Guidelines for Prevention and Management of Common Opportunistic Infections/Malignancies among HIV-Infected Adult and Adolescent

May 2007

NACO

Ministry of Health & Family Welfare
Government of India

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सत्यमेव जयते

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FOREWORD

HIV presently accounts for highest number of deaths attributable to any single infective agent. The rate of progression of an individual from HIV infection to AIDS depends on a number of viral and host factors including health status of person, type of risk behavior, type and frequency of exposure to opportunistic infections, accessibility to drugs for prevention and management of opportunistic infections and access to antiretroviral therapy. The profile of opportunistic infections varies from country to country depending on the infections already prevalent in the community. The early diagnosis and adequate management of opportunistic infections can slow down the progression to AIDS and need for ART. The current literature on management of OIs is based on infections seen in the developed countries. Tuberculosis, which is commonest opportunistic infection in our patients, is not seen commonly in western countries. Infections like histoplasmosis, MAC and blastomycosis seen in western countries are uncommon in our country. Also the profile of opportunistic infections has been changing over the years. There has been an increase in diagnosis of infections like PCP in our patients. This could be due to better diagnostic techniques as well as training of microbiologist in diagnosing these infections which were uncommon in pre-HIV era. Similarly certain new infections like penicillium marnefii have been reported from North-Eastern part of our country.

The above guidelines have been drafted by a wide consultative process involving experts from all over the country and keeping in view the infections commonly seen in HIV infected patients in India. The National AIDS Control Organisation would like to acknowledge the technical and funding support provided by the WHO Country Office (India) and CDC India in the development of these guidelines.

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ACRONYMS AND ABBREVIATIONS

ADA	adenosine deaminase
ADC	AIDS dementia complex
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
ART	antiretroviral therapy
ARV	antiretroviral
ASC-H	"atypical squamous cells – cannot rule out high-grade disease"
ASCUS	"atypical squamous cells of uncertain significance"
AST	aspartate aminotransferase
ATT	antituberculosis therapy
AZT	zidovudine
d4T	stavudine
ABC	abacavir
BAL	broncho-alveolar lavage
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CXR	chest X-ray
DOTS	Directly observed treatment, Short-course
EBV	Epstein–Barr virus
ELISA	enzyme-linked immunosorbent assay
ESLD	end-stage liver disease
FNAC	fine-needle aspiration cytology
HAART	highly active antiretroviral therapy
HAD	HIV-associated dementia
HBcAg	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCW	health-care worker
HHV 8	human herpesvirus 8
HPV	human papillomavirus
HSV	herpes simplex virus
IgG	immunoglobulin G
IRIS	immune reconstitution inflammatory syndrome
JC virus	James Canyon virus
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma-associated herpesvirus
LDH	lactate dehydrogenase
LP	lumbar puncture
MAC	*Mycobacterium avium* complex
MOTT	mycobacteria other than tuberculosis
MSM	men who have sex with men
MTB	*Mycobacterium tuberculosis*
O&P	ova and parasites
OHL	oral hairy leukoplakia
OI	opportunistic infection
PCP	*Pneumocystis jiroveci* (earlier *carinii*) pneumonia
PCR	polymerase chain reaction
PEG IFN	pegylated interferon
PET	positron emission tomography
PGL	persistent generalized lymphadenopathy
PID	pelvic inflammatory disease
PLHA	people living with HIV/AIDS
PPD	purified protein derivative
PTB	post-primary pulmonary TB
PUO	pyrexia of unknown origin
RIA	radioimmunoassay
RIBA	recombinant immunoblot assay
RNTCP	Revised National Tuberculosis Control Programme
RPR	Rapid Plasma Reagin
RSS	recurrent non-typhoidal *Salmonella* septicaemia
SPECT	single photon emission computed tomography
STI	sexually transmitted infection
TE	*Toxoplasma* encephalitis
TST	tuberculin skin test
VZV	Varicella zoster virus
VCT	voluntary counselling and testing
VDRL	Venereal Disease Research Laboratory
ZN	Ziehl–Neelsen

1 Section Introduction

HIV presently accounts for the highest number of deaths attributable to any single infective agent. India has an estimated 5.2 million HIV-infected people. The threat to their life is not from the virus alone. Opportunistic infections (OIs) and associated complications account for a considerable proportion of such mortality. Appropriate management of OIs is as important as antiretroviral therapy (ART) in preventing mortality and morbidity among HIV-infected persons.

The incidence of OI depends on the level of immunosuppression (occurring at CD4 cell counts of < 200/mm^3 or total lymphocyte count <1200/mm^3), and on the endemic prevalence of the causative agent. Also, apart from "true" OIs, which occur only among immunosuppressed individuals, infections such as tuberculosis (TB), amoebiasis and leishmaniasis occur more frequently in HIV-infected persons. Many of these OIs are seen in patients who are in WHO clinical stage IV and are referred to as "AIDS-defining illnesses".

Over 80% of OIs are caused by 28 pathogens. Health-care workers (HCWs) dealing with HIV-infected individuals need to recognize the characterisitc symptom patterns of these serious and frequent OIs to be able to institute prompt and effective treatment. Early recognition of the HIV status and periodic interaction between HCWs and those infected are needed for providing appropriate preventive advice and for timely recognition and treatment of OIs. Screening for OIs in persons at risk particularly before starting ART will reduce the incidence of immune reconstitution inflammatory syndrome (IRIS). Judicious use of chemo- and immunoprophylaxis to prevent various OIs favourably impacts the survival of HIV-infected people and is necessary to maximize benefits from the ART roll-out. More widespread availability of ART may then be expected to reduce OI, and decrease the hospitalization and mortality of HIV-infected persons.

Definition of opportunistic infections

An opportunistic infection (OI) 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/mm^3. The appearance of many OIs correlates with the CD4 count. Tuberculosis (TB) generally develops at CD4 counts of 200–500 cells/mm^3, as does *Candida albicans* infection *Pneumocystis jiroveci* pneumonia (PCP, earlier known as *Pneumocystis carinii*) generally occurs at CD4 counts <200 cells/mm^3 and cytomegalovirus (CMV) infection occurs when the CD4 count falls below 100 cells/mm^3.

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.

It is important to emphasize the strategies for diagnosis of OIs, their management in patients on ART, timing of initiation of ART in the presence of an OI, recommendations during pregnancy, geographically distinctive OIs (penicilliosis and leishmaniasis) and drug interactions during concomitant administration of treatment for OIs and ART. Simple preventive measures such as eating properly cooked food, drinking boiled water, hand-washing after toilet use, avoiding situations with a high risk of infection, and appropriate and timely immunizations go a long way in decreasing the disease burden of OIs.

ASSOCIATION BETWEEN OPPORTUNISTIC INFECTIONS AND CD4$^+$-LYMPHOCYTE COUNT

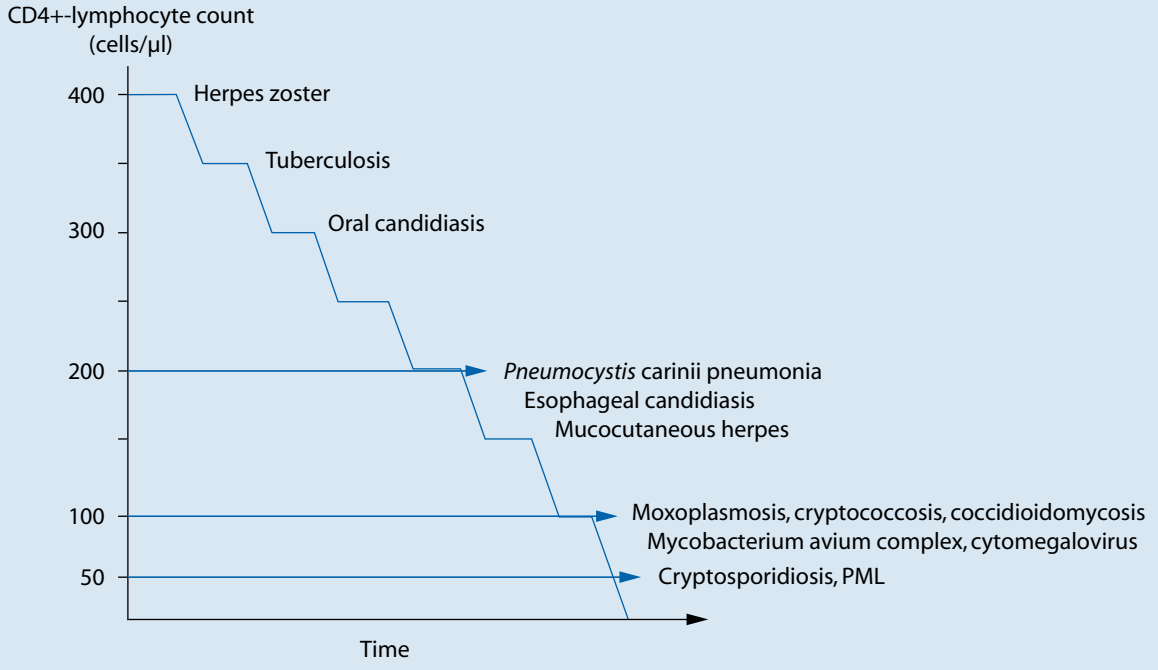


Table 1.1. HIV-related infections most frequently encountered in India

Bacterial	Viral	Fungal	Parasitic	Other illnesses
Tuberculosis	Herpes simplex virus infection	Candidiasis	Cryptosporidiosis	AIDS dementia complex
Bacterial respiratory infections	Oral hairy leukoplakia	Cryptococcosis	Microsporidiosis	Invasive cervical cancer
	Varicella zoster virus disease	*Pneumocystis* jiroveci pneumonia	Isosporiasis	Non-hodgkin lymphoma
Salmonella infection	Cytomegalovirus disease	Penicilliosis	Giardiasisww Stongyloides	
	Human papillomavirus infections		Toxoplasmosis	

* Rare infections include those due to *Bartonella henselae, Rhodococcus equii,* atypical mycobacterioses and human herpesvirus (HHS)-8 infections

Figure 1.1 Opportunistic infections among patients with AIDS in India

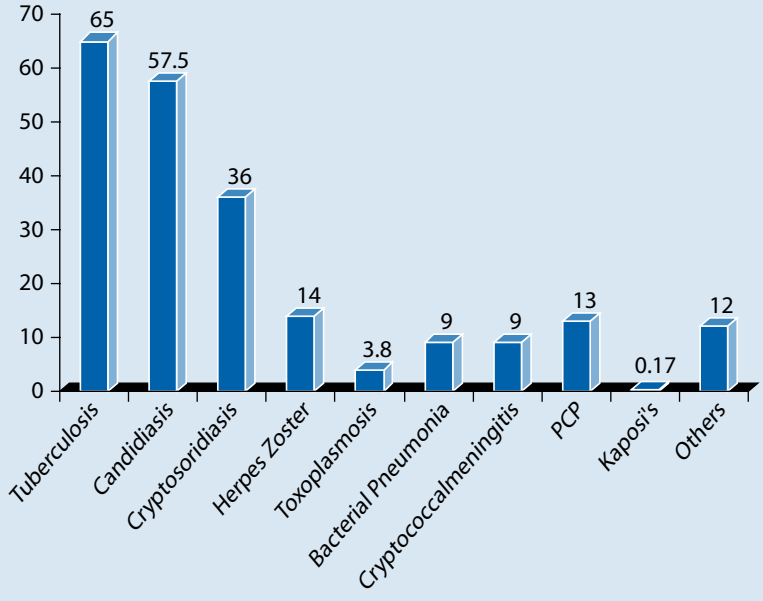
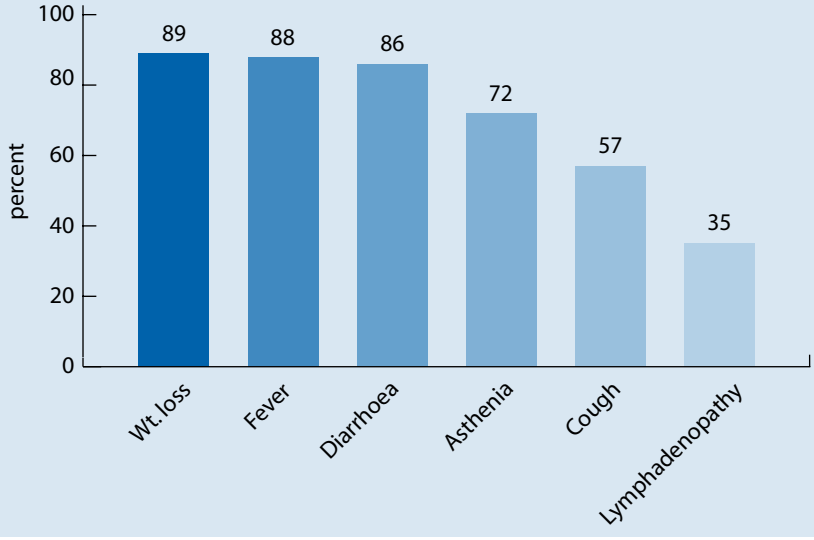


Figure 1.2 Presenting symptoms and signs in patients with AIDS



2 Section HIV and Respiratory Infection

Preventable and treatable respiratory infections are seen in up to two thirds of all HIV-infected individuals. Table 2.1 shows the pattern of pulmonary infections that emerge with falling CD4 counts.

Table 2.1. Association of pulmonary infections with CD4 counts in HIV-infected patients

Infection	CD 4 cell count (per mm^3)
Mycobacterium tuberculosis	<400
Bacterial pneumonia	<250
Suppurative lung and sinus disease	<100
Pneumocystis jiroveci pneumonia	<200
Mycobacterium avium complex	<100
Cytomegalovirus	<100

Although HIV-associated respiratory disease includes upper respiratory infections, sinusitis and bronchitis, the pneumonias are the most commonly diagnosed bacterial respiratory infection. In advanced stages of the disease, there is often more than one pathogen.

Table 2.2. Common infections of the respiratory system and their management

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and others)	Management and treatment	Unique features, prophylaxis
M. tuberculosis	Cough for >3 weeks, not responding to antibiotic treatment Purulent or blood-stained sputum Night sweats Weight loss Evening fevers	Chest X-ray: Miliary pattern Hilar adenopathy Pleural effusion Focal infiltrates in upper and hilar regions Multilobar infiltrates Interstitial infiltrates Cavitation With severe immunosuppression, X-ray might appear normal Sputum in adults: 3 samples recommended: one on the spot, one early morning (day 2), and another on the spot (day 2)	The management and treatment of TB is as per RNTCP guidelines following the DOTS regimen	More common with HIV and worsens HIV disease Atypical presentation if there is severe immunosuppression Pulmonary TB at any CD4 level; disseminated TB usually at CD4 <200 cells/mm^3

Table 2.2. Common infections of the respiratory system and their management

Streptococcus pneumoniae	Abrupt onset High fever Productive cough Pleuritic chest pain Purulent sputum Dyspnoea	Localized infiltrates limited to one lobe Often with pleural effusion Sputum Gram stain shows Gram-positive cocci Sputum for culture and sensitivity (C&S) Leukocytosis Blood cultures may be positive	Cefotaxime 2 g IV q6h Ceftriaxone 2 gm/day IV Amoxicillin 750 mg PO tid Fluoroquinolone: Levofloxacin 500 mg PO/IV qd; gatifloxacin 400 mg PO/IV qd; moxifloxacin 400 mg PO/day Alternative treatment: Macrolides (azithromycin clarithromycin, erythromycin) Vancomycin	Pneumonia in HIV-positive patients is more frequently associated with bloodstream infections and is a not uncommon cause of early death in HIV-infected patients in developing countries. Treat an acute respiratory illness accompanied by fever and chills in an HIV-infected person as an emergency.
Haemophilus influenzae	Fever Cough Purulent sputum Dyspnoea	Infiltrates more diffuse Reticular or granular pattern Leukocytosis Blood cultures may be positive Sputum for culture and sensitivity (C&S)	Cefuroxime Alternative regimens: TMP–SMX, cephalosporins (2nd- and 3rd-generation) or fluoroquinolones	
Staphylococcus aureus	Similar to *Streptococcus pneumoniae*	Bilateral patchy consolidation in critically ill patient Sputum Gram stain Sputum for culture and sensitivity (C&S)		Often other signs of staphylococcal infection, including pyomyositis, abscess
Protozoal				
Toxoplasmosis gondii	Fever Nonproductive cough Dyspnoea	Diffuse interstitial pattern or reticulonodular infiltrates confirmed by Giemsa staining of broncho-alveolar washings		Consider *Toxoplasma* pneumonitis where induced sputum fails to demonstrate PCP
Fungal				
Pneumocystis jiroveci (PCP) * NB: PCP is no longer classified as protozoal; current classification is fungal	Dry cough Progressive shortness of breath Fever Chest pain Patient becomes increasingly ill with fever,	Bilateral diffuse lace-like interstitial infiltrates extending from perihilar region Chest X-ray may be normal Signs of pneumonitis on CXR develop as disease slowly	TMP–SMX containing 15 mg/kg/day of trimethoprim PO or IV x 21 days + PO_2 <70 mmHg or A–a gradient >35 mmHg: prednisone 40 mg bid x 5 days, then 40 mg/day x 5 days, then 20 mg/day	PCP is the most frequently identified serious OI in HIV disease. Treatment is effective, but early recognition and treatment are important because

Table 2.2. Common infections of the respiratory system and their management

	severe dyspnoea/ hypoxia, confusion/ delirium Presentation is nonspecific and insidious	progresses Definitive diagnosis is by demonstrating cysts in induced sputum, broncho-alveolar lavage or biopsy specimens	to completion of treatment Alternative treatments: TMP 15 mg/kg/day PO + dapsone 100 mg/day x 21 days Pentamidine 4 mg/kg/ day IV x 21 days Clindamycin 600 mg IV q8h or 300–400 mg PO q6h + primaquine 15–30 mg base/day x 21 days Atovaquone 750 mg PO bid with meal x 21 days	of acute morbidity and mortality. More common in those with CD4 counts <200 cells/ mm^3; Chronic maintenance therapy (secondary prophylaxis) should be discontinued if CD4+ T lymphocyte count increases in response to ART from <200 to >200 cells mm^3 for >6 months
Penicillium marneffei	Abrupt onset of fever Anaemia Skin lesions Weight loss Cough, shortness of breath Local or generalized lymph-adenopathy, hepatomegaly or splenomegaly may occur (less common)	Diffuse nodular pulmonary infiltrates or cavitary disease		Skin involvement occurs in patients with disseminated disease The typical appearance is one of multiple, papular lesions, often with central umbilication or ulceration, resembling molluscum contagiosum. The lesions are typically on the face, scalp and upper trunk. The condition must be differentiated from TB and disseminated cryptococcal disease. If there are no skin lesions, the diagnosis is difficult CD4 <50 cells/mm^3

2.1 Bacterial pneumonias

Epidemiology

Bacterial pneumonias are common causes of HIV-related morbidity. Serious infections may occur even with relatively higher CD4 counts. The risk of developing bacterial pneumonia is increased in HIV-positive people who smoke, use crack cocaine, are intravenous drug users, or have alcoholic liver disease.

The common bacterial organisms causing pneumonia include *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Atypical pneumonia is common and in up to 33% of patients, no pathogen is isolated.

Clinical manifestations

The clinical manifestations are the same as in those without HIV, but they occur at a higher frequency and have higher complication rates. Such complications include bacteraemia, intrapulmonary cavitation, abscess, empyema and death.

Bacterial lower respiratory tract infections present with cough, sputum production, variable fever, chills and chest pain.

Lobar consolidation on chest X-ray is commonly observed in bacterial pneumonia. The presentation may be atypical with a multilobar, nodular or reticulonodular pattern.

Efforts should be made to exclude the presence of underlying TB in such patients as HIV-infected persons may have more than one OI at the same time and TB is the commonest.

Prompt and accurate diagnosis is essential. The outcome of HIV-associated bacterial pneumonia appears to be good with appropriate treatment.

Laboratory diagnosis

The diagnostic modalities used depend on available expertise, facilities and resources. Generally, microbiological investigations should precede initiation of therapy. Microscopy alone can be performed at routinely available laboratory services at health-care facilities. Culture of common pathogens may be possible at district/tertiary-level health centres while bacterial isolation and antimicrobial susceptibility testing may be possible only at tertiary/referral centres.

Chest X-ray and white blood cell (WBC) count aid in making a diagnosis of bacterial pneumonia. PCP may coexist with bacterial pneumonia. An induced sputum examination for *P. jiroveci* should be done to rule it out. AFB staining and TB cultures of sputum samples (either expectorated or induced) should be performed on all HIV-1-infected hospitalized patients with pulmonary infiltrates.

Specimen collection and transport

Deep, coughed-up sputum should be expectorated directly into a sterile, wide-mouth container. Sputum production may be assisted by postural drainage. In patients who are unable to produce sputum, aerosol-induced sputum may be collected by allowing the patient to breathe aerosolized droplets of a solution containing 15% sodium chloride and 10% glycerine for 10 minutes. The bronchial aspirate can be collected and broncho-alveolar lavage (BAL) performed during bronchoscopy but these are not recommended routinely.

Treatment

Pneumonia may require hospitalization for the administration of medications, oxygen and life support. Therapy should target the common pathogens, particularly *Strept. pneumoniae* and *H. influenzae*. Recommended empirical regimens include the use of extended-spectrum cephalosporins (cefotaxime or ceftriaxone) or a fluoroquinolone with activity against *Strept. pneumoniae* (levofloxacin or gatifloxacin).

Combination therapy with a macrolide or quinolone plus a cephalosporin should be considered for those with severe illness. Among patients with CD4 counts <100 cells/mm^3, previous *Pseudomonas* infection, bronchiectasis or neutropenia, empirical coverage should include agents such as ceftazidime, cefepime, piperacillin/tazobactam, carbapenems, or high-dose ciprofloxacin or levofloxacin. If ceftazidime and ciprofloxacin are used, other antimicrobial agents may be needed for optimal Gram-positive coverage.

Clinical improvement usually occurs within 2–3 days of treatment. However, completing the full course of antimicrobial therapy (7–10 days) is essential to ensure adequate control of infection and prevent the development of resistant strains. Failure of therapy is suspected in the presence of persistent pyrexia, persistently elevated total WBC count, persistent or worsening pulmonary signs or radiological abnormalities, and progressive hypoxaemia or other evidence of progressive disease. Antimicrobial therapy with agents with a broader spectrum of activity or new drugs should then be given, depending on the culture report.

Prevention of recurrence

The most effective strategy to prevent recurrence is to optimize ART. Adults and adolescents with CD4 counts ≤200 cells/mm^3 should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine if they have not received it during the preceding five years. Annual influenza vaccination may also help prevent superinfections.

Using antibiotics solely to prevent recurrence may lead to the development of drug-resistant strains and drug toxicity, and hence is not recommended.

2.1.1 Streptococcus pneumoniae infection

The disease is caused by a widely prevalent Gram-positive coccus. It usually occurs as a sequel to a viral bronchitis and is commoner in smokers. Infection with *Strept. pneumoniae* is far more common in those with HIV infection than in age-matched HIV-negative populations. Recurrent pneumococcal pneumonia is also more common among HIV-1-infected patients, with a rate of 8–25% within 6 months. Reinfection with a different strain is more common than relapse. Treatment is with Cap. amoxycillin, 500 mg q8h for 7–10 days or until improvement.

2.1.2 Haemophilus influenzae infection

H. influenzae is more likely to cause disease in smokers, patients with chronic obstructive pulmonary disease (COPD), or those who have chronic bronchitis. It responds to amoxycillin 500 mg q8h for 7 days.

2.1.3 Nocardiosis

It is caused by *Nocardia*, a Gram-positive branching bacterium found extensively in the soil and in decomposing organic matter. Human disease is usually caused by *N. asteroides* and *N. braziliensis*. It may produce cough, fever, haemoptysis, pleural involvement and empyema, and may be indistinguishable from TB. It can also cause disseminated disease. A high degree of clinical suspicion is needed to make a diagnosis. The organism is not easily detected in cultures or on sputum examination. When seen they may appear as partially acid-fast filaments.

