CHAPTER 7

# INFECTIONS – BACTERIAL, VIRAL AND OPPORTUNISTIC

## TETANUS

An acute neurological disorder resulting from contamination of a wound (may be a trivial one) by an obligate anaerobic organism *Clostridium tetani*.

### SALIENT FEATURES

- Generalized tetanus, the most common form usually starts with trismus or lockjaw followed by rigidity, violent, painful, generalized muscle spasms and seizures provoked by slightest stimulation. Generalized muscle spasms may compromise respiration. Fever and tachycardia may be present. Mentation is not impaired.
- Prognosis and management depend on grade. Poor prognostic features are age > 70 years, heart rate >140/min, BP >140 mmHg, temperature >38.5°C and severe tetanus.
- In neonatal tetanus, poor prognostic features are pneumonia, recurrent apnoea, cyanosis and opisthotonus.

**Grade I or mild**—muscle rigidity with few or no spasms.

**Grade II or moderat**e—trismus, dysphagia, rigidity, and short-lasting spasms.

**Grade III or severe**—frequent explosive spasms, autonomic dysfunction particularly sympathetic over-activity may be present.

**Grade IV or very severe**—features of grade III plus violent autonomic disturbances involving the CVS—severe hypo- or hypertension.

- Other presentations include local, cephalic (cranial nerves) or neonatal tetanus (within 2 weeks of life).
- Complications include respiratory failure, respiratory infections, barometric trauma due to prolonged ventilator support, persistent hypotension, labile hypertension, cardiac arrhythmia, sepsis and sudden death.

## Treatment

### *Nonpharmacological*

Admit in a quiet room/ICU with minimum stimulation, cardiopulmonary monitoring, protection of airways/respiratory support (intubation/tracheostomy) with or without ventilation, cleaning/exploration/debridement of wound. Maintain hydration and enteral/parenteral nutrition with high calorie and high protein diet.

### *Pharmacological*

**Grade I tetanus.** (1) As above.

(2) Tab. Diazepam 5-20 mg 3 times a day in mild tetanus; slow IV infusion; not to exceed a dose of 80-100 mg in 24 hours.

(3) If spasms not controlled.

Inj. Phenobarbitone 200 mg IM every 8-12 hours.

Or

Inj. Chlorpromazine 50 mg IM in adults 4 times a day.

The ideal sedative and muscle relaxant schedule for each patient should be individualized. An objective guide to decrease in rigidity is relaxation of abdominal muscles.

**Grade II.** (1) As above.

(2) Tracheostomy.

(3) Inj. Magensium sulphate 40 mg/kg IV loading dose followed by infusion of 1.5 mg/h to control muscle spasms.

**Grade III and IV.** (1) As above.

(2) Ventilator support.

(3) Inj. Pancuronium 2-4 mg IV.

Or

Inj. Gallamine 20-40 mg IV.

(4) In case of hypotension

Inj. Dopamine/Dobutamine 10-40 mcg/kg/min infusion titrated to maintain systolic BP of 100 mm Hg.

If bradyarrhythmias, Inj. Atropine 0.6-1.2 mg IV.

If hypertension, see Chapter 3 for details

(5) In addition, give following to all patients

Inj. Crystalline penicillin 2 mega units 6 hourly IV for 10 days.

Or

Inj. Metronidazole 500 mg 8 hourly or 1 g 12 hourly.

(Other antibiotics may be required according to need of infected wound).

(6) Inj. Human tetanus immunoglobulin (TIG) 3000-5000 units IV or IM.

Or

Inj. Equine antiserum, 10,000 units by slow IV Injection after sensitivity test (If human TIG is not available).

Antiserum should be given before local manipulation of the wound.

(**Caution**: Tetanus immunoglobulin does not produce natural immunity and a full course of immunization with tetanus toxoid should be administered once the patient has recovered).

**References**

1. Tetanus. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp. 1197-1200.
2. Tetanus. In: Oxford Textbook of Medicine. Warrell DA, Cox TM, Firth JD, Benz EJ Jr. (eds), 4th Edition, Oxford University Press, 2003; pp. 1.545-1.551.
3. New Trends in the management of Tetanus. Expert Rev Anti-Infect Ther 2004; 2: 73-84.

## HIV AND AIDS

HIV has emerged as a global pandemic and as on December 2008, more than 33.4 million people are living with HIV/AIDS worldwide. India has an estimated 2.4 million people living with HIV infection with adult (15-49 y) HIV prevalence at 0.31% in 2009. HIV infection leads to progressive immune deficiency that characterizes the disease and is responsible for the opportunistic infections that complicate the illness. The rate of disease progression is highly variable between individuals, ranging from 6 months to more than 20 years. The median time to develop AIDS after transmission is 10 years in the absence of antiretroviral therapy (ART). The availability of antiretroviral therapy (ART) has dramatically changed the outcome of the patients with HIV infection and has significantly reduced the disease mortality and morbidity.

