are seen despite treatment and secondary prophylaxis.

The common infections seen in this stage are those with M. Avium Complex (MAC), systemic histoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, CMV retinitis, CMV colitis and CMV encephalitis.

Many patients with CD4 count < 50/mm^3 present with direct neurological effects of HIV known as AIDS Dementia Complex (ADC). It is a subcortical dementing process which causes motor abnormalities, cognitive impairment and behavioural changes. The incidence of ADC is decreasing over years with use of ARV therapy. Many patients in this stage develop significant weight loss, wasting of muscles, various types of malabsorptions, various features of addison's disease etc. (HIV wasting syndrome).

Clinical Case Definition of AIDS in India

For persons (above 12 years of age)

A. Two positive tests for HIV infection by ERS test); and

B. Any of the following:

1. (a) Significant weight loss (10 per cent or more of body weight) within last one month) and/or cachexia (not known to be due to condition other than HIV infection) and

   (b) chronic diarrhoea (intermittent or continuous) or

   (c) prolonged fever (intermittent or continuous)

Perianal Discomfort	Herpes viral proctitis Herpes viral Ulceration

Respiratory Manifestations of AIDS

Persistent cough, dyspnoea, cyanosis, tachypnoea, fever haemoptysis, pleural effusions	Mycobacterium tuberculosis Bacterial Pneumonia Streptococcus, H. Influenzae atypical mycobacterium Cytomegalo virus Pneumocystitis carinii Legionella, candida Histoplasma Lymphoid interstitial pneumonitis Herpes simplex virus Kaposi's sarcoma

Neurological Manifestations of AIDS

Headache, lethargy	HIV Encephalopathy
Dementia, ataxia, altered personality, convulsions, incontinence	Cryptococcal meningitis Lymphoma Herpesvirus AIDS dementia complex
Meningism	Cryptococcal meningitis Tubercular meningitis Bacterial meningitis
Visual impairment Eye changes)	CMV retinitis Toxoplasmosis Keratoconjuctivitis Microsporidia
Focal seizures, hemiplegia & other focal Neurological deficits	Abscess due to toxoplasma, cryptococcus, mycobacteria, Lymphoma
Peripheral neuropathy	HIV vasculitis Lymphoma

Various haematological, renal, cardiac, endocranial, reproductive and other manifestations have also been reported and must be kept in mind.

INITIAL ASSESSMENT

Patients with HIV may present during the seroconversion phase or at any time later, perhaps not until they get an AIDS defining illness (or a major opportunistic infection). A thorough evaluation of patient is called for with a number of investigations and this may take more than one visit. Each visit of the patient must be utilised adequately for his counselling on various issues right from testing, antiretroviral therapy, various opportunistic infections, long term complications morbidity, psychological support, legal and ethical issues including his rights.

HISTORY

Psychological

Evaluate the patient for anxiety, depression, reduced self esteem, denial. Seek carefully details of his behaviour that put him at risk, including promiscuity, drug or alcohol dependence, I/V drug abuse. Assess him for his ability to adjust to the diagnosis and level of cooperation in medical management.

Social

Assess his relationships and supports, and understanding level of family members. Develop trust with patient and have him faith in you with regard to confidentially. Never rebuke him for his earlier high risk behaviour.

Risk Factors and Likely Contacts

Other Medical Conditions: (e.g. Herpes, STD, liver disorder, bronchiectasis) and medications (e.g. steroids) that may lead to complications.

Physical Examination

Weight	Skin
Oral cavity	Lymphadenopathy
Eyes	Systemic examination

Check for STDs etc.

Investigations

HIV: Atleast 2 different Antigen based ELISA tests (Western blot no longer required as a must in our country)

Immune functions: CD4+, CD8+ Cell counts, CD4/CD8 ratio

Plasma viral loads (where-ever possible)

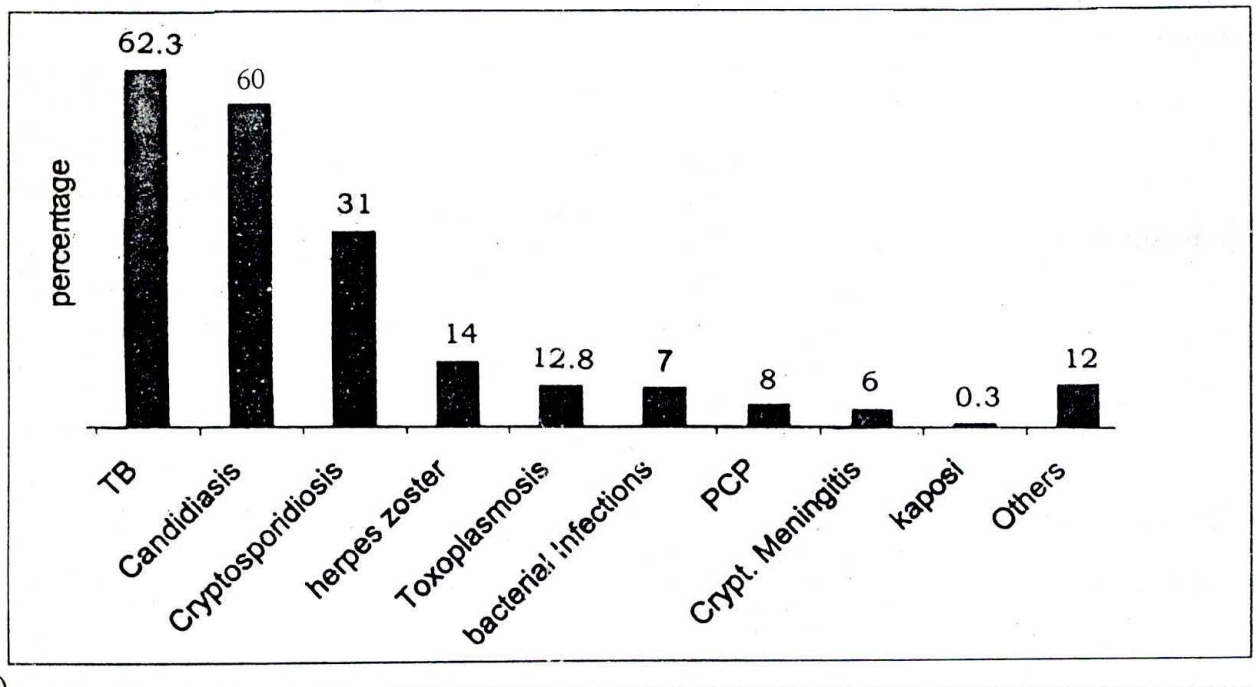
Full blood counts, Liver & renal functions tests
Mantoux test
X-ray chest

Co-infections: tests for syphilis, gonorrhoea, hepatitis A, B & C, Toxoplasma, E-B virus, papsmear for women.

SPECTRUM OF OPPORTUNISTIC INFECTIONS IN INDIA

Analysis of AIDS cases reported by various States to NACO, the spectrum of various opportunistic infections (OIs) is shown below:

OIs	Percentage
Tuberculosis	62.3
Candidiasis	60.0
Cryptosporidiasis	31.0
Herpes zoster	14.0
Toxoplasmosis	12.8
Bacterial pneumonia	7.0
Cryptococcal meningitis	6.0
PCP	8.0
Kaposi's sarcoma	0.3
Others	12.0



CHAPTER 14

Post Exposure Prophylaxis Guidelines

Introduction

Health Care Workers (HCW) are normally at a very low risk of acquiring HIV infection during management of the infected patient. However, inspite of a low statistical risk of acquisition of HIV, the absence of a vaccine or effective-curative treatment, makes the health care worker apprehensive. So, it is very necessary to have a comprehensive programme in place to deal with anticipated accidental exposure.

Most exposures do not result in infection. The risk of infection varies with type of exposure and other factors such as:

- The amount of blood/body fluid involved in the exposure
- The amount of virus in patient's blood/other body fluids at the time of exposure
- Whether post exposure prophylaxis (PEP) was taken within the recommended time.

Prevention is the mainstay of strategy to avoid occupational exposure to blood/body fluids. All the biosafety precautions emphasized in Universal Work Precautions must be practiced at all times for all patients, blood and body fluids while providing medical services.

Definition of an Occupational Exposure

An occupational exposure that may place a worker at risk of HIV infection is a percutaneous injury, contact of mucous membrane or contact of skin (when the skin is chapped, abraded or afflicted with dermatitis or the contact is prolonged or involving an extensive area) with blood, tissue or other body fluids to which universal precautions apply.

Steps to be taken on exposure to HIV infected blood/body fluids and contaminated sharps etc.

Immediately following an exposure:

- Needle sticks and cuts should be washed with soap and water;
- Splashes to the nose, mouth or skin, should be flushed with water;

- Eyes should be irrigated with clean water; saline, or sterile irrigants;
- Pricked finger should not be put into mouth, reflexly.

No scientific evidence exists as to the fact that the use of antiseptics for wound care or squeezing the wound will reduce the risk of transmission of HIV, However, this must always be done. The use of a caustic agent such as bleach is not recommended.

Report the exposure to the appropriate authority such as Infection Control Officer and condition must be treated as an emergency. Prompt reporting is eesentional because in same cases, HIV postexposure prophylaxis (PEP) may be recommended and it should be standard as soon as possible, preferably within two hours.

Based on animal models, the success of PEP therapy is reported to be maximal when started within matter of hours after the exposure. Althogh, any cutoff time i arbitrary initiating treatment more than 72 hours after the exposure is not recommeded. Although perhaps not as effective as prophylaxis, late PEP (after 72 hours) may still be useful as early treatment of HIV infection, in case infection has occurred.

Types of Occupational Exposure to HIV for which PEP is recommended

Most occuptional exposures do not lead to HIV infection. The change of possible serous side effects (toxicity) of the drugs used to prevent infection may be much greater then the chance of HIV infection from some kind of exposures. Both risk of infection and possible side effects of drugs should be carefully considered when deciding whether to take postexposure prophylaxis. Exposures with a lower infection risk may not be worth the risk of the side effects associated with these drugs. The decision to start PEP is made on the following basis:

1. Degree of exposure to HIV (determined by the Exposure Code – figure 1);
2. HIV status of the source from whom esposure/infection has occurred (figure 2);
3. PEP recommendations (figure 3).