Treatment

Severe pulmonary involvement or disseminated disease requires treatment with parenteral antibiotics such as ceftriaxone or amikacin. Local infection responds to long-term sulfonamides and surgical debridement.

2.2 Fungal pneumonia

2.2.1 *Pneumocystis Jiroveci* Pneumonia (PCP)

Epidemiology

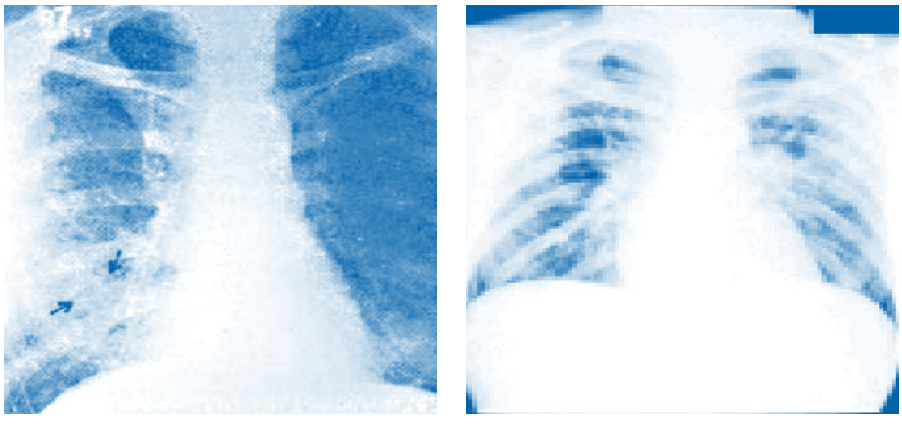
Pneumocystis jiroveci pneumonia (PCP) is a life-threatening respiratory disease caused by *P. jiroveci* (previously known as *Pneumocystis carinii*). Initial infection with *P. jiroveci* usually occurs in early childhood. Two-thirds of healthy children have antibodies to *P. jiroveci* by 2–4 years of age. Adult PCP results from reactiviation of latent infection or new exposure to the organism. Person-to-person spread occurs by the airborne route. PCP infection occurs in 20–30% of AIDS patients. Even with treatment, PCP is associated with a mortality of 20–40%.

Clinical features

PCP occurs in advanced HIV disease generally with a CD4 count <250 cells/mm^3. The onset is indolent with fever, non-productive cough and progressive dyspnoea out of proportion to the cough. Fever is present in the majority of cases. Fatigue and night sweats may appear before respiratory symptoms. In mild cases, pulmonary examination at rest may be normal. Tachypnoea, tachycardia and diffuse dry "cellophane" rales may be present. Physical signs and radiological changes occur in the late stage of the infection. Other symptoms are tightness of the chest and difficulty in breathing. Extrapulmonary disease is rare but can affect any organ. In 2–6% of cases, PCP may present with spontaneous pneumothorax.

Table 2.3. Clinical manifestations of *pneumocystis jiroveci* pneumonia (earlier known as *P. carinii*)

	Mild	Moderate	Severe
Symptoms	Cough, sweats, exertional dyspnoea	Dyspnoea on minimal exertion, fever, sweats, cough (nonproductive)	Dyspnoea at rest, tachypnoea, persistent fever
Blood gas analysis	PaO_2 normal	PaO_2 60–80 mmHg and 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



Pneumocystis jiroveci pneumonia

Diagnosis

Presumptive diagnosis: A presumptive diagnosis can be made in the presence of clinical symptoms, low CD4 count/presence of oral candidiasis and suboptimal prophylaxis in the past. The PaO_2 can be used to grade the severity. Chest X-ray may support the diagnosis but may also be normal. Diagnosis should be confirmed by sputum examination, if available. However, treatment should not be withheld for want of confirmation. Serum lactate dehydrogenase (LDH) is often raised. A high LDH level is an unfavourable sign and indicates severe PCP. However, its use as a parameter for prognosis of the disease is limited.

Definitive diagnosis: The diagnosis of PCP is confirmed by demonstration of the organism in pulmonary secretions. This may be achieved by (a) sputum induction with hypertonic saline (50–80% sensitive); (b) BAL (86–97% sensitive); (c) BAL and transbronchial lung biopsy (99% sensitive).

Sputum is often difficult to obtain. However, it can be collected by inhalation of hypertonic saline or by nebulization. All material coughed out (2–3 ml) is collected and diluted with an equal volume of sterile water. The specimen is liquefied with dithiothreitol or used as such for preparing smears and staining.

Staining techniques: The common staining techniques undertaken for demonstrating *P. jiroveci* include: (a) Wright–Giemsa staining: Cysts and trophozoites of *P. jiroveci* are seen, which are thick-walled 5–8 μm structures, with up to 8 intracystic bodies (1–2μm) termed sporozoites. Trophozoites are thin-walled, free-living, pleomorphic organisms containing a small nucleus. (b) Immunofluorescence (IF) staining: Organisms are visible either as a single cyst or aggregates of extracellular thick-walled cysts with a bright apple-green fluorescence. The cyst aggregates may or may not be embedded in a brightly stained extracellular matrix. Individual cysts may appear as comma shaped or parenthesis-like structures. (c) Silver impregnation: Gomori's methenamine silver stain is used.

Treatment

Trimethoprim (15–20 mg/kg daily) and sulfamethoxazole (75–100 mg/kg/day) in three or four divided doses is usually given for 21 days. In an adult, this usually is equivalent to **co-trimoxazole double strength (160/800) 2 tablets thrice daily**. Clinical worsening may occur during the first 3–5 days in some patients and *should not* lead to early change in treatment. Improvement usually occurs in 7–10 days.

If the patient is allergic to sulfamethoxazole, rapid desensitization should be carried out, using the procedure explained in Table 2.4.

Table 2.4. Desensitization regimen in patients allergic to sulfamethoxazole

Time in hours	Dose (TMP–SMX)	Dilution
0	0.004/0.02 mg	1:10,000
1	0.04/0.2 mg	1:1000
2	0.4/2 mg	1:100
3	4/20 mg	1:10
4	40/200 mg	tablet
5	160/800 mg	tablet

Alternative regimens for the treatment of PCP include:

a. TMP 15 mg/kg/day orally + dapsone 100 mg/day orally for 21 days
b. Clindamycin 600–900 mg intravenously q6–8h or 300–450 mg q6h orally + primaquine base 15–30 mg/day orally for 21 days.

In moderately severe or severe disease (PO_2<70 mmHg or A–a gradient >35 mmHg) prednisolone (40 mg orally twice daily for 5 days, then 40 mg once daily for 5 days, and then 20 mg per day to complete 21 days of treatment) should be given to all adult patients. Steroids should be started within 72 hours of initiation of specific treatment. It decreases alveolar oedema and improves oxygen perfusion across the alveoli. Oxygen is administered during the acute phase of the infection.

If there is no improvement within 10 days of treatment, the diagnosis of PCP should be reviewed. After clinical stabilization and completion of treatment, the patient should be referred for HAART.

Prophylaxis

Primary prophylaxis is recommended in patients with CD4 count <200 cells/mm^3, or in the presence of any other AIDS-defining illnesses. Secondary prophylaxis should be given to all patients after an episode of PCP. One double-strength tablet of trimethoprim–sulfamethoxazole (TMP–SMX) (160/800 mg) daily is used for prophylaxis.

Alternative regimens include dapsone 100 mg once a day. In the absence of other AIDS-defining illnesses, prophylaxis may be discontinued in a patient on ART with a CD4 count consistently >200 cells/mm^3 on two consecutive occasions over a period of 6 months.

2.3 Mycobacterial infections

2.3.1 Mycobacterium tuberculosis: TB and HIV–TB interaction

TB is the most common cause of death in people with HIV. In people with normal immune systems, initial contact with TB bacteria, usually in childhood, results in a robust granulomatous reaction and the infection is then contained and remains latent. In an HIV-infected person, because of immunosuppression, this response is modified leaving patients with a reduced ability to kill the bacteria. Simultaneously, active TB also promotes host HIV replication and progression to AIDS.

In India and other areas of the world where TB is endemic, TB infection is usually acquired in childhood. In any individual with latent infection, there is a 10% lifetime risk of reactivation of latent infection and progression to TB disease. However, in an HIV-infected person, the risk of reactivation varies between 5% and 10% yearly, which translates to a lifetime risk of 50% among HIV-infected individuals.

HIV-related TB can present with typical or atypical clinical and/or radiological features. Atypical features are usually found in persons with severe immunosuppression while those in the early stages of HIV infection present with typical signs and symptoms of TB. TB disease may become apparent at any time during HIV infection and may be pulmonary or extrapulmonary.

Pulmonary TB

This is most common form of TB disease. The presentation depends on the degree of immunosuppression:

- In patients with mild immunosuppression, chest X-ray (CXR) typically shows upper lobe and/or bilateral infiltrates, cavitation, pulmonary fibrosis and shrinkage. The clinical picture often resembles post-primary pulmonary TB (PTB), and the sputum smear is usually positive.
- In severely immunosuppressed patients, the features of the disease are atypical, resembling those of primary TB. The sputum smear can often be negative and CXR shows interstitial infiltrates, especially in the lower zones, with no features of cavitation and fibrosis. Unilateral or bilateral infiltrates are seen more often in the lower lobes than in the upper lobes and typical cavities are seen in only 25% of patients.

- In persons with advanced HIV infection, disseminated and extrapulmonary TB are more common. The most common forms are lymphadenitis, pleural effusion, pericarditis, miliary disease and meningitis.
- The most important symptoms are: cough lasting longer than 3 weeks and not responding to the usual antibiotic treatment, purulent/blood-stained sputum, evening fever, night sweats and weight loss.

Diagnostic tests

1. Sputum examination: Microscopic examination of sputum stained by the Ziehl–Neelsen (ZN) method is the diagnostic test of choice. A PTB suspect should submit three sputum samples for microscopy. At first visit, the patient should provide an on-the-spot sputum sample. Give the patient a sputum container to take home for an early morning sample on the following day (that is, on day 2). On day 2, when the patient brings in sample two, he or she provides another on-the-spot sample. An inpatient can provide three early morning sputum samples.
2. Radiological examination: The classical pattern seen on CXR in TB is upper lobe infiltrates with cavitation. However, in severe immunosuppression, the affected region is mostly extrapulmonary in the form of hilar adenopathy and pleural effusion. There may be upper zone infiltrates or a miliary pattern, and atypical lower zone infiltration of the lung fields as described above. Cavitation may not be seen in patients with severe immune suppression. It is not possible to make a confirmed diagnosis of TB based on the X-ray picture alone.
3. Purified protein derivative (PPD) test: PPD is likely to be positive at higher CD4 counts. As the count falls to less than 100 cells/mm^3 it may become negative. It has no diagnostic significance.
4. Fine-needle aspiration cytology (FNAC): An FNAC from a lymph node may show AFB in patients with HIV infection.
5. Other tests: An ultrasonography of the abdomen may show enlarged intra-abdominal lymph nodes and multiple hypoechoic lesions in organs such as the spleen or liver. A lumbar puncture (LP) done in suspected cases of TB meningitis may have a turbid or viscous appearance, with 100–300 lymphocytes/mm^3, 0–200 polymorphs/mm^3, 0.5–3 g/litre of protein, and half the blood value of glucose. A CT scan can pick up brain tuberculomas, hydrocephalus or enhancement of the basal meninges. Bone marrow biopsy and culture may demonstrate the presence of the organisms.

Treatment

Standard Directly observed treatment, Short-course (DOTS) regimens are to be followed according to the RNTCP programme in India. The patient should be referred to a DOTS centre for antituberculosis therapy (ATT). The regimens used for the treatment of pulmonary and extrapulmonary tuberculosis are same in both HIV-positive and -negative individuals. Around 6–8 months of treatment appears to be sufficient for extrapulmonary disease at many sites. Twelve months of therapy is recommended for miliary TB, bone or joint disease and tubercular meningitis. Persistently positive sputum culture after 2–3 months of therapy suggests the possibility of drug-resistant TB or non-compliance with therapy.

Revised National Tuberculosis Control Programme (RNTCP)

Treatment regimens followed vary according to the type of patient (whether the patient is a new case of TB or one who has been treated for TB previously), severity of illness and response to treatment.

Category I – Regimen used: $2(EHRZ)_3$ 4 $(HR)_3$

This regimen is recommended in patients with new sputum smear-positive TB, seriously ill smear-negative TB, seriously ill extrapulmonary TB, and all new TB patients who voluntarily disclose their HIV status.

Category II – Regimen used : 2 $(SEHRZ)_3$/1(EHRZ)/5 $(EHR)_3$

This regimen is recommended in patients with previously treated smear-positive TB (including relapse, failure and treatment after default).

Category III – Regimen used: $2(HRZ)_3/4(HR)_3$

This regimen is recommended in patients with new smear-negative TB, extrapulmonary TB and those who are not seriously ill.

In all categories, treatment is given in two phases.

- The first or **intensive phase** consists of treatment lasting for 2–3 months. In the intensive phase, three to five anti-TB drugs are administered depending on the category of treatment prescribed and all the thrice-weekly doses are given under direct observation.
- This is followed by the **continuation phase**, which lasts for 4–5 months. In the continuation phase, the number of anti-TB drugs administered is reduced to two or three drugs depending on the regimen prescribed and only the first dose of the week is given under direct supervision and the remaining two doses in the week are self-administered.
- E (ethambutol), H (isoniazid), R (rifampicin), Z (pyrazinamide) and S (streptomycin).
- The numbers before the bracket indicate the number of months for which the drugs are to be administered.
- The number "3" given as a subscript after the bracket indicates that the drugs are administered thrice weekly.
- Category I and Category III regimens are given for 6 months, while the Category II regimen is for 8 months.

Precautions

In HIV-infected TB patients, combining rifampicin with protease inhibitors and nevirapine has been found to decrease the levels of all the drugs, thereby decreasing the effectiveness of ART and increasing the rifampicin levels, leading to rifampicin-induced hepatotoxicity. In case ATT and ART are used together, an efaviranz-based ART regimen should be followed. If oral candidiasis is also present, administration of anti-TB drugs together with fluconazole can also result in hepatotoxicity. Close monitoring for serum transaminases and serum bilirubin is necessary for early detection of hepatotoxicity.

Dosages

In adults, the dosages of the drugs are as follows:

- isoniazid 600 mg thrice weekly
- rifampicin 450 mg (600 mg if weight >60 kg) thrice weekly
- pyrazinamide 1500 mg thrice weekly
- ethambutol 1200 mg thrice weekly
- Streptomycin 0.75 g thrice weekly (0.5 g in patients >50 years of age).

Tuberculous meningitis

Clinical features

The onset may be insidious or explosive, with fever, headache and vomiting. There may be TB elsewhere in the body or a history of close contact with persons suffering from TB.

Diagnosis

The diagnosis is established by an LP. The cerebrospinal fluid (CSF) pressure is high, proteins are increased and the sugar is low. There is pleocytosis with a predominance of lymphocytes. Acid-fast staining may not demonstrate the organisms and culture take several weeks.

Treatment

ATT with the standard drugs should be given for 1 year.

Relapse and resistance

This may be due to infection with resistant organisms, failure to adhere to therapy or inadequate dosage of the drugs.

Tuberculous diarrhoea

This is suspected if there is fever, diarrhoea, abdominal pain and loss of weight in an HIV-positive person with a positive Mantoux test or history of contact with a person having TB. The diagnosis is made by direct staining of the stools for AFB, barium studies and abdominal imaging studies.

Tuberculous lymphadenopathy

It is one of the most common forms of extrapulmonary TB in HIV-positive patients. The cervical nodes are most commonly involved. The lymph nodes are initially firm and discrete, and later become fluctuant and matted together. They may break down and form chronic sinuses which heal with scarring. FNAC of the involved lymph nodes are positive for AFB (high rate in HIV patients). In smear-negative pulmonary TB, it is worthwhile aspirating the extrathoracic lymph nodes to confirm the diagnosis of TB (80% positive).

2.3.2 Mycobacteria other than Tuberculosis (MOTT)

Mycobacterium Avium Complex (MAC)

Epidemiology: MAC can cause life-threatening symptoms in immunocompromised individuals. In advanced HIV disease, MAC usually causes disseminated disease. MAC is ubiquitous and is found in water, soil, food and in other animals. It is not seen very commonly in Indian patients with HIV. The patient may present with fever, night sweats, chills, weight loss, muscle wasting, abdominal pain, tiredness, pallor and diarrhoea. There may be enlargement of the liver, spleen and lymph nodes. The diagnosis is made by culture of the organism from the blood and/or bone marrow samples.

The diagnosis is *confirmed* if MAC is cultured from normally sterile body fluid, tissue or an organ. Diagnosis is considered *probable* if MAC is cultured from the bronchopulmonary, gastrointestinal, skin surface or other non-sterile sites (as the sole pathogen) *and* histopathological confirmation of AFB/MAC is obtained from the tissue specimen from which the culture was obtained.

A clinical MAC syndrome consists of one or more of the following: persistent fever <38°C for more than one week, night sweats, diarrhoea, weight loss or wasting, radiographically documented pulmonary infiltrates, hepatomegaly, splenomegaly, anaemia (haemoglobin <8.5 g/dl) and alkaline phosphatase more than twice the upper limit of normal.

Treatment: Combination therapy is generally used to prevent resistance. Clarithromycin is highly effective and results in rapid clearance of MAC from the blood. Azithromycin is an excellent substitute in cases where drug interactions or side-effects prevent the use of clarithromycin. Ethambutol is active against MAC, but it has to be combined with either clarithromycin or azithromycin. It has side-effects such as cause nausea, vomiting and visual problems. To prevent drug resistance and increase the potency of anti-MAC therapy, a third and sometimes a fourth antibiotic can be added. Rifampicin is used but has drug interactions, particularly with protease inhibitors or non-nucleoside analogues used to treat HIV. Ciprofloxacin can also be used. Lifelong maintenance therapy is necessary to prevent recurrence, but may be discontinued at a CD4 count >100 cells/mm^3.

Prophylaxis: Prophylaxis against MAC is usually started at a CD4 count <75 cells/mm^3. Macrolides are effective drugs for prophylaxis with risk reduction rates of 70%. The benefits of prophylaxis with macrolides outweigh the risks of resistance with prolonged use of antibiotics. Both azithromycin and clarithromycin cause similar side-effects.

To prevent MAC, clarithromycin must be taken once a day, whereas azithromycin only needs to be taken once a week. However, routine prophylaxis for MAC is presently not recommended in India.

2.3.3. Diagnostic modalities for mycobacterial infections

Specimens

Sputum is the **best sample in patients with pulmonary disease**.

The utility of *gastric lavage* is limited to senile, non-ambulatory patients, children less than three years and other patients who may have swallowed sputum or are unable to produce sputum by aerosol induction. Three consecutive specimens are to be submitted within three days for processing.

Blood: HIV-infected patients can have disseminated mycobacterial infection, the most common species in India being *M. tuberculosis*. Blood is collected in broth such as radiometric BACTEC 13 A or the lysis centrifugation system.

Urine: Three consecutive morning specimens (entire volume) must be collected in sterile containers after proper precautions in suspected cases of urogenital tuberculosis.

Fecal specimens: Patients with AIDS at risk for developing disseminated MAC disease can be identified by acid-fast staining and culture of fecal specimens.

Serodiagnostic techniques

Enzyme-linked immunosorbent assay (ELISA): Although the specificity of ELISA exceeds 95%, its sensitivity is only 53–62% in smear-negative pulmonary TB and 30–40% in extrapulmonary TB. Hence, antibody detection by ELISA is of limited use for the detection of TB and is not advocated as routine.

Radioimmunoassay (RIA): RIA has a higher sensitivity than ELISA for both antigen and antibody detection. However, it is very expensive with the added disadvantage of radioactivity and hence is of limited use.

Adenosine deaminase detection: The enzyme adenosine deaminase (ADA) is found in ten times greater amounts in lymphocytes than in RBCs. In addition, its activity is more in T cells than in B cells. The activity

of ADA is the maximum in rapidly proliferating lymphocytes and increases whenever an antigen stimulates cell-mediated immunity.

Newer diagnostic techniques

DNA probes: A nitrocellulose membrane filter is laden with DNA extracted from clinical specimens. A radiolabelled DNA probe complementary to a chosen sequence of the target *Mycobacterium* is added. After hybridization the radioactivity is measured by autoradiography. At least 10^4 bacilli/ml must be present for detection by this method.

Polymerase chain reaction (PCR): PCR is a sensitive and specific method of diagnosis. The technique consists of repetitive cycles of denaturation of the native double-stranded target DNA at 94 °C, annealing of DNA primers to the complementary sequences at 50 °C and extension of the annealed primers by Taq polymerase at 72 °C. Since the technique is expensive and requires trained personnel, it is used mainly by referral centres.

3 Section HIV and Gastrointestinal Infection

Conditions of the mouth and throat

Introduction

a. Overview

Patients with AIDS may have different conditions involving the oral cavity. An examination of the mouth needs to be part of the physical examination of every patient suspected of having HIV infection. Even in the absence of complaints, oral lesions and difficulty in swallowing can develop rapidly. Patients often present with another complaint, and it is the presence of oral thrush that raises the suspicion of HIV infection.