### SALIENT FEATURES

I) Case Definition of AIDS in Children (up to 12 years of age)

- The positive tests for HIV infection by ERS (ELISA/RAPID/SIMPLE) in children above 18 months or confirmed maternal HIV infection for children less than 18 months. **AND** Presence of at least two major and two minor signs in the absence of known causes of immunosuppression.
- Major signs:
  (a) Loss of weight or failure to thrive which is not known to be due to medical causes other than HIV infection,
  (b) Chronic diarrhoea (intermittent or continuous) >1 month duration,
  (c) Prolonged fever (intermittent or continuous) > 1 month duration.
- Minor signs:
  (a) Repeat common infections (e.g. pneumonitis, otitis, pharyngitis, etc.),
  (b) Generalised lymphadenopathy,
  (c) Oropharyngeal candidiasis,
  (d) Persistent cough for more than 1 month,
  (e) Disseminated maculopapular dermatosis

II) Case Definition of AIDS in adults (for persons above 12 years of age)

- Two positive tests for HIV infection by ERS test (ELISA/RAPID/SIMPLE) AND
- Any one of the following criteria:
  (a) Significant weight loss (>10% of body weight) within last one month/ Cachexia (not known to be due to a condition other than HIV infection) AND chronic diarrhoea (intermittent or continuous) >1 month duration or prolonged fever (intermittent or continuous) >1 month duration
  (b) Tuberculosis: Extensive pulmonary, disseminated, miliary, extrapulmonary tuberculosis
  (c) Neurological impairment preventing independent daily activities, not known to be due to the conditions unrelated to HIV infection (e.g. trauma)
  (d) Candidiasis of the oesophagus (diagnosable by oral candidiasis with odynophagia)
  (e) Clinically diagnosed life-threatening or recurrent episodes of pneumonia, with or without aetiological confirmation
  (f) Kaposi sarcoma
  (g) Other conditions: Cryptococcal meningitis, neurotoxoplasmosis, CMV retinitis, *Penicillium marneffei*, recurrent herpes zoster or multi-dermatomal herpes infection and disseminated molluscum
- HIV disease is characterized by three phases: acute primary illness, asymptomatic chronic illness and symptomatic chronic illness.
- **Essential laboratory investigations:** HIV serology, CD4+, T lymphocyte counts (if available) or total lymphocyte count (TLC), complete blood count and chemistry profile, pregnancy test.
- **Supplementary tests indicated by history and physical examination:** Chest X-ray, urine for routine and microscopic examination, hepatitis C virus (HCV) and hepatitis B virus (HBV) serology (depending on test availability and resources).

**Note**: It is most important to confirm the diagnosis of HIV infection by tests performed by a trained technician, preferably in a diagnostic laboratory (pre- and post-test counselling is a must). The test results should include the type of test performed to establish the diagnosis based on WHO guideline. In case there is any doubt, the test should be repeated in a standard/referral laboratory.

## PRE- AND POST-TEST HIV COUNSELLING

Counselling is the confidential dialogue between a client and a care provider aimed at enabling the client to cope with stress and take personal decision related to HIV/AIDS. The counselling process includes an evaluation of personal risk of HIV transmission

and facilitation of preventive measures. This includes information, education and psychosocial support and allows individuals to make decisions that facilitate coping and preventive behaviours. Counselling is an integral part of prevention, diagnosis, management and support of people living with HIV/AIDS. Counselling aims to enable the person to prevent the spread of infection by helping in change of behaviour and lifestyle and provide psychosocial support to individual and family.

**Components of pretest counselling:**

1. Assessment of risk and likelihood and meaning of positive, negative and indeterminate test result.
2. Assess and educate regarding the understanding of HIV transmission and natural history, window period and differentiation between HIV infection and full-blown AIDS.
3. Discuss confidentiality provisions and anonymous testing.
4. Assess psychological stability, social support and impact of a positive result.
5. Ensure follow up and discuss risk reduction plan and referral to other services, if needed.
6. Obtain informed consent for HIV antibody testing.

**Components of post-test counselling:**

1. The results of HIV testing should always be given in person and under all precautions of keeping confidentiality.
2. Disclose test results and provide interpretation (positive, negative, indeterminate) in the context of that person's risk of infection.
3. If test is negative, readdress and reinforce risk reduction plan especially regarding safer sexual practices. Discuss the need for repeat testing for those with recent (<6 months) exposure or ongoing risk behaviour.
4. If test is positive, counsel about the meaning of a positive HIV test; differentiate with full-blown AIDS and ways to avoid transmitting HIV to others. Assess need for psychological support and provide referrals for medical, psychological or social service, if necessary. Emphasize the importance of early clinical intervention and schedule follow-up visit to assess psychological status and to address partner notification issues.

