EUROPE

2 Management of Opportunistic Infections and General Symptoms of HIV/AIDS

Clinical Protocol for the WHO European Region

Contents

I. Principles

- Management of opportunistic infections (OIs) is an essential component of comprehensive HIV/AIDS treatment and care.
- *All* patients with OIs – irrespective of gender or social class and including injecting drug users (IDUs), sex workers, prisoners, immigrants and other vulnerable populations – should be treated. The decision of whom to treat should be based exclusively on medical considerations.
- Treatment for comorbidities should not stop while OI prevention and/or treatment is being provided.

II. Management of opportunistic infections

1. General information

HIV-related infections and illnesses include the following (Table 1).

Table 1. HIV-related infections and illnesses

Bacterial infections	Fungal infections	Viral infections	Parasitic infections	Other illnesses
Tuberculosis Bacterial respiratory infections Bacterial enteric infections Atypical mycobacteriosis Bartonellosis	*Candida* oesophagitis Cryptococcosis Histoplasmosis *Pneumocystis jirovecii* pneumonia (PCP) Coccidioidomycosis	Herpes simplex virus (HSV) disease Varicella-zoster virus (VZV) disease Cytomegalovirus (CMV) disease Human herpesvirus 8 (HHV8) infection, also known as the Kaposi sarcoma herpes virus (KSHV) Human papillomavirus (HPV) infection Progressive multifocal leukoencephalopathy Hepatitis B and C (natural course of infection is worsened by HIV coinfection)	Toxoplasmosis Cryptosporidiosis Microsporidiosis Isosporiasis Leishmaniasis	Kaposi sarcoma (KS) Non-Hodgkin lymphoma (NHL) Cervical cancer Encephalopathy Vacuolar myelopathy

The most common OIs in the WHO European Region include:
- tuberculosis (TB)
- bacterial infections
- PCP
- herpes infections (including herpes zoster, CMV, HSV 1 and 2 (HSV 1/2)
- *Candida* oesophagitis
- *Cryptococcus* meningitis
- toxoplasmosis.

Less frequent opportunistic infections and cancers include:
- *Mycobacterium avium* complex (MAC or MAI) disease
- KS
- NHL
- CMV infection (retina, gastrointestinal (GI) tract, encephalitis).

The order of infections and cancers in the list may change, due to factors that may or may not be related to the HIV/AIDS epidemic.

2. Initial evaluation

Patients with unknown HIV status who present with infections or illnesses that are associated with HIV infection should be offered HIV testing and counselling. The physician should explain to the patient the reasons for offering an HIV test and the importance of knowing the results for correct clinical management. However, patients have the right to refuse testing (opt out).

The initial assessment of HIV status should include:
- HIV pretest counselling;
- serological testing (typically ELISA and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test (which indicates HIV infection if the result is positive); and
- post-test counselling – whether the result is positive or negative – including information on reducing risky behaviour.

If the patient is HIV-positive, an initial clinical evaluation should be made to determine the clinical stage of the infection and identify comorbidities and conditions. (For more information please refer to Protocol 1, *Patient evaluation and antiretroviral treatment of adults and adolescents*).

3. Counselling patients on OIs and other conditions

- Physicians and nurses should counsel all patients and/or families about the chronic nature of HIV infection and the possible appearance of OIs.
- Patients should be informed that some OIs can be prevented (see Table 2 below).
- They should know that it is essential to diagnose an opportunistic infection early, so that they consult their physician when they suspect any disease progression may be occurring.
- They should be counselled on symptoms that might indicate OIs and the need to inform their physician about them:
  - dyspnoea: *Pneumocystis jirovecii* pneumonia (PCP), TB, pneumonia;
  - cough: PCP, TB, pneumonia;
  - bloody sputum: TB, pneumonia;
  - neurological changes: cerebral toxoplamosis, cerebral lymphoma or meningitis/ encephalitis;
  - weight loss, fever, night sweats: TB, atypical TB, lymphoma;
  - visual impairment: CMV retinitis;
  - painful swallowing: candida oesophagitis; or
  - diarrhoea: CMV colitis, infection with cryptosporidiae, microsporidiae, salmonellosis, etc.
  - visual field loss (reading a newspaper is a good and sensitive test);
  - weakness of arms or legs: cerebral toxoplasmosis;
  - any change of mental status or behavioural signs that may signal mental health problems (as observed by friends and family members): herpes meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy (PML), etc.
  - change in skin conditions or (more often) oral thrush (possible antiretroviral treatment (ART) failure).
- Patients should know the importance of monitoring their chronic conditions.
  - Patients with chronic hepatitis should have an abdominal ultrasound twice a year because of the risk of hepatocellular carcinoma.
  - Patients with a history of tuberculosis should have a chest X-ray once a year.
  - Older overweight HIV patients who have hypertension and are on an ART regimen that includes a protease inhibitor (PI) must be checked for cardiovascular disease, diabetes and other conditions.
- Patients should be given a checklist that includes a schedule of laboratory and clinical tests to be undertaken on a regular basis. The content of this list may vary due to comorbidities.

For further information on counselling issues please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

4. OI prophylaxis in HIV-infected patients

- Certain OIs that may develop in people living with HIV (PLHIV) can be prevented.
- Prophylaxis of OIs in PLHIV should be an integral part of OI management.
- After initiating ART, it is possible to discontinue primary prophylaxis if the CD4 count has risen over the relevant indication level for 3–6 months (e.g. PCP: >200 cells/mm^3, toxoplasmosis: >100 cells/mm^3, MAI: >50 cells/mm^3). See Table 2 below. Discontinuation of secondary prophylaxis should also be possible in the same situation with close monitoring. Always restart prophylaxis when CD4 counts fall below the indication level.