Fig. 1: Determination of the Exposure Code (EC)

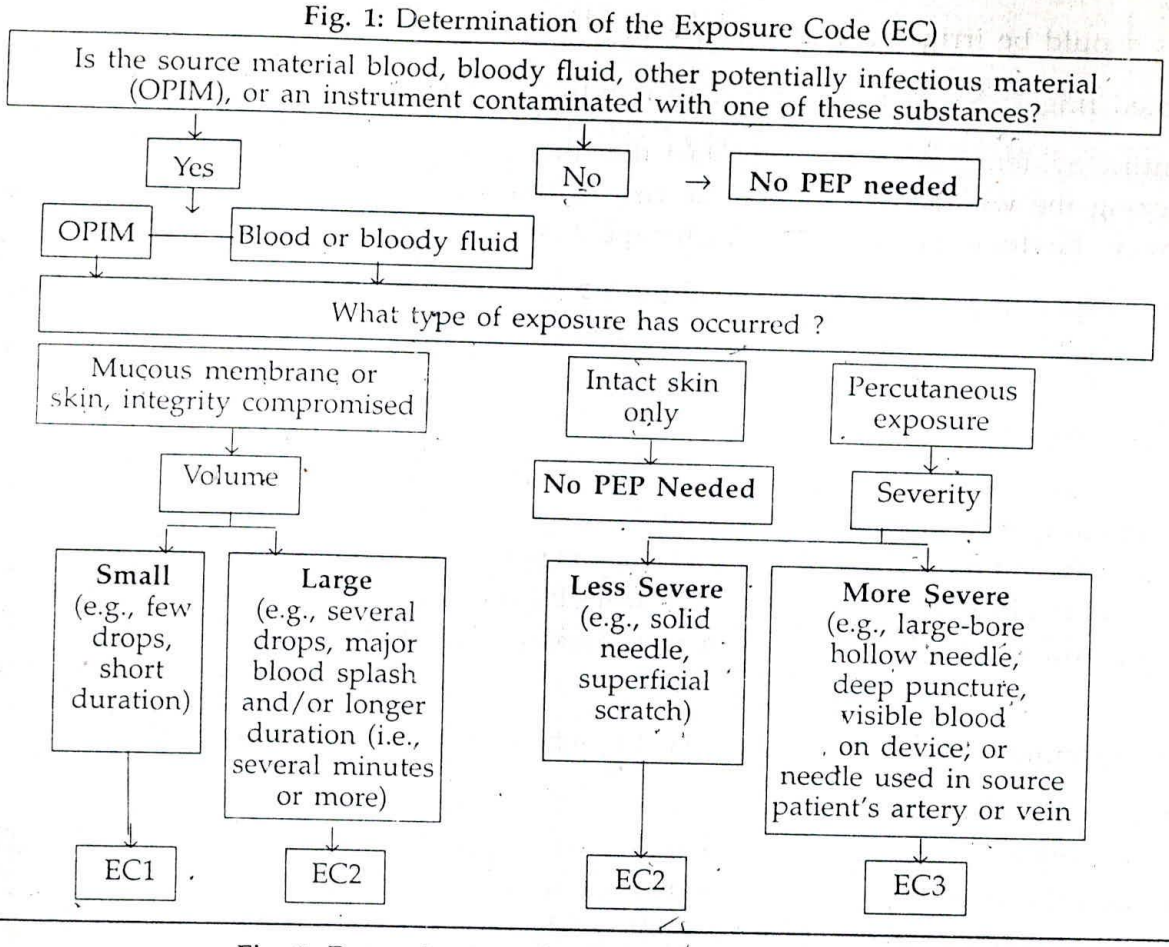


Fig. 2: Determination of the HIV Status Code (HIV SC)

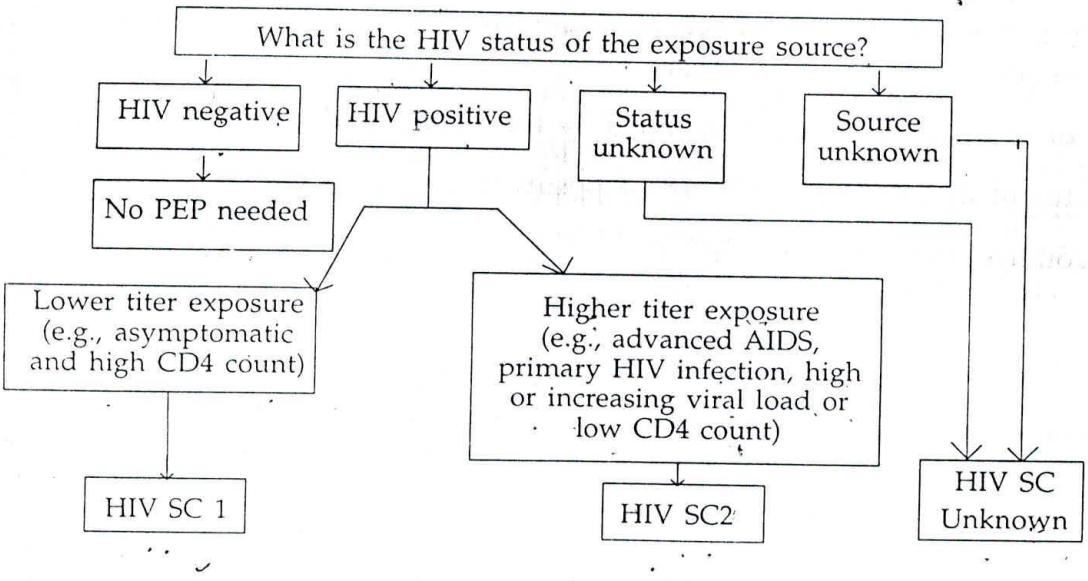


Fig. 3. Determine the PEP recommendation

EC	HIV SC	PEP recommendation
1	1	PEP may not be warranted. Exposure type does not pose a known risk for HIV transmission. Whether the risk for drug toxicity outweighs the benefit of PEP should be decided by the exposed HCW and treating clinician.
1	2	Consider basic regimen. Exposure type poses a negligible risk for HIV transmission. A high HIV titre in the source may justify consideration of PEP should be decided by the exposed HCW and treating clinician.
2	1	Recommend basic regimen. Most HIV exposures are in this category; no increased risk for HIV transmission has been observed but use of PEP is appropriate.
2	2	Recommend expanded regimen. Exposure type represents an increased HIV transmission risk.
2/3	UNKNOWN	If the source, (in the case of an unknown source), the setting where the exposure occurred suggests a possible risk for HIV exposure and the EC is 2 or 3, consider PEP basic regimen.

Pre and Post test counselling and testing

The person should be provided with pre test counselling and AZT be started as discussed above. Before starting AZT, 33-5 ml. of person's reference blood sample is taken and tested for anti-HIV antibodies immediately after the exposure. In case the sample tests are positive as per the strategy on the HIV testing the individual is referred to the clinician for management, as a case of HIV infection. In case the sample tests are non-reactive, a 2nd sample is collected at 6 weeks and 3rd at 12 weeks after the exposure and tested for HIV antibodies. The facilities for RT-PCR are available presently at NARI, Pune and AIIMS, New Delhi and this can give us results even at 2nd week after exposure. Post-test counselling is done in all cases.

During the follow-up period, especially the first 6-12 weeks when most infected persons are expected to show signs of infection, the recommendations for preventing transmission of HIV are to be followed by the HCW. This includes refraining from blood, semen and organ donation and abstaining from sexual intercourse it is undertaken, a latex condom must be used correctly and consistently. This reduces the risk of HIV transmission. In addition, women should not breast-feed their infants during the follow-up period after exposure to prevent exposing their infants to HIV in breast milk.

Drugs recommended for postexposure prophylaxis/treatment

It is recommened that in India zidovudine (ZDV – 300 mg BD) and lamivudine (3TC – 150 mg BD) be used as basic regimen. Both these drugs should be cosidered for treatment of all exposuers involving HIV infected blood, fluid containing visible blood, or other potentially infectious fluids or tissue. Used in combination, ZDV and 3TC are very effective in treating HIV infection after exposure and considerable information shows, that they are safe when used for a short time.

In selected cases (HIV Status Code 2 and Exposure Code 2 and 3), and ZDV – 800 mg TDS indinavir (or one of the other protease inhibitors) is also being used as per PEP guideline (in advanced regimen).

Duration for which drugs need to be taken

The optimal course of treatment is unknown if tolerated, treatment should be taken for 4 weeks.

Pregnancy and PEP

Based on limited information, ZDV taken during 2nd and 3rd trimesters of pregnancy has not caused serious side effects in mothers or infants. There is very little information of the safety of ZDV when taken during the 1st trimester or on the safety of other antriviral, drugs taken during pregnancy. If the HCW is pregnant at the time of occupational exposure to HIV, the designated authority/physician must be consulted about the use of antiviral drugs for PEP.

Facts known about the safety and side effects of these drugs

Most of the information known about the safety and side effects of these drugs is based on studies of their uses in HIV-infected individuals. For these individuals, ZDV and 3TC have usually been tolerated well except for nausea, vomiting, diarrhoea, tiredness or headache for people taking ZDV.

Steps to be undertaken by the Infection Control Officer on receiving information about occupational exposure

- All the needle stick injuries should be reported to the State AIDS Control Society giving the exposure code and the HIV status.
- The State AIDS Control Socities should in turn inform NACO about the cases periodically.

- A registry is planned to be opened in NACO soon, for follow-up of all such cases.
- NACO has decided in principle to supply antiretroviral drugs to all cases for PEP in Govt. Hospital setting for HCW.
- Infection Control Officers in all hospitals have been directed to ensure that entireretroviral drugs for PEP are available in casualty at all the time.

CHAPTER 18

Management of Opportunistic Infections in AIDS

Acquired Immunodeficiency Syndrome (AIDS) has been defined as the occurrence of life threatening opportunistic infections, malignancies, neurological diseases and other specific illnesses in patients with human immunodeficiency virus (HIV) infection and/or with CD4 count less than 200/cmm.

The timing and development of opportunistic infections in people with HIV are product of the immune defect of the host and the microbial environment within which we all live. Although virtually all aspects of the immune system are altered by HIV, defects in cellular immunity are prominent (involving T-cells and macrophages).

In the west there has been significant decline in the opportunistic infections because of highly active antiretroviral therapy (HAART).

However, opportunistic infections still significantly contribute to morbidity and mortality in HIV disease.

Till the time highly active antiretroviral therapy (HAART) becomes more widely available to the developing countries, managing opportunistic infections would constitute the mainstay of managing HIV disease.

Opportunistic infections in these patients are as a rule disseminated, recurrent and persistent and are seen to be influenced by economy and race e.g. PCP, MAC, Cryptococcus, cytomegalovirus and toxoplasma gondii are common in developing countries like Africa, Asia and Southeast Asia.

HIV AND RESPIRATORY DISEASES

Upto 2/3rd of people with HIV will have a respiratory illness associated with their infection. Many of these illnesses are treatable and preventable.

Table 1. Pulmonary diseases in HIV infection

Condition	CD 4 cell count/mm^3
Infection	
Mycobacterium tuberculosis	< 400
Bacterial pneumonia	< 350
Suppurative lung and sinus disease	< 100
Pneumocystis carini pneumonia	< 200
Mycobacterium avium complex	< 100
Cytomegalovirus	< 100

MYCOBACTERIUM INFECTIONS

Tuberculosis is the most common opportunistic infection in AIDS cases in our country and can present at any stage of HIV infection. In immunosuppressed, tubercular infection can be rapid taking months rather than years.

HIV infection represents the greatest risk factor for the development of active tuberculosis. Instead of a lifetime risk of developing TB of 10%, those with HIV infection have a risk of 8% to 10% per year.

Extrapulmonary tuberculosis is much more common in HIV and can present as

- lymphadenitis
- miliary disease
- CNS TB
- bonemarrow TB
- genitourinary tract TB

DIAGNOSIS

- clinical history in form of low grade fever, weight loss, anorecia, fatigue
- X-ray chest may show:
  - hilar adenopathy
  - pleural effusion
  - upper zone infiltrates
  - cavitation or miliary pattern
- sputum for AFB (positive in 80% of patients)

  (3 samples should be tested)

TB lymphadenopathy FNAC - AFB positive in 65%

Treatment standard regimen to be followed.

- 4 drug regime for 2 months – INH
  Rifampicin
  PZA
  Ethambutol or streptomycin

  Followed by 2 drugs for 4 months – INH
  Rifampicin

Do not give thiacetazone to HIV-positive patients (increased risk of severe and sometimes fatal skin reaction).

Regimens which are adequate for treatment of pulmonary tuberculosis are generally effective in treating extra-pulmonary tuberculosis also.

Around 6 to 9 months of treatment appears to be sufficient to many sites of extra-pulmonary disease, a longer duration of therapy (12 months) is recommended for some sites including:

- miliary TB
- bone or joint disease
- tubercular meningitis

Persistently positive sputum culture after 2-3 months of therapy suggests the possibility of drug resistant tuberculosis or non-compliance with therapy.

PNEUMOCYSTIS CARINII PNEUMONIA (PCP)

PCP occurs in advanced HIV disease, when CD4 count falls below 250 cells/cmm.

It has an indolent onset with fever, non-productive cough and progressive dyspnoea.

Physical signs such as crackles and radiological changes such as bilateral pulmonary infiltrates tend to be late manifestations.