**Antiretroviral therapy–Assessment for initiation:**

Prior to starting antiretroviral therapy in any HIV infected patient, a thorough assessment of the patient should be performed. The goals of this assessment are:

1. Determine the clinical stage of HIV infection.
2. A detailed history and physical examination that focus on past significant illness (especially related to HIV), identify current, ongoing HIV associated illnesses or opportunistic infections (OI) that require treatment, identify other co-existing medical conditions.

3. Determine the eligibility and need for ART and OI prophylaxis.
4. Laboratory investigations – including a CD4 count that will help in staging the disease and determining the need to start ART.
5. Identify and manage other high-risk behaviours—injecting drug use, unprotected sex, etc.

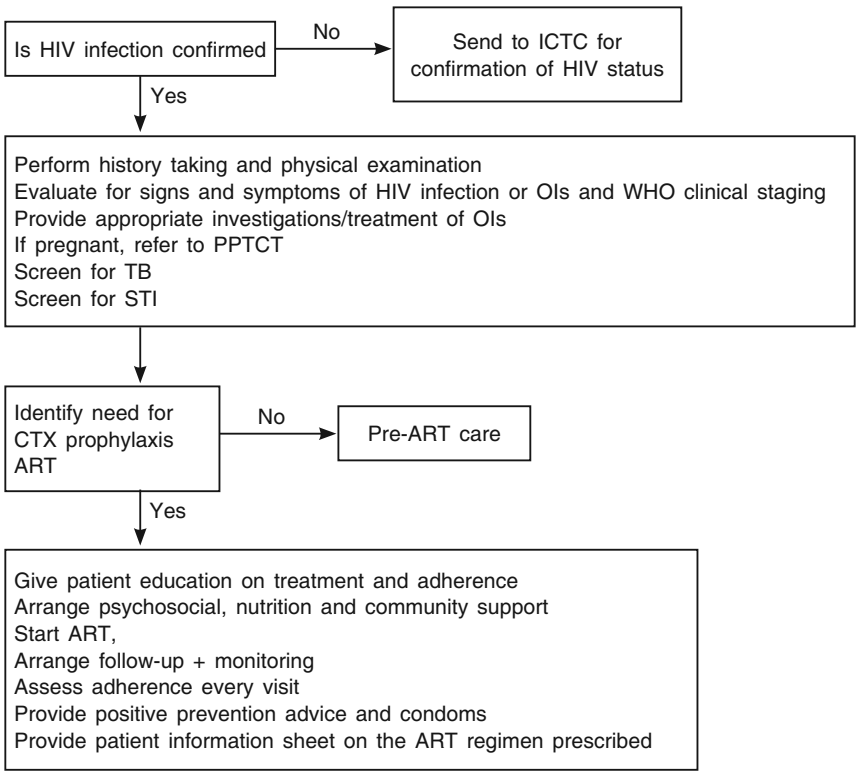


**Fig. 7.1.** Assessment and management of HIV-infected person.

## WHO Clinical staging of HIV/AIDS for adults and adolescents

### Clinical stage 1

Asymptomatic

Persistent generalized lymphadenopathy

### Clinical stage 2

Unexplained moderate weight loss (<10% of presumed or measured body weight)

Recurrent respiratory tract infections—sinusitis, tonsillitis, otitis media, pharyngitis

Herpes zoster

Angular cheilitis
Recurrent oral ulceration
Papular, pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections

**Clinical stage 3**

Unexplained severe weight loss >10% of presumed or measured body weight
Unexplained chronic diarrhoea of more than 1 month
Unexplained persistent fever >37.5° C intermittent or constant for >1 month
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections—pneumonia, empyema, pyomyositis, bone or joint infections, meningitis, bacteremia
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia < 8 g/dl, neutropenia < 500 /cumm, and/or chronic thrombocytopenia

**Clinical stage 4**

HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection–orolabial, genital or anorectal >1 month or visceral infection at any site
Oesophageal candidiasis
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection–any site
CNS toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis–including meningitis
Disseminated non-tuberculous mycobacterial infections
Progressive multifocal leucoencephalopathy
Chronic cryptosporidiosis, isosporiasis
Disseminated mycosis
Lymphoma – cerebral or B cell NHL
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Recurrent septicaemia
Symptomatic HIV associated nephropathy or cardiomyopathy

## Antiretroviral therapy

The goals of ART are:

1. ***Clinical goals*** **–** prolongation of life and improvement in quality of life.
2. ***Virological goals*** **–** Prolonged suppression of viral replication to undetectable levels (HIV RNA <50-75 copies/ml).
3. ***Immunological goals*** **–** immune reconstitution that is both qualitative and quantitative.
4. ***Therapeutic goals*** **–** rational sequencing of drugs in a fashion that achieves clinical, virological and immunological goals while maintaining treatment options, limiting drug toxicity and facilitating adherence.
5. ***Epidemiological goals*** **–** reduction of transmission of HIV in individuals and in the community.