Table 2 summarizes the most recent recommendations for prophylaxis strategy.

Table 2. OI prophylaxis for HIV-infected patients

Pathogen	Indication	First choice	Alternatives
Pneumocystis jirovecii	CD4 count <200 cells/mm^3 *or* oropharyngeal candidiasis	TMP-SMZ (cotrimoxazole) double-strength tablet PO[a] OD[b]	• TMP-SMZ single-strength tablet PO OD *(1)* • TMP-SMZ double-strength tablet PO TIW[c] (Monday, Wednesday and Friday) • Dapsone 50 mg PO BID[d] • Dapsone 100 mg PO OD *(2)* • Pyrimethamine 50 mg + dapsone 50 mg + folinic acid 15 mg OD • Pentamidine inhalation 300 mg every three weeks *(3)* • Also possible: clindamycin or atovaquone *(4, 5)*
M. tuberculosis	Purified protein derivative (PPD) reaction ≥5 mm *or* recent contact with a case of active TB	Isoniazid (INH) 300 mg PO + pyridoxine 50 mg PO OD for 6 months *(6)*	Further research is needed for developing alternative prophylaxis treatment for TB in areas with high prevalence of INH resistance.
Toxoplasma gondii, primary	CD4 count <100 cells/mm^3	TMP-SMZ double-strength tablet PO OD	• TMP-SMZ single-strength tablet PO OD *(7, 8)* • Dapsone 50 mg PO OD + pyrimethamine 50 mg PO QW[e] + folinic acid 25 mg PO QW
Toxoplasma gondii, secondary	CD4 count <100 cells/mm^3	TMP-SMZ double-strength tablet PO OD	Dapsone 50 mg PO OD + pyrimethamine 50 mg OD + folinic acid 15–25 mg OD
M. avium complex	CD4 count <50 cells/mm^3	Azithromycin 1200 mg PO QW	Clarithromycin 500 mg PO BID *(9, 10)*
Cryptococcus neoformans	CD4 count <50 cells/mm^3	Fluconazole 100–200 mg PO OD *(11)*	

[a] PO: per os.
[b] OD: once daily.
[c] TIW: three times weekly.
[d] BID: twice daily.
[e] QW: once weekly.

5. Diagnosis and treatment of OIs

5.1. Respiratory infections

- Lower respiratory tract infections are the most common recurrent infections in PLHIV. They are usually life-threatening and can be caused by bacteria, viruses (rarely) and fungi (also rarely).

- Patients may present early in the course of HIV infection with bacterial pneumonias, which respond readily to antibiotics *(12)*.
- Patients with HIV infection appear to be particularly prone to infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae (13)*.
- Later, and with the onset of immune suppression, patients may develop opportunistic pulmonary infections, the most important of which is pulmonary TB.
- As cell-mediated immunity deteriorates, patients may develop life-threatening opportunistic infections such as PCP and severe fungal and viral pneumonias. Table 3 summarizes the respiratory illnesses associated with HIV infection.

Table 3. Respiratory illness in PLHIV

Type of infection	Possible complications[a]
Bacterial	
Pneumococcal pneumonia	Empyema[b], pleural effusion, lung abscess
H. influenza pneumonia	Pleural effusion[b], lung abscess, empyema,
Klebsiella pneumonia	Empyema[b], pleural effusion
Staphylococcal pneumonia	Lung abscess[b], empyema, pleural effusion
M. tuberculosis pneumonia	Pericardial effusion, lung abscess, empyema, pleural effusion
MAC pneumonia	Rare complications: Abscesses especially with IRIS
Viral	
Cytomegalovirus	Pneumonitis[b] (highly lethal)
Herpes simplex virus	Pneumonitis[b] (highly lethal)
Fungal	
Pneumocystis pneumonia	Pneumothorax
Cryptococcosis	
Histoplasmosis	
Aspergillosis	Lung abscess
Other conditions	
KS	Pleural or pericardial effusion
Lymphoma	Pleural or pericardial effusion
Carcinoma (non-HIV-related)	Pericardial effusion

[a] Possible complications are in the order of the frequency the occur.
[b] Complications that occur most frequently.

5.1.1. Bacterial respiratory infections

- Bacterial lower respiratory tract infections are common in the general population, but they are more frequent and more severe in immunosuppressed persons with HIV infection.
- *S. pneumoniae* is the most common lower respiratory tract pathogen.
- Patients with bacterial pneumonia present with cough and fever and often have chest pain, difficulty in breathing and tachypnoea.
- Chest X-rays may show classic lobar pneumonia, bronchopneumonia or atypical (or absent) infiltrates.

5.1.1.1 Diagnosis

The diagnosis of pneumonia is usually made on clinical grounds and by a chest X-ray, which may reveal:

- lobar or patchy consolidation
- diffuse lung infiltrates or
- atypical changes, including cavitary disease.

5.1.1.2. Treatment

- If the patient is not severely ill and no PCP is suspected, treatment may be provided at home according to Tables 4 and 5 below.

Table 4. First-line antibiotic treatment of bacterial pneumonia

Antibiotic	Dose	Frequency	Route	Duration
Amoxicillin (Use a penicillin in combination with beta lactamase inhibitor if there is a chance of penicillin/ampicillin resistance.)	500–1000 mg	TID[a]	PO	7 days or longer until resolved
or:				
Erythromycin	500 mg	QID[b]	PO	7 days
or:				
Clarithromycin	500 mg	BID	PO	7 days
or:				
Azithromycin	500 mg	OD	PO	3–4 days
or:				
Quinolone with pneumococcal activitiy (e.g. moxifloxacin)	400 mg	OD	PO	7 days
or:				
Doxyciclin	100 mg	BID	PO	7 days

[a] TID: three times daily.
[b] QID: four times daily.