Table 2. Manifestations of pneumocystis carinii pneumonia

	Mild	Moderate	Severe
Symptoms	Cough, sweats exertional dyspnoea	Dyspnoea on minimal exertion, fever sweats, cough	Dyspnoea at rest, tachypnoea, persistent fever
Blood gas analysis	PaO_2 normal	PaO_2 60-80 mmHg SaO_2 falls on exertion	PaO_2< 60 mmHg
Chest x-ray	Normal or minor perihilar markings	Diffuse bilateral interstitial shadowing	Extensive bilateral interstitial and alveolar markings

PaO_2 = Partial pressure of arterial oxygen and SaO_2 = arterial oxygen saturation.

DIAGNOSIS

Diagnosis is often made on clinical grounds but should be confirmed by sputum examination. However, treatment should not be withheld for want of confirmed diagnosis.

DEFINITIVE DIAGNOSIS

a) Sputum Induction with hypertonic saline (50-80% sensitive).

b) Broncho-alveolar lavage (BAL) (86-97% sensitive).

c) Broncho-alveolar lavage + transbronchial biopsy (99% sensitive).

Clinical worsening during the first 3-5 days of starting treatment is common, but generally there is improvement by 7-10 days, so avoid early change in treatment.

Trimethoprim 15-20 mg/kg daily + sulfamethoxazole 75-100 mg/kg/day in divided doses.

(Co-trimoxazole – Double strength tablets, 2 x TDS)

If allergic to sulfamethoxazole, alternative regimens are

IV pentamidine 4 mg/kg/day

Dapsone 100 mg daily + trimethoprim 300 mg daily

Start steroids within 48-72 hours of specific treatment. Prednisolone 40 mg twice daily for days and then reduce gradually. This helps in reducing alveolar oedema and improving oxygen perfusion across alveoli.

PRIMARY PROPHYLAXIS IS RECOMMENDED

1. When CD+4 count less than 200 cells/cmm.
2. In patients with higher CD 4 count and persistent fever with.
   a) Oral candidiasis.
   b) Along with other AIDS defining conditions.

SECONDARY PROPHYLAXIS

All patients after an episode of PCP.

Oral trimethoprim-sulfamethoxazole 1 double strength tablet (160/800 mg) daily

Alternative

Pentamidine 300 mg IV or Inhaled monthly.

BACTERIAL INFECTIONS

Pyogenic bacterial infections occur more frequently in HIV infected patients than in general population.

Common infecting organisms are similar and include

- Streptococcus pneumoniae
- Haemophilus influenzae
- Staphylococcus aureus

Bacterial chest infections tends to have a very different clinical course as compated to PCP, with an abrupt onset of fever, productive cough, purulent sputum, dyspnoea and typical signs of consolidation signs and X-ray findings.

TREATMENT WITH STANDARD AGENTS IS EFFECTIVE AND INCLUDES

- Penicillin
- Ampicillin
- Erythromycin
- Cefotaxime
- Adequate oxygenation and chest physiotherapy

DIARRHOEAL DISEASES

Diarrhoea is the most common gastrointestinal symptom in HIV infection affecting 90% of patients and becoming more frequent as immune deficiency progresses.

Diarrhoea and weight loss are independent predictors of mortality.

Gastrointestinal infections are predominant cause of diarrhoea.

Table 3. Common pathogens in HIV related diarrhoea

	Small bowel (duodenum/jejunum)	Large bowel (colon/terminal ileum)
Bacteria	Mycobacterium avium complex Salmonella species	Campylobacter species Yersinia species Aeromonas species Clostridium difficile
Protozoa	Cryptosporidium species Microsporidia Cyclospora species Giardia lamblia	Entamoeba histolytica Cytomegalovirus
Viruses	Rotavirus Astrovirus Caliicivirus Picornavirus HIV	Adenovirus Herpesvirus

MANAGEMENT OF DIARRHOEA

Management has three basic aims

1. Detection of treatable cause.
2. Relief of symptoms.
3. Prevention of malnutrition

Table 5. Principles of managing HIV related gut infection

* Remember pathogens may be involved concurrently
* Dissemination from the gut can occur in some bacterial infections (MAC, Salmonella, Shigella, Campylobacter)
* Relapse following successful treatment is frequent (CMV Salmonella, Shigella, Campylobacter, MAC, cryptosporidia, microsporidia, Cyclospora)
* Progressive weight loss and reduced performance status are frequent if there is no resolution of diarrhoea pathogen is not identified. The symptomatic therapy is indicated.

Table 4. Managing HIV related diarrhoea

1. Take history :
   * Nutritional status, medication, previous opportunistic infections
   * Diarrhoeal symptoms: Small bowel disease (enteritis) usually causes watery, large volume diarrhoea associated with bloating and often profound weight loss. Large bowel disease (colitis) usually causes cramping lower abdominal pain, urgent, frequent small volume stool which often contains blood, mucus and pus, and the presence of fever. In many clinical situations, the distinction is not possible and indeed , some pathogens cause significant disease throughout the gut (panenteritis).
2. Withdraw drugs associated with diarrhoea
3. Examine faecal specimen:
   * Microscopy: blood/pus cells; parasites (special stains for microsporidia if initial specimen is not diagnostic)
   * Culture: Salmonella/Shigella/Campylobacter/Yersinia
   * Toxin assay: Clostridium difficile
4. Blood cultures (2):
   * Standard broth and, if CD 4 cell count < 100 µL, mycobacterium-supporting media
5. Manage according to the findings:

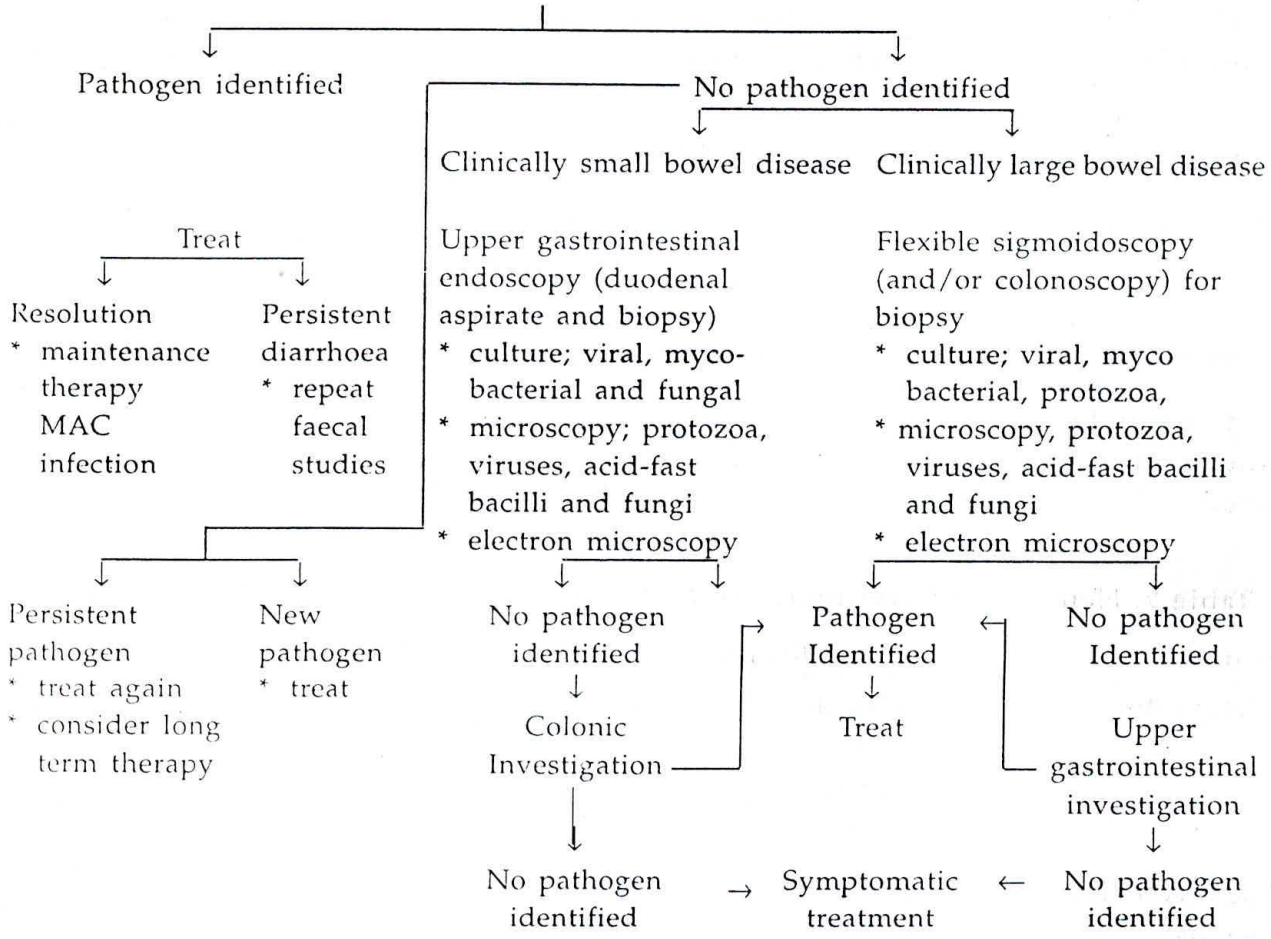


Table 6. Specific treatment for diarrhoea

CMV colitis: Ganciclovir 5 mg/kg intravenously every 12 hours for 14 days, or, if unresponsive or intolerant foscarnet 90 mg/kg per day intravenously for 14 days

Salmonella Shingella enterocolitis: (May cause bacteraemia or focal extraintestinal infection). Ciprofloxacin 500 mg orally every 12 hours for 14 days

Campylobacter colitis: (May cause bacteraemia). Erythromycin 500 mg orally every 6 hours

Cryptosporidiosis: Paromomycin 500 mg orally every 8 hours for two weeks. No proven effective therapy; other possible treatment includes azithromycin and leetrazuril. The response rate is poor with all available therapies.

Microsporidiosis: Albendazole 400 mg orally every 12 hours for 14 days. No proven effective therapy; the response rate is poor and relapse is common.

Isospora belli infection: Trimethoprim-sulfamethoxazole 160/800 mg orally every 6 hours for 10 days, then twice daily for 21 days. Relapse is common.

CHRONIC DIARRHOEA LEADS TO MALNUTRITION

Adequate nutritional supplements and specific vitamins and minerals replacement is essential.

HIV AND OPPORTUNISTIC NEUROLOGICAL INFECTIONS

Opportunistic infection of the central nervous system particularly toxoplasmosis and cryptococcosis are common. There are usually complications of advanced immunodeficiency when CD count has fallen below 150/cmm or even lower.

Table 7. Neurological syndromes and opportunistic infections in AIDS

Syndrome	Clinical features	Aetiology
Meningitis	Headache Fever Nausea/vomiting Altered consciousness	Cryptococcosis Syphilis Listeria Tuberculosis
Focal cerebral lesions	Headache Focal signs	Toxoplasmosis Progressive multifocal-

	Convulsions	leukoencephalopathy Syphilis Cytomegalovirus
Encephalitis	Cognitive impairment Psychiatric features Altered consciousness	Cytomegalovirus Herpes simplex Toxoplasmosis
Myelitis	Sensory Paraparesis Sphincter disturbance	Cytomegalovirus Herpes simplex Varicella zoster Syphilis Toxoplasmosis

CRYPTOCOCCAL MENINGITIS

Cryptococcosis is the most common cause of meningitis in AIDS affecting around 10% patients.

Common presentation includes

- headache
- fever
- nausea and vomiting
- confusion and impaired consciousness, but
- signs of meningism are seen in less than 40% of patients, so diagnosis is missed quite often.