The currently available antiretroviral drugs are classified as:

**Nucleoside reverse transcriptase inhibitors (NRTIs):** Zidovudine (AZT, ZDV); Stavudine (d4T); Lamivudine (3TC); Didanosine (ddI); Zalcitabine (ddC); Abacavir (ABC); Emtricitabine (FTC); Tenofovir (TDF)

**Non-nucleoside reverse transcriptase inhibitors (NNRTI):** Nevirapine (NVP); Efavirenz (EFV); Delavirdine (DLLV)

**Protease inhibitors (PIs):** Saquinavir (SQV); Ritonavir (RTV); Nelfinavir (NFV); Amprenavir (APV); Indinavir (INV); Lopinavir/ritonavir (LPV); Fosamprenavir (FPV); Atazanavir (ATV); Tipranavir (TPV)

**Fusion inhibitors (FI):** Enfuviritide (T 20)

**CCR5 antagonist:** Maraviroc

**Integrase inhibitor:** Raltegravir

**Initiation of ART based on CD4 count and clinical staging (Table 7.1)**

Though CD4 count is used as a guide to initiate ART, ART must not be delayed in any patient, if he is clinically eligible according to WHO clinical staging. However a CD4 count must be ordered as soon as possible.

### Important points to consider:

1. Offer ART to symptomatic patients if, CD4 count is 200-350 cells/cu mm.
2. Consider ART in asymptomatic patients with CD4 count 200-350 cells/cu mm and monitor closely for new symptoms.
3. The optimum time to start ART is when the patient is symptomatic and develops the first opportunistic infection (OI).
4. Ensuring good adherence is essential to the success of ART regimen. The patient must be assessed for readiness to start ART and must be counselled in detail about adherence – its benefits and the harms of non-adherence. Patients need at least 2 counselling sessions prior to ART initiation. Many patients may need more than this.

**Table 7.1.** Guidelines for the initiation of ART based on CD4 count and clinical staging

| Classification of HIV disease | WHO clinical stage | CD4 not available or pending result | CD4 available |
|---|---|---|---|
| Asymptomatic | 1 | Do not treat | Treat, if CD4 < 200 |
| Mild symptoms | 2 | Do not treat | Treat, if CD4 < 200 |
| Advanced symptoms | 3 | Treat | Consider treatment If CD <350 and initiate before CD 4 < 200 |
| Severe / advanced symptoms | 4 | Treat | Treat irrespective of CD4 count |

It is recommended that all patients should be started with a three drug combination from two different classes, namely NRTI and NNRTI (Table 7.2.). Different ART regimen approved for use by NACO are as shown in Table 7.3.

**Table 7.2.** Preferred ART regimen available through the NACO

| Recommendation | Regimen | Comments |
|---|---|---|
| Preferred first-line regimen | AZT + 3TC + NVP | AZT may cause anaemia, which requires Hb monitoring, but is preferred over d4T because of d4T toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy)<br>Patients who develop severe anaemia while on an AZT-based regimen should not be re-challenged with AZT. In such cases, the patient should receive either d4T or TDF in place of AZT<br>For women with CD4 > 250 cells/$mm^3$, monitor for hepatotoxicity closely, if started on the NVP-based regimen |
| Alternative first-line regimens | AZT + 3TC + EFV | EFV is substituted for NVP in cases of intolerance to the latter or if patients are receiving rifampicin-containing anti-TB treatment.<br>EFV should not be used in patients with grade 4 or higher elevations of ALT |
| | D4T + 3TC + (NVP or EFV) | If the patients have anaemia, a d4T-based regimen should be prescribed |

**Table 7.3.** The ART regimen approved for use by NACO

| National ART regimen | Regimen | Indications | Availability |
|---|---|---|---|
| Regimen I | Zidovudine + Lamivudine + Nevirapine | "Preferred regimen" | First line regimens available at all ART centers Alternate first line ART made available at 10 centers of excellence |
| Regimen I(a) | Stavudine* + Lamivudine + Nevirapine | For patients with Hb < 9 g/dl | |
| Regimen II | Zidovudine + Lamivudine + Efavirenz | Preferred for patients on anti-tuberculosis treatment and Hb > 9 g/dl | |
| Regimen II (a) | Stavudine* + Lamivudine + Efavirenz | For patients on anti-tuberculosis treatment and Hb < 9 g/dl | |
| Regimen III | Tenofovir + Lamivudine + Nivirapine | For patients not tolerating ZDV or d4T on an NVP-based regimen | |
| Regimen III (a) | Tenofovir + Lamivudine + Efavirenz | For patients not tolerating ZDV or d4T on an EFV-based regimen | |
| Regimen IV | Zidovudine + Lamivudine + Atazanavir/Ritonavir | For patients not tolerating both NVP and EFV, and Hb > 9 g/dl | |
| Regimen IV (a) | Stavudine + Lamivudine + Atazanavir/Ritonavir | For patients not tolerating both NVP and EFV, and Hb < 9 g/dl | |
| Regimen V | Tenofovir + Lamivudine + Atazanavir/Ritonavir | | Second line ART made available at 10 centres of excellence |