- If patients do not respond to first line treatment over a period of 72 hours (no fever, C-reactive protein (CRP) elevation resolved, leukocyte count is not reliable), the patient should be referred to the hospital and second line treatment prescribed as indicated below. Patients may also require oxygen (in this case PCP should be suspected).
- Severely ill patients should be referred for hospital admission immediately.

Table 5. Second-line treatment of bacterial pneumonia

Antibiotic	Dose	Frequency	Route	Duration
Ceftriaxone + erithromycin	2 g 500 mg	OD QID	IV*	7 days
or:				
Ampicillin + sulbactam + erythromycin	1500 mg 500 mg	TID QID	IV	7 days
or:				
Quinolone with pneumococcal activitiy (e.g. moxifloxacin)	400 mg	OD	IV/PO	7 days
or:				
Chloramphenicol (if other drugs are not available)	12.5 mg (base) per kg of body weight	QID	IV	7 days

*Intravenously.

- If patients do not respond to this treatment, consider PCP or TB as a possible diagnosis. The diagnostic gold standard is lavage by bronchoscopy to define the pathogen before starting antibiotics *(14)*. Also helpful are blood cultures, which have a higher rate of pneumococcal identification and may be done up to five times.

5.1.2. Atypical mycobacteriosis

Mycobacterium avium complex (MAC or MAI) disease is less common than some other OIs. It presents with:

- fever
- weight loss
- night sweats
- diarrhoea
- wasting.

MAC organisms may be found in the blood and excreta of infected persons. A definite infection can be shown with acid-fast bacilli (AFB) in sterile fluids or specimens (blood, cerebrospinal fluid, bone marrow and liver).

5.1.2.1. Diagnosis

- Blood cultures on special media are the cornerstone of MAC diagnosis.
- In most symptomatic patients, the intensity of mycobacteraemia is such that most or all blood cultures are positive.
- Because the liver and bone marrow are often involved in disseminated MAC infection, the bacteria may be visible in acid-fast-stained biopsy samples from these sites.
- Presumptive diagnosis by examination of a biopsied liver specimen saves time.

5.1.2.2. Treatment

Table 6. Atypical mycobacteriosis treatment

Antibiotic	Dose	Frequency	Route	Duration
First-line treatment *(15, 16)*				
Clarithromycin + ethambutol + rifabutin	500 mg–1000 mg	BID	PO	6 months; decide on clinical grounds
	15 mg/kg	OD	PO	6 months; decide on clinical grounds
	300–450 mg	OD	PO	6 months; decide on clinical grounds
Other drugs active against MAC[a]				
Azithromycin	500–1200 mg	OD	PO	6 months
Ciprofloxacin	500 mg	BID	PO	6 months
Amikacin	15 mg/kg/day or 7.5 mg/kg/day	OD BID	IV IV	No longer than 4 weeks

[a] Rifampicin is not effective against MAC.

- Once MAC treatment has been started, and there is indication that the condition is improving and the drugs are well tolerated, ART should be initiated.
- Standard procedure is to start on ART 4–6 weeks after MAC treatment has begun. After six months with an improved immune response (CD4 count >100 cells/mm^3), reduce MAC treatment or stop it and use a secondary prophylaxis.
- Stopping the secondary prophylaxis is possible when the immune system is stable and responsive for more than 3–6 months.
- MAC treatment or secondary prophylaxis should be administered for six months to ensure a successful treatment and avoid relapse.
- It is important to begin with treatment for MAC to avoid confusion about whether any side-effects come from MAC drugs or ART.

- There is the possibility of immune reconstitution inflammatory syndrome (IRIS) after starting ART (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, sections Clinical failure and Immune reconstitution inflammatory syndrome).

5.1.3. Pneumocystis pneumonia

- PCP is a common HIV-associated OI, caused by the fungus *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii)*.
- Patients usually present with cough, shortness of breath and fever.
- Occasionally patients with PCP have no chest signs.
- Patients with PCP often have features of respiratory failure such as shortness of breath and cyanosis.
- Symptoms may be very severe; an attack of PCP may lead to death if not treated early and effectively.

5.1.3.1. Diagnosis

- Diagnosis is often made on clinical grounds when a febrile PLHIV presents with respiratory distress, with or without cyanosis.
- The patient may have a non-productive cough, but the main feature of the condition is shortness of breath, with minimal or absent chest signs on physical examination.
- Chest X-rays:
  - There is not always a ground-glass opacification in the lower zones of both lung fields.
  - There may be evidence of patchy infiltrates in both lung fields that mimics bacterial pneumonia or TB.
  - A considerable proportion of patients with confirmed PCP show no changes at all on the X-ray.
- Bronchial lavage is the gold standard of diagnosis *(14)*. Diagnosis is confirmed upon finding cysts of *Pneumocystis* in forced sputum or in bronchial lavage aspirate.
- If diagnosis cannot be established due to the lack of a bronchoscope, deteriorating pulmonary function tests or blood gas analysis can be used as indicators.
- Treatment should be started immediately upon diagnosis.

5.1.3.2. Treatment

Patients should be admitted to hospital for management. Supportive therapy including oxygen may be necessary. Details of treatment are given in Tables 7 and 8 below.