DIAGNOSIS

Cryptococcal meningitis is confirmed by CSF examination

- positive India ink staining
- CSF cryptococcal antigen titre will provide rapid diagnosis
- Increase CSF white cell count
- decreased CSF glucose

Table 8. Treatment of cryptococcosis

Primary therapy

Severe case (*i.e. altered consciousness, CSF white blood cell count > 20/ml, CSF antigen titre > 1:1024 and a positive blood culture)*

Amphotericin β 0.7 mg/kg daily by intravenous injection
± 5-flucytosine 100 mg/kg daily by mouth or intravenously for 2 weeks, followed by fluconozole for 10 weeks

Mild case

Fluconazole 800 mg loading dose by mouth, then 400 mg daily by mouth
± 5-flucytosine 100 mg/kg daily by mouth

Most patients respond clinically within 1-2 weeks, with an early mortality of 5%-10%. Continue therapy for four to six weeks or until the CSF is sterile. Without maintenance therapy, relapses will occur in 50%-60% of patients within six months. With maintenance therapy, relapses are uncommon and usually related to non-compliance with treatment, but may also occur because of development of drug resistance and drug interactions which lower fluconazole levels. Monitoring serum cryptococcal antigen titres is not useful in predicting relapse

Maintenance therapy (Life long)
Fluconazole 200-400 mg daily by mouth

TOXOPLASMOSIS

Commonest cause of focal cerebral lesions in HIV/AIDS is toxoplasmic encephalitis and in most cases, it is almost always due to reactivation of past infection.

It usually manifests with subacute development of focal neurological deficit but may present with seizures, intracranial haemorrhage, disorientation, altered mental state and coma, CT brain scan shows multiple bilateral ring enhancing cerebral lesions.

Table 9. Treatment of toxoplasmosis.

Primary therapy

Sulfadiazine 100 mg/kg per day, in 4 divided doses up to 8 g daily by mouth or intravenously

+ Pyrimethamine 200 mg loading dose, then 75 mg daily by mouth

+ Folinic acid 7.5 mg daily by mouth

Or

Clindamycin 600 mg 4 times a day by mouth or intravenous injection

+ Pyrimethamine and folinic acid

Maintenance therapy (Life long)

Sulfadiazine 500 mg 4 times a day by mouth

+ Pyrimethamine 25 mg daily by mouth

+ Folinic acid 7.5 mg daily by mouth

Or

Clindamycin 600 mg 4 times a day by mouth

+ Pyrimethamine and folinic acid

The dose of clindamycin is not reduced during the maintenance phase as lower doses are less effective.

COMMON OPPURTUNISTIC INFECTIONS-DR.RAO

(CHEST &MATERNITY CENTER.

Candidacies is an opportunistic endogenous infection caused by yeast like fungus Candida albicans and other Candida species

nSeen in CD4<250,Commonest OI in immuno-compromised.
nWhite painless plaques seen on the buccal, pharyngeal mucosa and tongue surface. (Pseudomembranous form)
nSome times can present as smooth red patches on the hard or soft palate, buccal mucosa and dorsal surface of the tongue (Erythematous form)
nOesophagitis can present as heartburn, odynophagia- dysphagia.
nVaginitis can present as foulsmelling discharge, pruritus, and Erythema of interoitus.

DIAGNOSIS
KOH smear shows yeast and chlamydiospores.
nCulture is used for antifungal sensitivity
(not for diagnosis)

TRATMENT

- Oral Candida
- Mild ones are better off with Clotrimazole oral paints, Nystatin paint.
- Flucanozole PO 100mg od/ Itraconazole 200mg /day X 10 to 14 days.
- In Severe Ressistant Cases Higher dose of flucanozole and IV Amphotorecin B.
- Oesophageal/ Tracheo Bronchial Candidiosis.
- Flucanozole 200 to 800mg/day X 14 to 21 weeks.
- Amphotericin B, Caspfungin, Voriconazole.
- 85% relapse rate with in One year, which requires maintenance Anti-fungal therapy usually Flucanozole 100-200mg/day.

- Candida Vaginitis
- Treatment is identical for women with and without HIV.
- Clotrimazole 100mg per vaginal tablets X7 – 14 days.
- Miconozole vaginal suppositories 100g/day X 7days.
- Flucanozole150mg od single dose / Itraconazole 200g od X 3 days.

HERPES SIMPLEX (DNA VIRUS)

- Oral (HSV 1), Perirectal and Genital (HSV 2)
- Presents with multiple, recurrent vesicles, some times non healing ulcers.

▪Dx- Characteristic Mucocutaneous lesions, Swab for tzank smear, PCR.▪In immunocompromised it's recurrant.

TREATMENT

▪Acyclovir 400mg PO tid X 7-10 days.
▪Valcyclovir 1g bid X 7- 10 days.
▪Severe Mucocutaneous lesions, Disseminated infection – Acyclovir IV 5- 10mg/kg q 8th hrly till the lesions or symptoms subside.
▪Herpes encephalitis- Acyclovir 10mg/kg q8th hrly X 14 to 21 days.
▪For recurrant cases needs Chronic Acyclovir 400mg bid , Valacyclovir 500mg /day.

HERP[ES ZOSTER

▪Its reactivation of latent varicella virus infection.
▪Usually presents as multiple, grouped vesicles along the dermatomal distribution.
▪In immunocompromised patients Herpes Zoaster is Recurrant, Multidermatomal, and more severe.
▪Dx- Characterstic Dermatoal distribution of the vesicles. Tzank smear and PCR are suportive.

TREATMENT

▪Val acyclovir 1g tid X 7-14 days.
▪Acyclovir 800mg 5 times/ day X 7-14 days.
▪In Severe Cases Acyclovir IV 30mg/kg/day X 7 days.
▪Supportive care.
▪Antibiotics for Sec. infections if any.
▪Analgesics for Neuralgia.
▪Antihistamines for pruritus.
▪Gabapentin /Carbamazepine /Tricyclics for severe post herpetic neuralgia.

CRYPTOCOCOSIS

▪Its subacute/Chronic systemic infection caused by yeast-Cryptococcus neoformans.

- It can present as Meningitis / Meningoencephalitis / Cutaneous Cryptococcosis / Pneumonia and Disseminated Cryptococcosis.
- Commonest and most fatal of all these is cryptococcal meningitis and meningo-encephalitis , usually seen in patients with CD4 < 100.
- Cutaneous Cryptococcosis can present as flesh coloured, umbellicated, papules ressembling Molluscum contagiosum.

Cryptococcal meningitis

- Presents as subacute fever, headache and altered sensorium.
- LP is diagnostic- CSF showing pleocytosis, low glucose, high protein, Indian ink smear showing budding yeast, CSF Cryptococcal Ag +ve, confirmed by CSF fungal culture.
- Sometimes Cryptococcoma seen in CT/MRI Brain.
- Elevated CSF opening pressure, WBC < 20, Positive Indian Ink Smear, Cryptococci isolated from extra neural sites.

Cryptococcal Meningitis Treatment

- Amphotericin B at 0.7mg/kg/day +5FC PO 100mg/kg/day x 14days followed by Flucanozole 400mg/day x 8 weeks followed by maintenance therapy of flucanozole 200mg/day.
- Mild cases Flucanozole 800mg od followed by 400mg/day x 10 weeks followed by chronic therapy with flucanozole 200mg od.
- Repeated LP to control elevated ICT. Anti-Oedema initially may be helpful. Steroids are containdicated.
- Regular monitering of renal functions. Hydration.
- Ambisome 4mg/kg/day IV X 14 days (lipid amphotericin reduces the side effects of Amphotericin B.

Pneumocystis Pneumonia

- Caused by **Pneuocystis Jerovicii**, a fungus, Usually seen in patients with CD4 < 150
- Sub acute course, presents with low grade fever, progressive cough and dyspnoea.
- Dx - CLINICAL SUSPECION Confirmation by Induced sputum smear either giemsa stain or immunofloroscence. CXR can be normal, sometimes prominent interstitial shadows – nodular. CXR rarely can show consolidation or perihilar cysts or pneumothorax. Desaturation after exercise. Increased LDH.
- Rx. TMP/SMX at 15mg/kg of TMP tid IV or PO (ie 2 DS TMP/SMX tid). With good hydration.
- Severe Cases my require Steroids, Oxygen, and sometmes Invasive or non invasive ventillation.

Toxoplasmosis

▪Toxoplasma gondii is an obligate intra cellular protozoan parasite which causes latent infection of brain, skeletal muscle and heart. Reactivation infection can be seen with CD4 < 100.

▪Encephalitis is the commonest and fatal manifestation of the Toxoplasmosis.

▪Presents with subacute onset of focal neurological abnormalities with headache, altered mental status, and fever.

Toxoplasmosis

▪Diagnosis :

▪CT/MRI showing multiple ring enhancing lesions in the basal ganglia and hemispheric conticomedullary junction.

▪Positive Anti Toxoplasma IgG Ab.

▪D/D : Cryptococcoma, Tuberculoma, CNS lymphoma, Neurocysticercosis, Brain abscess.

Toxoplasmosis

▪Pyrimethamine 200mg loading dose , then 50 to 75mg/day + 10 -15mg Folinic acid /day + SD 1 to 1.5gPO q 6th hrly X > 6 weeks.

▪Pyrimethamine + Leucovorin + Clindamycin 600mg PO/IV 6th hrly for 6 weeks.

▪Azithromycin, TMP/SMX, Atovaquone also have anti toxo properties.

▪Maintenance with Pyrimethamine 25-50mg/day + SD 500-750mg q 6th hrly (50% of acute dose.)

▪Primary prophylaxis with TMP/SMX DS .

Cytomegalovirus (CMV-DNA Virus)

▪Occular manifestations are commonly presented manifestations of CMV. Extra Occular manifestations may be CMV colitis, CMV oesophagitis, CMV encephalitis, CMV Dementia, CMV polyradiculomyelopathy, CMV Pneumonitis.

CMV Retinitis

▪May be asymtpmatic or can have floaters, field defects, scotomata or decreased acquity. Seen in patients with CD4 < 50.

▪Fundus showing Cottage cheese and ketchup (peri vascular yellow white retinal infiltrates±Intra retinal haemorrhages) Retinal thinning and sometimes detachment.
▪Diagnosis is by fundoscopy. Vitreous PCR CMV may be rarely considered.

CMV Retinits Treatment ▪Intra-Ocular Gancyclovir every 6-8 months + Valgancyclovir 900mg Po bd X 14 – 21 days
▪Gancyclovir 5mg/kg IV q 12th hrly x 14–21 days then valgancyclovir Po 900mg qd.
▪Forcarnet, Cidofovir, Intraoccular Fomivirensen are alternate treatments.
▪As relapse is common, maintenance therapy with Valgancyclovir 900mg po qd

CMV Oesophagitis / Colitis▪One of the important cause of odynophagia and AIDS Cholangiopathy. Can present with Fever, diarrhoea and abdominal pain.
▪Rx
▪Valgancyclovir 900 mg PO bd with food X 3 to 4 weeks . Maintenance with Valgancyclovir PO 900mg od .

CMV

Encephalitis-Polyradiculomyelopathy-Dementia.▪Progressive leg paresis, bladder/bowel dysfunction.
▪Delerium with Cranial nerve defects, ataxia and nystagmus.
▪Dx by CSF showing increased protein and mononuclear pleocytosis. MRI showing periventricular enhancement. CSF PCR CMV is also helpful.
▪Treatment Gancyclovir 5mg/kg bid X 3 to 6 weeks + Foscaranet 90mg IV bid x 3 to 6 weeks then maintenance with Gancyclovir or Val gancyclovir

CMV Pneumonitis▪Fever, cough , dyspnoea and interstitial infiltrates.
▪DX by pulmonary infiltrates, Characteristic inclusions in lung tissue.

▪Treatment by Gamcyclovir 5mg / kg bid X 21 days or Valgancyclovir 900mg PO bid X 21 days.

Mycobacterium avium Complex (MAC)

▪Disseminated disease seen in CD4 < 50.

▪Presents with Fever, night sweats, weight loss, diarrhoea and abdominal pain.

▪Diagnosis by culture of MAC from non pulmonary site.

▪RX: Clarithromycin 500mg bid PO + ethambutal 15mg/kg/day PO + Rifabutin 300mg/day or Levofloxacin 500mg qd till immune reconstitution after early HAART.