Oral lesions may be debilitating because they interfere with feeding and increase the risk of weight loss. (Painful eating and swallowing, and decreased appetite are signs.) These decrease the quality of life considerably. Oesophageal complaints are common and are frequently misdiagnosed as peptic ulcer. The incidence is higher in patients with CD4 counts <200 cells/mm^3.

b. Differential diagnosis includes the following:

- Bacterial infection: Anaerobic infections causing gingivitis
- Fungal infections: *Candida albicans*
- Viral infections: Epstein–Barr virus (EBV, oral hairy leukoplakia [OHL]), herpes simplex virus (HSV), CMV
- Oncological conditions: Kaposi sarcoma

Table 3.1. Conditions of the mouth and throat

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, cave-ats, prophylaxis
Oral hairy leukoplakia (OHL)	Non-removable whitish plaques with vertical folds, mostly on the lateral surface of the tongue			This condition is caused by EBV. It is neither dangerous nor painful and does not require any treatment. It is a sign of immune suppression and heralds a poor prognosis
Candida albicans	**Oral (thrush)** • Pseudomembranous: white/yellow colonies or clusters appearing any-where in the oral cavity. May be discrete or extensive, and can be easily removed by wiping	• Microscopic examination of scrapings from lesions • Microscopic examination of scrapings will be KOH-positive	Oral (thrush) Nystatin (1 tablet of 500 000 IU) gargled 4–5 tmes/day x 7–14 days Clotrimazole troche 10 mg 5 times/day (7–14 days)	Oral candidiasis is a rare condition in a healthy person, but is frequently the first indication of immune impairment in HIV-infected patients. It is often used as an indicator disease for starting

Table 3.1. Conditions of the mouth and throat

	• Erythematous: red patches on mucosal areas; if the tongue is involved it may lose its usual surface texture. • Hyperplastic: similar to pseudomembranous, but usually adheres to the tissue • Angular cheilitis: fissuring at corners of mouth with or without visual colonization • Oesophageal • Pseudomembranous lesions extend into lower pharynx and esophagus, causing difficulty in swallowing, nausea, and retrosternal and epigastric pain	• Endoscopic biopsy • Tissue invasive mycelia on endoscopic examination	Fluconazole 100 mg/day PO x 7–14 days Fluconazole 200 mg/day x 14–21 days. 2nd choice — Itraconazole (100 mg bid, doses can be increased to a maximum of 400 mg a day x 14–21days) Use intermittent therapy for as long as possible to delay the emergence of resistant candidiasis	TMP–SMX prophylaxis. The diagnosis of oral candidiasis in an HIV-positive patient classifies the patient as being in WHO stage III Recurrent episodes of oral candidiasis usually occur in patients with CD4 counts <300 cells/mm^3 Suppressive therapy generally nsot recommended unless patients have frequent severe recurrences of oropharyngeal candidiasis Oesophageal candidiasis will develop in 10–20% of AIDS patients with CD4 counts <100 cells/mm^3 and is the most common cause of dysphagia (inability or difficulty in swallowing) This indicates the patient is in WHO stage IV
CMV oesophagitis	Pain on swallowing	Endoscopic examination Oesophageal ulcers are usually single or few in number, large and deep, and are located in the lower third of the oesophagus	If treatment of suspected oesophageal candidiasis does not improve symptoms after seven days, the patient may have CMV or HSV infection or infection with another species of *Candida* Increase fluconazole to 200 mg/day and add acyclovir 800 mg thrice daily for 10 days If not resolving, and ganciclovir is not available to treat CMV, consider prednisone 1 mg/kg/day in the morning to relieve pain	The most frequent clinical manifestation of CMV disease is retinitis, followed by gastrointestinal symptoms Clinically, if it cannot be distinguished from *Candida* oesophagitis, consider CMV infection in patients with oesophageal symptoms that do not respond to empirical antifungal therapy Most oesophageal ulcers result from CMV infection, the other main cause being aphthous ulcers. In the presence of fever, CMV infection is more likely than aphthous lesions

Table 3.1. Conditions of the mouth and throat				
Necrotizing gingivitis	Inflammation of the gums that can become very extensive and necrotic and lead to tooth loss			Caused by bacteria of the oral cavity.
Herpes simplex virus (HSV) (stomatitis and oesophagitis)	Painful mucocutaneous lesions. Small painful crops of vesicles in the mouth that evolve into destructive gingivostomatitis Retrosternal pain and pain on swallowing	Biopsy and tissue culture		HSV oesophagitis is a rare cause of viral oesophagitis in AIDS patients. Without biopsy and tissue culture, it is difficult to make a differential diagnosis between HSV and CMV ulcerative oesophagitis. Often there is bacterial and fungal secondary infection. Empirical antifungal treatment may improve symptoms slightly
Epstein–Barr virus infection (EBV)	Fever of unknown origin. Other minor symptoms similar to the common cold are malaise, pharyngitis, pharyngeal hyperplasia, lymphadenopathy	CBC Total white blood count can be normal or low; patient can be lymphopenic and/or have evidence of reactive lymphocytes on blood smear. Endoscopic examination Ulcers are located in the mid-oesophagus	Primarily symptomatic	Often the patient has OHL
Kaposi sarcoma	Lesions appear as red or purple macules or nodules Sometimes they are painful and interfere with food intake and speech		Ganciclovir, foscarnet, cidofovir *See* section 6.4	When Kaposi sarcoma (KS) involves the oral cavity, it is considered to be an aggressive form of KS. Lesions can be stable for a long time, however
Aphthous ulcers and aphthous oesophagitis	Oral ulcers that can lead to painful giant lesions Oesophageal ulcers		Topical treatment 2– 4 times/day: lidocaine, triamicinolone Oral and intralesional prednisolone, colchicine, dapsone, thalidomide	Of unknown origin. Herpes simplex and CMV should be excluded After CMV infection, oesophageal ulcers are most often due to aphthous ulcers May be very debilitating. CMV is more likely in the presence of fever

3.1 Fungal infections

3.1.1 Candidiasis

Epidemiology

Candida spp. are found on the skin, in the stomach, colon and rectum, vagina, mouth and throat. Although a non-invasive commensal which keeps other microbes in check, candidal overgrowth can cause a variety of problems.

Stress, poor diet, inadequate rest, use of antibiotics, inhaled steroids, poor oral hygiene, smoking, and excessive alcohol and sugar consumption have all been found to be associated with a higher risk of infection.

In HIV-positive people, oral candidiasis occurs regardless of the CD4 counts, and in the absence of other risk factors, although it is more likely to recur and produce invasive infections at CD4 counts <200 cells/mm^3.

Although the majority of infections are caused by *C. albicans*, a gradual emergence of non-*albicans* species, particularly *C. glabrata*, has been noticed. This causes refractory mucosal candidiasis, especially in those with advanced immunosuppression.

The introduction of HAART has led to a dramatic decline in the prevalence of oropharyngeal candidiasis and a marked diminution of refractory disease.

Clinical manifestations

Oral candidiasis: Painless, creamy-white, plaque-like lesions are seen on the buccal or pharyngeal mucosa or tongue. The lesions can be easily scraped off with a tongue depressor.

Less commonly, erythematous patches without white plaques are seen on the anterior or posterior upper palate or diffusely on the tongue. Angular cheilosis may also be seen.

Oesophageal candidiasis: This condition presents with fever, retrosternal burning pain, discomfort and odynophagia. Endoscopic examination reveals white plaques similar to those observed in oropharyngeal disease. These may progress to superficial ulceration with central whitish exudates.

Diagnosis

Diagnosis is usually clinical and based on the characteristic appearance of the lesions and the ease with which the superficial whitish plaques can be scraped off. Microscopical examination of the scrapings using a potassium hydroxide (KOH) preparation shows yeast forms. The diagnosis of oesophageal candidiasis requires endoscopic visualization of the lesions with histopathological demonstration of yeast forms in tissue, as well as culture confirmation.

Treatment

Oral candidiasis: Clotrimazole troche is given in a dose of 10 mg five times/day until the lesions resolve (usually 7–14 days). Nystatin oral suspension 500 000 units gargled 4–5 times/day may be used topically. Oral medications include fluconazole 100–200 mg/day (150 mg tab x 1–2 times daily) for 7–14 days.

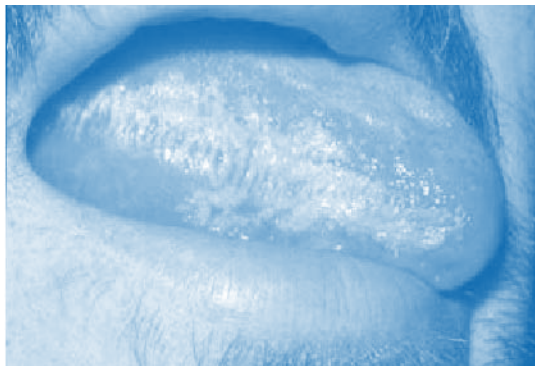
Oesophageal candidiasis: For oesophageal candidiasis, fluconazole 200–400 mg/day orally or itraconazole 200 mg/day PO x 14–21 days may be used. The duration of treatment should not exceed 21 days and treatment should be prescribed again in case of relapse. If the patient fails to respond to treatment, alternative diagnoses such as HSV or aphthous ulcers should be considered. Relapses occur very frequently in patients who are not on ART. However ART decreases the risk of relapse once the CD4 counts are >200 cells/mm^3.

Prophylaxis: Primary or secondary prophylaxis is not indicated.

3.1.2 Oral Hairy Leukoplakia (OHL)

Epidemiology

OHL is caused by Epstein–Barr virus (EBV) infection. Although most people are infected with EBV, it causes disease mainly in immunocompromised individuals. More than 25% of HIV-positive people develop OHL at some point. It is most common among HIV-positive men and smokers. OHL is among the earliest OIs to occur in HIV-positive people. It can occur at any level of T-cell count, but is more common at CD4 counts <200 cells/mm^3. It can also occur in people not infected with HIV.



Oral Hairy Leukoplakia

Clinical features

White patches develop along the sides, top and undersurface of the tongue or along the inside of the cheek. They can be shaggy in appearance and may contain a number of ridges. OHL may resemble oral candidiasis. However, candidal patches usually come off when lightly scraped with a toothbrush, whereas those due to OHL do not.

OHL is asymptomatic, and is usually discovered during a routine clinical inspection. It does not cause discomfort or affect taste sensation. Rarely, mild pain, alterations in taste and heightened sensitivity to food temperature may be present.

Diagnosis

The diagnosis is usually based on clinical inspection. A simple scrape test can be performed using a tongue depressor or a toothbrush. If the patch appears to come off with scraping, it is probably not OHL. A sample of the patch should be sent to the laboratory to confirm the diagnosis of EBV.

Diagnosis is *confirmed* if EBV is identified in the epithelial cells of an oral lesion by electron microscopy, in situ hybridization or immunocytochemistry.

Diagnosis is *probable* when there is a (a) white lesion (classically described as hairy, shaggy or furry) that cannot be scraped off with a tongue depressor blade, *and* (b) its location is limited to the lateral margin(s) of the tongue *or* the lesion extends beyond the lateral margin(s), but oral candidiasis has been excluded *or* the lesion persists after antifungal therapy and without antiherpes therapy.

Treatment

OHL usually does not require treatment. Acyclovir orally for 1–2 weeks may cause the lesions to disappear temporarily. Tretinoin and podophyllin resin can be applied directly to the patches. Tretinoin is usually

applied 2–3 times a day until the patches have disappeared. Podophyllin is applied 1–2 times over a 2–3-week period by a health-care provider. Liquid nitrogen cryotherapy and surgery are other alternatives.

3.2 Diarrhoeal diseases

Diarrhoea is among the most common symptoms of HIV infection and is experienced by over 90% of patients with AIDS. It becomes more frequent as immune deficiency progresses. Some of these diarrhoeal diseases are likely to be severe, recurrent and persistent, and associated with extra-intestinal disease. Diarrhoea and weight loss are independent predictors of mortality. Enteric pathogens recovered from HIV-infected persons include: *Shigella flexneri*, other *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., enterohaemorrhagic *E. coli*, enteroinvasive *E. coli*, *Clostridium difficile, Vibrio cholerae*, *Staph. aureus*, *Plesiomonas shigelloides*, *Aeromonas hydrophila* and *Yersinia enterocolitica*.

Laboratory diagnosis of diarrhoea

Specific pathogens may be isolated in up to 75–80% of patients in developed countries, with bacterial causes being identified in approximately 20%. Stool analysis of three samples will identify the majority of the aetiological agents. The frequency of finding "pathogen-negative" diarrhoea depends upon the extent of investigations undertaken. A minimum evaluation should consist of a careful search for routine bacterial enteric pathogens by culture and examination of the stool. Enteric bacteria are usually detected by routine stool cultures but are occasionally found only in the blood. *C. difficile* toxin should be looked for if the patient has received antibiotics within the past 2–3 months.

Specimen collection and transport

A freshly passed stool sample should be collected in a clean, waxed, cardboard or plastic container. About 1 teaspoon of liquid stool or pea-sized amount of formed stool is sufficient. The sample should be delivered to the laboratory within 1–2 hours of collection. If a delay >2 hours is expected, the specimen should be placed in a transport medium (Cary–Blair medium or buffered glycerol saline) and kept at 4 °C until it can be processed. In case a stool sample is unavailable, a rectal swab may be collected and transported in Cary–Blair medium containing reduced agar (1.6 g/litre).

Table 3.2. Common pathogens in HIV-related diarrhoea

	Small bowel (duodenum/jejunum)	Large bowel (colon/terminal ileum)
Bacteria	*Mycobacterium avium* complex, *Salmonella* spp	*Campylobacter* spp., *Yersinia* spp. *Aeromonas* spp., *Clostridium difficile*
Protozoa	*Cryptosporidium* spp., *Microsporidia*, *Cyclospora* spp., *Giardia lamblia*	*Entamoeba histolytica*
Viruses	Rotavirus, astrovirus, calicivirus, picornavirus, HIV	Adenovirus, herpesvirus, CMV

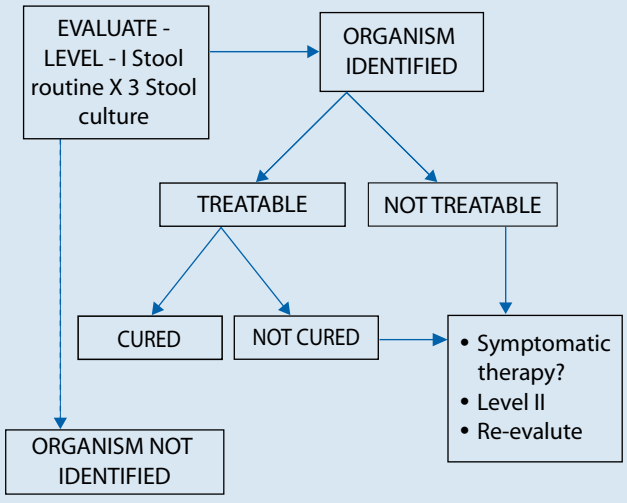
Principles of management

Supportive therapy with fluids and electrolytes is important even before antimicrobial therapy is initiated. Evaluation should proceed as given above. Specific therapy is preferred to empirical therapy.

Empirical therapy

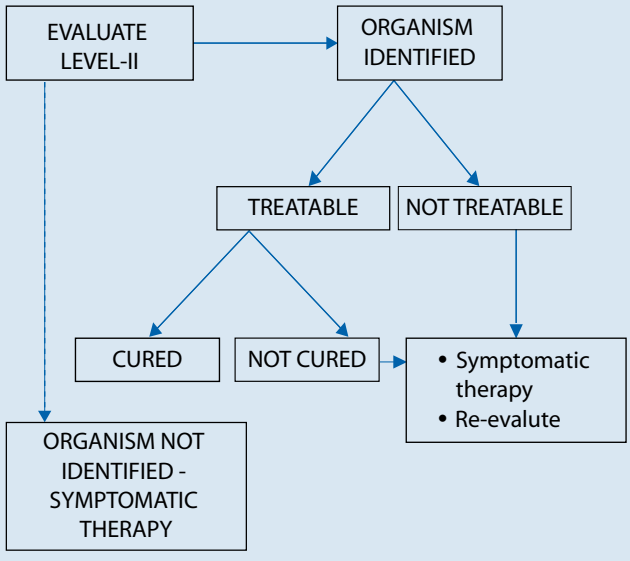
When a definite organism cannot immediately be identified, start treatment with sulfamethoxazole/trimethoprim (SMX–TMP) 2 double-strength tablets orally twice daily for 5 days. This is active against many bacterial and

Fig. 3.1. Evaluation of HIV-related diarrhoea



Level 1

- Stool culture
- Stool examination for parasites
  Saline & Iodine
  Modified AFB
  Trichrome



Level 2

- Gastroscopic biopsy
- Colonoscopic biopsy
  H & E stain
  AFB stain
  Giemsa
- AFB culture
- Duodenal fluid examination

a. Take history of nutritional status, medication, previous OIs. History should also differentiate between small and large bowel diarrhoea. 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 stools which often contain blood, mucus and pus, accompanied by fever. In many clinical situations, the distinction is not possible. Some pathogens cause significant disease throughout the gut (panenteritis).
b. Withdraw drugs associated with diarrhoea.
c. Examine fecal 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*
d. Blood cultures (2): Standard broth; if CD4 cell count <100/cells/mm^3 *Mycobacterium*-supporting media
e. Manage according to the findings

parasitic infections. If there is no response, metronidazole 400 mg thrice daily orally for 7 days is added. If there is still no response, and/or fever and bloody stools are present at the onset, ciprofloxacin 500 mg twice daily orally for 5 days is given. Anti-diarrhoeal agents (loperamide, maximum daily dosage 16 mg) are contraindicated in the presence of bloody diarrhoea. In case of suspected helminthic infections, mebendazole 100 mg thrice daily orally for 7 days is given. If the diarrhoea is disabling, look for intestinal TB and refer to a centre with better facilities.

Please refer to Annexes 4 and 5 for management of acute and chronic diarrhoea in HIV-infected patients.

Chronic diarrhoea

a. Overview

Diarrhoea in HIV-infected individuals may be either *acute* (<7 days), or *chronic* (three or more liquid stools daily for >14 days).

Chronic diarrhoea leads to malabsorption, malnutrition and contributes to mortality. Initial clinical evaluation includes assessment of hydration, skin elasticity, weight, pulse, blood pressure, respiration, eyes, mucous membranes and urine output. Chronic diarrhoea is a very frequent and frustrating problem in PLHA; at least 50% experience it sometime during the evolution of the disease.

Diarrhoea is often accompanied by nausea, weight loss, abdominal cramps and dehydration. There is often an intermittent watery diarrhoea, without blood or mucus. In one-third to two-thirds of cases, no cause is identified. Wherever possible, establish the cause and give specific treatment. The step-up diagnostic approach consists of examination of the stool for ova and parasites (with special stains – modified AFB, trichome and monoclonal stains) and endoscopic biopsy (gastroscopic/colonoscopic) if referred. The key to good management is rehydration including replacement of electrolytes. High-energy and high-protein intake reduces the degree of muscle wasting.

Prevention consists of attention to personal hygiene, hand-washing, drinking boiled water and eating only thoroughly cooked meat and vegetables.

b. An infectious agent can be identified in about 50% of patients with AIDS-associated diarrhoea. Differential diagnosis includes diarhoea due to the following pathogens:

• **Bacterial infection:**	• *Campylobacter, Shigella* and *Salmonella*
• **Protozoal infection:**	• *Cryptosporidium* spp., *Giardia lamblia, Isospora belli, Entamoeba histolytica, Microsporidium* spp.
• **Toxin induced:**	• *E. coli* and *Clostridium difficile*
• **Mycobacterial infection:**	• *M. tuberculosis, M. avium* complex
• **Helminthic infection:**	• *Strongyloides stercoralis*
• **Fungal infection:**	• *Candida* spp. (seldom a cause of diarrhoea)

These conditions should be differentiated from:

AIDS enteropathy: Direct cytopathic effect of HIV

Non-infectious disorders: Kaposi sarcoma, lymphoma

Table 3.3. Common infections of the gastrointestinal system: chronic diarrhoea

Aetiology Bacterial	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, caveats
Salmonella	Fever; general malaise Sometimes no GI symptoms, but if so, will have: bloody diarrhoea, abdominal pain and weight loss	Stool culture: *Salmonella* bacilli may be found in stool/blood cultures Serology: positive Widal test with increasing titres	In case of signs of sepsis, IV therapy is necessary Ciprofloxacin 500 mg bid or ofloxacin 400 mg bid or ceftriaxone 2 g IV for 7–10 days Many patients often relapse after treatment, and chronic maintenance therapy (TMP–SMX 1 double-strength tablet daily) is sometimes necessary	Salmonellosis is a frequent cause of bacteraemia in people living with HIV/AIDS (PLHA).
Shigella	High fever Abdominal pain Bloody diarrhoea	Stool microscopy— fresh examination and after concentration Multiple stool samples may need to be examined. *Shigella* bacillus found in stool	TMP–SMX (160/800) mg bid x 5 days or amoxicillin 500 mg tid x 5 days If resistant to the above, give ciprofloxacin 500 mg bid, or norfloxacin 400 mg bid x 5 days or nalidixic acid 1 g qid x 10 days	In many developing countries, resistance of *Shigella* (and *Salmonella*) to TMP–SMX has increased
Protozoal				
Cryptosporidium	Recent and prolonged history of severe diarrhoea—usually large-volume, watery stools with a lot of abdominal pain, bowel noise and activity Severe weight loss/wasting in those with longer history May be the AIDS-defining presentation in patients who previously had few symptoms of HIV infection	Stool samples x 3 for staining/AFB smear Oocysts present on stool examination No fecal WBCs	Rehydration (IV and/or ORS) Paramomycin 500 mg qid for 2–3 weeks; maintenance with 500 mg bid often required Codeine phosphate 30–60 mg tid until under control (or other antidiarrhoeal agents such as loperamide 2–4 mg tid or qid—maximum of 32 mg in 24 hours) ARV is protective against cryptosporidiosis	Cryptosporidia are highly infectious and transmitted through water, food, animal-to-human and human-to-human contact. Special precautions should be taken to prevent exposure. People with HIV infection and a CD4 count <200 cells/mm^3 should boil tap water for at least one minute to reduce risk of ingestion of oocysts in potentially contaminated drinking water

Table 3.3. Common infections of the gastrointestinal system: chronic diarrhoea				
Entamoeba histolytica	Colitis Bloody stools Cramps Can be asymptomatic	Stool for ova and parasite examination Ova and parasites (O&P) seen on stool examination No fecal WBCs	Metronidazole 400 mg tid x 7 days	*E. histolytica* may be common in the general population in developing countries, but may be recurrent or more severe in HIV-infected patients
Giardia lamblia	Enteritis Watery diarrhoea ± malabsorption Bloating Flatulence	Stool for O&P O&P on stool examination	Metronidazole 200 mg PO tid x 10 days	Common cause of diarrhoea in general population, but may be recurrent or more severe in HIV-infected patients
Isospora belli	Enteritis, watery diarrhoea No fever Wasting, malabsorption	Stool x 3: unstained wet preparation *Isospora belli* oocysts are relatively big (20–30 µm) and can be easily identified in unstained wet stool preparation No fecal WBCs	Most cases are readily treated with TMP–SMX (160/800 mg qid for 10 days) followed by 1 double-strength tablet (160/800 mg bid for 3 weeks) then chronic suppression with TMP–SMX (160/800 mg) daily. High dose of pyrimethamine with calcium folinate required to prevent myelosuppression Long-term maintenance therapy may be necessary to prevent relapse.	
Microsporidium	Profuse, watery, non-bloody diarrhoea Abdominal pain and cramping Nausea Vomiting Weight loss Species of microsporidia have been linked to disseminated disease, for example, cholangitis, keratoconjunctivitis, hepatitis, peritonitis and infections of the lungs, muscles and brain	Fresh stool microscopy with modified trichrome stain Spores present on stool examination	Disseminated disease Itraconazole 400 mg PO od and albendazole 400 mg PO bid	Chronic maintenance therapy may be discontinued if patients remain asymptomatic; sustained CD4+ T-lymphocyte counts >200 cells/mm^3 for >6 months on ART

Table 3.3. Common infections of the gastrointestinal system: chronic diarrhoea				
Helmenthic				
Strongyloides stercoralis	Serpiginous erythematous skin lesions (larva currens) Diarrhoea Abdominal pain Cough Full-blown hyper-infection syndrome has the characteristics of a Gram-negative sepsis, with acute respiratory distress syndrome, disseminated intravas-cular coagulation, secondary peritonitis and cough	Chest X-ray: CXR may reveal diffuse pulmonary infiltrates Stool microscopy (multiple stool samples may need to be examined) Sputum sample In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, BAL fluid, pleural fluid, peritoneal fluid and surgical drainage fluid.	Ivermectin 12 mg daily for 3 days. This is also the drug of choice for the treatment of systemic strongyloidiasis An alternative treatment is albendazole 400 mg bid x 5 days Maintenance therapy once a month is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once a month)	In immuno-compromised patients, *Strongyloides* can cause overwhelming infection. This serious complication is called *Strongyloides* hyper-infection syndrome and has a high case-fatality rate

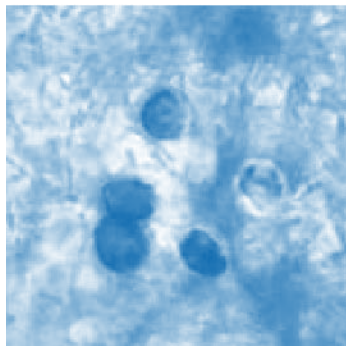
3.2.1 Cryptosporidiosis

Cryptosporidiasis is caused by a protozoon that infects the lining of the small intestine, causing severe diarrhoea and malabsorption.

In immunocompromised individuals it also infests the large bowel and exraintestinal sites. Several genotypes exist, all of which cause similar disease.

Patients with CD4 counts <100 cells/mm^3 are at greatest risk.

Cryptosporidium is spread by food or water contaminated with animal feces. Oral–anal sex and fecal contamination of water supply also causes spread of the disease. Young children with diarrhoea can transmit the infection to susceptible adults.



Cryptosporidium

Clinical manifestations

Watery diarrhoea, abdominal pain, nausea, vomiting, weight loss, loss of appetite and dehydration are common manifestations. If the biliary and pancreatic ducts are infected, cholangitis and pancreatitis can occur. Rarely, papillary stenosis and scelrosing cholangitis may occur.

For diagnosis, a stool sample is stained with acid-fast dye (to differentiate the organisms from fungi with a similar appearance) and examined under a microscope. Immunofluorescence, ELISA and genotyping by PCR are specialized techniques. Endoscopy/colonoscopy with sampling of intestinal tissue for histopathology and electron microscopy may be needed. Cryptosporidia cannot be grown in culture.