Table 7. PCP first-line treatment

Antimicrobial agent	Dose	Frequency	Route	Duration
TMP-SMZ	240/1200 mg <60 kg 320/1600 mg ≥60 kg	QID	PO/IV	21 days

Table 8. PCP second-line treatment

Antimicrobial agent	Dose	Frequency	Route	Duration
Clindamycin + primaquine	600 mg 15 mg	QID BID	PO/IV PO	21 days *(17)*
or:				
Pentamidine (in combination with a broad-spectrum antibiotic to prevent bacterial superinfection, e.g. ampicillin + sulbactam for 10 days)	4 mg/kg IV daily. Dose reduction to 2 mg/kg after 5 days of treatment *(18)*	OD	IV	21 days

- Severely ill patients will require prednisolone, 80–250 mg PO/IV daily for 1–2 weeks (reduces interstitial oedema).
- Combination treatment should also be considered in severe cases, for example, TMP-SMZ and pentamidine. This treatment has incurred a high risk of toxicity according to case reports only. A severe case of PCP requires artificial ventilation or an oxygen saturation (SO_2) <92%.

Side-effects should be monitored, especially the kidneys (both), pancreas (with pentamidine) and bone marrow (with TMP-SMZ). Lab analysis should be required twice weekly.

After successfully treating an acute episode of PCP:
- it is necessary to continue secondary prophylaxis with TMP-SMZ 160/800 mg PO OD on a long-term basis;
- prophylaxis may be discontinued when the patient's CD4 count remains stable at >200/mm^3 for at least three months.

5.1.4. Other causes of pneumonia in immunosuppressed people

- Other causes of pneumonia include fungal and viral infections. They are difficult to diagnose without sophisticated laboratory facilities and are difficult to treat.
- Viral pneumonia may be caused by herpes simplex virus, varicella-zoster virus or cytomegalovirus.
- In addition to PCP, other fungal causes of pneumonia include *Histoplasma capsulatum*, *Cryptococcus neoformans* and *Aspergillus*.

5.1.4.1. Diagnosis

- When pneumonia fails to respond to standard treatment, TB or pneumonia caused by viruses, fungi or protozoa should be suspected.
- Making a specific diagnosis of fungal or other infections requires sophisticated laboratory tests:
  - pp65 early CMV antigen from peripheral blood or bronchial lavage;
  - polymerase chain reaction (PCR) for viruses of the herpes family (CMV, HSV 1/2, VZV, Epstein-Barr virus (EBV), human herpes virus 8 and 6 (HHV8, HHV6))
  - special cultures for slow-growing pathogens, such as nocardia.
- Close collaboration between physician and microbiologist is needed.

5.1.4.2. Treatment

Treatment will depend on the cause, for example foscarnet for CMV infection or long-term antibiotics (eight weeks) for nocardia.

5.2. Gastrointestinal infections (GIIs)

- GIIs in PLHIV may be the result of any of the following infections:
  - HIV (direct infection of the GI tract)
  - bacterial
  - fungal
  - viral
  - protozoal
  - parasitic.
- Some of the problems may arise from atrophy of the intestinal villi, which commonly leads to malabsorption.
- The most common GI problem encountered is diarrhoea, which can be acute, acute-on-chronic or chronic.
- Diarrhoea is persistent or chronic in people with AIDS, and an important cause of death among them.
- Acute diarrhoea leads to dehydration unless properly treated.
- The passing of bloody or blood-stained stools occurs in persons with shigellosis or amoebic dysentery.
- Other common GI problems in PLHIV include:
  - poor appetite
  - nausea
  - vomiting
  - progressive weight loss.

Table 9 summarizes the clinical features, diagnosis and treatment of some of the more common gastrointestinal infections seen in immunosuppressed PLHIV.

Table 9. Gastrointestinal infections commonly encountered in PLHIV

Infection	Clinical features and diagnosis	Treatment
Non-typhoid salmonelloses	Fever, abdominal pain, diarrhoea with or without blood, weight loss, anorexia, hepatosplenomegaly Diagnosis upon blood or stool culture	Ciprofloxacin 500 mg PO BID for >2 weeks *(19)*
Shigelloses	Fever, abdominal pain, bloody diarrhoea Diagnosis upon blood or stool culture	Ciprofloxacin 500 mg PO BID for 7–10 days *or:* Nalidixic acid 500 mg PO QID for 7–10 days *or:* TMP-SMZ 160/800 mg PO BID for 7–10 days
Cryptosporidiosis	Watery diarrhoea, loss of appetite; afebrile Diagnosis upon stool microscopy	Paromomycin 1 g PO BID + azithromycin 600 mg PO OD for 4 weeks *then:* Paromomycin alone for 8 weeks *(20, 21)*. Treatment often fails *(22)*.
Microsporidiosis	Watery diarrhoea, loss of appetite; afebrile Diagnosis upon stool microscopy	Albendazole 400 mg PO BID for 4 weeks. *If this does not work try:* Mebendazole 200 mg PO TID (albendazole tends to be more successful) *(23)*.

5.3. Candidiasis

- *Candida albicans* colonizes primarily the GI tracts of both men and women. Up to one third of all normal women also carry *C. albicans* in the vagina.
- Women with vaginal candidiasis may develop a vaginal discharge and vulvovaginal pruritus.

- Men with genital candidiasis will develop balanitis or balanoposthitis and will complain of a subpreputial discharge and itchiness of the penis and foreskin.
- Oral candidiasis (thrush) leads to inflammation of the mucosal surface together with the appearance of adherent white plaques.
- *C. albicans* can infect the skin and cause pruritic dermatitis.
- Depending on the level of immune suppression, oral infection may extend to involve the oesophagus.
- Bronchial and disseminated infections are rare.