Diarrhoea

▪Causes of chronic Diarrhoea in HIV patients.

▪**Protozoa** (70%)

▪Isosporabelli, Giardia lamblia, Cryptosporidia, Microsora, Cyclospora, E. Histolytica, Blastomycosis.

▪▪**Bacteria** (23%)

▪Shigella, Salmonella, Aeromonas.

▪**Helimenths** (6%)

▪Strongoloids stercoralis.

Evaluation of Chronic Diarrhoea

▪Stool culture for bacteria

▪Stool specimens for parasites using saline, iodine, trichrome and acid fast preparations.

▪Consider emparic therapy if all tests are negative.

▪Gastodudenoscopic or colonoscopic inspection of tissues and biopsy.

▪Biopsy stained with H&E for protozoa, Giemsa or Methanamine silver for fungii, AFB staining for mycobacteria.

▪Duodenal/colonoscopic biopsy culture for Mycobacteria.

▪Duodenal fluid examination for parasites.

▪Biopsy specimen examined by electron microscopy.

Immune Reconstitution Inflammatory Syndrome

▪Blurring of vision following ART.

▪Crypto meningitis, TE following ART.

▪Flaring of Tb following ART.

- Rised AST/ALT in HBsAG+ve, seropositive individuals following ART.
- PUO following ART.
- HZ following ART.

Primary Prophylaxis
- TMP/SMX DS od CD4 < 200 (for prevention of PCP, TE, Diarrhoeal diseases, Skin infections)
- Azithromycin 1.2g od once a week CD4 < 50 (MAC)
- INH prophylaxis (not practicised in INDIA)

Secondary Prophylaxis
- Flucanozole 200mg PO od (following Cryptococcal meningitis).
- Valgancyclovir 900 mg PO od (following CMV infection).
- SD+Pyrimethamine (50% of treatment dose) (following Toxoplasmosis.

For any querries

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UNAIDS
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World Health Organization

UNAIDS/WHO Policy Statement on HIV Testing

The Context

As access to antiretroviral treatment is scaled up in low and middle income countries, there is a critical opportunity to simultaneously expand access to HIV prevention, which continues to be the mainstay of the response to the HIV epidemic. Without effective HIV prevention, there will be an ever increasing number of people who will require HIV treatment. Among the interventions which play a pivotal role both in treatment and in prevention, HIV testing and counselling stands out as paramount.

The current reach of HIV testing services remains poor: in low and middle income countries only 10 per cent of those who need voluntary counselling and testing, because they may have been exposed to HIV infection, have access to it. Even in settings in which voluntary counselling and testing is routinely offered, such as programmes for prevention of mother-to-child transmission, the number of people who avail themselves of these services remains low in many countries. The reality is that stigma and discrimination continue to stop people from having an HIV test.

To address this, the cornerstones of HIV testing scale-up must include improved protection from stigma and discrimination as well as assured access to integrated prevention, treatment and care services. The conditions under which people undergo HIV testing must be anchored in a human rights approach which protects their human rights and pays due respect to ethical principles. (cf Appendix 1). Young people require special attention to their needs through the provision of confidential youth friendly health services. Public health strategies and human rights promotion are mutually reinforcing.

The conditions of the **'3 Cs'**, advocated since the HIV test became available in 1985, continue to be underpinning principles for the conduct of HIV testing of individuals. Such testing of individuals must be:

- **confidential**
- be accompanied by **counselling**
- only be conducted with informed **consent**, meaning that it is both informed and voluntary.

In many low and middle income countries, the primary model for HIV testing has been the provision of **client-initiated** voluntary counselling and testing services. Increasingly, **provider-initiated** approaches in clinical settings are being promoted, i.e. health care providers routinely initiating an offer of HIV testing in a context in which the provision of, or referral to, effective prevention and treatment services is assured. To reach people in need of treatment, tens of millions of tests will have to be conducted among those who may have been exposed to HIV.

UNAIDS/WHO recommend that the following four types of HIV testing be clearly distinguished:

1) **Voluntary counselling and testing**

Client-initiated HIV testing to learn HIV status provided through voluntary counselling and testing, remains critical to the effectiveness of HIV prevention. UNAIDS/WHO promote the effective promotion of knowledge of HIV status among any population that may have been exposed to HIV through any mode of transmission. Pre-testing counselling may be provided either on an individual basis or in group settings with individual follow-up. UNAIDS/WHO encourage the use of rapid tests so that results are provided in a timely fashion and can be followed up immediately with a first post-test counselling session for both HIV-negative and HIV- positive individuals.

2) Diagnostic HIV testing is indicated whenever a person shows **signs or symptoms** that are consistent with HIV-related disease or AIDS to aid clinical diagnosis and management. This includes HIV testing for all **tuberculosis** patients as part of their routine management.

3) A routine offer of HIV testing by health care providers should be made to all patients being:

- assessed in a **sexually transmitted infection** clinic or elsewhere for a sexually transmitted infection - to facilitate tailored counselling based on knowledge of HIV status
- seen in the context of pregnancy - to facilitate an offer of **antiretroviral prevention of mother-to-child transmission**
- seen in clinical and community based health service settings where **HIV is prevalent and antiretroviral treatment is available** (injecting drug use treatment services, hospital emergencies, internal medicine hospital wards, consultations etc.) but who are **asymptomatic.**

Explicit mechanisms are necessary in provider-initiated HIV testing to promote **referral to post-test counselling services** emphasising prevention, for all those being tested, and to **medical and psychosocial support,** for those testing positive. The basic conditions of confidentiality, consent and counselling apply but the standard pre-test counselling used in VCT services is adapted to simply ensure informed consent, without a full education and counselling session. The minimum amount of information that patients require in order to be able to provide **informed consent** is the following:

- the clinical benefit and the prevention benefits of testing
- the right to refuse
- the follow-up services that will be offered and
- in the event of a positive test result, the importance of anticipating the need to inform anyone at ongoing risk who would otherwise not suspect they were being exposed to HIV infection

For provider-initiated testing, whether for purposes of diagnosis, offer of antiretroviral prevention of mother-to-child transmission or encouragement to learn HIV status, patients retain the right to refuse testing, i.e. to 'opt out' of a systematic offer of testing.[1]

[1] HIV testing without consent may be justified in the rare circumstance in which a patient is unconscious, his or her parent or guardian is absent, and knowledge of HIV status is necessary for purposes of optimal treatment.

4) Mandatory HIV screening

UNAIDS/WHO support mandatory screening for HIV and other blood borne viruses of all blood that is destined for transfusion or for manufacture of blood products. Mandatory screening of donors is required prior to all procedures involving transfer of bodily fluids or body parts, such as artificial insemination, corneal grafts and organ transplant.

UNAIDS/WHO do not support mandatory testing of individuals on public health grounds. Voluntary testing is more likely to result in behaviour change to avoid transmitting HIV to other individuals. Recognising that many countries require HIV testing for immigration purposes on a mandatory basis and that some countries conduct mandatory testing for pre-recruitment and periodic medical assessment of military personnel for the purposes of establishing fitness, UNAIDS/WHO recommend that such testing be conducted only when accompanied by counselling for both HIV-positive and HIV-negative individuals and referral to medical and psychosocial services for those who receive a positive test result.

Appendix 1 Ensuring a rights based approach

The global scaling up of the response to AIDS, particularly in relation to HIV testing as a prerequisite to expanded access to treatment, must be grounded in sound public health practice and also respect, protection, and fulfilment of human rights norms and standards.

The voluntariness of testing must remain at the heart of all HIV policies and programmes, both to comply with human rights principles and to ensure sustained public health benefits.

The following key factors, which are mutually reinforcing, should be addressed simultaneously:

1. Ensuring an *ethical process for conducting the testing,* including defining the purpose of the test and benefits to the individuals being tested; and assurances of linkages between the site where the test is conducted and relevant treatment, care and other services, in an environment that guarantees confidentiality of all medical information;

2. Addressing the *implications of a positive test result*, including non-discrimination and access to sustainable treatment and care for people who test positive
3. Reducing *HIV/AIDS-related stigma and discrimination* at all levels, notably within health care settings;
4. Ensuring a supportive *legal and policy framework* within which the response is scaled up, including safeguarding the human rights of people seeking services;
5. Ensuring that the *healthcare infrastructure* is adequate to address the above issues and that there are sufficient trained staff in the face of increased demand for testing, treatment, and related services.

UNAIDS Global Reference Group on HIV/AIDS and Human Rights

NACO Guidelines

Guidelines on HIV Testing

HIV testing carried out on a voluntary basis with appropriate pre-test and post-test counselling is considered to be a better strategy and is in line with the WHO guidelines on HIV testing. The basis and objectives of testing are to :

- monitor the trend of HIV infection in a population or subgroup for facilitation of intervention using unlinked anonymous testing.
- test blood or organs or tissue for ensuring safety of the recipients.
- identify an individual with HIV infection for diagnosing or voluntary testing purposes.

There is an active debate in the country on the issue as to whether there should be mandatory testing of people suspected of carrying HIV infection. Considerable thought has been given to this issue. Testing for HIV is more than a mere biological test for it involves ethical, human and legal dimensions. The government feels that there is no public health rationale for mandatory testing of a person for HIV/AIDS. On the other hand, such an approach could be counter productive as it may scare a large number of suspected cases from getting detected and counselled to take appropriate measure to improve his quality of life and prevent spread of infection to other persons in the community. HIV testing carried out on a voluntary basis with appropriate pre-test and post-test counselling is considered to be a better strategy and is in line with the national policy on HIV testing and also the WHO guidelines.

GENERAL PRINCIPLES OF HIV TESTING

It should be a part of the overall comprehensive preventive and promotive programme.

Testing by itself does not result in behavioural changes that restrict transmission of HIV to others and therefore, testing should be a part of the total control programme which is conducive for behavioural change of the individual by providing social support, means and skills to reduce or eliminate risk behaviour.

Testing without 'explicit' consent of the patients (mandatory testing) has proved to be counter productive in the long run in the control of HIV epidemic. Social support and intervention must be directed to anybody vulnerable to risk behaviour irrespective of whether an individual or group participate in testing procedure or not. Otherwise such testing can drive the target people underground and make it more difficult for launching intervention.

Any health programme which does not maintain the dignity of a patient or deprives him of his basic right to employment or access to medical care or social support is a harmful on a long term basis.

The question which must be asked before a testing procedure is undertaken is how this result will be used for the benefit of individual or of the community; if there is a policy and means to support the group under testing following the test result; and does the same principle of intervention apply even if people refuse testing ?

POSITIVE ANSWER TO ALL THE ABOVE QUESTIONS ARE PREREQUISITE FOR TESTING TO BE AN EFFECTIVE TOOL

THE TESTING SHOULD BE TECHNICALLY SOUND AND APPROPRIATE

No test in biological system is foolproof even under the best laboratory conditions. For example if we wish to detect an asymptomatic HIV positive person by using ELISA (2nd ELISA done on sera reactive to first ELISA) in a population where the prevalence of infection is 1%, the chance that a person detected positive is actually positive (positive predictive value) is only 50% after one ELISA test and 99% turly after two tests. This means one result will be falsely positive in every 100 tests, even by two tests if we use a western blot as supplemental test instead of 2nd ELISA, the chance of detcting truly positive increased to 99.998% which means there will be one false positive out of 10,000 declared positive.

If we appreciate the limitation of any test which could measure the HIV status the cheaper test could be considered (e.g. three ERS instead of ELISA and Western Blot) to achieve yield. Presently three types of tests are available on similar principle to ELISA which have been broadly categorized, as one which can be completed within half an hour.

- Dip stick rapid test-similar to that done for examination of sugar in urine for diabetic.
- A simple test is one which does not involve any sophisticated instrument and even could be carried out in conditions without electricity.