Treatment

No antimicrobial agent has been found to be completely effective against *Cryptosporodium*. However, some drugs such as paramomycin, azithromycin and nitazoxanide are of benefit in some patients.

Specific treatment includes nitazoxanide (500 mg twice daily) or azithromycin 500 mg daily for 5 days. Paramomycin in a dose of 1500–2000 mg daily can cure the infection and reduce diarrhoea. Dapsone in a dose of 750 mg daily is also helpful. Nitozoxanide has been approved by the FDA for the treatment of cryptosporidiosis in children.

To help control the diarrhoea, antimotility drugs such as octreotide, loperamide and paregoric may be used. Since the diarrhoea is the direct result of intestinal inflammation caused by the infection, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen may be helpful.

Weight loss requires nutritional supplementation. Total parenteral nutrition may be necessary in severe cases. Supportive treatment and optimization of HAART are the only approaches for treatment failure.

Cryptosporidial infection is easier to eradicate if the CD4 count increases to more than 100 cells/mm^3 following HAART. Malabsorption due to the infection may reduce the absorption of HIV drugs and reduce their level in the bloodstream. No drug regimens have been proven to prevent recurrence.

In patients with CD4 counts >100 cells/mm^3, symptoms usually resolve. Even a mild increase in the CD4 count will lead to symptom resolution and pathogen elimination.

Prevention

The most effective way of preventing cryptosporidial infection is to avoid contaminated drinking water. HIV-positive people with severely compromised immune systems should be encouraged to drink bottled or boiled water. Fruits and vegetables should be peeled and washed thoroughly in boiled water. Routine methods of water purification are ineffective against *Cryptosporidium* because the organisms are not filtered by municipal water systems and are resistant to chlorine and ozone. The risk of contracting cryptosporidial infection can be minimized by using microstraining filters (0.1–1 μm), boiling water for 1 min, or using high-quality bottled water.

3.2.2 Isosporiasis

Epidemiology

It is caused by the protozoon *Isospora belli* which infects the lining of the small intestine and causes severe diarrhoea and malabsorption.

It may be an initial AIDS-defining illness.

It spreads by food or water contaminated by animal feces, and by oral–anal sex. It is common in tropical countries where water contamination is a problem. At a CD4 count <150 cells/mm^3 it can cause prolonged, severe diarrhoea and malabsorption.

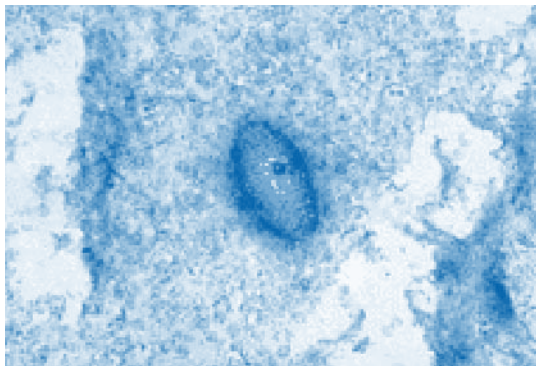
Clinical features

Watery diarrhoea, flatulence, abdominal pain, weight loss, loss of appetite and dehydration are the presenting features.

Diagnosis

Examination of a stained stool sample may demonstrate the organism.

Endoscopic or colonoscopic biopsy of the small or large intestine may be helpful.



Isospora belli

Treatment

Two double-strength TMP–SMX tablets 160/800 mg taken twice daily, or one double-strength tablet four times daily for 10 days and then 3 times daily for 3 weeks is the treatment of choice.

Sulfa allergy with fever and rash may occur and may be severe enough to necessitate stoppage of therapy. In such cases, pyrimethamine and folinic acid may be tried for a month. Symptomatic treatment with antimotility agents may be necessary. Intestinal inflammation may be reduced by NSAIDs such as ibuprofen.

3.3 Bacterial infections

3.3.1 Shigella infections

The incidence of *Shigella flexneri* infections has increased among men who have sex with men (MSM) in the United States. *Shigella* bacteraemia, a rare complication of shigellosis in adults, may be more common in HIV-infected patients. Treatment is with ciprofloxacin 500 mg twice daily orally for 5 days or TMP–SMX 160/800 mg orally twice daily for 5 days.

3.3.2 Salmonella infections

Epidemiology

Salmonellosis may cause severe invasive disease in HIV-infected persons. HIV-positive people are 20–100 times more likely to acquire disease. The common strains are *S. typhimurium* and *S. enteritidis*. Recently, recurrent non-typhoidal *Salmonella* septicaemia (RSS) has been included as an AIDS-defining illness. Not all serotypes produce RSS.

Transmission is through contaminated food or water or by anal–oral contact with infected people. It can also be contracted from animals, especially cattle and poultry. It can be acquired from contaminated raw poultry, eggs, unpasteurized milk and cheese products.

Clinical features

Salmonella septicaemia may manifest like typhoid fever, with few gastrointestinal symptoms. Symptoms appear after an incubation period of 3 days. Severe diarrhoea which may be bloody, and fever, chills, abdominal pain, vomiting and weight loss are other manifestations. If there is co-infection with other GI pathogens, the intestinal inflammation may predispose to bacteraemia. Focal suppurative complications such as abscesses in the spleen or bones, osteomyelitis, pneumonia, cholangitis, endarteritis and endocarditis also may occur.

Diagnosis

A stool culture may grow the organism. There may be leukocytosis. Liver function tests may reveal raised levels of enzymes. Imaging studies may show abscesses. Cultures may be done from aspirated pus.

Treatment

TMP–SMX 160/800 mg for 7–14 days is the initial treatment of choice. People with suppressed immune systems and evidence of endovascular disease may require 4–6 weeks of antibiotic therapy. Ciprofloxacin or ceftriaxone should be used if resistance is suspected. Long-term suppressive antibiotic therapy is needed for recurrence, usually at the lower dose of 500 mg ciprofloxacin a day. This may have to be continued for several months. Abscesses may have to be drained surgically.

4 Section HIV and Neurological Disorders

Epidemiology

Neurological manifestations are the initial symptoms of HIV infection in about 10–20% of patients. HIV enters the brain as early as two days after infection, and persists throughout the course of the disease. About 60% of those with advanced AIDS will have clinically evident neurological dysfunction. Autopsy studies have demonstrated pathological abnormalities of the nervous system in 75–90% of cases. All levels of the nervous system may be involved, and the degree of involvement is independent of the CD4 level (*see* Table 4.2).

Table 4.1. Neurological involvement in HIV infection

HIV related	OI related
• Acute aseptic meningitis • Chronic meningitis • HIV encephalopathy (AIDS dementia) • Vacuolar myelopathy • Peripheral neuropathy (sensory) • Myopathy	• Cryptococcal meningitis • Cerebral toxoplasmosis • CMV retinitis and encephalitis • Progressive multifocal leukoencephalopathy (PML) • Primary CNS lymphoma • TB • Syphilis

Table 4.2. Neurological syndromes and opportunistic infections in AIDS (aetiological diagnoses)

Syndrome	Clinical features	Aetiology
Meningitis	Headache, fever, nausea/vomiting Altered consciousness	Cryptococcosis, syphilis, listeriosis, tuberculosis
Focal cerebral lesions	Headache, focal signs, convulsions	Toxoplasmosis, progressive multifocal leukoencephalopathy (PML), syphilis, cytomegalovirus
Encephalitis	Cognitive impairment, psychiatric features, altered consciousness	Cytomegalovirus, herpes simplex, toxoplasmosis
Myelitis	Sensory disturbances, paraparesis, sphincter disturbance	Cytomegalovirus, herpes simplex, varicella zoster, syphilis, toxoplasmosis

Table 4.3. Conditions of the neurological system

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, caveats
***Toxoplasma gondii* (toxoplasmosis)**	**Clinical symptoms may evolve in less than 2 weeks** Headache (severe, localized) Fever Confusion Myalgia Arthralgia Focal neurological defects such as seizures, hemiparesis, hemiplegia, cerebellar tremor, cranial nerve palsies, hemisensory loss, visual problems or blindness, personality changes and cognitive disorders	Where available: CT scan or MRI Toxoplasma IgG titre In a resource-constrained setting: diagnosis based on clinical symptoms CT scan or MRI findings: multiple ring lesions in the cerebral hemispheres An HIV-infected individual presenting with typical symptoms and normal cerebrospinal fluid (CSF) findings should be given treatment for toxoplasmosis. CSF values Protein: 10–150/ml WBC: 0–40 (monocytes) Blood: full blood count (FBC)	Treatment for acute phase: >6 weeks Pyrimethamine 100–200 mg loading dose, then 50–100 mg/day PO + folinic (or folic) acid 10 mg/day po + sulfadiazine 1–2 g qid (Dexamethasone 4 mg PO or IV q 6 h for mass effect) OR TMP/SMX 5/25mg/kg daily OR Clindamycin (600 mg tid) + pyrimethamine 100 mg daily loading dose followed by 50 mg daily + folinic acid 10 mg daily *Maintenance* Preferred regimen: suppressive therapy required after a patient has had toxoplasmosis: Pyrimethamine 25–75 mg PO qid + folinic acid 10 mg qid + sulfadiazine 0.5–1.0 g PO qid (50% of acute dose) If allergic to sulfa Give dapsone PO 100 mg once daily or clindamycin IV (or oral) 600 mg qid or atovaquine 750 mg PO qid Eptoin 50–100 mg bid or tid or tegretol 100–200 mg bid or tid (to be started only if the patient has convulsions)	Usually occurs when CD4 count <100 cells/mm^3 Clinical response in 1 week and MRI reponse expected in 2 weeks Check blood picture regularly as the relatively high doses of drugs can lead to toxicities. Leukopenia, ombocytopenia and rash are common. Folinic acid reduces the risk of yelosuppresion During treatment, advise patients to maintain a high fluid intake and urine output Secondary *prophylaxis* may be discontinued if free of *Toxoplasma* encephalitis; and sustained CD4+ T lymphocyte count of >200 cells/mm^3 for >6 months of ART
Mycobacterial infection – *M. tuberculosis* (TB meningitis)	Gradual onset of headache and decreased consciousness	Lumbar puncture/ CSF microspcopy: CSF may be cloudy		CD4<350 cells/mm^3 Up to 10% of AIDS patients who present with TB

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, caveats
	Low-grade evening fever Night sweats Weight loss Neck stiffness and positive Kernig sign Cranial nerve palsies result from exudate around base of the brain	Protein: High (40–100 mg/dl) WBC: 5–2000 (average is 60–70% monocytes) Glucose: low (<20 mg/dl) AFB smear positive: 20%		show involvement of the meninges. This results from rupture of a cerebral tuberculoma or is blood-borne Always exclude cryptococcal meningitis by CSF microscopy (India ink stain)
***Strept. pneumoniae, Neisseria meningitidis* (Bacterial meningitis)**	Fever Headache Stiff neck Photophobia Vomiting Malaise Irritability Drowsiness Coma Symptoms tend to present within 1 week of infection. May be preceded by a prodromal respiratory illness or sore throat	CSF examination Full blood count Common findings: Leukocytosis; CSF shows increased pressure, cell count (100 –10 000/mm^3), protein (>100 mg/dl), and decreased glucose (<40 mg/dl or <50% of the simultaneous glucose blood level) Gram-stained smear of a spun sediment of CSF can reveal the aetiological agent	Penicillin (24 million units daily in divided doses every 2–3 hours) or ampicillin (12 g daily in divided doses every 2–3 hours) or chloramphenicol (4–6 g IV/day). Treatment should be continued for 10–14 days Crystalline penicillin 2–3 mega units and chloramphenicol 500–750 mg 6 hourly for 10–14 days	Often encountered during late stages of HIV disease. Prompt diagnosis and aggressive management and treatment ensure a quick recovery
***Cryptococcus neoformans* (cryptococcal meningitis)**	Presentation usually nonspecific at onset, which may be true for > 1 month Protracted headache and fever may be the only signs Nausea, vomiting and stiff neck may be absent and focal neurological signs uncommon. Extraneural symptoms include skin lesions, pneumonitis,	CSF values: Protein 30–150 mg/dl WBC: 0–100 (monocytes) Glucose decreased: 50–70 mg/dl Culture positive: 95–100% India ink positive: 60–80% Crypt Ag nearly 100% sensitive and specific India ink staining of spinal fluid Test spinal fluid and/or serum	Preferred regimen: Amphotericin B 0.7 mg/kg/day IV + flucytosine 100 mg/kg/day PO x 14 days, followed by fluconazole 400 mg/day x 8–10 weeks Finally, maintenance therapy with fluconazole 200 mg/day for life Alternate regimen: Amphotericin B 0.7 mg/kg/day IV + flucytosine 100 mg/kg/day PO x 14 days followed by itraconazole 200 mg bid for 8 weeks Fluconazole 400 mg/day	If untreated, it is slowly progressive and ultimately fatal. It occurs most often in patients with a CD4 count <100 cells/mm^3 Headache is secondary to fungal accumulation, so the headache increases gradually over time, goes away and then comes back and is harder to get rid of. Then it becomes continuous, and this is what the patient reports

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, caveats
	pleural effusion and retinitis Fever, malaise and nuchal pain signify a worse prognosis, and nausea, vomiting and altered mental status occur in the terminal stages	for cryptococcal antigen	PO x 8 weeks, followed by 200 mg once daily Itraconazole 200 mg PO tid x 3 days, then 200 mg PO bid x 8 weeks after initial treatment with amphotericin Fluconazole 400 mg/day PO + flucytosine 100 mg/kg/day PO	Repeated LP might be indicated as adjunctive therapy among patients with increased intracranial pressure Discontinuation of antifungal therapy can be considered among patients who remain asymptomatic, with CD4+ T-lymphocyte count >100–200 cells/mm^3 for >6 months
Cytomegalovirus (CMV)	Fever ± delirium, lethargy, disorientation, malaise. Headache most common Stiff neck, photophobia, cranial nerve deficits less common No focal neurological deficits Gastrointestinal symptoms: diarrhoea, colitis, oesophageal ulceration appear in 12–15% of patients Respiratory symptoms, i.e. pneumonitis, present in ~1%	Retinal exam to check for changes Consult an ophthalmologist. CMV retinitis, characterized by creamy yellow white, haemorrhagic, full-thickness retinal opacification, which can cause visual loss and lead to blindness if untreated; patient may be asymptomatic or complain of floaters, diminished acuity or visual field defects. Retinal detachment if disease is extensive UGI endoscopy when indicated	Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h x 14–21 days; ganciclovir 5 mg/kg IV bid x 14–21 days, then valganciclovir 900 mg PO qid Patients without immune recovery will need to be on maintenance therapy lifelong for retinitis Extraocular: ganciclovir and/or foscarnet	Evolution <2 weeks CD4 count <100 cells/mm^3 Although any part of the retina may be involved, there is a predilection for the posterior pole; involvement of the optic nerve head and macular region is common Treatment is very expensive and usually not available. CMV management needs special care. Therefore, early referral is essential
Progressive multifocal leukoencephalopathy (PML)	Afebrile, alert, no headache Progressively impaired speech, vision, motor function Cranial nerve deficits and	CT brain scan may be normal or remarkable for areas of diminished density or demyelination (deterioration of the covering of the nerve)	There is no treatment for this illness ART can improve symptoms and prolong life	**An end-stage complication of HIV, caused by the JC virus** PML is rare in the general community, but relatively common

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, caveats
	cortical blindness Cognition affected relatively late	PCR of CSF for detection of the James Canyon (JC) virus JC virus PCR positive in about 60% of cases Differential diagnosis: Toxoplasmosis, primary CNS lymphoma Definitive diagnosis is by brain biopsy (if available)		in HIV infection (affecting 4% of all AIDS patients). Routine testing for HIV should be considered for any patient with PML. Evolution: weeks to months Usually occurs when CD4 count <100 cells/ mm^3
Others				
Primary CNS lymphoma	Disease progresses slowly over a few weeks Afebrile; headache Focal and multifocal neurological	CT scan/MRI Location: preventricular in one or more sites Prominent oedema, irregular and solid on enhancement	There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients, but is considered palliative Corticosteroids can also help some patients	Primary CNS lymphoma is rare in the general community, but affects about 2% of AIDS patients
	deficits (confusion, hemiplegia, seizures) Mental status change (60%, personality or behavioural Seizures (15%)	CSF: Normal—30–50% Protein—10–150/ml WBC—0–100 (monocytes) Cytology positive in <5% Suspect when toxoplasma IgG is negative or there is failure to respond to empirical treatment for toxoplasmosis		Survival after diagnosis is usually limited (a few months only). Typical end-stage complication of HIV disease Evolution: 2–8 weeks Usually occurs when CD4 count <100 cells/ mm^3
AIDS dementia complex (ADC) (HIV-associated dementia [HAD])	In up to 10% of patients, it is the first manifestation of HIV disease. Afebrile; general lethargy Triad of cognitive, motor and behavioural dysfunction Early: concentration and	Neuropsychological tests show subcortical dementia Mini-mental examinations not very sensitive	Possible benefit from antiretroviral regimens with agents that penetrate the CNS (AZT, d4T, ABC, nevirapine) Benefit of AZT at higher dose for mild or moderately severe cases is established; monitor therapy with neurocognitive tests	Prevalence increases with improvement in general management of various OIs because patients live long enough to develop severe immune suppression. Patients present with a demeanour

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, caveats
	memory deficits, inattention, motor incoordination, ataxia, depression, emotional lability Late: global dementia, paraplegia, mutism The frequency in all patients is 10–15%		Anecdotal experience indicates response to ART, if started early Sedation for those who are agitated and aggressive—use smaller doses initially to avoid oversedation Close monitoring: to prevent self-harm to ensure adequate nutrition to diagnose and treat OIs early	similar to Parkinson disease and may even be misdiagnosed as such

4.1.1 Aseptic meningitis

It may occur as one of the manifestations of acute HIV syndrome. The onset may be several weeks after the other manifestations of the acute HIV syndrome. There may be retro-orbital pain, confusion, irritability, polyneuropathy, polyradiculopathy, facial palsy and weakness. Seizures and Guillain–Barre syndrome may occur. HIV can be demonstrated and cultured in the CSF but not in the blood. Treatment is supportive.

4.1.2 Acute bacterial meningitis

Acute bacterial meningitis occurs with equal frequency in HIV-infected and -uninfected persons. Common organisms include *S. pneumoniae, H. influenzae* and *N. meningitides*. The symptoms and signs include fever, headache, stiff neck, photophobia, vomiting, malaise, irritability, drowsiness and coma. Symptoms tend to present within one week of infection, and may be preceded by a prodromal respiratory illness or sore throat. On examination, the CSF shows increased pressure, a high cell count (100–10 000/mm^3), increased protein (>100 mg/dl) and decreased glucose (<40 mg/dl or <50% of the simultaneous glucose blood level). A Gram-stained smear of a spun sediment of the CSF may reveal the aetiological agent. A full blood count should also be done. Where available, CT scan or MRI may be performed to evaluate focal neurological deficits. Specific treatment depends on the aetiological agent.

4.2 Chronic meningitis

4.2.1 Tuberculous meningitis

Please *see section 2.3.1*.

4.2.2 Cryptococcal meningitis

It is caused by *Cryptococcus neoformans* var *neoformans*. It is the most common fungal meningitis in AIDS and affects about 10%. The majority of cases are seen when the CD4+ counts are <50 cells/mm^3. It commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise and headache. Classical symptoms and signs such as neck stiffness or photophobia occurs only in one-fourth to one-third of AIDS patients. Some patients may present with encephalopathic symptoms such as lethargy, altered mentation,

personality changes and memory loss. Some patients have disseminated disease without concurrent meningitis. Approximately half of them have pulmonary involvement. Skin lesions may be seen.

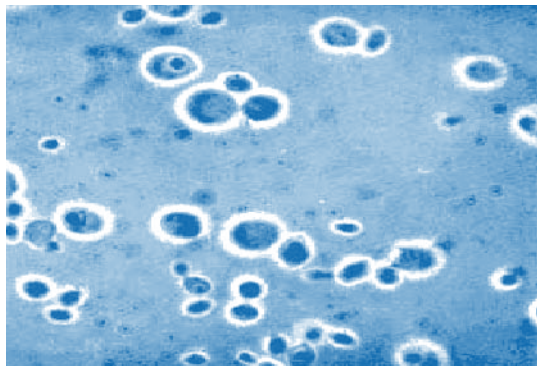
Diagnosis

Analysis of the CSF usually shows mildly raised protein, normal or slightly low glucose, with an increased white cell count (5–100 cells: predominantly mononuclear lymphocytes). The opening pressure of the CSF is elevated. India ink staining demonstrates the organism. Culture of the CSF grows *Cryptococcus*. Up to 75% of those with HIV-associated cryptococcal meningitis have positive fungal blood cultures. Serum cryptococcal antigen might be useful in making an initial diagnosis.

Diagnosis is said to be *confirmed* when *Cryptococcus* is identified in the CSF or CNS tissue by positive culture or histopathology.

Diagnosis is said to be *probable* in the presence of:

1. Compatible clinical syndrome that includes fever and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures and/or focal deficits.
2. Positive serum cryptococcal antigen
3. Specific antifungal therapy initiated or recommended.



Cryptococcus neoformans

Diagnosis is considered *possible* when:

1. There is a compatible clinical syndrome that includes fever and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures and/or focal deficits, and
2. Specific antifungal therapy initiated or recommended.

Treatment

Untreated, cryptococcal meningitis is fatal. The recommended initial treatment for acute disease is amphotericin B for 2 weeks, followed by fluconazole alone for an additional 8 weeks. This approach has a mortality of <10% and a mycological response of 70%. If new symptoms or clinical findings occur after 2 weeks of treatment, a repeat LP should be performed. Serial measurement of CSF cryptococcal antigen might be useful but require repeated LPs and is not routinely recommended. Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances.

Lipid formulations of amphotericin B are fairly effective in doses of 4 mg/kg daily. However, under the national programme, non-lipid formulations of amphotericin B are provided. Combination therapy with fluconazole (400–800 mg/daily) and flucytosine is also effective for treating AIDS-associated cryptococcal meningitis but the latter is not available in India.

Primary therapy

Acute – Induction: Amphotericin B (0.7 mg/kg/d) ± 5- flucytosine 25 mg/kg qid x 14 days
Consolidation: Fluconazole 400 mg/day for 8–10 weeks or until the CSF is sterile.
Maintenance: Fluconazole 200 mg/day lifelong (stop when the CD4+ count is >200 cells/mm^3 for 3 months)

Lumbar puncture: Repeated LPs are needed if the CSF opening pressure is >250 mmH_2O. The initial LP should reduce the opening pressure by 50%. Daily LPs are needed to maintain the opening pressure at <200 mmCSF. LP may be stopped once the opening pressure has been normal for several consecutive days. CSF shunting should be considered when daily LPs are no longer tolerated or when the signs and symptoms of cerebral oedema are not relieved. Acetazolamide has no role in reducing the intracranial pressure.

Maintenance therapy

Without maintenance therapy, relapse occurs in 50–60% of patients within 6 months. Maintenance therapy is given with fluconazole at a dose of 200 mg daily lifelong or until the CD4+ count remains above 200 cells/mm^3 for 3–6 months in a patient on HAART. Alternative therapy is possible with amphotericin B, voriconazole, and high-dose fluconazole + terbinafin.

Fluconazole has drug interactions with nevirapine used in HAART and leads to hepatotoxicity in 25% of patients receiving both drugs. This combination has to be used with caution and with regular monitoring of liver function tests.

Failure of therapy

With maintenance therapy, relapses are uncommon and usually related to noncompliance. Rarely, drug resistance and drug interactions which lower fluconazole levels may be responsible. Monitoring serum cryptococcal antigen titres is not useful in predicting relapse.