## Dosages:

Stavudine – 30 mg twice daily

Zidovudine – 300 mg twice daily

Lamivudine – 150 mg twice daily

Nevirapine – 200 mg once daily as lead in dose for 2 weeks followed by 200 mg twice daily

Efavirenz – 600 mg once daily

**Drug combinations and strategies NEVER to be used:**

1. Monotherapy or dual therapy for the management of HIV infection
2. Combination of AZT and 3TC
3. d4T and ddI
4. Unboosted PIs
5. Structured treatment interruptions

**Important considerations:**

1. Nevirapine is the first choice NNRTI in ART regimens. Efavirenz is preferred over NVP when:
   a. There is significant NVP toxicity
   b. Patients have associated TB
2. Efavirenz is contraindicated in pregnant HIV-infected women.
3. Do not start ART in the presence of an active, ongoing OI. OIs should be treated or at least stabilized before ART is started.
4. Follow-up and monitoring is essential in patients initiated on ART.
5. Monitor for clinical effect, adverse effects and toxicities.
   The Table 7.4 highlights the major toxicities observed with the ARVs.

Definition of ART failure (first line regimen):

1. **Clinical failure:** New or recurrent WHO stage 4 condition after at least 6 months of ART
2. **Immunological failure**:
   a. Fall of CD4 count to pre-therapy or baseline
   b. 50% fall from the on treatment peak value
   c. Persistent CD4 levels below 100 cells/cu mm
3. **Virological failure**: Plasma viral load > 10,000 copies/ml

**Table 7.4.** Major drug toxicities

| Toxicity | Possible drug responsible |
|---|---|
| Hepatitis | NVP, EFV, uncommon with NRTIs |
| Acute pancreatitis | ddI, Lamivudine |
| Lactic acidosis | All NRTIs |
| Hypersensitivity | NVP, Abacavir |
| Rash, Stevens Johnson syndrome | NVP, EFV (rarely) |
| Peripheral neuropathy | Stavudine, ddI |
| Haematological toxicity—anaemia | ZDV |
| Lipodystrophy | All NRTIs especially d4T |
| Neuropsychiatric symptoms | EFV |
| Dyslipidaemia, insulin resistance | All protease inhibitors |
| Renal toxicity | Indinavir |
| GI intolerance | Most ARVs |

## OCCUPATIONAL HIV EXPOSURE AND HIV POST-EXPOSURE PROPHYLAXIS (PEP)

**PEP** refers to the comprehensive management given to minimize the risk of infection following potential exposure to blood-borne pathogens (HIV, HBV, HCV). This includes counselling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person, first aid and depending on the risk assessment, the provision of short term (4 weeks) of antiretroviral drugs, with follow-up and support. The following stepwise approach to occupational exposure is recommended:

**Step 1: Management of exposure site–first aid**

**For skin–if the skin is broken after a needle-stick or sharp instrument:**

Immediately wash the wound and surrounding skin with water and soap, and rinse. Do not scrub; do not use antiseptics or skin washes (bleach, chlorine, alcohol, betadine).

**After a splash of blood or body fluids to unbroken skin:**

Wash the area immediately; do not use antiseptics.

**For the eye:**

Irrigate exposed eye immediately with water or normal saline.

Sit in a chair, tilt head back and ask a colleague to gently pour water or normal saline over the eye. If wearing contact lens, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean them in the normal manner. This will make them safe to wear again; do not use soap or disinfectant on the eye.

**For mouth:**

Spit fluid out immediately; rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times; do not use soap or disinfectant in the mouth.

**Step 2: Define the category of exposure**

**Category definition**

**Mild exposure:** Mucous membrane/non-intact skin with small volumes, e.g. a superficial wound (erosion of the epidermis) with a plain or low caliber needle, or contact with the eyes or mucous membranes, subcutaneous injections following small-bore needles.

**Moderate exposure:** Mucous membrane/non-intact skin with large volumes or percutaneous superficial exposure with solid needle, e.g. a cut or needle stick injury penetrating gloves.

**Severe exposure:** Percutaneous with large volume, e.g. an accident with a high caliber needle (>18 G) visibly contaminated with blood; a deep wound (haemorrhagic wound and/or very painful); transmission of a significant volume of blood; an accident with material that has previously been used intravenously or intra-arterially.