THE TEST PROCEDURE MUST BE APPROPRIATE TO THE FIELD SITUATION

Places where electricity is not available for major part of the working hours, use of techniques dependent on a sophisticated procedures will be inappropriate. Rapid or simple tests are recommended where infrastructure is minimal or where quick screening of sample is needed.

THE TESTING PROCEDURE MUST BE COST EFFECTIVE

It is generally seen that costly mass screening programme often spread a false sense of security without any public health impact and often delays the proper intervention measures. For example, mass screening for HIV patient seeking hospital admission can only delay implementation of measures for hospital infection control procedures that could have prevented more infective disease like hepatitis 'B' & 'C'.

LABORATORY PROCEDURE MUST BE MONITORED FOR ENSURING QUALITY

NACO POLICY ON HIV TESTING

TRANSFUSION SAFETY

A single ERS test is sufficient to ensure transfusion safety with the provision of simple tests in places without electricity. The objective of the transfusion safety does not require identification of donor of the infected unit of blood and in low prevalence settings of HIV single ERS would detect at least 50% SAMPLES FALSELY POSITIVE. However the same test gives more than 99.9% surety that blood found negative is actually free of infection. Therefore, while we can label blood as safe it is risky to label any donor HIV positive on such test result and employees of blood bank must be well aware of interpretation of the test. Often employees of blood bank are confronted with situation where a donor might ask why his blood has been rejected. In such situation the donor could be referred to the voluntary HIV testing centre with pre and post test counselling and supplemental test facilities for HIV (3ERS).

SURVEILLANCE

The objective of surveillance is best achieved by annual cross sectional survey of same risk group in the same place over few years by unlinked anonymous testing, following test procedures by 2 ERS. The main purpose of the survey is to monitor the trend of infection of HIV. Unlinked anonymous tests are only possible if blood is drawn for some other purpose and a portion of that is tested for HIV without identification data.

IDENTIFICATION OF HIV POSITIVE INDIVIDUALS

This testing procedure must offer pre and post test counselling of the client and involve explicit

consent. Voluntary HIV testing and counselling when offered to any asymptomatic person must have any of the following purposes:

- to permit early institution of an specific drug therapy if found to be effective (however at present no such therapy has proved to be beneficial including antiretroviral drugs or chemo-prophylaxis).
- to help infected or non-infected persons be more aware of their health status and prognosis to take decisions of child bearing, breast feeding and reduce or eliminate risk behaviour.

Increasing number of AIDS cases in the country calls for availability of diagnostic facilities for clinically suspected cases of AIDS. However, such testing procedure must be of highest specificity, accuracy and coupled with trained man power for counselling. The result of the test must be kept confidential and even health care workers who are not directly involved in care of the patient should not be told about the result. Surveillance of AIDS cases in the country does not require reporting of the identification data of the patient.

In the case of diagnosis of clinically suspected cases and for voluntary testing, the testing is done with 3 ERS using HIV kits with different antigens.

RESEARCH

Testing procedure for research are designed according to specific objectives and could be decided by the researcher. However, all the studies undertaken must follow ethical standards which primarily involves full explicit consent of the patient and pre decided mutually agreed terms for any eventuality of the patient due to research activities.

Govt. of India has earlier issued a comprehensive HIV testing policy and the following issues are reiterated here:-

- No individual should be made to undergo a mandatory testing for HIV.
- No mandatory HIV testing should be imposed as a precondition for employment or for providing health care facilities during employment.
- Adequate voluntary testing facilities with pre tests and post test counselling should be made available throughout the country in a phased manner. There should be at least one HIV testing centre in each district in the country for voluntary testing in the Governmental sector.

Top

HOME

National Aids Control Program || Speeches of PM/MOH || NACO Officials || State AIDS Control Societies || About HIV/AIDS || Indian Scenario || Global Scenario

Ask the Doctor || Announcements || Letter from the Project Director || Feedback || Site Map || Related Sites || Newsletter

Asha-Jyothi UVI Reach Clinics Dates & Address

	Gangavathi Monday	Sindhanur Tuesday	Deo Durga Wensday	Lingasagur Thursday	Koppal. Friday.
June	20-06-05	21-06-05	22-06-05	23-06-05	24-06-05
July	4-07-05 18-07-05	5-07-05 19-07-05	06-07-05 20-07-05	07-07-05 21-07-05	08-07-05 22-07-05
Aug	01-08-05 15-08-05	02-08-05 16-08-05	03-08-05 17-08-05	04-08-05 18-08-05	05-08-05 19-08-05
Sep	05-09-05 19-09-05	06-09-05 20-09-05	07-09-05 21-09-05	08-09-05 22-09-05	09-09-05 23-09-05
Oct	03-10-05 17-10-05	04-10-05 18-10-05	05-10-05 19-10-05	06-10-05 20-10-05	07-10-05 21-10-05
Nov	07-11-05 21-01-05	08-11-05 22-11-05	09-11-05 23-11-05	10-11-05 24-11-05	11-11-05 25-11-05
Dec	05-12-05 19-12-05	06-12-05 20-12-05	07-12-05 21-12-05	08-12-05 22-12-05	09-12-05 23-12-05
	Taluka Govt Hospital VCTC Centre Time-2-00 PM to 5-00 PM.	Taluka Govt Hospital Samraksha Information Centre Time-10-00AM to 4-00PM to	Taluka Govt Hospital Deo Durga Time-2-00 PM to 5-00 PM	Taluka Govt Hospital VCTC-centre Time-10-00 AM to 4-00 PM	Samraksha office Sadhasiva Nagar Near, Bannikatti Koppal Time-2-00PM to 5-00 PM

Service Providing In Out Reach clinics

→ All out Reach clinics supported by Taluk health officer, Doctors & YCTC counsellors.

→ OIs Treatment giving.

→ Counselling support for every client.

→ Conducted Group Education sessions In every clinic

→

1. INTRODUCTION

Treatment is now perceived as a critical component of a comprehensive program to combat HIV/AIDS, along with prevention and improvement of health care infrastructure for the delivery and monitoring of care and support. This integration has recently become, more feasible. Political leadership and commitment has shifted significantly in favor of providing access to anti-retroviral treatment (ART) for people living with HIV/AIDS. Earlier, high costs, demanding treatment regimens, and the absence of basic health infrastructure were repeatedly cited as potentially insurmountable barriers.

The "Call to Action" at the UN General Assembly Special Session on HIV/AIDS (June 2001), pushed forward a new global consensus on the need for ART. This led to a cumulative response from diverse quarters. It put pressure on pharmaceutical manufacturers, and ever since, we are witnessing dramatic reductions in drug prices. Brazil's national ART distribution programme added to the public debate. WHO released guidelines for anti-retroviral use in resource constrained settings in April 2002, added 10 ART drugs to its list of "essential medicines" for all countries, and for the first time qualified a number of generic manufacturers. WHO declared the lack of access to ARV treatment for HIV/AIDS a "global health emergency" in September, 2003, and announced that it would release an emergency plan to scale up access to ARV treatment for at least three million people by the end of 2005. This joint WHO/UNAIDS announcement popularly came to be known as the 3 by 5 initiative. The WHO guidelines for anti-retroviral use in resource constrained settings have since been revised in Dec 2003.

Admittedly, antiretroviral therapy is no cure for HIV/AIDS. Effective antiretroviral regimens inhibit replication of HIV virus, reduce viremia to undetectable levels and significantly lower the frequency of opportunistic infections, thus reducing the cost of management of HIV. This helps people lead more productive lives, with perceptibly reduced stigma and discrimination. Successes achieved in delaying the onset of AIDS by ART, has now transformed the common perception about HIV from being an immediately fatal scourge to somewhat more manageable, chronic illness.

9.1. First line regimens

The overwhelming short term priority is for first-line regimens which will facilitate the scaling up of treatment. Second-line treatment is not a priority in the short-term. The characteristics of an ideal first-line ARV combination should:

- Be effective and well tolerated, with minimal side effects
- Be potent, even in advanced disease, and favourable resistance profile
- Have no drug interactions or contra indications
- Be safe for use in patients with TB and in pregnant or lactating women
- Be available in a fixed dose combination (once or twice a day)
- Be stable in tropical conditions
- Do not require laboratory monitoring
- Be affordable

The first recommended choice for first-line combinations is d4T/3TC/NVP (Stavudine + Lamivudine + Nevirapine), taken twice daily (BID) as a fixed dose combination (FDC)

Advantages: It is well tolerated in most cases, has few contra-indications and is appropriate for use in women of child bearing age. It has proven efficacy under actual field conditions, is affordable, and is easy to take.

Limitations: The major side effects with d4T (stavudine) are neuropathy and pancreatitis. Nevirapine causes hepatotoxicity and severe rash. NVP has drug interaction with rifampicin. It should therefore be avoided with rifampicin for both reasons of interaction as well as possibility of haepatoxiciticty. It is ineffective on HIV2.

9.2. Alternate to first-line combinations

1. AZT/3TC and NVP (Zidovudine + Lamividine) and Nevirapine taken twice daily.

Advantages: Largest experience with Zidovudine use, easy to take, well tolerated. Can be used where d4T (Stavudine) use is contraindicated.

Limitations: Major potential toxicities with AZT are anemia and neutropenia. In resource poor settings where anaemia is common it may be an issue for concern. The treatment requires Hb monitoring. Zidovudine is more expensive than d4T (Stavudine) and therefore this combination is also more expensive.

2. d4T/3TC + EFV (Stavudine+Lamivudine) and Efavirenz, taken as EFV (600 mg) once per day plus d4T/3TC as twice daily fixed dose combination.

Advantages: can be used with rifampicin, and easy to take.

Limitations: EFV has potential for CNS toxicity and teratogenecity. It is therefore contra-indicated in pregnant women and women of child bearing age who are not on contraception.

In both regimens d4T + 3TC + NVP and AZT + 3TC + NVP fixed dose combinations, Nevirapine should be administered in 200 mg dose as a single drug for 15 days as lead-in dosing and if tolerated only then FDC should be started.

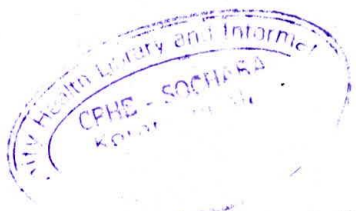
9.3. Fixed dose combination.

Fixed dose combinations are considered important tools for scaling up in resource-poor, high HIV prevalence settings. These medicines are preferable because they are easy to use, have distribution advantages (procurement and stock management), improves adherence ensuring intake of all medicines and reduces the chances of development of resistance. Though once-a-day dosing is an ultimate goal, however it is not essential as field experience clearly has shown that BID regimens with co-formulations are easy for patients to adhere to. Therefore, WHO must guide both commercial and non-commercial efforts by communicating attributes of the ideal future first-line ARV therapy.

Up to the present the Government provides first line regimen(s), consisting of fixed does combinations of the following ARV drugs:

Zidovudine/ Lamivudine and Stavudine/ Lamivudine alongwith Nevirapine and Efavirenz.

(i) Stavudine(30mg) + Lamivudine(150mg) + Nevirapine(200 mg)
(ii) Stavudine(40 mg) + Lamivudine(150mg) + Nevirapine(200 mg)
(iii) Stavudine(30 mg) + Lamivudine(150mg)
(iv) Stavudine(40 mg) + Lamivudine(150mg)
(v) Zidovudine (300mg) + Lamivudine(150mg)



(vi) Nevirapine (200mg) for lead in dosage and combination with (v)

(vii) Efavirenz (600mg) for single dose

The physician will prescribe one of the regimens of first line ARV drugs indicated above. The assumption is that 80% of the people seeking treatment for HIV/AIDS require Stavudine+Lamivudine+Nevirapine combination; 10% require Zidovudine+ Lamivudine+Nevirapine fixed dose combination; the remaining 10% of people seeking treatment may require Efavirenz combinations on account of toxic reaction to Nevirapine.