4.3 Cerebral toxoplasmosis

It is caused by the protozoon *Toxoplasma gondii*. Although *T. gondii* usually causes encephalitis, it also causes disease in various organs including the eyes and lungs. Infection is acquired by contact with cats or birds, and eating undercooked meat, especially pork, lamb or venison. Encephalitis occurs from reactivation of latent cysts, and is most common among HIV-positive people with CD4 counts <50 cells/mm^3. Anti-*Toxoplasma* antibodies are not protective and only indicate prior infection.

Clinical features

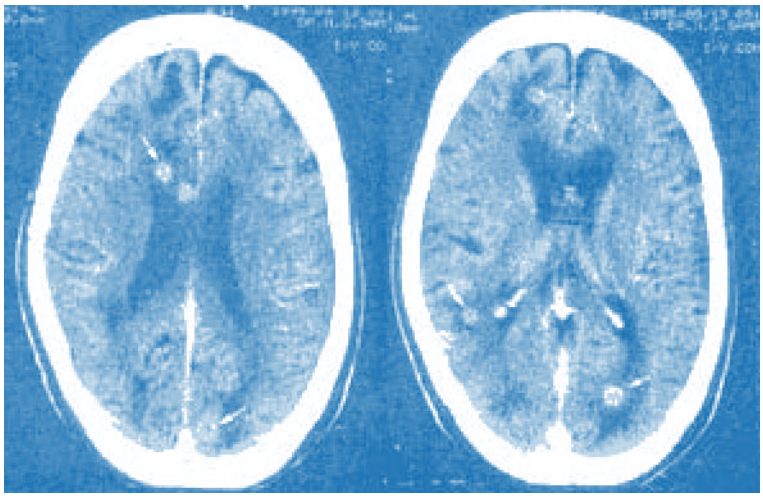
Symptoms include headache, fever, confusion, progressive focal neurological deficits, seizures, abnormal behaviour, motor weakness and coma.

Diagnosis

Serum IgG and IgM anti-*Toxoplasma* antibodies can be estimated, but do not indicate active disease. Polymerase chain reaction (PCR) tests have high specificity but low sensitivity. CT or MRI scans showing focal lesions may be helpful in making a diagnosis, although differentiation from other CNS diseases such as lymphoma may be difficult. Newer imaging devices such as positron emission tomography (PET) or single photon emission computed tomography (SPECT) scans may be more helpful, although more expensive. Stereotactic CT-guided brain biopsy is reserved for patients who fail to respond to therapy.

Treatment

If CNS toxoplasmosis is suspected, treatment should precede confirmation of diagnosis. Brain biopsy is required only if the patient does not respond to treatment. Biopsy may be required to diagnose toxoplasmosis of other tissues such as the lungs.



Cerebral toxoplasmosis

A combination of pyrimethamine, sulfadiazine and leucovorin is the recommended initial regimen. Pyrimethamine is started orally at a dose of 100–200 mg daily, followed by a lower dose. It penetrates the brain parenchyma even if there is no inflammation. Leucovorin contains folate, and decreases the haematological side-effects of pyrimethamine. Sulfadiazine is given orally four times a day at a dose of 4–8 g/day. Clindamycin or TMP–SMX can be used in case sulfadiazine is not available.

Other combnations used include: atovaquone + sulfadiazine; atovaquone + pyrimethamine + leucovorin; azithromycin + pyrimethamine + leucovorin. Dapsone, 5-fluorouracil, clarithromycin, and minocycline have all been used with in various permutations and combinations.

Initially, high doses of these medications are given for 4–6 weeks followed by lower doses as maintenance therapy to prevent recurrence. Maintenance therapy can be discontinued in an asymptomatic patient on HAART with a CD4 count >200 cells/mm^3 for at least 6 months. It has to be restarted if the CD4 count falls or the MRI/CT shows persistent cerebral mass lesions.

Corticosteroids such as dexamethasone may help control inflammation of the brain in patients with focal neurological symptoms. However, they need to be used carefully, given that corticosteroids may precipitate other OIs. Anticonvulsants should be administered only if there is a history of seizures and should not be used prophylactically.

Adverse events

Pyrimethamine can cause rash, nausea and bone marrow suppression. Sulfadiazine and TMP–SMX can cause rash, fever, leucopenia, hepatitis, nausea, vomiting, diarrhoea, crystalluria, hepatotoxicity and *Clostridium difficile* colitis. Drug interactions between anticonvulsants and ART may necessitate adjustment of dosages.

Prevention

The best way to prevent toxoplasmosis is to avoid contact with *T. gondii*. Meats such as pork, lamb or venison should be well cooked. Precautions should be followed while handling cats and birds.

Daily TMP–SMX is the most effective regimen to prevent toxoplasmosis. For patients who are allergic, dapsone + pyrimethamine + folic acid once a week is a good alternative.

4.4 AIDS Dementia Complex (ADC)

ADC or HIV-associated dementia (HAD) is different from other OIs in that the disease is caused by the HIV itself, which enters the brain as early as two days after infection. HIV can then damage the nerve cells in the brain. ADC is more likely with CD4 counts <200 cells/mm^3. Between 20% and 35% of all HIV-positive people eventually develop ADC at CD4 counts of 100–200 cells/mm^3.

There is acquired and slowly progressive cognitive decline, motor and behavioural changes, and non-focal or diffuse CNS signs. Signs of early dementia include: trouble learning new things, difficulty remembering things that happened in the past, changes in behaviour, confusion and depression. Advanced dementia produces abnormalities of speech, balance, vision, gait, and loss of bladder control. It can also lead to mania (exaggerated feeling of well-being) or psychosis (loss of contact with reality).

Diagnosis

ADC is a *diagnosis of exclusion*. The CSF findings are non-specific and CT/MRI shows only cerebral atrophy and ventricular dilatation. Several AIDS-related diseases such as toxoplasmosis, lymphoma and PML can cause symptoms similar to those of ADC.

Treatment

HAART is the most effective treatment and ARV regimens should include agents that penetrate the CNS (AZT, d4T, ABC, nevirapine). Even though HAART can treat the underlying cause, it may not effectively treat the symptoms, and may actually worsen them in some cases. Additional supportive treatment strategies may be needed in some cases. Sedation is required for those who are agitated and aggressive, with smaller initial doses to avoid oversedation. Close monitoring to prevent self-harm, adequate nutrition, early diagnosis and treatment of other OIs, and psychological support for caregivers are important accessories to therapy.

4.5 Primary CNS lymphoma

Primary CNS lymphoma is rare in the general community, but affects about 2% of HIV/AIDS patients. Survival after diagnosis is usually limited to a few months only. It is a typical end-stage complication of HIV disease. The disease evolves over 2–8 weeks. It usually occurs when the CD4 count is <100 cells/mm^3.

Disease progression occurs over a few weeks. Patients are afebrile, with headache and focal neurological deficits (confusion, hemiplegia, seizures). They may present with mental status changes (60%), and personality or behavioural changes. Seizures occur in 15%.

Diagnosis

CT scan/MRI shows periventricular irregular lesions which appear solid on enhancement in one or more sites. There is prominent oedema. Lymphoma is suspected when the *Toxoplasma* IgG is negative or there is failure to respond to empirical treatment for toxoplasmosis. Neuropsychological tests show subcortical dementia. Mini-mental status examinations are not very sensitive. CSF analysis is normal in 30–50% of patients. The CSF cytology is positive for malignant cells in <5% of patients.

Treatment

There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients, but is considered palliative. Corticosteroids can also help some patients.

4.6 Progressive Multifocal Leukoencephalopathy (PML)

PML results from multifocal demyelination caused by the James Canyon (JC) virus.

It is a neurological condition that progresses relatively rapidly over weeks to months with cognitive dysfunction, ataxia, aphasia, cranial nerve deficits, hemiparesis or quadriparesis, and eventually coma.

Diagnosis

Typical CT scan findings include single or multiple hypodense, non-enhancing cerebral white matter lesions. Diagnosis is *confirmed* if histopathology or in situ hybridization from a brain biopsy or CSF PCR shows the JC virus.

Diagnosis is considered *probable* if the clinical presentation (subacute progressive focal neurological deficits including hemiparesis, field deficits, ataxia, or other abnormality referable to dysfunction of a specific brain region, and does not include cognitive impairment alone) and MRI findings are compatible with PML.

Diagnosis is considered *possible* if the clinical presentation is consistent with PML, and focal lesions without mass effect or enhancement are seen on CT or MRI of brain.

Treatment

HAART is the only effective treatment and many studies have used even more than three drugs in HAART (mega HAART) but the current recommendation is triple-drug ART only.

4.7 Cytomegalovirus infection

Cytomegalovirus (CMV) or herpesvirus type 4 is a double-stranded DNA virus. Infection is common, and latency follows infection. Almost all homosexual or bisexual men and more than 75% of all HIV-infected people carry the virus. A small percentage with severely compromised immune systems actually develops CMV disease when immunosuppression reactivates inherent CMV to cause disseminated or localized end-organ disease. Around 30% of patients with AIDS develop CMV retinitis some time between the diagnosis of AIDS and death.

Clinical manifestations

Retinitis is the most common manifestation. CMV retinitis usually occurs unilaterally, but may be bilateral. Peripheral retinitis might be asymptomatic, or may present with floaters, scotomata or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula are associated with decreased visual acuity or central field defects. The characteristic ophthalmological appearance includes perivascular fluffy yellow–white retinal infiltrates, and focal necrotizing retinitis with or without intraretinal haemorrhage. There is very little inflammation of the vitreous. Blood vessels near the lesions might be sheathed. The lesions might have a granular appearance. In the absence of HAART or specific anti-CMV therapy, retinitis progresses and causes a characteristic brushfire pattern, usually within 10–21 days after presentation. A granular, white leading edge forms, eventually resulting in an atrophic and gliotic scar leading to blindness.

CMV colitis is the second most common manifestation, and occurs in 5–10% of patients with CMV infection. The most frequent clinical manifestations are fever, weight loss, anorexia, abdominal pain, diarrhoea and malaise. Extensive mucosal haemorrhage and perforation can cause life-threatening complications.

CMV oesophagitis occurs in less than 5% and causes fever, odynophagia, nausea and mid-epigastric or retrosternal discomfort. Pneumonitis is uncommon, but can cause shortness of breath, dyspnoea on exertion, a nonproductive cough and hypoxaemia.

CMV neurological disease causes dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy. Patients with dementia typically have lethargy, confusion and fever. The condition might mimic HIV dementia.

Diagnosis

CMV viraemia can be detected by PCR, antigen assays or blood culture. A negative IgG antibody suggests that CMV is unlikely to have caused disease. Patients with advanced immunosuppression might serorevert from being antibody-positive to -negative.

The diagnosis of CMV retinitis is based on characteristic retinal changes in the fundus.

CMV colitis is recognized by mucosal ulcerations on endoscopic examination and colonoscopic or rectal biopsy. Histopathology demonstrates characteristic intranuclear and intracytoplasmic inclusions. The diagnosis of CMV oesophagitis is established by the presence of extensive large, shallow ulcers in the distal oesophagus. Biopsy shows intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer. Culturing CMV from a biopsy or cells brushed from the colon or the oesophagus is not sufficient to establish the diagnosis.

The diagnosis of CMV pneumonitis should be made with X-ray evidence of pulmonary interstitial infiltrates. CMV inclusion bodies can be identified in the lung tissue.

CMV neurological disease is diagnosed on the basis of the clinical syndrome and the presence of CMV in the CSF or brain tissue. The use of PCR enhances the detection of CMV. The CSF generally demonstrates lymphocytic pleocytosis; there may be a mixture of neutrophils and lymphocytes. The glucose levels may be low-to-normal, and protein levels normal-to-high. Periventricular enhancement on CT or MRI images helps to distinguish CMV ventriculoencephalitis from HIV-1-related neurological disease.

Laboratory diagnosis

The diagnosis of CMV infection requires laboratory confirmation and cannot be made on clinical grounds alone. CMV antigen detection can be done using commercially available kits. Virus isolation and PCR can be done by State/National Laboratories.

The presence of CMV IgM antibody is useful but not a reliable indicator of an acute infection. IgM antibodies may not be present during an active infection (false-negative) or may persist for such a long time that the finding may not be diagnostic (false-positive).

Polymerase chain reaction (PCR): PCR using primers from a part of a genome coding for immediate early antigen has been used but this method is oversensitive. RT-PCR for CMV RNA or quantitative PCR to determine the CMV load is more useful in detecting active infection or monitoring antiviral therapy.

Treatment

Treatment suppresses the infection and prevents relapse. It cannot reverse damage that has already occurred. Treatment for CMV retinitis can be given intravenously, orally, or directly into the eye(s). It consists of two phases: induction therapy and maintenance therapy. Induction therapy usually takes two or three weeks.

Maintenance therapy is intended to prevent the virus from causing a relapse. This may be discontinued once the CD4 count increases to more than 200 cells/mm^3 for at least 6 months following HAART. The treatment of choice is ganciclovir 5 mg/kg twice daily IV (induction) followed by capsules (maintenance), and can treat all forms of CMV disease. IV ganciclovir is given twice daily for two to three weeks and then IV once daily 5–7 days a week. Oral treatment is given as 1000 mg capsules three times daily.

Intravenous foscarnet can be used to treat CMV retinitis and all other forms of CMV disease. It is given 2–3 times daily for two to three weeks and then once a day.

Intravenous cidofovir with probenecid (to help prevent kidney damage) is given once a week for two weeks. It has been studied only in CMV retinitis but might be effective in other forms of the disease.

Valganciclovir may be given orally as two 450 mg tablets twice a day for three weeks, followed by two 450 mg tablets once a day. It is the only treatment for CMV that can be given orally. It has been shown to be as effective as IV ganciclovir for the treatment of CMV retinitis. It has many of the side-effects of IV ganciclovir.

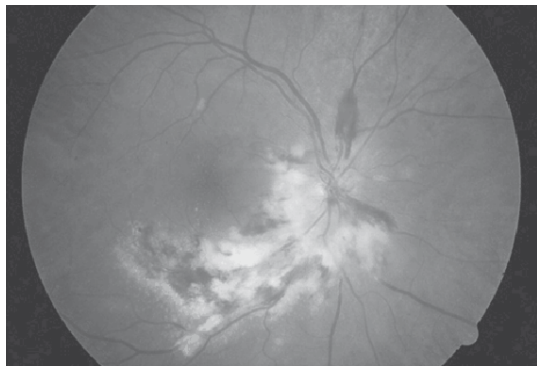
Ganciclovir implants have been used in the past, although they have a high incidence of recurrence and retinal detachment.

CMV pneumonitis

The presentation and diagnosis is similar to that of HSV pneumonitis (*see* section 6.1.1).

CMV retinitis

CMV retinits occurs in 50–75% of AIDS patients, often before the appearance of other systemic features. To diagnose the condition, examination by torch light, ocular motility, flash light and pupil examination are needed. Fundus examination after dilatation is also necessary for diagnosis.



CMV retinitis

Treatment may be given by intravitreal injection of 0.1 ml ganciclovir at a dose of 200–4000 µg thrice weekly for induction and 200–4000 µg weekly for maintenance. The induction dose of foscarnet is 1.2–2.4 mg twice weekly, and maintenance dose 1.2 mg/week. The dose of cidofovir is 20 µg/5 weeks in divided doses for induction and maintenance.

5 Section

Lymphadenopathy (Generalized/localized)

Swelling of the lymph nodes is often encountered in HIV infected person. It requires a careful history and physical examination. The cause usually becomes obvious, but in more complicated cases, laboratory tests and lymph node biopsy may be necessary to establish a definitive diagnosis.

Differential diagnosis of lymphadenopathy includes the following:

- HIV-related: Persistent generalized lymphadenopathy (PGL)
- Opportunistic infections: Tuberculous lymphadenitis, CMV, toxoplasmosis, infections due to *Nocardia* spp., fungal infections (histoplasmosis, penicilliosis, cryptococcosis, etc.)
- Reactive lymphadenopathy: Pyomyositis, pyogenic skin infections, ear, nose and throat (ENT) infections
- STI: Syphilis, inguinal lymphadenopathy resulting from donovanosis, chancroid or lymphogranuloma venereum (LGV)
- Malignancies: Lymphoma, Kaposi sarcoma, carcinomatous metastases
- Other infections: Brucellosis, visceral leishmaniasis (kala-azar), sarcoidosis, trypanosomiasis, rickettsial disease, infectious mononucleosis
- Drug reactions (for example, phenytoin hypersensitivity).

Further evaluation of the lymph nodes is indicated if the following features are present:

- Large (>4 cm diameter) or rapidly growing lymph nodes
- Asymmetrical lymphadenopathy
- Tender/painful lymph nodes not associated with a local infection
- Matted/fluctuant lymph nodes
- Obvious constitutional symptoms (fever, night sweats, weight loss)
- Hilar or mediastinal lymphadenopathy on chest X-ray
- Suspicion of pulmonary TB
- Evidence of abscesses (cutaneous, pulmonary, etc.)

Table 5.1. Common conditions causing lymphadenopathy

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, prophylaxis
Persistent generalized lymphadenopathy (PGL)	Lymph nodes >1.5 cm in diameter in 2 or more extrainguinal sites of 3 or more months' duration Nodes are non-tender, symmetrical and often involve the posterior cervical, axillary, occipital and epitrochlear nodes	Where possible, do a CBC and chest X-ray before making a diagnosis of PGL. Hilar or mediastinal lymphadenopathy on CXR	There is no specific treatment for PGL.	Develops in up to 50% of HIV-infected individuals. Up to one-third do not have any other symptom on presentation (WHO clinical stage I) In HIV-positive patients, PGL is a clinical diagnosis. No

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, prophylaxis
	Lymph nodes that require further evaluation: Large (>4 cm diameter) Rapidly growing nodes Tender/painful nodes not associated with a local infection Matted/fluctuant lymph nodes Obvious constitutional symptoms (fever, night sweats, weight loss)			further examination is necessary, unless there are features of another disease. PGL may slowly regress during the course of HIV infection and may disappear before the onset of AIDS
Tuberculous lymphadenopathy	Cervical nodes most commonly involved Usual course of lymph node disease is as follows: Firm, discrete nodes ↓ Fluctuant nodes matted together ↓ Skin breakdown, abscesses ↓ Chronic sinuses with healing and scarring	Fine-needle aspiration of the involved lymph node Extrathoracic lymph node aspiration Positive smears for acid-fast bacilli on fine-needle aspirates of the involved lymph nodes (high rate in HIV-infected patients) In smear-negative pulmonary TB, it is worthwhile aspirating the extrathoracic lymph nodes to confirm the diagnosis of TB (80% positive)	Treatment should be started following the national TB guidelines	One of the most common forms of extrapulmonary TB in HIV-infected patients Miliary TB is an important consideration in patients with generalized lymphadenopathy Abdominal lymph nodes might be enlarged even in the absence of peripheral lymphadenopathy and CXR changes
Nocardiosis	Chronic lymphadenopathy Abscesses (skin, pulmonary, etc.)	Fine-needle aspiration of the involved lymph node Organism may stain weakly on acid-fast staining. The organisms are different from Koch bacilli because of their thread-like filaments. *Nocardia* organisms are easily recognized on Gram stain.	TMP–SMX 10/50 mg/kg bid >6 months or In sick patients, intitially ceftriaxone 2 g daily combined with amikacin 15–25 mg/kg daily for 2 weeks to be followed by TMP–SMX	Consider the diagnosis in HIV-infected patients with chronic lymphadenopathy and abscesses (skin, pulmonary, etc.) Most show clinical response in 5 days

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, prophylaxis
Fungal infections (histoplasmosis, penicilliosis, cryptococcosis)	Fever Lymphadenopathy Often skin or lung lesions	Biopsy for histology and culture of skin lesions or lymph nodes often reveals the diagnosis	Initial treatment for histoplasmosis and penicilliosis: For moderate-to-severe cases: Amphotericin B 0.6 mg/kg/day x 2 weeks, then itraconazole 200 mg PO bid x 10 weeks Maintenance therapy: itraconazole 200 mg daily is the preferred therapy given lifelong. For cyptococcosis give: Amphotericin B (IV) 0.7 mg/kg daily for 14 days, followed by fluconazole 400 mg daily for 8–10 weeks After that, maintenance therapy consists of fluconazole 200 mg once a day	Clinical response to therapy takes 5–7 days
Secondary syphilis	Generalized, painless lymphadenopathy Maculopapular, papular or pustular rash on entire body, especially on palms and soles Highly infectious lesions on mucous membranes (lips, mouth, pharynx, vulva, glans penis) which are silvery grey superficial erosions with a red halo and not painful, unless there is secondary infection. 40% of these patients will have	On examination, CSF shows increased protein and lymphocytic pleocytosis	Although there is some doubt about treatment efficacy in HIV-infected patients, CDC rec-ommends the same treatment for primary and secondary syphilis as in HIV-negative individuals: Benzathine penicillin 2.4 million units IM single dose In case of penicillin allergy, give:	All patients should be evaluated for ocular and CNS involvement. If either is positive, then an LP must be done to obtain CSF to rule out CNS disease

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, prophylaxis
	CNS involvement with headache and meningismus		Doxycycline 100 mg PO bid for 14 days OR Ceftriaxone 1 g IM/IV daily for 10 days	
Lymphoma and Kaposi sarcoma	Lymphadenopathy Characteristic skin lesions in oral cavity, GI tract and respiratory tract	Diagnosis confirmed by histopathology	For treatment and management, Refer section 6.4	

Section 6

Dermatological Conditions in HIV Disease

Dermatological diseases are common in the setting of HIV disease. Some dermatological conditions may be more severe or resistant to treatment in the context of HIV disease. The organisms causing disease are diverse. Skin manifestations may be part of a broader systemic infection. Many infections are hospital acquired and may be due to a mixture of organisms. Therapy often fails because of incorrect diagnosis, resistant organisms, deeper and complex infection.

Table 6.1. Skin conditions

Aetiology	Presenting signs and symptoms	Diagnostics (laboratory, X-ray and other)	Management and treatment	Unique features, prophylaxis
Bacterial				
Skin abscess or pyomyositis	Abscess or affected area is fluctuant and warm		Surgical drainage and care of the lesion Antibiotics: Cloxacillin 500 mg PO qid for 10 days or cloxacillin 1–2 g IV qid for 10 days Vancomycin in case of severe sepsis	
Furunculosis or folliculitis	Skin sepsis around hair follicles Carbuncles (clusters of furuncles) with multiple openings form as a result of invasion and necrosis of the subcutis.		Local lesion care Antibiotics: cloxacillin 500 mg PO qid for 10 days	Usually caused by staphylococci Needs careful management in HIV-infected patients because life-threatening disseminated infections may occur. WHO stage II
Syphilis	Primary: A painless, indurated genital ulcer (chancre) Inguinal lymphadenopathy Secondary: Rash, usually involves the palms and soles and is maculopapular. Condyloma lata Oral lesions	Diagnostics: Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR) test	Benzathine penicillin 2.4 million units IM single dose Follow-up VDRL q 6 months until negative	About 25% of untreated patients develop a systemic illness (weeks to months later) with fever, rash, condyloma lata, lymphadenopathy and oral lesions (mucous patch). VDRL or RPR is not positive until 7–10 days after appearance of chancre

Table 6.1. Skin conditions				
Bacillary angiomatosis (BA)	Angioproliferative lesions that look like Kaposi sarcoma Cutaneous lesions start with small red papules that gradually expand into large papular, nodular, pedunculated forms Lesions have a vascular appearance and the surface is friable and bleeds easily Symptoms include fever, malaise, headache, hepatomegaly and skin lesions	Diagnosis: Tissue histology using silver stain to detect *Bartonella*	Erythromycin 500 mg PO qid or doxycycline 100 mg PO or IV x >3 months. Alternative: Azithromycin 600 mg qid	It is recommended that syphilis testing be offered to all clients presenting for voluntary counselling and testing (VCT) in high-prevalence areas because it is treatable in the early stages, and has an accelerated course in HIV infection. Bacillary angiomatosis (BA) and bacillary peliosis are caused by tiny Gram-negative bacilli *Bartonella henselae and Bartonella quintana*, which are difficult to cultivate in the laboratory BA is epidemiologically linked to exposure to cats, especially young cats infested with fleas. Differential diagnosis from Kaposi sarcoma is not always easy Clinical response is slow and relapse is common
Impetigo	Multiple superficial skin sores		Gently keep the lesions clean with soap and water As impetigo is highly contagious, maintain good hygiene and hand-washing techniques to prevent spread to others In severe cases, give cloxacillin or erythromycin 50 mg/kg/day qid for 5 days	
Mycobacterial diseases	Suspect if patient presents with papulopustular eruption on trunk and extremities and is extremely ill	Diagnostics: Aspiration and/or biopsy of lymph nodes Skin biopsy		Disseminated miliary tuberculosis of the skin is a rare form of TB.