5.3.1. Symptoms

- Oral thrush can include infection of the:
  - buccal mucosa
  - tongue
  - oropharynx
  - gums
  - hard and soft palates.
- Patients may have no symptoms at all or may complain of a burning sensation in the mouth when eating.
- Some patients may complain of white patches in the mouth.
- If the thrush has extended into the oesophagus, patients may complain of:
  - pain on swallowing food
  - retrosternal pain
  - excessive salivation.

Patients in whom candidiasis occurs most frequently are:

- healthy pregnant women and healthy women on oral contraceptives
- healthy neonates, especially pre-term infants
- those on prolonged courses of broad-spectrum antibiotics
- those receiving steroids systemically
- those with diabetes mellitus
- those with congenital or acquired immunodeficiencies
- those suffering from chronic debilitating conditions
- the severely malnourished
- those with cancer and those receiving chemotherapy or radiotherapy.

5.3.2. Diagnosis

- The diagnosis of oropharyngeal candidiasis is made on clinical grounds, based on direct observation and microscopic examination of material obtained from lesions.
- Examination of the oral cavity may reveal redness and inflammation of the mucosa, with or without patches of white plaques.
- Inflammation may be seen on the palate, throat, gums, tongue and/or the inside of the cheeks. When the tongue is affected, it may be smooth and red, and the papillae normally found on the tongue may be absent.
- Diagnosis has to be confirmed by histological examination of tissue biopsies only in cases of suspected *Candida* oesophagitis or aspergillosis of the lungs.
- The symptoms of *Candida* oesophagitis are:
  - difficulty in swallowing
  - pain in the chest that increases with swallowing.
- Disseminated candidiasis causes fever and symptoms in the affected organs (for example, blindness when it affects the eyes).

5.3.3. Treatment

- Localized candidiasis is treated first with relatively inexpensive topical drugs such as nystatin, miconazole or clotrimazole.
- In patients with disseminated candidiasis and in those in whom topical treatment has failed, systemic antifungal agents such as ketoconazole, fluconazole, itraconazole or amphotericin B may be given.
- For treatment of drug-dependent patients receiving methadone as opioid substitution therapy, see Table 4 of Protocol 5, *HIV/AIDS treatment and care for injecting drug users*, for the interactions of fluconazole, itraconazole and ketoconazole with methadone.

Table 10. Oral candidiasis

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment *(24)*				
Myconazole	Buccal tablets	Once a day	Gum patch	7 days
or:				
Fluconazole	100 mg	BID for 3 days followed by OD for 4 days	PO	7 days
Second-line treatment *(25)*				
Itraconazole	200–400 mg	OD	PO	7 days

Table 11. Vaginal candidiasis

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment				
Fluconazole	100 mg	Single dose	PO	Once
Clotrimazole	500 mg	Single dose	Vaginal	Once
Second-line treatment				
Ketoconazole	200 mg	BID	PO	3 days
Ketoconazole	200 mg	OD	PO	7 days
Maintenance therapy				
Nystatin	2–4 million IU	BID	PO	10 days
or:				
Fluconazole	50–200 mg	OD	PO	10 days
Third-line treatment				
Ketoconazole	200 mg	OD	PO	Depends on response, usually 7–10 days
Itraconazole	100 mg	OD	PO	Depends on response, usually 7–10 days

Table 12. Oesophageal and disseminated candidiasis

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment				
Ketoconazole	200–400 mg	BID	PO	21 days
or:				
Fluconazole (more effective than ketoconazole)	200–400 mg, reduce on clinical grounds after 3 days to 100 mg/day	OD	PO/IV	14 days
Second-line treatment				
Amphotericin B	0.3–0.5 mg/kg		IV	10–14 days
or:				
Itraconazole	200–400 mg	OD	PO	2 weeks

- Long-term maintenance treatment with fluconazole 50–100 mg OD PO, itraconazole 100 mg OD PO or ketoconazole 200 mg OD PO may be necessary for patients who have been treated for candidal oesophagitis.
- If the patient fails to respond to this treatment, a diagnosis of CMV or HSV oesophagitis should be considered, and the patient should be referred for an oesophagoscopy.
- *Candida glabrata*, *C. krusei* and *C. tropicalis* are resistant to fluconazole to some extent. A specimen is needed for culture; susceptibility testing is possible and prescribing of amphotericin B makes more sense. Voriconazole, posaconazole and caspofungin are new drugs encountering rare resistance in any fungi, including *Aspergillus*; all are very expensive. Voriconazole can interact with ARV drugs, and it should not be prescribed to patients taking efavirenz (EFV) or ritonavir (RTV). Patients receiving both PIs and voriconazole should be closely monitored for possible side-effects *(26)*.

5.4. Cryptococcal meningitis

- Cryptococcosis most often appears as meningitis, and occasionally as pulmonary or disseminated disease.
- Cryptococcal meningitis is a common systemic fungal infection in PLHIV.
- **Without treatment, the life expectancy of patients with cryptococcal meningitis is probably less than a month.**

5.4.1. Diagnosis

Cryptococcosis is relatively easy to diagnose. Patients usually present with headache, fever, neck stiffness and/or cranial nerve palsies, or they may be comatose. However, signs of meningeal inflammation such as fever and neck stiffness often do not occur. A centrifuged deposit of the cerebrospinal fluid (CSF) should be examined microscopically after adding a drop of India ink.

- The yeasts are visible as organisms surrounded by thick capsules.
- The CSF may be cultured for cryptococci.
- The cryptococcal antigen test is useful in assessing patients for cryptococcosis and can be performed on serum or cerebrospinal fluid.