9.4. Criteria for starting ARV therapy in adolescents and adults:

Confirmed HIV infection and one of the following conditions:

- WHO Stage IV HIV disease irrespective of CD4 cell count
- WHO Stage III disease with consideration of using CD4 cell counts < 350/mm^3 to assist decision making
- WHO stage I or II HIV disease with CD4 cell counts < 200/mm^3

If CD4 Testing Available:

- WHO Stage IV disease irrespective of CD4 cell count
- WHO stage III disease with consideration of using CD4 cell counts < 350/mm3 to assist decision making

If CD4 Testing Unavailable:

- WHO Stage IV disease irrespective of total lymphocyte count
- WHO Stage III disease irrespective of total lymphocyte count
- WHO Stage II disease with a total lymphocyte count = 1200/mm3

9.5. Side Effects

Side effects could be caused by the followings:

- A side effect of the ARV therapy;
- A new opportunistic infection;
- An immune reconstitution syndrome (stronger immune system reacting to infection that had been invisible; usually within 2-3 months after starting treatment).

Clinical monitoring at the first-level facility requires the ability to consult with the district clinician on higher level clinical team. This will require support for cell phone or radio telephone communications. The followings are signs or symptoms of the side effects and suggested response.

Signs or symptoms	Response:
Nausea	Take the medicines with food (except for ddi or IDV). If on zidovudine, reassure the patient that this is common, usually self-limited. Treat symptomatically.
Headache	Give paracetamol. Assess for meningitis. If on zidovudine or EFV, reassure that this is common and usually self-limited. If persists more than 2 weeks, call for advice or refer.
Diarrhea	Hydrate. Follow diarrhea guidelines. Reassure patient that if due to ARV, will improve in a few weeks. Follow up in 2 weeks. If not improved, call for advice or refer.
Fatigue	This commonly lasts 4 to 6 weeks especially when starting ZDV. If severe or longer than this, call for advice or refer.
Anxiety, nightmares, psychosis, depression	This may be due to efavirenz. Give at night; counsel and support (usually lasts < 3 weeks). Call for advice or refer if severe depression or suicidal or psychosis. Initial difficult time can be managed with amitriptyline at bedtime
Blue /black nails	Reassure. It's common with zidovudine
Rash	If on nevirapine or abacavir, assess carefully. Is it a dry or wet lesion? Call for advice. If generalized or peeling, stop drugs and refer to hospital
Fever	Call for advice or refer. (This could be a drug side effect, an opportunistic infection a new infection, or immune reconstitution syndrome.)
Yellow eyes (jaundice) or abdominal or flank pain	Stop drugs. Call for advice or refer. (Abdominal pain may be pancreatitis from ddi or d4T.) If jaundice or liver tenderness, send for ALT test and stop ART (nevirapine is most common cause.) Call for advice or refer.
Pallor: anemia	If possible, measure hemoglobin. Refer if sever pallor or symptoms of anemia or very low hemoglobin (<8 grams).
Tingling, numbers or painful feet/legs	If new or worse on treatment, call for advice or refer. Patient on d4T/3TC/NVP should have the d4T discontinued - substitute ZDV if no anemia (check hemoglobin).
Cough or difficult breathing	This could be immune reconstitution syndrome. Call for advice. If on abacavir, this could be life-threatening drug reaction. (Stop drug and consult/refer.)
Changes in fat distribution	Discuss carefully with your patient- can he or she accept it?

The following table indicates the possible side effects caused by the ARV therapy and the suggested drug substitution:

Regimen	Toxicity	Drug Substitution
D4T/3TC/NVP	• d4T – related neuropathy or pancreatitis	• Switch d4T to ZDV
	• d4T –related lipoatrophy	• Switch d4T to TDF or ABC
	• NVP – related severe hepato-toxicity	• Switch NVP to EFV (except in pregnancy)
	• NVP – related severe rash (but not life threatening)	• Switch NVP to EFV
	• NVP – related life threatening rash (Stevens – Johnson syndrome)	• Switch NVP to PI
ZDV/3TC/NVP	• ZDV relate to persistent gastro-intestinal intolerance or severe hematological toxicity	• Switch ZDV to d4T
	• NVP – related severe hepato-toxicity	• Switch NVP to EFV (except in pregnancy. In this situation switch to NFV, LPV/r or ABC.)
	• NVP – related severe rash (but not life threatening)	• Switch NVP to EFV
	• NVP – related life threatening rash (Stevens - Johnson syndrome)	• Switch NVP to PI
D4T/3TC/EFV	• d4T – related neuropathy or pancreatitis	• Switch d4T to ZDV
	• d4T – related lipoatrophy	• Switch d4T to TDF or ABC
	• EFV –related persistent CNS toxicity	• Switch EFV to NVP
ZDV/3TC/EFV	• ZDV –related persistent GI intolerance or severe hematological toxicity	• Switch ZDV to d4T
	• EFV – related persistent CNS toxicity	• Switch EFV to NVP

9.6. First line ARV Drug Interaction

If patient is taking:	Do not co-administer with these drugs[1]:	Other cautions:
Nevirapine (NVP)	• Rifampin • Ketoconazole	Do not rely on estrogen-based oral contraceptives-switch or use additional protection. If on methadone, will need to increase dose. Monitor for withdrawal signs.

[1] Call for advice for alternative medicines

Lamivudine (3TC)	No major drug interactions	
Stavudine (d4T)	Do not give with ZDV (zidovudine, AZT)	Higher risk of d4T neuropathy when also taking INH
Zidovudine (ZDV, AZT)	Do not give with d4T or ganciclovir	Higher risk of anaemia when also taking acyclovir or sulpha drugs
Efavirenz (EFV)	• Diazepam (OK for convulsions in emergency) • Other benzodiazepines other than lorazepam • Phenobarbitol • Phenytoin • Protease inhibitor ARV	Do not take with high fat meal If on methadone, will need to increase dose. Monitor for withdrawal signs

9.7. ART for Women at Reproductive Age

ARV Regimen	Usage in women in child bearing age or who are pregnant	Major Potential Toxicities
d4T/3TC/NVP	• Can be used	• d4T related neuropathy, pancreatitis and lipoatrophy • NVP related hepato-toxicity and severe rash
ZDV/3TC/NVP	• Can be used	• ZdV related GI, intolerance, anemia and neutropenia • NVP related hepato-toxicity and severe rash
d4T/3TC/EFV	• Should be avoided	• d4T related neuropathy, pancreatites and lipoatrophy • EFV related CNS toxicity and potential for teratogenicity
ZDV/3TC/EFV	• Should be avoided	• ZDV related GI intolerance, anemia and neutropenia • EFV related CNS toxicity and potential for teratogenicity.

9.8. Second line regimens

In the event of treatment failure, a number of second line regimens have been found to be effective in prolonging the benefits of ART. Here, the programme needs to guard against cross resistance. Ideally, second line regimens should include at least

three new drugs. WHO's recommended second line regimens corresponding to each failed first line regimen are summarized below.

First-line regimen	Second-line regimen
d4T or ZDV	TDF or ABC
+	+
3TC	ddI [1]
+	+
NVP or EFV	LVP/r or SQV/r [2]

[1] dose of ddI should be reduced from 400 mg to 250 mg when administered with TDF

[2] LVN/r and SQV/r require secure cold chain. NFV can be considered as an alternative in resource settings without cold chain.

10. TREATMENT OF HIV/AIDS WITH ART IN CHILDREN

Laboratory diagnosis of HIV infection in infants less than 18 months of age is difficult due to the persistence of maternal antibody, for which a virological test is required to make a definitive diagnosis. In resource-limited settings, CD4 cells assay can be used for making a decision for starting antiretroviral (ARV) treatment. As CD4 absolute is affected by various factors, it is recommended that CD4 percentages should be used. It should be noted that the breastfeeding infants are at risk of HIV infection during the entire period of breastfeeding, and a negative virological or antibody test does not exclude possibility of the child becoming infected at a later stage if breastfeeding is continued.

The total lymphocyte count significantly corelates with the risk of mortality in the HIV-infected children. The 12-month risk of mortality is more than 20% for children less than 18 months of age having a total Lymphocyte count < 2500/mm^3 and for children >18 months of age with a total lymphocyte count of less than 1500/mm^3. In cases where the CD4 cell count cannot be assessed, the total lymphocyte count may be used as a substitute for an indication of treatment of infants and children with documented HIV infection in the presence of symptomatic disease – Stage II and Stage III of the WHO Clinical Classification. An abnormal total lymphocyte count or CD4 cell count or percentages should be confirmed with a second test prior to taking a therapeutic decision, but this may not always be possible.

10.1. WHO Staging System for HIV Infection and Disease in Children

Clinical Stage I:

- Asymptomatic
- Generalized lymphadenopathy

Clinical Stage II:

- Chronic diarrhea >30-days, duration in absence of known etiology
- Severe persistent or recurrent candidiasis outside the neonatal period
- Weight loss or failure to thrive in the absence of known etiology
- Persistent fever >30-days, duration in the absence of known etiology
- Recurrent severe bacterial infections other than septicemia or meningitis (e.g. osteomyelitis, bacterial (non-TB) pneumonia, abscesses)

Clinical Stage III:

- AIDS-defining opportunistic infections
- Severe failure to thrive (wasting) in the absence of known etiology
- Progressive encephalopathy
- Malignancy
- Recurrent septicemia or meningitis

10.2. HIV pediatric immune category classification system

	<12 months		1-5 yrs		6-12 yrs	
Immune category	No./mm^3	(%)	No./mm^3	(%)	No./mm^3	(%)
Category 1: No suppression	(≥1500)	(≥25%)	≥1000	(≥25%)	≥500	(≥25%)
Category 2: Moderate hsuppression	750 – 1499 (1000)20%	(15%-24%) 20%	500-999 (650)	(15%-24%) 20%	200-499 275	(15%-24%) 20%
Category 3: Severe suppression	<750	(< 15%)	< 500	(<15%)	<200	(<15%)

10.3. Criteria for starting ARV therapy in infants and children

(i) For HIV seropositive infants aged below 18 months, WHO recommends initiation of ARV therapy if:

- The infant has virologically proven infection (using HIV DNA PCR, HIV RNA or p24 antigen) and has:

  (a) WHO paediatric Stage III HIV disease (e.g. clinical AIDS) irrespective of CD4 percentage.

  or

  (b) WHO paediatric Stage II disease with consideration of using CD4<20% to assist in decision-making.

  or

  (c) WHO paediatric Stage I (e.g. asymptomatic) and CD4<20% (to be treated only if CD4 assay available).

- If virological tests to confirm the HIV-infection status are not available but CD4 cell assays are available, WHO recommends that the ARV therapy can be initiated in HIV-seropositive infants who have WHO Stage II or III disease and the CD4 percentage is less than 20%. In such cases, HIV antibody testing must be repeated at age 18 months to definitively confirm that the child is HIV-infected. Only infants with confirmed infection should have ARV therapy.

(ii) For HIV-seropositive children aged >18 months, WHO recommends the initiation of ARV therapy if:

(a) WHO paediatric Stage III HIV disease (e.g. clinical AIDS) irrespective of CD4 %.

or

(b) WHO paediatric Stage II disease with consideration of using CD4< 15% to assist in decision making.

or

(c) WHO paediatric Stage I (e.g. asymptomatic) and CD4<15%.

- The penetration of ARVs into human milk in lactating women has not been quantified for most of ARV drugs Although some ARVs, such as nevirapine, are known to be present in breast milk, the concentration and the quantity of the drug that would be ingested by infants would be less than that needed to achieve therapeutic levels. Thus, if a breastfeeding infant is ill enough to require ARV treatment, then ARVs at the standard paediatric doses should be initiated regardless of whether the mother is receiving ARV therapy or not.