Table 6.1. Skin conditions

		Microscopic examination of skin biopsy reveals numerous acid-fast bacilli Aspiration and/or biopsy of lymph nodes has a higher diagnostic yield than skin biopsy in extrapulmonary TB		
Fungal skin infections				
Dermatophytosis	Hyper- or hypopigmented patches that are itchy, with or without a ring pattern and with scaling	Direct microscopy of KOH preparation	Use a broad-spectrum antifungal topically, such as clotrimazole cream 1% daily bid for 2–4 weeks Explain to the patient that local treatment may take a long time Widespread dermatophytosis may necessitate systemic treatment with terbinafine 250 mg qid x 2–4 weeks or itraconazole 100–200 mg qid x 2–4 weeks. for skin lesions and up to 12 weeks for lesions of the nails	Tinea corporis, tinea pedis, tinea cruris and onycho-mycosis all occur more frequently in HIV-infected patients. The most frequent is tinea pedis Onychomycosis requires long-term therapy, and not all patients with dystrophic nails have a fungal infection Therefore, it is necessary to make the correct diagnosis. Direct microscopy of a KOH preparation is sufficient to confirm diagnosis
Seborrhoeic dermatitis or generalized erythroderma	Generalized, greasy scaling with excessive dandruff on the scalp, face and chest		Topical steroids: Triamicinolone 1% with or without ketoconazole 2% cream twice daily for the duration of the flare Shampoos: Tar-based or selenium sulfide or ketoconazole-based twice weekly	A very common complaint and one of the earliest clinical markers of HIV infection
Skin candidiasis	Itchy, wet lesions prominent in armpits, groin and under breast	Diagnostics: KOH preparation of affected areas may show pseudohy-phae and budding yeasts	Topical antifungal drug, such as clotrimazole 1% cream or ketoconazole In severe cases, or if there still is no response to therapy, fluconazole 100– 200 mg PO bid x 10 days may be required	Severely immunocompromised patients may have balanitis, distal urethritis or paronychia (nail infection)

Table 6.1. Skin conditions				
Deep mycosis	70% of patients with disseminated *Penicillium marneffei* infection will have skin lesions Histoplasmosis and cryptococcosis can also present with pustules, nodules, ulcers and papules. Patients with cryptococcosis and penicilliosis may have molluscum contagiosum-like, centrally umbilicated lesions typically located on the face and trunk	Diagnostics: Organisms can be seen by microscopic examination of skin scrapings, touch preparations of skin biopsy or lymph node aspirate stained with Wright or Cotton blue stain Diagnosis is confirmed by culturing the fungus from clinical specimens		Diagnostic techniques are not readily available in developing countries Diagnosis is suggested by clinical picture: high fever, severe anaemia, cough, lymphadenopathy, hepatomegaly and meningeal signs WHO stage IV
Viral				
Chronic mucocutaneous herpes simplex (HSV)	Painful clusters of vesicles, ulcers or lesions on the mouth or anogenital area Herpes simplex in HIV disease runs a chronic ulcerative course		Acyclovir 400 mg tid daily for 7 days (14 days if disseminated mucocutaneous herpes simplex infection) Treat local lesion by using local antiseptics such as gentian violet or cleaning the ulcerative vesicles with salt water and keeping them dry Recurrences occur frequently (more than 6/year) in some patients: administer chemosuppression with oral acyclovir 400 mg bid or famciclovir 250 mg bid	Chronic ulcers (>3 weeks) are seen only with advanced immune suppression If untreated, they can last for months and finally involve most of the genital and perianal skin and mucous membranes WHO stage IV
Shingles (herpes zoster)	Painful cluster of vesicles on an erythematous		For extensive lesions present for less than 48 hours, use	Herpes zoster in a young person is highly predictive of HIV infection

Table 6.1. Skin conditions

	patch of skin in a localized neurodermatomal distribution Lesions can become necrotic and extensive, and take a long time to heal		famciclovir 500 mg tid or acyclovir 800 mg x 5 times x 7–10 days to avoid post-herpetic pain Local application of lidocaine gel 2% may help relieve pain in some patients Calamine lotion is cheap, soothes the skin, reduces intense pruritus and accelerates the drying up process	If the ophthalmic branch of the trigeminal nerve is involved, the cornea may get involved leading to corneal scarring with loss of vision in that eye WHO stage II Post-herpetic neuralgia should be treated with pain-modifying agents: phenytoin 100 mg slowly increasing to 250–300 mg daily or carbamazepine 100 mg daily, increasing to 400 mg daily in 10 days
Molluscum contagiosum	Centrally umbilicated non-pruritic papules on the face, neck and anogenital areas. Lesions on the face tend to proliferate, especially if injured during shaving.		Prick each lesion with a needle dipped in phenol; follow by expression of the central core Alternatively, where available, cryotherapy with liquid nitrogen or curettage is recommended The recurrence rate is high	Differential diagnosis: disseminated cryptococcosis, histoplasmosis and penicilliosis These systemic mycoses are usually associated with fever, pulmonary or meningeal involvement Remission following treatment with ARVs
Condylomata acuminata (genital warts)	Finger-like projections on surface with cauliflower appearance Can be very extensive, involving both the genital and perianal region		Treat with podophyllin 20% solution twice weekly until cleared Podophyllin 20% can be corrosive to the surrounding unaffected skin It should only be applied to the tips of the warts and washed away no later than 6 hours after application. For warts on the genital mucosa and mouth, a lower concentration of podophyllin (10%) may be applied.	The lesions are caused by the human papillomavirus, which can give rise to cervical and anal cancer Patients with a small number of warts may be asymptomatic Other patients may have pruritus, bleeding or pain The recurrence rate is high

Table 6.1. Skin conditions

			Alternatively, glacial trichloracetic acid may be applied 1–2 times a week until the lesion has cleared. Where available, cryotherapy with liquid nitrogen is recommended	
Others				
Scabies	Parasitic skin infection: superficial burrows, intense pruritus (most intense at night) and secondary inflammation	Diagnosis: KOH preparation of skin scales Mites can be seen on microscopic examination	Topical permethrin cream (5%) applied to total body, neck down, and washed off 8–14 hours later. Re-treat after 1–2 weeks. All household contacts must be treated. Avoid contact with the eyes	Scabies can lead to extensive disease in AIDS patients with hypertrophic, hyperkeratotic lesions that become secondarily infected with bacteria It can be life-threatening when secondary infection is severe
Kaposi sarcoma	Dark, patchy, painless swelling or nodules that are not itchy and no ring pattern, with or without similar oral lesions		Discrete, solitary or few lesions are best left alone Lesions of the face or exposed parts of the body may be treated locally with cryotherapy (topical liquid nitrogen), intralesional therapy with either vinblastine (0.2–0.4 mg at two-week intervals) or alpha interferon, and surgical excision In single lesions, the results with any of the treatment choices mentioned are promising If lesions are disseminated or extensive and if treatment is envisaged, do a biopsy	Remission reported with ARVs Association with HHV type 8 Visceral disease with lung involvement may mimic TB

Table 6.1. Skin conditions				
			Radiotherapy: for localized intraoral or pharyngeal KS, painful cutaneous KS, and lymphoedema of the face and extremities	

6.1 Viral infections

Disease	Manifestations
Acute HIV exanthema (primary HIV infection)	Fever, myalgias, urticaria; truncal, palmar, plantar maculopapules
Herpes simplex	Relapsing with persistent erosions
Varicella zoster	May be recurrent; usually dermatomal
Molluscum contagiosum	Clusters of white umbilicated papules
Oral hairy leukoplakia (OHL)	Whitish, nonremovable verrucous plaques on sides of tongue
Warts (HPV)	Increased number and size of verrucous lesions

6.1.1 Herpes simplex

Patients with AIDS are particularly prone to severe and progressive herpesvirus (HSV) infections. Herpes viruses also contribute to the progression of HIV disease as co-factors, though the exact mechanism is unknown. Serological studies have found that >95% of homosexual men with AIDS have a history of HSV infection. Genital ulcerative disease due to HSV is also an important risk factor for the acquisition of HIV infection.

The course of herpesvirus infection can be divided into three phases:

i. Primary infection: The host acquires infection for the first time; viral replication occurs leading to death of cells and is controlled by the host's immune system.
ii. Latent infection: The virus genome remains in the host's cells in an inactive form.
iii. Reactivation: The latent viral genome becomes active resulting in viral replication when the host's immune system is impaired. Most HSV infections among AIDS patients result from reactivation of latent virus.

Clinical features

Genital and oral infections with extensive tissue damage account for the majority of lesions due to HSV in HIV-infected individuals. Progressive HSV perianal ulcers, proctitis, colitis, oesophagitis, oral lesions, pneumonia and a variety of neurological disorders have been observed in AIDS patients. HSV-induced mucocutaneous ulcers lasting for more than 1 month, or bronchitis, pneumonitis or oesophagitis are AIDS-defining criteria.

Skin and mucosal manifestations include vesicular eruptions in crops, quickly progressing to ulcerations, frequently localized in or around the genital organs, rectum and colon, oral cavity and perioral areas. Occasionally, there is spread to the oesophagus which causes dysphagia and odynophagia. Sometimes the infection can extend to the trachea and bronchi. The disease is generally severe with frequent relapses.

The manifestations of HSV encephalitis are nonspecific with focal symptoms suggestive of frontal–temporal lobe involvement.

Treatment

Acyclovir 200 mg 5 times per day for 7–10 days (14 days in case of recurrence) or acyclovir 5 mg/kg IV q8h for 10 days for severe cases (including encephalitis).

6.1.2 Herpes zoster

It is caused by the Varicella zoster virus (VZV) or herpesvirus type 3, and is also the causative agent of chicken pox. Zoster develops only if the person has been previously infected with chicken pox. The virus remains dormant in the nerve roots of the spinal cord. A person immunized against chicken pox will not develop chicken pox or zoster. Herpes zoster occurs in 8–11% of HIV-infected individuals. In most, it is a self-limited infection, although severe complications can arise with advanced HIV disease. Disseminated lesions of the lungs, liver or nervous system leading to pneumonitis, hepatitis, retinitis and encephalitis may occur. The course of herpes zoster is also more prolonged, with a higher risk of scarring and post-herpetic neuralgia in HIV-infected individuals.

Clinical features

The incidence of herpes zoster is 15–25 times higher in HIV-1-infected persons than in the general population. The symptoms of zoster start with a burning, sharp pain, tingling, numbness, itching or aching in or under the skin of one side of the body or face. There may be constitutional symptoms of tiredness with fever, chills, headache and an upset stomach. The prodrome of severe pain may resemble a burn or muscle injury. It may be recurrent, or multiple dermatomes may be affected. After several days a rash that does not cross the midline develops. The rash is made up of grape-like clusters of small, clear, fluid-filled blisters on red skin. Within three days of development of the rash, the blisters turn yellow, dry up and form crusts. The rash takes longer to crust in HIV-positive people. The skin lesions are similar to chicken pox in appearance and evolution. In severely immunocompromised individuals the rash can resemble burns. Recurrent disease can occur in 3–5% and is usually in the same dermatome. Extensive cutaneous dissemination and visceral involvement can occur.

Progressive outer retinal necrosis is a VZV-associated entity that typically occurs among HIV-1-infected persons with CD4+ counts <50 cells/mm3. It is characterized by multifocal retinal opacification with little or no ocular inflammation and rapid visual loss.

Diagnosis

Zoster is diagnosed empirically based on the appearance of characteristic lesions. When lesions are atypical or the diagnosis is uncertain, swabs are taken from a fresh lesion and a Tzanck preparation made to look for for multinucleate giant cells. Alternatively, biopsied tissue is submitted for viral culture. Growth in culture is very slow. PCR is being evaluated as a diagnostic tool.

Treatment

Treatment of zoster reduces healing time and pain, and delays or prevents additional flare-ups. To be effective, medication needs to be started within 3 days of the symptoms. Typically, treatment is used only during a flare-up. Oral acyclovir is the recommended treatment (20 mg/kg body weight up to a maximum dose of 800 mg four or five times daily). This is called "episodic therapy". The area around the lesions should be kept clean and dry. If cutaneous lesions are extensive or if clinical evidence of visceral involvement is observed, IV acyclovir 10 mg/kg q8h is given for 7–10 days and continued until the lesions are clearly resolving. Switching to oral therapy with valacyclovir or famciclovir after the patient has defervesced might be permissible, if

there is no evidence of visceral involvement. Analgesics can be used to manage the discomfort of zoster. Adjunctive corticosteroid therapy to prevent postherpetic neuralgia is not recommended.

Multidermatomal herpes zoster

The condition is often difficult to treat and frequently relapses. The lesions can spread on both sides and affect multiple areas of the body to cause disseminated zoster. Topical dyes (methylene blue, millian) are used to combat superinfection. Topical antivirals are often not effective and can irritate the lesions. Systemic therapy is preferred and is most useful when given early in the course of the illness, within 72 hours after the onset of the lesions. Treatment is similar to that of herpes zoster.

6.1.3 Molluscum contagiosum (pox virus)

Molluscum contagiosum (MC) is a common skin problem caused by a viral infection of the upper layers of the skin. MC is caused by the molluscum contagiosum virus (MCV), a DNA pox virus. It can be spread through skin-to-skin contact, especially during sexual activity that involves friction and skin irritation.

MC causes one or more lesions on the skin that resembles warts or pimples. They usually form in clusters, notably on the thighs, buttocks, groin and lower abdomen, and may occasionally appear on the external genital and anal region, and on the face and eyelids. The clear liquid pearl-like nodules are 2–10 mm in diameter with central umbilication. MC looks like small flesh-coloured or pink dome-shaped bumps that are shiny in appearance. The lesions may be itchy or tender.

Diagnosis is usually based on the clinical apperance. Giant confluent lesions may have a bizarre appearance and require biopsy. Local anaesthetic is not required as the lesion is painless.

Treatment

Cryotherapy using liquid nitrogen to freeze the lesions, laser treatment, curettage, scraping of the lesions and electrocautery can be used to remove the lesions. Incision and drainage can be done using tincture of iodine.

Topical gels and creams such as podophyllum, trichloroacetic acid, cantharidin, tretinoin, tincture of iodine, silver nitrate or phenol can be applied directly to the lesions. Repeated application may be required until the lesions clear. The normal skin around may need to be protected with parafiin wax. Griseofulvin and cimetidine are effective in MC lesions. Cimetidine can be used if the area becomes inflamed or itchy. If the lesions are extensive HAART needs to be initiated.

6.1.4 Genital warts and human papillomavirus disease

Human papillomavirus (HPV) infection of the anogenital tract results in a spectrum of disease, ranging from self-limited, transient infection to squamous cell cancer. It is the aetiological agent of genital warts and condyloma acuminata. HIV-positive people are more likely to be infected with HPV. The principal manifestations of genital HPV infection is a cauliflower-like, pedunculated lesion(s) measuring a few millimeters to 1–2 cm in diameter; or flat, keratotic plaques and dome-shaped papules. Lesions often occur in clusters, and might occur at multiple sites in the anogenital tract. Patients may be asymptomatic, although those with perineal lesions often have pain on defecation or perianal itching. Diagnosis is usually by clinical inspection and further diagnostic testing is not generally required. However, dysplastic lesions cannot be seen by the naked eye. The entire anogenital region should be carefully inspected for visual signs of warts. Digital examination of the vulvar, vaginal and perineal regions, and the anal canal should

be performed routinely. Digital examination should be done after taking a cervical or anal Papanicolou (Pap) smear because the lubricant may cause errors in the interpretation of Pap smears. Routine Pap smear and colposcopic monitoring should be done to detect dysplasia among HIV-infected women. If the Pap smear has a cytological interpretation of "atypical squamous cells of uncertain significance" (ASCUS) or "atypical squamous cells—cannot rule out high-grade disease" (ASC-H), colposcopy and directed biopsy are recommended.

Treatment

Therapy is not required for genital warts and low-grade dysplasia, but is recommended to prevent these lesions from advancing. Intermediate and high-grade dysplasia, as well as cervical or anal cancer, requires therapy to prevent these from becoming life-threatening problems. Treatment depends on the location and severity of the disease.

No treatment for genital warts is uniformly effective, and recurrence rates are high. Patient-applied methods are generally recommended for uncomplicated external lesions, and consist of topical gels and creams such as podophyllum, trichloroacetic acid and imiquimod. They are 30–80% effective in reducing the size of the wart(s).

Podofilox is an antimitotic agent applied topically to lesions as a 0.5% solution or a 0.5% gel twice daily for 3 consecutive days. Treatment is repeated weekly for up to 4 weeks. The efficacy is 40– 60% in immunocompetent subjects. Skin irritation may occur.

Imiquimod is a topical cytokine inducer that recruits an inflammatory response to the site of the wart.

Trichloroacetic or bichloroacetic acids are caustic agents that kill wart tissue. They can be made in an 80–95% aqueous solution and applications are repeated weekly for 3–6 weeks.

Podophyllin resin is a crude extract that contains podophyllotoxin and other cytoxins and induces wart necrosis after topical application. It is prepared as a 10–25% suspension in tincture of benzoin, and applied and removed by washing a few hours later.
Cryotherapy with liquid nitrogen may be used until each lesion is thoroughly frozen.
Surgical treatment comprises excision with scissors, shaving or curetting, or electrosurgery.

6.2 Fungal infections

6.2.1 *Tinea versicolor*

The disease is caused by a yeast-like organism which is a commensal on the skin. Colonization occurs in the scalp, flexures and upper trunk. Three types are seen: *Pityrosporum ovale, P. orbiculare* and *Malassezia furfur*. They cause pityriasis versicolor (thick, scaly, hypopigmented or light-brown plaques on the trunk), seborrhoeic eczema and folliculitis. Diagnosis is clinical. It can be confirmed by histopathological examination of skin scrapings or by examination under Wood light. Treatment is with selenium sulfide shampoo. The shampoo is applied and left for 30 minutes and then washed off. Application is repeated daily for a week. A topical imidazole cream can be applied twice daily for 2 weeks. Oral itraconazole 100 mg daily for 1 week can be used for resistant, widespread infestation. The pigmentation takes months to return to normal. Folliculitis can be treated with ketoconazole shampoo or a topical imidazole cream applied twice daily for 2 weeks.

6.3 Bacterial infections

6.3.1 Staphylococcal infections

S. aureus causes superficial and subcutaneous infections in HIV-infected individuals. These include staphylococcal pyomyositis and impetigo.

Pyomyositis

This is caused mainly by *S. aureus* and there is pus in individual muscle groups. It may also be due to *S. pneumoniae* or Gram-negative enteric bacteria. Blood culture is positive in 5–30% of the cases.

It usually presents in an extremity. Any muscle group may be involved, including the trunk muscles and the psoas. The infection begins with localized pain, muscle spasm and fever. Later, the muscles have a firm wooden feel, with pain and tenderness. Ultrasound or CT scan may be needed to diffentiate the condition from deep vein thrombosis.

Treatment involves incision and drainage, and appropriate antibiotic therapy (usually cloxacilin).

6.4 Kaposi sarcoma

Human herpesvirus 8 (Kaposi sarcoma)

Also called Kaposi sarcoma-associated herpesvirus (KSHV), HHV 8 is non-pathogenic in the majority of healthy individuals but is highly oncogenic in immunosuppressed patients. It is involved in the pathogenesis of Kaposi sarcoma, primary effusion lymphoma and some cases of multicentric Castleman disease. Approximately 30% of all HIV-positive gay and bisexual men are infected with HHV 8, whereas 2–3% of HIV-positive transfusion recipients or haemophiliacs are infected. Only 3–4% of HIV-positive heterosexual women are infected. The overall incidence of Kaposi sarcoma was as high as 20% among patients with AIDS before the advent of effective ART. KS has been known to occur in some HIV-positive people with relatively high T-cell counts (>500 cells/mm^3). The incidence of KS is very low in India.

Clinical features

In young children, primary HHV 8 infections are asymptomatic or very mild, but become severe in case of immunodeficiency. Its principal clinical manifestations are neoplastic disease. KS blotches on the skin range in colour from pinkish-red to brownish-blue and are usually flat, painless lesions that do not blanch on pressure. This helps to differentiate them from bruises. Eventually, these lesions may become elevated and painful. New lesions usually evolve very slowly. KS lesions inside the mouth can create soreness and cause bleeding. Eating becomes difficult and painful. Pulmonary KS can cause severe breathing problems. Lesions in the large intestine and colon can cause diarrhoea and cramping discomfort. KS lesions in the gut and lungs can be fatal if not treated or disease progression controlled.

Diagnosis

Confirmed mucocutaneous and visceral: Positive histopathology on tissue from any site/organ.

Probable mucocutaneous and/or visceral: Characteristic lesion(s) on skin or mucous membrane noted by an experienced physician. Characteristic appearance may include erythematous pigmentation (reddish to purplish brown), flat, papular, plaque-like and nodular lesions.

Treatment: Ganciclovir, foscarnet and cidofovir can be used and may produce regression.

7 Section HIV and Liver Diseases

Liver diseases have important co-morbidities with HIV.
HBV/HCV and HIV co-infection is common in some states of India

7.1 Acute and chronic hepatitis B

Epidemiology

It is the leading cause of chronic liver disease and is transmitted through sexual contact and IV drug use. HIV infection is associated with an inceased risk of developing hepatitis B. Patients with chronic hepatitis B infection are at increased risk of hepatocellular carcinoma.

Clinical features

Acute infection may present with fatigue, right upper quadrant abdominal pain, nausea, vomiting, fever, arthralgia and jaundice. The disease may remain asymptomatic until the onset of end-stage liver disease (ESLD) which is heralded by ascites, coagulopathy, palmar erythema, jaundice, hepatospenomegaly, variceal bleeding or encephalopathy. There may also be polyarteritis nodosa, glomerulonephritis and vasculitis.

Diagnosis

Tests for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc) and antibody to hepatitis B surface antigen (anti-HBs) will identify the majority of patients. It will also determine which individuals require vaccination. A chronic stage is said to occur when HBsAg is present for more than six months. Once detected, the severity of the liver disease must be followed with assessment of alanine transaminase (ALT), serum albumin, prothrombin time, platelet count, complete bloodcount and bilirubin levels. Patients should also be monitored every six months with alpha-fetoprotein levels and ultrasound of the liver, especially if they are older than 45 years, alcoholic, have cirrhosis or have a family history of chronic liver disease. Liver biopsy should be done to assess the grade and stage of liver disease. Transient elevation of enzymes can occur as a result of the hepatotoxicity of various drugs used in HAART. It may also occur as a result of concomitant infection with hepatitis A, hepatitis C or hepatitis delta virus.

Treatment

Patients should avoid alcohol. All their contacts – sexual, household and needle-sharing – need to be immunized. If the person also develops hepatitis A, it is likely to be fulminant and therefore active immunization with two doses of hepatitis A vaccine should be administered before the CD4 count falls to <200 cells/mm^3. Antiviral treatment is advised if there is actively replicating virus in the blood, indicated by a positive hepatitis B core antigen (HBcAg) or HBV DNA levels >10^5 copies/ml and a raised ALT level that is twice the normal. Pegylated interferon (PEG IFN)-alpha 2, 5–10 MU can be given thrice a week subcutaneously (SC) for 16–24 weeks. If the patient is HAART-naive, lamivudine is the preferred drug along with other ARV drugs. Adefovir dipivoxil 10 mg OD can be used in patients who do not require HAART. Tenofovir 300 mg OD can also be used. Emtricitabine 200 mg OD is also active against replication of the hepatitis B virus. If the patient is infected with HBV, HBC and HIV-1, starting HAART should be the first priority. If HAART is not required then treatment for HBV should be considered first.