5.4.2. Treatment

Table 13. Cryptococcal meningitis treatment

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment *(27)*				
Amphotericin B + 5-flucytosine	0.7–1.0 mg/kg 25 mg/kg	OD QID	IV IV	14 days
then: fluconazole	400 mg	OD	PO	At least 10 weeks
then: fluconazole	200 mg	OD	PO	Lifelong
Second-line treatment				
Amphotericin B + 5-flucytosine	0.7–1.0 mg/kg 25 mg/kg	OD QID	IV IV	6–10 weeks
or:				
Amphotericin B	0.7–1.0 mg/kg	OD	IV	6–10 weeks
or (in mild cases):				
Fluconazole	400–800 mg	OD	PO	10–12 weeks
then: fluconazole	200 mg	OD	PO	Lifelong

5.4.3. Secondary chemoprophylaxis or maintenance therapy

- Lifelong secondary chemoprophylaxis is necessary; it may be achieved with fluconazole 200 mg orally once daily for life.
- Alternate long-term secondary prophylaxis may be achieved with itraconazole 200 mg orally once daily for life.
- The need for maintenance therapy with patients who have an improved immune system (CD4 count >200) is presently neither supported nor refuted by concrete evidence.
- For treatment of drug-dependent patients receiving methadone as opioid substitution therapy, see Table 4 of Protocol 5, *HIV/AIDS treatment and care for injecting drug users*, for the interaction of fluconazole with methadone.

5.5. Histoplasmosis

This uncommon acute or chronic infection is caused by inhaling spores from the fungus *Histoplasma capsulatum*.

- The outcome of exposure depends on the immune status of the host as well as the size of the inoculum.
- Intact cell-mediated immunity is essential for preventing its dissemination. The acute illness is influenza-like, with:
  - fever
  - anorexia
  - arthralgia
  - myalgia
  - dry cough
  - chest pain.
- Dissemination occurs soon after initial infection in immunosuppressed patients, who develop:
  - weight loss
  - oral and skin lesions
  - chest symptoms
  - liver, spleen and lymph node enlargement.

- Oral lesions may appear as protruding, necrotic ulcers. There may also be perforation of the palate and extensive soft tissue destruction.

5.5.1. Diagnosis

Diagnosis is made on clinical grounds and is confirmed by fungal cultures or histological examination of biopsied tissues.

- A chest X-ray in acute illness may show:
  - hilar lymphadenopathy
  - scattered infiltrates
  - lower lobe nodules.
- Blood and skin tests have been developed for the diagnosis of histoplasmosis, but they are not widely available.

5.5.2. Treatment

In normal immune systems, acute histoplasmosis is self-limiting and does not require treatment. In immunosuppressed patients it may be treated as shown in Table 14.

Table 14. Treatment of histoplasmosis

Antifungal agent	Dose	Frequency	Route	Duration
Amphotericin B	0.7–1 mg/kg	OD	IV	10 days

Source: Johnson et al. *(28).*

This initial treatment is followed, three months after immunoreconstitution with >100 CD4 cells, with one of the following long-term treatments:

- itraconazole 200 mg BID PO
- fluconazole 200 mg BID PO
- amphotericin B 1 mg/kg IV weekly.

An alternative is itraconazole 200 mg TID PO x 3 days, then 200 mg PO BID x 12 weeks (taken with a meal and an acidic drink).

5.6. Kaposi sarcoma (KS)

- KS is caused by the human herpes virus type 8 (HHV8), also known as the Kaposi sarcoma herpes virus (KSHV).
- Any patient suspected of KS should be examined by an oncologist and referred to an oncology clinic as needed.
- In HIV-associated immunosuppression, KS is more aggressive, disseminated and rapidly progressive than the endemic disease found in people without HIV infection.

5.6.1. Diagnosis

The diagnosis of KS is made on clinical suspicion and confirmed by histological examination of biopsied tissue.

Clinical signs include the following.

- Lesions may be found anywhere on skin and on any mucosal surface. Skin lesions are hyperpigmented, blue or purplish papules or nodules and can be associated with lymphoedema. Systemic lesions are commonly found on the palate, gastrointestinal tract, lungs or lymph nodes.
- Oral lesions of KS may be found on the hard palate and occasionally on the tongue, throat, tonsils or gums. The lesions are purple papules, usually painless and sometimes large and pedunculated.

- Pulmonary lesions are infiltrative with pleural effusion and often lead to respiratory failure. The condition may be confused with bacillary angiomatosis (bartonellosis), an infective condition seen in PLHIV.

5.6.2. Treatment

- KS is a cancer and should accordingly be treated by an oncologist.
- It is treatable with radiotherapy if lesions are localized and with cytotoxic chemotherapy if it is generalized.
- Cytotoxic drug combinations that have been used with varying degrees of success include:
  - liposomal doxorubicin monotherapy (best results) *(29–31)*
  - bleomycin
  - vincristine
  - daunorubicin
  - vinblastine
  - etoposide.
- Remission is difficult to achieve, and relapses are common.
- Localized lesions may be surgically excised or treated with liquid nitrogen (high relapse rate), laser therapy or radiation. Intralesional injection with bleomycin has also been shown to be effective.
- KS is usually treatable with ART alone; after successful initiation of ART, KS becomes inactive and slowly disappears.