**Step 3: Determination of risk in source**

**Source HIV– status definition of risk in source**

**HIV negative**–source is not HIV infected but consider HBV and HCV.

**Low risk**–HIV positive and clinically asymptomatic.

**High risk**–HIV positive and clinically symptomatic (see WHO clinical staging)

**Unknown**–status of the patient is unknown, and neither the patient nor his/her blood is available for testing (e.g. injury during medical waste management the source patient might be unknown). The risk assessment will be based only upon the exposure (HIV prevalence in the locality can be considered).

**Table 7.5.** Determine the risk for exposure to assess need for PEP

| **Exposure** | **Status of source** | | |
|---|---|---|---|
| | **HIV + and asymptomatic** | **HIV + and clinically symptomatic** | **HIV status unknown** |
| Mild | Consider 2-drug PEP | Start 2-drug PEP | Usually no PEP or consider 2-drug PEP |
| Moderate | Start 2-drug PEP | Start 3-drug PEP | Usually no PEP or consider 2-drug PEP |
| Severe | Start 3-drug PEP | Start 3-drug PEP | Usually no PEP or consider 2-drug PEP |
| **Regimens of PEP:** | | | |
| **Medication** | **2-drug regimen** | **3-drug regimen** | |
| Zidovudine (AZT) | 300 mg twice a day | 300 mg twice a day | |
| Stavudine (d4T) | 30 mg twice a day | 30 mg twice a day | |
| Lamivudine (3TC) | 150 mg twice a day | 150 mg twice a day | |
| | | 1st choice: | |
| | | Lopinavir/ritonavir (LPV/r) | |
| | | 400/100 mg twice a day or | |
| | | 800/200 mg once daily with meals | |
| | | 2nd choice: Nelfinavir (NLF) | |
| | | 1250 mg twice a day or<br>750 mg three times a day with empty stomach | |
| | | 3rd choice: Indinavir (IND) | |
| | | 800 mg every 8 hours and drink 8-10 glasses (≥ 1.5 litres) of water daily | |

**Note:** If protease inhibitor is not available and the 3rd drug is indicated, one can consider using Efavirenz (EFV 600 mg once daily).

**Table 7.6.** Tuberculosis and HIV infection

| Aetiology | Presenting signs and symptoms | Diagnostics (laboratory, X-ray and others) | Management and treatment | Unique features, prophylaxis |
|---|---|---|---|---|
| *Pulmonary tuberculosis* | Cough for >2 weeks,<br>not responding to antibiotic treatment<br>Purulent or blood-stained sputum<br>Night sweats<br>Weight loss<br>Evening fevers | Chest X-ray: Miliary pattern, hilar adeno-pathy, pleural effusion,<br>focal infiltrates in upper and hilar regions<br>Multilobar infiltrates<br>Interstitial infiltrates<br>Cavitation<br>with severe immunosuppression, X-ray might appear normal.<br>Sputum in adults: 2 samples recommended:<br>one on the spot, one early morning (day 2) | The management and treatment of TB is as per RNTCP guide-lines following the DOTS regimen<br>Start ART after 2 weeks of intitation of ATT for all patients with CD4 <350 cells/cu mm (as soon as patient is stabilized.<br>For patients with CD4 >350, defer ART | More common with HIV and worsens HIV disease<br>Atypical presen-tation if there is severe immuno-suppression<br>Pulmonary TB at any CD4 level;<br>disseminated TB usually at CD4 <200 cells/cu mm |

***Extrapulmonary TB and HIV***: Start ART after 2 weeks of initiation of ATT in all patients irrespective of CD4 count (as soon as patient is stabilized, special attention to monitoring hepatotoxicity).

***For details of prevention of parent to child HIV transmission (PPTCT), see Chapters 15 and 19.***

## OPPORTUNISTIC INFECTIONS

### Definition of opportunistic infections (OIs)

An opportunistic infection is a disease caused by a microbial agent in the presence of a compromised host immune system. Acquired immunodeficiency syndrome (AIDS) is defined as the occurrence of life-threatening OIs, malignancies, neurological diseases and other specific illnesses in patients with HIV infection and CD4 counts <200 cells/cu mm. The appearance of many OIs correlates with the CD4 count. Tuberculosis (TB) generally develops at CD4 counts of 200–500 cells/cu mm, as does *Candida albicans* infection *Pneumocystis jiroveci* pneumonia (PCP, earlier known as *Pneumocystis carinii*) generally occurs at CD4 counts <200 cells/cu mm and cytomegalovirus (CMV) infection occurs when the CD4 count falls below 100 cells/cu mm.

In the West, the incidence of OIs has markedly declined because of the widespread availability of highly active antiretroviral therapy (HAART). However, OIs continue to contribute significantly to the morbidity and mortality in resource-limited countries, though the increasing availability of ART will help reduce this.