Lamivudine resistance occurs at the rate of around 20% per year. Adefovir or tenofovir may be better drugs. If ESLD develops it is managed in the same way as in HIV-negative individuals. IFN is contraindicated in ESLD. Liver transplantation can be done.

7.2 Acute and chronic hepatitis C

Epidemiology

Chronic hepatitis C infection is caused by the single long-stranded RNA hepatitis C virus. There are 6 genotypes and 50 subtypes. It is transmitted sexually, through infected blood products, needle-sharing and from mother to child. Cirrhosis sets in approximately 20 years after infection. The incidence of cirrhosis is higher in males, those >45 years and with concomitant alcoholism. Co-infection with HIV increases the rapidity of progression to ESLD.

Clinical features

Patients may be asymptomatic or only mildly symptomatic so that acute infection is not recognized. There may be low-grade fever, fatigue, anorexia, right upper quadrant pain, nausea, vomiting, dark-coloured urine and frank jaundice. ALT and aspartate aminotransferase (AST) may be elevated. Serum cryoglobulins are present in 60% but may not cause symptoms. As liver disease progresses, signs of portal hypertension may appear. There may be leukocytoclastic vasculitis and porphyria cutanea tarda. Fibrosing cholestatic hepatitis might occur.

Diagnosis

Qualitative HCV RNA assay in the blood shows >50 copies/ml. A recombinant immunoblot assay (RIBA) can be performed if the HCV RNA is negative but the immunoassay for anti-HCV is positive. HCV viral load does not correlate with the degree of histological injury. Co-infected persons should be checked for other co-morbid liver conditions such as hepatocellular carcinoma by serum alfafetoprotein level and ultrasound examinations of the liver. ALT is the simplest and least expensive test to evaluate the activity of liver disease.

Treatment

All patients should be counselled to stop alcohol consumption. Fulminant hepatic failure occurs if there is co-infection with hepatitis A. Hence, all patients should receive two doses of hepatitis A vaccine before the CD4 count falls to <200 cells/mm^3. In addition, they should also receive hepatitis B vaccine.

Treatment should be offered to patients at increased risk of developing cirrhosis, patients with detectable plasma HCV RNA levels, and in those in whom liver biopsy shows inflammation, necrosis, portal or bridging fibrosis and elevated ALT levels.

IFN alfa-2b 180 µg weekly by subcutaneous injection plus ribavirin 600–1400 mg daily might eradicate HCV infection. Patients with unstable cardiopulmonary disease, anaemia unresponsive to erythropoietin or haemoglobinopathy cannot be given ribavirin. The exact duration of treatment is not known but it is usually continued for 48 weeks. The critical CD4 level is 500 cells/mm^3. Before it falls below this level, treatment for HCV should be started. If the CD4 count is already below this level, HAART should be started first. Liver transplantation is a primary treatment option.

Quantitative HCV RNA levels are the best estimate for treatment. A sustained virological response means an absence of detectable HCV RNA (<50 IU/ml) after antiviral treatment for 2 weeks. Relapse is defined as the presence of detectable HCV RNA at the end of treatment.

Section 8

Management of Common Syndromes, Symptoms and Signs seen among HIV-infected Persons

8.1 Syndromes

8.1.1 Acute undiffirentiated fever

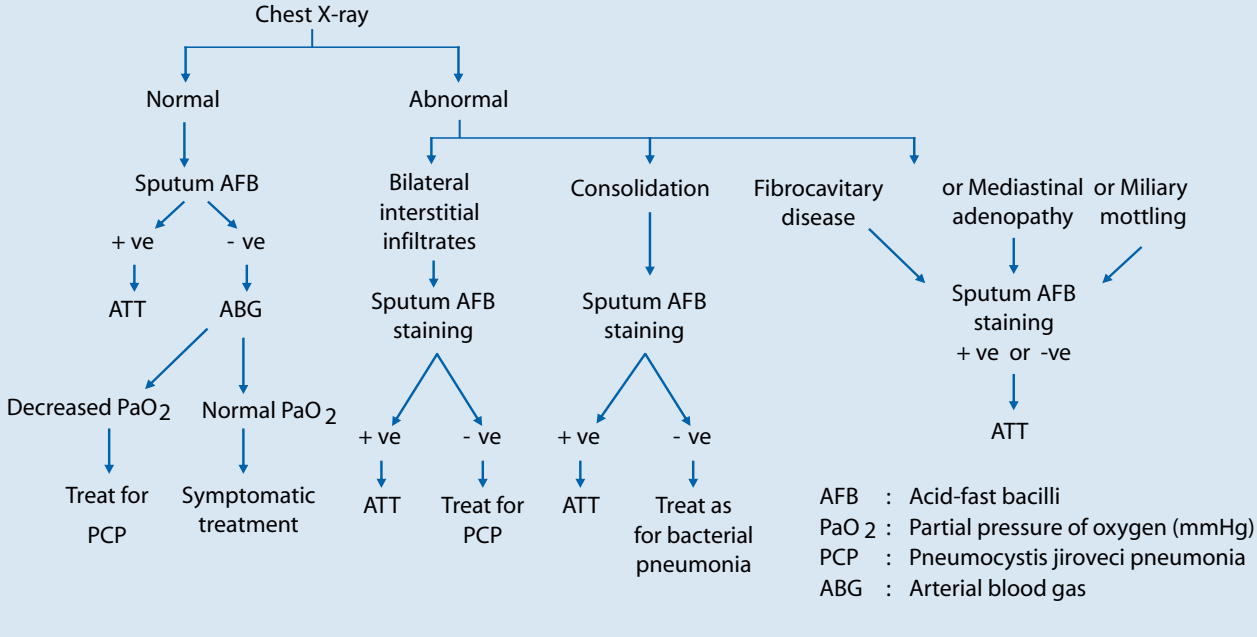
An acute undifferentiated fever needs evaluation only in the presence of other symptoms or signs that indicate a more serious aetiology. Symptomatic treatment may be given. In case of fever for >14 days, evaluation may be done as for prolonged fever.

8.1.2 Prolonged fever

This is a common sign in those with HIV infection and is usually caused by a treatable OI. A recent study found the causes of prolonged fever among HIV-infected individuals in India to be TB (69%), cryptococcosis (10%), PCP (7%), pneumonia, amoebic liver abscess (2% each), and histoplasmosis, sinusitis, spontaneous peritonitis, pyogenic meningitis and malaria (1% each). For evaluation, ultrasound abdomen was helpful in 85%, bone marrow trephine biopsy in 42%, and lymph node FNAC in 75% of cases.

Diagnostic evaluation of pyrexia of unknown origin (PUO) in an HIV-infected individual requires a comprehensive history, repeated physical examinations, complete blood counts, tests for malarial parasites, urine analysis, CXR, sputum examination, blood cultures, liver function tests, ultrasound of the abdomen, imaging of the chest, if necessary, CD4 counts and tuberculin skin tests (Fig. 8.1).

Figure 8.1 Prolonged fever and pulmonary symptoms



8.2 Symptoms

8.2.1 Headache

In a patient with a CD4 count ≥200 cells/mm^3, headache is predominantly due to causes other than an OI (e.g. muscle tension, vascular, sinus-related). In an individual with a lower CD4 count, OIs also must be considered in the differential diagnosis. The three most common OIs are cryptococcal meningitis, *Toxoplasma* encephalitis and CNS lymphoma; less frequent infections include coccidioidomycosis, histoplasmosis and TB.

History should include duration, location and precipitants of headache, associated symptoms and potential exposures (e.g. travel, TB, drug use). Physical examination should focus on the head and neck, and a detailed neurological assessment is needed.

For a patient with a CD4 count <200 cells/mm^3 and significant or persistent headache, neuroimaging with a contrast-enhanced brain MRI/CT scan should be performed to rule out the presence of a mass lesion. If this is normal, an LP with CSF analysis, including cell count, chemistry, cryptococcal antigen, syphilis serology, cytology, and stains and cultures for specific suspected pathogens, is indicated. PCR may identify pathogens such as CMV, HSV, JC virus and EBV (for lymphoma). Other useful tests include serum cryptococcal antigen and *Toxoplasma* IgG antibody.

The presence of a mass on radiological imaging narrows the differential diagnosis to toxoplasmosis or lymphoma. Toxoplasmosis appears as multiple ring-enhancing lesions with minimal oedema in the grey matter, whereas lymphoma lesions are usually solitary, periventricular, non-enhancing, and have substantial surrounding oedema.

In patients who are positive for *Toxoplasma* IgG or in seronegative individuals with characteristic CNS lesions, empirical anti-*Toxoplasma* therapy is usually warranted. If a clinical and radiological response is not seen within 10–14 days, brain biopsy is indicated to establish a definitive diagnosis.

8.2.2 Jaundice

The causes of jaundice include:

1. Hepatitis: Drug-induced, alcohol-induced, HBV, HCV, *Mycobacterium avium* complex (MAC) (*see* section 7).
2. Acalculus cholecystitis and cholangitis: CMV, *Cryptosporidium, Microsporidium*

8.2.3 Gynaecological symptoms

These complaints may be the initial manifestation of HIV infection in women. Many conditions, including vulvovaginal candidiasis, cervical abnormalities, cancer and pelvic inflammatory disease (PID) have an increased incidence and are more difficult to treat in HIV-infected women.

Vaginal discharge and pelvic pain: Vaginal discharge can be due to vaginitis or the initial manifestation of more complicated problems such as PID. Recurrent vaginal candidiasis, a common problem, is characterized by pruritus and a thick white discharge. Other causes of vaginal discharge, including bacterial vaginosis and trichomoniasis, are seen at the same rates in HIV-infected and uninfected women.

Genital HSV infection, which is more common and severe in HIV disease, usually manifests with localized discomfort. Pelvic pain can be associated with PID, ectopic pregnancy, HSV infection and other gynaecological abnormalities, including uterine fibroids, ovarian cysts and endometriosis.

Women with HIV infection are also at increased risk for cervical dysplasia and neoplasia. Although usually asymptomatic, advanced cervical lesions can present with vaginal symptoms.

Evaluation of HIV-infected women presenting with vaginal discharge or pelvic pain requires a careful history, and abdominal and pelvic examinations. The history should focus on the location and nature of symptoms, characteristics of the discharge if any, and the presence of fever and other associated symptoms. Testing should be done for gonorrhoea and *Chlamydia*. The discharge should be examined with KOH for yeast and with normal saline for trichomoniasis or evidence of bacterial vaginosis (clue cells). A urinary pregnancy test should be performed if clinically indicated. Pelvic or abdominal ultrasound may be needed.

Menstrual irregularities: Menstrual symptoms are not more frequent when compared with seronegative controls. Evaluation of menstrual symptoms may include screening for pregnancy, uterine fibroids, and endocrinological abnormalities. Referral to a gynaecologist is appropriate.

Section 9

Management during Clinical Latency

9.1 Primary prophylaxis for opportunistic infections

HIV-infected individuals become susceptible to a multitude of opportunistic microorganisms, including protozoa, fungi, viruses and bacteria, which are generally innocuous in healthy individuals. HIV-infected subjects tend to contract OI during the course of the disease, which roughly corroborates with the CD4 cell counts. Although no definitive relationship between OIs and CD4 cell count has yet been established, cumulative information points towards a relationship. Also, since opportunistic events tend to recur, irrespective of previous successful treatment, prophylaxis needs to be continually given.

Primary prophylaxis needs to be started in all HIV-infected patients when they come under stage III WHO classification, or stage II when the CD4 count is <200 cells/mm^3. It may be discontinued when the CD4 cell count is >200 cells/mm^3 for six months. It is given lifelong if the CD4 cell count is not estimated.

Primary prophylaxis for *Cryptococcus* is not routinely recommended due to the relatively low incidence of the disease, lack of a definite survival benefit, drug interactions, development of resistance to the azole class of antifungals, cost and absence of mortality benefit.

Co-trimoxazole (sulfamethoxazole/trimethoprim [SMX–TMP]) 800 mg/160 mg PO once daily is effective in preventing PCP and toxoplasmosis. It could help in the prevention of certain bacterial pneumonias, nocardiosis and enteric pathogens (isosporiasis). In case of allergy to co-trimoxazole, an alternative for primary prophylaxis against PCP and toxoplasmosis is dapsone 100 mg once daily with pyrimethamine 50 mg weekly. Desensitization may be suggested for sulfa allergy.

10 Section

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS refers to atypical manifestations of OIs with paradoxical clinical deterioration following initiation of HAART. The syndrome is well-described for TB, cryptococcosis and PCP. Occurrence of IRIS with *P. marneffei* infection has also been reported.

IRIS following treatment of infection due to *C. neoformans* presents with aseptic meningitis and raised intracranial pressure, mediastinal lymphadenopahty and cavitary pulmonary lesions. With PCP the presentation includes worsening dyspnoea, and pulmonary infiltrates and cavitation or cystic lesions.

IRIS must be distinguished from failure of treatment or prophylaxis, as the management is very different. Emphasis is on primary prevention of OI transmission to the HIV-infected spouse and other noninfected family members.

Immune Reconstitution Disease (IRD)/Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution disease (IRD) can be described as an adverse clinical phenomenon following rapid restoration of immune function in a previously severely immunocompromised individual. This is not specific to HIV-infected persons on HAART but can follow recovery from neutropenia (chemotherapy/transplantation) or dose reduction/withdrawal of steroids. It is associated with many pathogens, most frequently (>40% in the literature) mycobacterial infections (MTB, MOTT, leprosy).

It is reported in up to 23% of HIV-seronegative patients on ATT, and often starts within two months of commencing ATT. In 75% of patients it manifests at the initial site of infection. It occurs predominantly as extrapulmonary disease and is associated with tuberculin skin test (TST) conversion. The clinical presentation is diverse. Clinical/radiological deterioration of pre-existing tuberculous lesions and development of new lesions (e.g. fever, lymph node enlargement, respiratory failure, neurological deterioration) are seen in those who initially responded to effective ATT.

In HIV-infected patients, IRD can be described as a deterioration of OIs due to restoration of pathogen-specific immune responses. A temporal relationship with commencement of HAART and exclusion of an alternative explanation (lack of compliance with treatment of OI, drug resistance, development of a new OI) must be established. Often, evidence of preceding immune restoration (rising CD4 count, decreasing viral load) are observed but these are neither diagnostic or specific, nor essential for diagnosis.

Treatment

There is accumulating evidence that HIV-positive patients recently started on HAART who develop IRD (both during antituberculous therapy for mycobacterial co-infection as well as non-tuberculous IRD) must continue on treatment, both ART and treatment of OI. Steroids are used in life-threatening conditions (*see Annex 10*).

11 Section Home-based Care

People suffering from HIV/AIDS require long and continuous treatment. Hospital care in such a situation is not feasible. Home-based care and a continuum of care are necessary for such patients. Home-based care has some specific objectives:

1. Formation of interdisciplinary groups that will train family members and provide social support and teach prevention. They will develop a referral network linking health services with NGOs.
2. Clinical management starts after proper diagnosis and treatment, and includes follow up, nursing care, medical and palliative care, infection control practices and educating family members.
3. Counselling has to be done before and after HIV testing to reduce stress and anxiety, and plan for the future. Home care includes training of family members, providing moral support, and linkages to social welfare.

Home care has to be monitored regularly. Care providers are members of the family and NGO volunteers. Ordinary ailments such as cough and diarrhoea can be treated by the family members. They know the medicines for controlling loose motions, dehydration and how to adjust the nutritional requirements of the patient. They and NGO volunteers look after the patient at home and are trained to know when to refer the patient to a dispensary for community care. The dispensary staff doctor and primary health care doctors know when to refer the patient to a tertiary-care hospital and the health-care persons at tertiary hospitals know about counselling, diagnosis, medical treatment and nursing care. At home, family members are trained to deal with excreta, secretions and blood spills and moderate universal care is taught. If this is done, then home care is possible in the real sense.

Table 11.1. Drugs needed for important pathogens at the three levels of care

Pathogen	Primary	Secondary (non-ART centre)	Secondary (ART centre)	Tertiary
PCP	TMP–SMX	TMP–SMX and alternative drugs	TMP–SMX, and alternative drugs	TMP–SMX and alternative drugs
Cerebral toxo-plasmosis	Sulfadiazine + pyrithmeth-amine	Sulfadiazine + pyrithmethamine	Sulfadiazine + pyrithmethamine	Sulfadiazine + pyrithmethamine
Cryptococcal meningitis		Amphotericin B IV IV and oral fluconazole	Amphotericin B IV IV and oral fluconazole	IV Amphotericin B IV and oral fluconazole
Candidiasis – oral and oesophageal	Fluconazole	Fluconazole, amphotericin B IV fluconazole for oesophageal	Fluconazole, amphotericin, IV fluconazole for oesophageal	Fluconazole, amphotericin IV fluconazole for oesophageal
Herpes simplex	Acyclovir PO, famcyclovir	Acylovir PO, famcyclovir IV acyclovir	Acylovir PO, famcyclovir IV acyclovir	Acyclovir, famcyclovir IV acyclovir
Herpes zoster	Famcyclovir	Famcyclovir	Famcyclovir	Famcyclovir

Table 11.1. Drugs needed for important pathogens at the three levels of care

Pathogen	Primary	Secondary (non-ART centre)	Secondary (ART centre)	Tertiary
Post-herpetic neuralgia		Carbamazepine Amitriptyline	Carbamazepine Amitriptyline	Gabapentin Carbamazepine Amitriptyline
CMV			HAART	HAART, IV Ganciclovir Intravitreal Ganciclovir
Norwegian scabies	Benzyl benzoate, permethrin	Ivermectin, permethrin	Ivermectin, permethrin	Ivermectin, permethrin
Molluscum contagiosum	Podophyllin	Chemical cautery	Chemical cautery	Chemical/ cryocautery
MAC				Rifabutin, azithromycin Clarithromycin Ethambutol
Isosporiasis	TMP–SMX Ciprofloxacin	TMP–SMX Ciprofloxacin	TMP–SMX Ciprofloxacin	TMP–SMX Ciprofloxacin
Cryptosporidiosis	Nitazoxanide	Nitazoxanide	Nitazoxanide	Nitazoxanide
Microsporidiosis	Albendazole	Albendazole	Albendazole	Albendazole
Strongyloidiasis	Albendazole Ivermectin	Albendazole Ivermectin	Albendazole Ivermectin	Albendazole
TB	DOTS	DOTS	DOTS	DOTS

1 Annex

WHO Clinical Staging of HIV/AIDS for Adults and Adolescents (2006)

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2
Unexplained moderate weight loss (<10% of presumed or measured body weight)[1]
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[2] severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.5 °C intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 10^9/litre) and/or chronic thrombocytopenia (<50 X 10^9/litre[3])
Clinical stage 4[3]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis

Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or Symptomatic HIV-associated cardiomyopathy

[1] Assessment of body weight in pregnant woman needs to consider expected weight gain of pregnancy.

[2] Unexplained refers to where the condition is not explained by other conditions.

[3] Some additional specific conditions can also be included in regional classifications (e.g. reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in Americas region, penicilliosis in Asia).

2 Annex

Case Definition of AIDS in Adults (for persons above 12 years of age) (NACO October 1999)

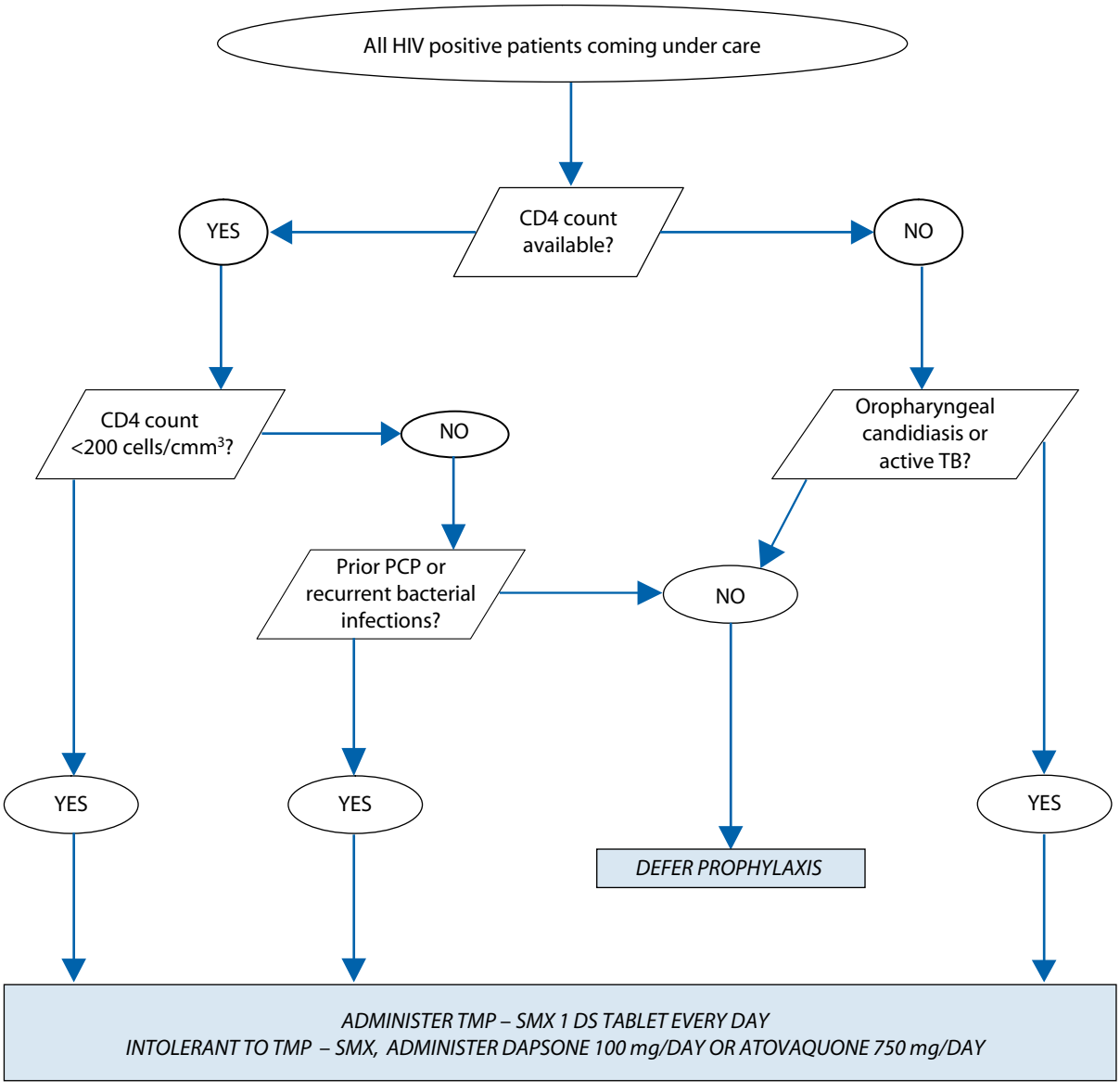
1. Two positive tests for HIV infection by ERS test (ELISA/RAPID/SIMPLE)

AND

2. 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) for >1 month or prolonged fever (intermittent or continuous) for >1 month
   b. Tuberculosis: Extensive pulmonary, disseminated, miliary, extrapulmonary
   c. Neurological impairment preventing independent daily activities, not known to be due to 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
      - Cerebral toxoplasmasis
      - CMV retinitis
      - *Pencillium marneffei* infection
      - Recurrent herpes zoster or multidermatomal herpes infection
      - Disseminated molluscum contagiosum