5.7. Cervical cancer

- Cervical cancer is one of the most common types of cancer, causing deaths among women worldwide. The estimated number of new cases per year is 500 000 *(32)*.
- Human papillomavirus (HPV) infection is the leading etiologic agent in the development of premalignant and malignant lower genital tract disease, including cervical cancer.
- The relative risk of cervical intraepithelial neoplasia (CIN) is 5–10 times higher for women with HIV/AIDS, and abnormal pathology is observed in 20–40% of their Pap smears *(33, 34)*.

5.7.1. Diagnosis

When a woman is diagnosed with HIV, a gynaecologic evaluation with pelvic examination and Pap smear should be performed. The examination and Pap smear should be repeated at six months and then annually.

For further information, please refer to Protocol 9, *Support for sexual and reproductive health of people living with HIV*.

5.8. Other cancers

Lymphomas – including non-Hodgkin, intracranial and Burkitt types – and squamous cell carcinoma are more commonly found in immunosuppressed PLHIV than in people who do not have HIV. Any patient suspected of cancer should be examined by an oncologist and referred to the oncology clinic as needed.

5.8.1. Non-Hodgkin lymphoma (NHL)

NHL – usually B-cell, very rarely T-cell – occurs commonly in immunosuppressed PLHIV, but its appearance is independent of CD4 cell count. It is thought that EBV or some other virus plays a role in the pathogenesis of this disease.

- Malignant NHL cells may be detected in all locations, most often in the lymph nodes, as well as the muscles; organs such as the liver, spleen, lung, heart, brain and GI tract; and (more rarely) the bones.
- Symptoms may vary.
- Swollen lymph nodes may be palpable in different locations.

- Fever, weight loss and fatigue are common, but not inevitable.
- Determining the stage of the disease (I–IV) requires thorough examination – cerebral, cervical, thoracic and abdominal computerized axial tomography (CAT) scans, bone marrow and cerebrospinal fluid biopsies and gastroscopy.
- Diagnosis is performed by biopsy of a suspect (enlarged) lymph node, followed by histological examination.

5.8.2. Burkitt-type lymphoma in PLHIV

Burkitt-type lymphomas, actually a subgroup of NHLs, are associated with HIV infection and may occur before advanced immunosuppression sets in. This type of tumour is associated with EBV.

5.8.2.1. Diagnosis

The diagnosis of Burkitt-type lymphoma is made on careful examination of lymph node and tumour biopsies, confirmed by histological examination.

5.8.2.2. Treatment of non-Hodgkin, Burkitt-type and CNS lymphomas

- For NHL, the CHOP regimen is effective and should be administered through six cycles (the number usually needed for complete remission) of the following:
  - prednisolone 100 mg/day OD for five days
  - vincristine (Oncovin) 1.4 mg/m²/day (maximum 2 mg/day) in one dose on Day 1 of treatment
  - cyclophosphamide 750 mg/m²/day in one dose on Day 1
  - doxorubicin (hydroxydaunomycin) 50 mg/m²/day in one dose on Day 1.

Begin a new cycle every 21 days (Day 22 becomes Day 1, etc.).

- The EPOCH regimen, which includes etoposide, prednisolone, vincristine, cyclophosphamide and daunorubicin or doxorubicin, has been shown to be effective in combination with ART. It is based on a regimen of continuous infusion for 96 hours, as follows:
  - etoposide 50 mg/m² per day (via central venous line)
  - doxorubicin 10 mg/m²/day (via central venous line)
  - vincristine 0.4 mg/m²/day (max 2 mg/week) (via central venous line)
  - cyclophosphamide 375 mg/m² on Day 5 only, in a bolus (via IV)
  - prednisolone 100 mg/day on Days 1–5 OD PO.

Repeat the regimen every 21 days until six cycles have been performed.

- Burkitt-type lymphoma is managed in the same manner as other lymphomas, and responds to CHOP or EPOCH. Treating this fast-growing lymphoma with more aggressive chemotherapy (such as the B-ALL regimen) is under discussion so there are no specific recommendations at the present time *(35, 36)*.
- In Burkitt-type lymphomas, chemotherapy should be followed by radiation of the suspected primary location.
- It is possible to treat NHL independently of CD4 cell count, but for prolonged success, ART should be started early. Even during chemotherapy with CD4 count >350, there is a high rate of relapse without ART *(37)*.
- For intracranial lymphoma (metastasis), cranial radiation in conjunction with cytotoxic chemotherapy and steroids is advised *(38)*.
- For primary central nervous system (CNS) lymphoma, radiation is the only effective evidence-based therapy. Most patients show CD4 counts <50 with diagnosis. In multivariate analysis, highly active antiretroviral treatment (HAART) is the only additional factor in prolonged remission. There are some reports of the effectiveness of HAART alone, so it should be started immediately *(39, 40)*.

5.9. Neurological infections

Invasion of the nervous system by HIV leads to encephalopathy, myelopathy and peripheral neuropathy. Numerous neurological syndromes have been ascribed to HIV, including:

- cerebral atrophy and degeneration
- AIDS dementia complex
- cerebellar atrophy
- vacuolar myelopathy
- facial nerve paralysis
- Guillain-Barre syndrome
- painful sensory and motor peripheral neuropathy.

A number of opportunistic infections, including bacterial, viral and fungal infections, also affect the central nervous system. (For cryptococcal meningitis, please refer to section II.5.4 above.)

5.9.1. Toxoplasmosis

Toxoplasmosis is frequently encountered in PLHIV in industrialized countries. It leads to the development of multiple inflammatory lesions in the brain. In PLHIV, it mainly appears as encephalitis or as disseminated disease.