**Table 7.7.** Common opportunistic infections and their management

| **I. Pneumocystis carinii pneumonia (PCP)**<br>*Pneumocystis carinii* pneumonia is a fungus that infects the lungs | |
|---|---|
| Symptoms | Typically fever, dry cough and progressive difficulty breathing. Also weight loss, night sweats and fatigue. |
| Presentation time frame | Subacute onset of symptoms over a period of weeks |
| CD4 count | <200 |
| Diagnosis | X-ray, induced sputum or bronchoscopy, serum LDH. |
| Severity of disease | Severe disease – breathless at rest or $PaO_2$<50 mmHg breathing room air.<br>Moderate disease – breathless on minimal exertion, $PaO_2$ 50-70 mmHg breathing room air at rest.<br>Mild disease – breathless on moderate exertion, $PaO_2$ > 70 mmHg breathing room air at rest. |
| Preventive therapy (prophylaxis) | Indicated when CD4+ cell counts equal or are below 200 and/or symptomatic HIV.<br>Preferred: TMP/SMX (two single-strength tablets daily or one double-strength tablet daily or three times a week). A gradual increase in TMP/SMX dose may help reduce the incidence of an adverse reaction to the drug. |
| Stopping preventive therapy | Able to stop, if CD4 cell count remain above 200 for more than 3 months measured on 2 separate occasions over at least 3 months on highly active antiretroviral therapy. |
| Treatment | Management of PCP depends on the degree and severity of disease<br>1. Severe disease – hospitalize, intravenous TMP/SMX (3-4 mg/kg/day for 21 days), supplemental oxygen. Patients with severe hypoxaemia ($PaO_2$ <70 mm Hg breathing room air at rest) should be given corticosteroids (prednisolone 1 mg/kg per day for 5 days with gradual tapering of dose until completion of acute treatment.<br>2. Moderate disease – an oral regimen can be used and management can proceed on an out-patient basis, although hospitalization should be considered. Recommended oral regimen: TMP/SMX 480 mg 2 tabs twice a day for 21 days.<br>3. Mild disease – Oral TMP/SMX as above. |
| Toxicities of treatment | TMP/SMX – hypersensitivity (typically fever and maculopapular rash), nausea and vomiting, bone marrow toxicity, hepatitis, Dapsone– hypersensitivity, haemolysis in people with G6PD deficiency<br>Clindamycin – hypersensitivity, diarrhoea |

| | |
|---|---|
| | Atovaquone – hypersensitivity, GI, hepatitis |
| | Pentamidine – renal impairment, pancreatic, cardiac dysrhythmias, hypotension |
| Alternative therapies | Dapsone 100 mg once a day for 21 days – preferred second line option |
| | Clindamycin 450 mg 4 times a day + primaquine 15 mg once daily for 21 days |
| | Trimethoprim 300 mg once a day for 21 days |
| | Atovaquone 750 mg once a day for 21 days |
| | Pentamidine (intravenous) 3-4 mg/kg/day for 21 days |
| Maintenance therapy | Everyone who has had PCP should be on maintenance therapy. The choice is the same as those for primary preventive therapy. |
| Stopping maintenance therapy | There is some evidence that it may be possible to stop maintenance therapy, if CD4 cell counts stay above 200 on antiretroviral therapy. |
| | However, there is insufficient data to make a current recommendation. |

**II. Oesophageal candidiasis**

Candidiasis is a fungal infection that frequently occurs in the mouth and vagina. It is considered to be an opportunistic infection when it occurs in the oesophagus.

| | |
|---|---|
| Symptoms | Difficulty in swallowing, painful swallowing, or retrosternal discomfort. Weight loss is common. |
| Presentation time frame | Subacute over weeks |
| CD4 count | <100 |
| Diagnosis | Usually made clinically in the presence of oral candidiasis and dysphagia. Endoscopy is only indicated in those who fail to respond to a clinical trial of appropriate treatment. The diagnosis of oesophageal candidiasis should be reconsidered, if oral candidiasis is not present. Associated fever and oral ulceration are not common. |
| Preventive therapy (prophylaxis) | Not recommended because current drugs effectively treat the disease, antifungal resistance may develop, and drug-drug interactions may occur. |
| Treatment | Fluconazole 100-200 mg once a day for 2 weeks is the treatment of choice. |
| Alternative treatment | Amphotericin 0.3-0.5 mg/kg/day; |
| Maintenance therapy | Fluconazole (50-100 mg once a day) |
| Stopping maintenance therapy | There is evidence that patient who achieves CD4 counts >100 on ART may cease maintenance therapy. |

**III. Cryptococcosis**

*Cryptococcus* is a fungus that is inhaled but has a predilection for the meninges