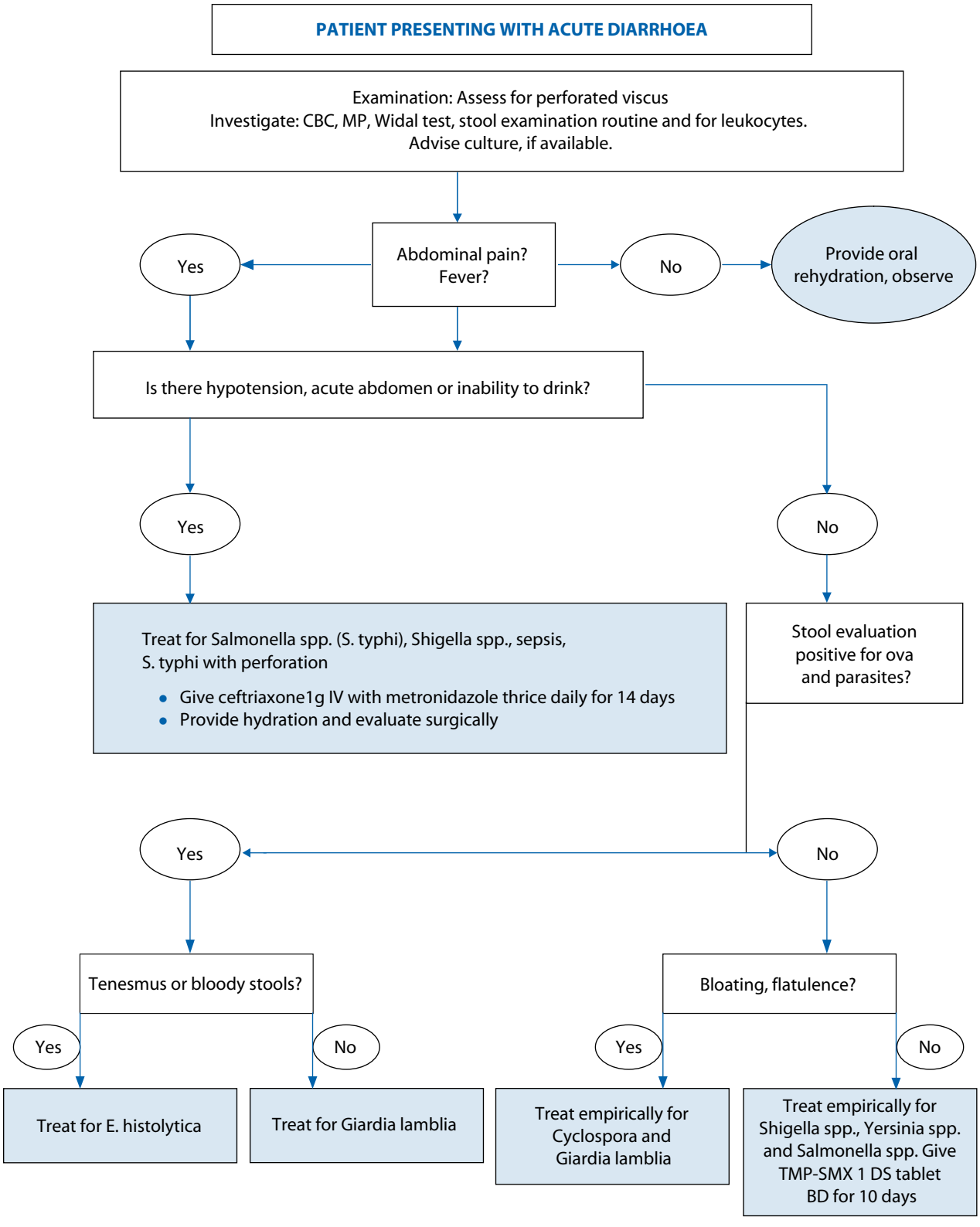
3 Annex

Prophylaxis against PCP and Invasive Bacterial Infections in HIV-positive Patients (See also Section 2.2.1)



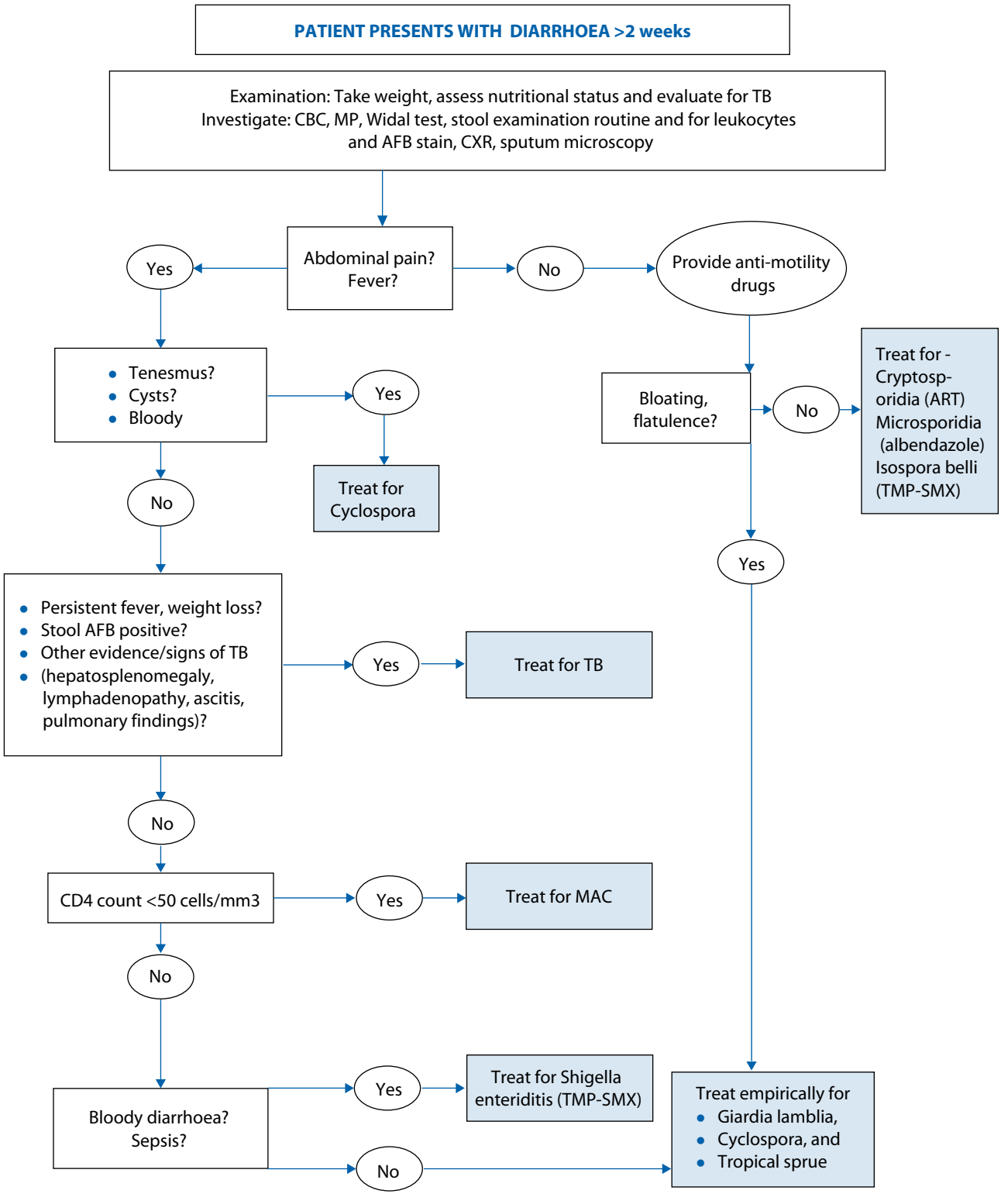
4 Annex

Approach to an HIV-positive Patient with Acute Diarrhoea



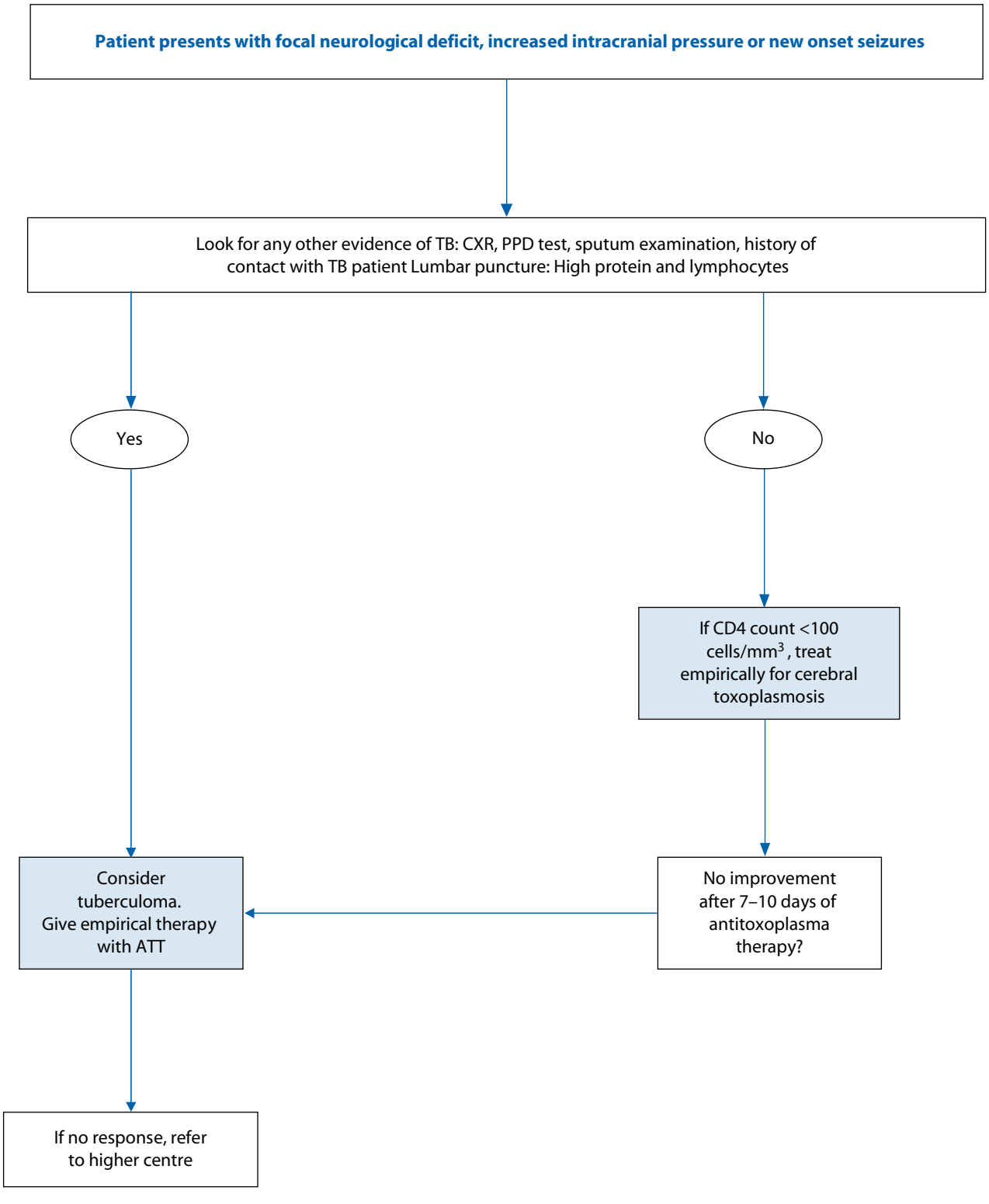
5 Annex

Approach to an HIV-positive Patient with Chronic Diarrhoea (>2 weeks)



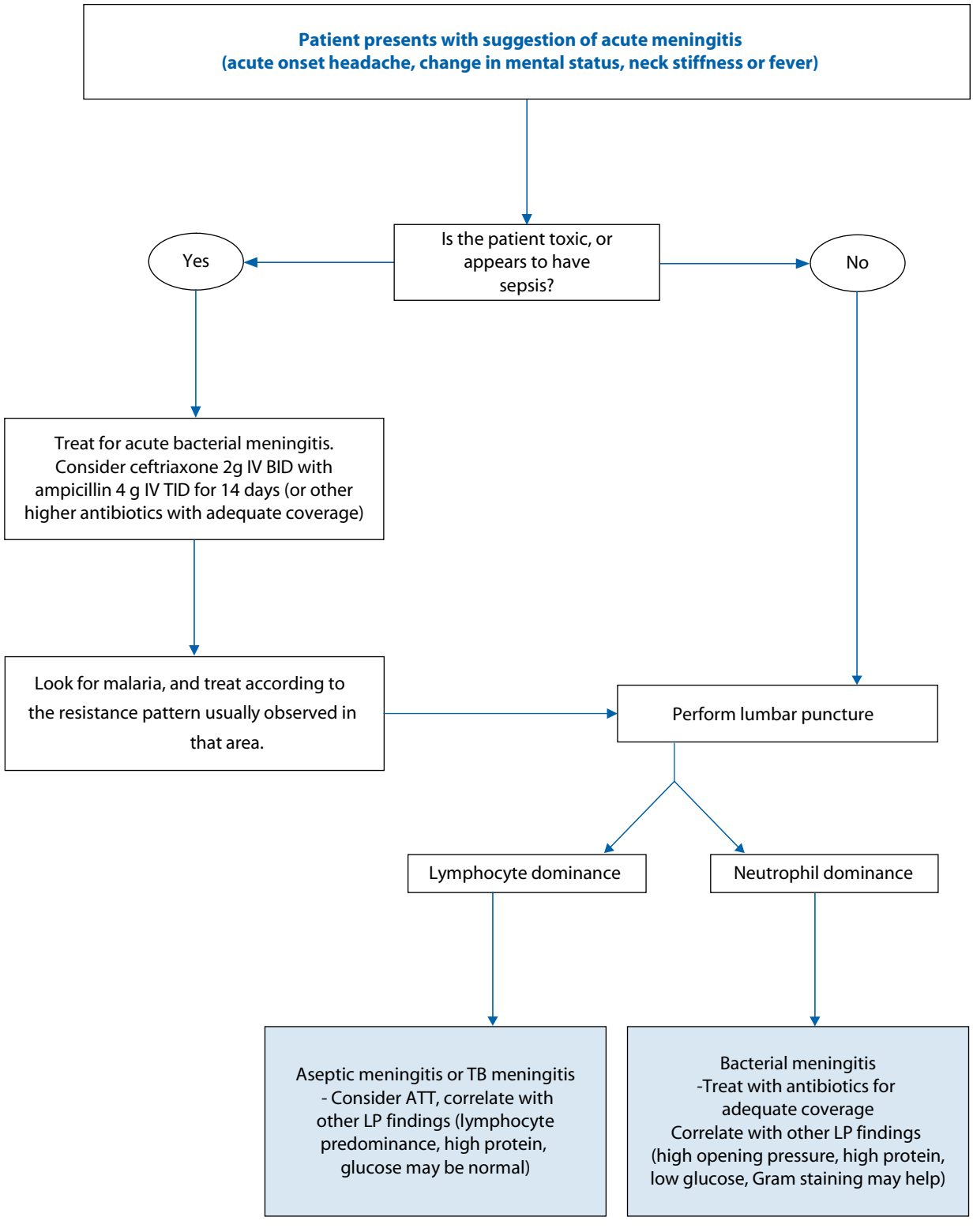
6 Annex

Management of Focal Neurological changes in an HIV-positive Patient



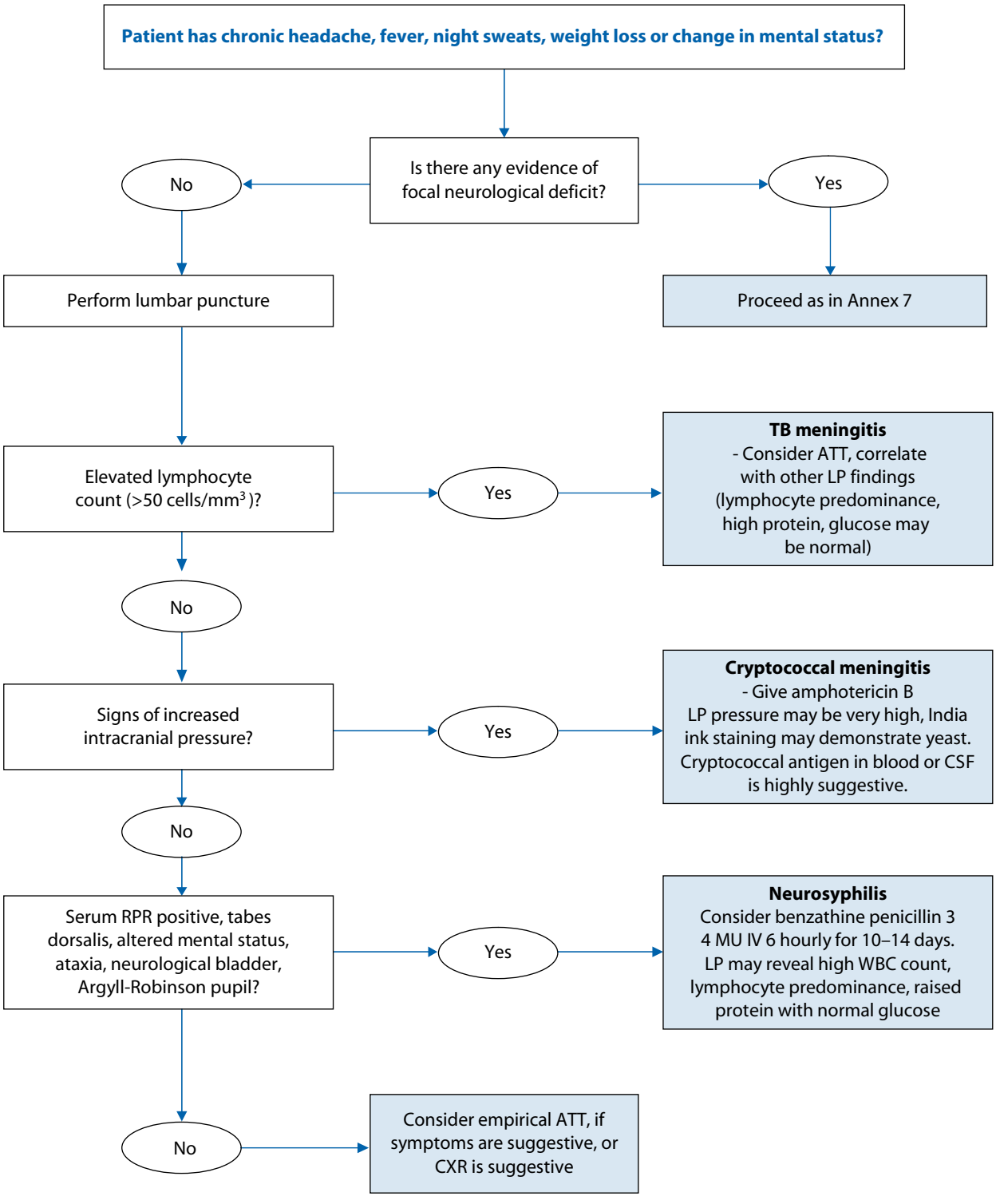
7 Annex

Management of an HIV-positive Individual with Suspected Acute Meningitis



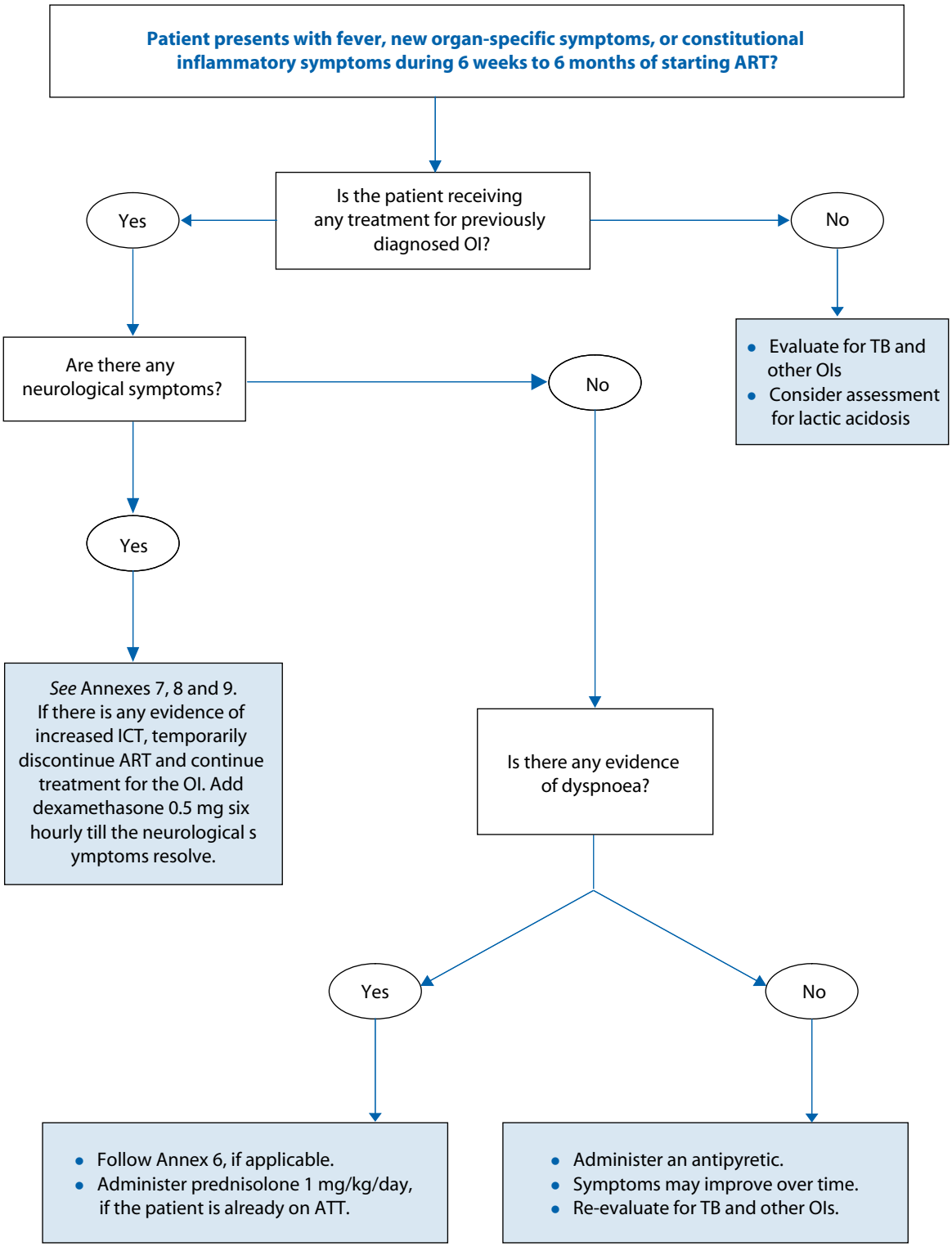
8 Annex

Management of an HIV-positive Patient with Suspected Chronic Meningitis



9 Annex

Management of Immune Reconstitution Inflammatory Syndrome (IRIS)



10 Annex

List of OI Drugs available under National Programme

Drugs to be supplied by the Institution where ART center is located		Drugs to be procured by NACO and supplied to ART centers)		Drugs to be procured by SACS/ centre as per requirement)	
1	Metronidazole 400mg	1	Nitazoxanide 500 mg	1	Fluconazole IV- 200 mg
2	Albendazole 400 mg	2	TMP-SMX DS 160/800mg	2	Acyclovir IV 250mg
3	Ciprofloxacin 500mg	3	Azithromycin 500mg	3	Inj. Gancyclovir 500mg
4	Prednisolone 10 mg	4	Fluconazole 150 mg	4	Cap. Gancyclovir 250 mg
		5	Fluconazole 400mg	5	Itraconazole 200mg
		6	Clotrimazole tubes	6	Clarithromycin 500mg
		7	Clindamycin 300 mg	7	Ethambutol 800mg
		8	Sulfadiazine 500 mg		
		9	Inj Amphotericin B 50 mg		
		10	Acyclovir 400 mg		
		11	Cefotaxime 1g		
		12	Levofloxacin 500 mg		
		13	Cap. Amoxyclav 625		