10.4. Recommended First-line ARV Regimens for infants and Children:

Formulations appropriate for use by young children who cannot swallow whole tablets or capsules are currently widely available. However, National AIDS Control Organization (NACO) and (SHI) recognize that until such time as appropriate formulations can be made more widely available, the splitting of adult dose solid formulations, ARV's should be resorted to. While such dosages may be suboptimal in their effect, this is the only way a severely ill child can receive therapy when no other alternatives are available. The pharmacokinetics of crushed tablets or sprinkled capsule contents in children has been evaluated.

In order to improve adherence, regimens chosen for children should take into account those eventually used by the patients to avoid different timings, and, if possible, to permit the use of same drugs. The drug doses must be adjusted as the child grows, otherwise there is a risk of under-dosage and development of resistance. Therefore, dosing in children should be based either on body surface area or weight.

The preferred first-line treatment option for children includes d4T or ZDV + 3TC plus an NNRTI (NVP or EFV) for the same rationale as discussed for the adult initial ARV regimen. A caveat is that EFC cannot be used for children under three years of age due to lack of appropriate formulation and dosing information. Thus, for children aged <3 years or weighing <10 kg, NVP should be the NNRTI of choice.

For Fixed-dose Combination (FDC) containing 30 mg of stavudine, the recommended fractions will be:

Wt.	Sta 30	Stavudine	Lam	NVP
7.5 – 12.5 kg	0.33	10	50	66
12.5 – 17.5 kg	0.5	15	75	100
17.5 – 22.5 kg	0.66	20	100	133
22.5 - 27.5 kg	0.75	22	112	150
27.5 – 32.5 kg	1 m	30	150	200
> 32.5 kg	1	30	150	200

FDC 30:
Stavudine : 30 mg
Lamivudine : 150 mg
Nevirapine : 200 mg

These doses will be administrated twice a day.

For FDC containing 40 mg of stavudine, the recommended fractions will be:

Wt.	Sta 30	Stavudine	Lam	NVP
7.5 – 12.5 kg	0.25	10	37.5	50
12.5 – 17.5 kg				
17.5 – 22.5 kg	0.5	20	75	100
22.5 – 27.5 kg	0.66	26	100	133
27.5 – 32.5 kg	0.75	30	112	150
> 32.5 kg	1	40	150	200

FDC 40:
Stavudine : 40 mg
Lamivudine : 150 mg
Nevirapine : 200 mg

The use of ZDV+3TC+ABC as the first line of therapy is now considered a secondary alternative.

- For children <3 years who require ARV therapy while receiving anti-TB therapy, the use of ADV+3TC=ABC should be considered, as SQV/r is not available in a formulation appropriate for children of this age.
- Because of the age-related decline in the CD4 absolute count upto 6 years of age, when nearly adult levels are reached, it is difficult to use the CD4 cell count to assess the failure of the therapy in younger children. For children aged 6 years or more, a similar CD4 count criteria as used in adults is appropriate.

10.5. Assessment of Infants and Children Receiving ARV Therapy

Important clinical signs of response to the ARV therapy in children include: improvement in the growth of children who were failing to grow; improvement in the

neurological symptoms and in general development of children who were demonstrating delay in developmental milestone or encephalopathy; and/or decreased frequency of infections (bacterial infections, oral thrush, and / or other opportunistic infections).

Laboratory assessments in children on ARV therapy should be done routinely to monitor the side-effects of drugs. It should also include monitoring of

- Nutrition and nutritional status
- Weight and height growth
- Developmental milestones
- Neurological symptoms

10.6. Side Effects and Drug Interaction

ARV regimen	Major potential toxicities	Usage in TB co-infection	Availability as three-drug fixed-dose combination	Laboratory monitoring requirements
D4T/3TC/NVP	D4T-related neuropathy, pancreatitis and lipoatrophy NVP-related hepatotoxicity and severe rash	Yes, in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens	Yes Dose escalation required	No
ZDV/3TC/NVP	ZDV-related neuropathy, pancreatitis and lipoatrophy EFV-related CNS toxicity and potential for treatogenicity	Yes, in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens	Yes	Yes
D4T/3TC/EFV	ZDV-related GI intolerance, anaemia and neutropenia	Yes, but EFV should not be given to pregnant	No, EFV not available as part of FDC. However,	No

	EFV-related CNS toxicity and potential for teratogenicity	women or women of childbearing potential, unless effective contraception can be assured	partial FDC available for d4T/3TC	
ZDV/3TC/EFV	ZDV-related GI intolerance, anaemia and neutropenia EFV-related CNS toxicity and potential for teratogenicity	Yes, but EFV should not be given to pregnant women or women of childbearing potential, unless effective contraception can be assured	No, EFV not available as part of FDC. However, partial FDC available for ZDV/3TC	Yes

10.7. Reason for changing ART in children

ART may need to be changed for either toxicity or drug failure. ***Toxicity*** is related to the inability to tolerate the side-effects of the medication and to significant organ dysfunction that may result. This can be monitored clinically and by laboratory tests.

If a change in regimen is necessary because of treatment failure, a new second-line regimen may be used. When the toxicity is related to a single drug, the offending drug can be replaced with the other drug that does not have the same side-effects.

Regimen	Toxicity	Drug substitution
D4T / 3TC / NVP	• D4T-related neuropathy or pancreatitis	• Switch d4T ZDV
	• D4T-related lipoatrophy	• Switch d4T TDF or ABC
	• NVP-related severe hepatotoxicity	• Switch NVP EFV
	• NVP-related severe rash (but not life-threatening	• Switch NVP EFV
	• NVP-related life-threatening rash (Stevens-Johnson syndrome)	• Switch NVP PI

Drug Failure: Important clinical signs of drug failure in children include a lack of growth, loss of neuro developmental milestones, development of enuphalopathy and recurrence of new opportunistic infections that is refractory to treatment. Before an ARV regimen is considered to be failing based on clinical criteria, the child should have had a reasonable trial on the ARV regimen for at least 24 weeks.

Due to age-related CD4 count changes in children aged less than 6 years, it is difficult to use the CD4 cell count to assess the failure of ARV therapy in young children.

10.8. Second-line ARV therapy for Infants and Children:

The second-line therapy for children in the event of the first-line regimen failure would include: change in nucleoside backbone based on the same principles as for adults (e.g. from ZDV+3TC to ABC+ddI) plus a protease inhibitor (LPV/r or NFV). TDF cannot be recommended for paediatric use at the current time due to limited data available on appropriate dosing in children, particularly children under 8 years of age.

First -line regimen	Second-line regimen
D4T or Zidovudine + 3TC + NNRTI: Nevirapine or Efavirenz	ABC + Didanosine + LPV/r or NFV or SQV if weight >25 kg

10.9. Adherence to ART

Structured HIV management conducted by trained and committed health care workers, together with informed patients, can result in improved adherence to ART. This can lead to:

- delayed onset of viral resistance
- delayed virological failure
- delayed treatment failure
- improved quality and length of life

A large number of ART-related adverse effects have a direct or indirect impact on the treatment outcomes. Differences in diet, environment and physiology are important factors. The population-level occurrence of ART-related adverse effects should be

monitored in new populations taking ART. At any rate, the occurrence of adverse effects in individuals needs to be anticipated and planned for. Patients taking ART should be counselled in advance about these effects so that their occurrence is not totally unexpected.

Compliance can be a special problem in paediatrics, yet rigorous adherence to the prescribed regimen is essential to achieve an effective antiretroviral effect from therapy. Unpalatable liquid formulations can cause the child to reject medications; therefore, innovative techniques may be needed to ensure compliance.

Paediatric patients depend on their care takers for drug administration and the families of paediatric HIV patients may face many challenges that can affect their ability to deliver effective care. Close family and medical follow up are essential to ensure compliance with ARV regimens.

10.10. Children with Tuberculosis and HIV Co-infection

If the child's condition permits, anti-tubercular therapy (ATT) should be completed before starting the NVP-based ART. In case a child's clinical or immunological status warrants administration of ART along with ATT, efavirenz based regimens are recommended. The dose of efavirenz should be:

Weight	**Dosage**
10-15 kg	200mg once a day
15-20 kg	250mg once a day
20-25 kg	300 mg once a day
25-35 kg	350mg once a day
35-40 kg	400mg once a day
> 40 kg	600mg once a day

This should be given with the combination of two NRTI drugs: zidovudine and lamivudine or stavudine and lamivudine.

13. MANAGING HIV/TB CO-INFECTION

HIV/TB co-infection is one of the most challenging issues in the scale-up efforts since more than 25% of people living with HIV develop TB. Likewise, in some high-prevalence countries like South Africa, 55-60% of people with TB are HIV positive.

Patients with TB merit special consideration because co-management of HIV and TB is complicated by rifampicin drug interactions with NNRTIs and PIs, pill burden, adherence and drug toxicity. Data to support specific treatment recommendations are incomplete and research is urgently needed in this area.

The management of patients with HIV and TB poses many challenges including patient acceptance of both diagnoses. Pending ongoing studies, WHO recommends that ART in patients with CD4 cell counts < 200 / mm^3 be started 2 weeks to 2 months after the start of TB therapy, when the patient has stabilized on TB therapy. This provisional recommendation is meant to encourage rapid initiation of therapy in patients who may have a high mortality rate. However, deferral of ARV initiation may be reasonable in a variety of clinical scenarios. For example, patients with higher CD4 cells may wait to start ART until after the induction of first phase of TB is completed in order to simplify management of their treatment.

ART Recommendations for individuals with Tuberculosis disease and HIV co-infection:

	Recommended Regimen	Comments
CD4< 200 mm^3	Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months) [1] EFV containing regimens [2,3,4]	Recommended ART. EFV is contraindicated in pregnant women or women of childbearing potential without effective contraception

CD4 between 200-350 mm ^{3}	Start TB treatment. Start one of the below regimens after initiation phase (if severely compromised start earlier): EFV containing regimens [2] or NVP containing regimens in case of rifampicin-free continuation phase TB treatment regimen	Consider ART
CD4> 350 mm 3	Start TB treatment	Defer ART [3]
CD4 not available	Start TB treatment	Consider ART [1,6]

[1] Timing of ART initiation should be up to clinical judgement based on other signs of immunodeficiency as per WHO guidelines. For extra pulmonary TB, ART should be started as soon as TB treatment is tolerated irrespective of CD4 cell count.

[2] Alternatives to the EFV portion of the regimen include SQV/r (400/400 mg bid or 1600/200 qd in sge), LPV/RTV (400/400 mg bid) and ABC (300 mg bid).

[3] NVP (200 mg qd for 2 weeks followed by 200 mg bid) may be used in place of EFV in absence of other options. NVP containing regimens include d4T/3TC/NVP or ZDV/3TC/NVP.

[4] EFV containing regimens include d4T/3TC/EFV or ZDV/3TC/EFV

[5] Unless non-TB stage IV conditions are present as per WHO guidelines. Otherwise start ART upon completion of TB treatment.

[6] If no other signs of immunodeficiency are present and patient is improving on TB treatment. ART should be started upon completion of TB treatment

Since TB may be masked in people with advanced HIV disease, new innovative tools that are more sensitive and specific are needed to support diagnosis, so that TB can be definitively diagnosed before ARVs are considered.

A number of service delivery strategies can be used for improving adherence to ARV treatment and safe behavior. Experience from TB and Leprosy prevention and control programmes has shown that early community involvement is essential for good treatment outcomes. Much experience has been gained from the Revised National Tuberculosis Control Programme (RNTCP) in which the DOTS strategy is used for delivery of anti TB drugs. However, in RNTCP twice weekly regimen is provided and during first eight weeks patients are administered drugs in the presence of a DOTS provider. But in case of antiretroviral treatment the drugs have to be taken on daily basis and at least twice a day. It may, therefore not be possible to translate the DOTS

strategy used in RNTCP for application in HIV treatment. New strategies and tools have to be developed to support treatment adherence and safe behavior to prevent transmission of HIV.

Treatment education is an important component of this strategy. It is important that the patient on ART knows how drugs work in the body and why it is important to adhere to treatment regimens. It should be done in a setting where the person is morally supported to integrate this into his or her life.