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| Symptoms | Meningitis – headaches, nausea, fever, malaise, altered mental status, irritability and seizures. Lung involvement may co-exist – cough, chest pain, breathlessness. |
| Presentation time frame | Subacute with progressive symptoms over weeks to months or acute with symptoms over days. |
| CD4 count | <100 |
| Diagnosis | Usually by lumbar puncture to test for presence of *Cryptococcus* or cryptococcal antigen in cerebral spinal fluid, India Ink preparation.<br>ICP is often raised, CSF protein and glucose are generally normal and there may be few white blood cells. |
| Preventive therapy (prophylaxis) | Not currently recommended |
| Treatment | Preferred: IV Amphotericin B (0.5-0.8 mg/kg daily) + Flucytosine (100 mg/day) 4 times a day) for 2 weeks then Fluconazole (400 mg daily) for 8 to 10 weeks. |
| Alternative treatment | Liposomal Amphotericin |
| Maintenance therapy | Fluconazole 200 mg once a day.<br>Pregnant women should avoid azole drugs. |
| Stopping maintenance therapy | Not currently recommended because of the few people studied.<br>Cohort studies suggest that maintenance therapy can be ceased in patients with sustained CD4 response to ART (CD4 >200) for >3 months. |

**IV. Toxoplasmosis**

Toxoplasmosis is a parasite that has a predilection for the brain

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| Symptoms | Altered mental state (confusion, unusual behaviour), headache, fever, seizures, paralysis and coma. |
| Presentation time frame | Acute to subacute over days to weeks |
| CD4 count | <100 |
| Diagnosis | Typical appearance on CT (computed tomography) or MRI (magnetic resonance imaging) scan. Diagnosis is frequently presumptive on the basis of appearance on scan. If no response to appropriate empirical anti-toxoplasmosis therapy after 2 weeks, then consider brain biopsy to rule out CNS lymphoma. |
| Preventive therapy (prophylaxis) | Indicated when CD4+ cell counts are below 200 (for primary PCP prophylaxis).<br>Preferred: TMP/SMX (1 double-strength every 12 hours three times a week; or a single-strength or 1 double-strength tablet once a day). |
| Stopping preventive therapy | CD4+ cell counts above 200 for over 3-6 months. |

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| Treatment | Pyrimethamine 100-200 mg loading dose and then 50-75 mg once a day given in combination with sulphadiazine 4-6 g/day 4 times a day or Clindamycin 2.4 g /day 4 times a day for 6 to 8 weeks duration depending upon response if sulphadiazine is used then Folinic acid 25 mg once a day should be given to prevent haematological toxicity |
| | Corticosteroids may be used in the presence of significant cerebral oedema. |
| Alternative treatment | Pyrimethamine in combination with one of the following:<br>Azithromycin 1-1.5 mg/day |
| | Atovaquone 3 g/day |
| | Dapsone 100 mg/day |
| | Clarithromycin 2 g/day |
| Maintenance therapy | Preferred: Pyrimethamine (25-75 mg once a day) + sulphadiazine (500-1,000 mg four times a day for several days with leucovarin.) |
| Stopping maintenance therapy | Stopping maintenance therapy is not currently recommended |

**V. Cryptosporidiosis**

Cryptosporidiosis is a parasite that infects the GI tract and can cause symptoms

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| Symptoms | Chronic diarrhoea with frequent watery stools, abdominal cramps, nausea, fatigue, weight loss, loss of appetite, vomiting, dehydration, electrolyte imbalance (especially sodium and potassium) and fever. |
| Presentation time frame | Acute to chronic presentation over days to weeks or months in some cases |
| CD4 count | <100 |
| Diagnosis | Stool examination for detection of acid-fast oocysts in the stool or biopsy of small intestine. A specific request for examination for Cryptosporidiosis is required (special lab techniques are needed) |
| Preventative therapy (prophylaxis) | There are no proven effective therapies.<br>There is no good evidence that boiling water or the use of water filters prevents disease |
| Treatment | There are no proven effective therapies. |
| | Symptomatic treatment includes Loperamide, codeine and somatostatin analogues. Nitazoxanide up to 2 g/day can be used. |
| | Immune recovery induced by ART alone results in excellent clinical responses. |
| Maintenance therapy | There are no proven therapies that prevent cryptosporidiosis. |

## OI Prophylaxis:

| Opportunistic infection | Primary prophylaxis indicated when CD4 is | Drug of choice | Discontinue primary prophylaxis when CD4 is | Discontinue secondary prophylaxis when CD4 is |
|---|---|---|---|---|
| PCP | <200 | TMP-SMX 1 daily | >200 | |
| Toxoplasmosis | < 100 | TMP-SMX 1 DS daily | >200 | |
| CMV retinitis | Not indicated | Secondary: oral ganciclovir | Not applicable | >100 |
| Cryptococcus meningitis | Not indicated | Secondary: fluconazole | Not applicable | >100 |
| Oral and oesophageal candidiasis | Not indicated | Not applicable | Not applicable | Not indicated |

DS—double strength

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