5.9.1.1. Diagnosis

- Toxoplasmosis may be suspected through clinical findings, and patients may present with:
  - altered mental status
  - fever
  - seizures
  - headaches
  - focal neurological findings, including motor deficits, cranial nerve palsies, movement disorders, dysmetria, visual-field loss and aphasia.
- Patients who present with evidence of diffuse cortical dysfunction develop evidence of focal neurological disease as the infection progresses.
- CAT or MRI brain scans may reveal multiple ring-enhancing lesions.
- Serological tests for *Toxoplasma* antibody (immunoglobulin G, or IgG) may help in establishing the diagnosis in the absence of neuro-imaging techniques.
- Most patients with cerebral toxoplasmosis have serological evidence of prior infection with *Toxoplasma gondii* (IgG-positive).
- If toxoplasmosis is suspected, patients should be given a trial of treatment.
- Only if they do not respond to this treatment within two weeks should a brain biopsy be considered.
- The diagnosis can be confirmed by histological examination of tissue obtained by brain biopsy.

5.9.1.2. Treatment

Table 15. Treatment of toxoplasmosis

Drug	Dose	Frequency	Route	Duration
Pyrimethamine	200 mg	Once (loading dose)	PO	Single dose
Then: pyrimethamine + folinic acid + sulfadiazine	25 mg or 50 mg	TID BID	PO	6–8 weeks
	15 mg	OD	PO	6–8 weeks
	1 g	QID	PO	6–8 weeks

Sources: Katlama et al., Dannemann et al. Chirgwin et al. *(41–43).*

- In the regimen above, sulfadiazine may be replaced by any of the following:
  - clindamycin 600 mg QID IV/PO for six weeks
  - azithromycin 1200 mg OD PO for six weeks
  - clarithromycin 1 g BID PO for six weeks
  - atovaquone 750 mg QID PO for six weeks.
- Some patients need a very long period of acute treatment. There is no rule for treatment duration. The decision has to be made on clinical grounds and CAT scan if available.
- Secondary prophylaxis is given using half the dosage of the acute treatment from the effective regimen, until CD4 count is over 200 cells/mm^3 for three months.

5.9.2. Herpes simplex virus (HSV)

- HSV infection is commonly encountered in clinical practice.
- Following an initial attack, there are frequent recurrences.
- In immunosuppressed people the infection may be extensive and persistent and possibly disseminated.
- Dissemination may lead to infection of the lungs, oesophagus and brain.
- HSV may also cause meningoencephalitis and meningitis.

5.9.2.1. Diagnosis

- The diagnosis of HSV infection is usually made based on the typical clinical presentation of vesicles and painful superficial sores around the mouth, nose, lips and/or genitals.
- It is often difficult to make a diagnosis of disseminated herpes. Special laboratory tests – such as viral culture, radio-immunoblot assay and fluorescent and monoclonal antibody tests – may be necessary.
- Typical changes may be seen on CAT scans of the brain, where herpes simplex encephalitis leads to multiple lesions.

5.9.2.2. Treatment

Table 16. Treatment of herpes simplex virus: mild infection

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	400 mg	TID	PO	7–10 days
or:				
Famciclovir	250 mg	TID	PO	7–10 days
or:				
Valaciclovir	1 g	BID	PO	7–10 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

Table 17. Treatment of herpes simplex virus: recurrences

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	800 mg	5 times per day	PO	7–10 days
or:				
Famciclovir	500 mg	TID	PO	7–10 days
or:				
Valaciclovir	1 g	BID	PO	7–10 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

Table 18. Treatment of herpes simplex virus: severe infection

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	10 mg/kg	TID	IV	7–10 days
or:				
Valaciclovir	1 g	BID	PO	7–10 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

Table 19. Treatment of herpes virus: severe and visceral infection

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	10 mg/kg	TID	IV	14–21 days
Second-line treatment				
Foscarnet (when resistance to aciclovir is suspected)	40–60 mg/kg	TID	IV	14 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

5.9.3. Herpes zoster *(48)*

- Varicella-zoster virus (VZV) often causes disseminated infection after initial exposure.
- In children, initial infection results in the development of chicken pox, though most who become infected develop no symptoms or signs of infection.
- The virus lies dormant in the paraspinal ganglia for years.
- With immune suppression, regardless of cause, the virus replicates and produces lesions along the length of a cutaneous nerve in a dermatomal distribution.

- Dissemination can also occur at the same time, with involvement of skin, nervous system, lungs and mucous membranes.
- In immunosuppressed patients, zoster is often multidermatomal in distribution, persistent, extensive and associated with severe pain and debility.

5.9.3.1. Diagnosis

The diagnosis is usually made on clinical grounds.

5.9.3.2. Treatment

Table 20. Treatment of dermatomal zoster

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	800 mg	5 times a day	PO	7–10 days or until lesions crust
or:				
Famciclovir	500 mg	TID	PO	7–10 days

Table 21. Treatment of disseminated, visceral or ophthalmic zoster

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	10 mg/kg	TID	IV	7–10 days
or:				
Famciclovir	500 mg	TID	PO	7–10 days
Second-line treatment				
Foscarnet	60 mg/kg or 40 mg/kg	BID TID	IV	7–10 days

- Post-herpetic neuralgia is a common and seriously debilitating problem. It causes severe pain in dermatomal distribution, usually at the site of the lesions.
- Pain control is often necessary and may be achieved with non-steroidal anti-inflammatory drugs (NSAIDs).
- If pain control is not achieved, amitryptiline, carbamazepine or phenytoin may be tried.

5.9.4. Cytomegalovirus (CMV) infection

CMV may affect multiple systems and organs in immunosuppressed individuals. Symptoms may include:

- fever and diarrhoea from CMV colitis
- dyspnoea from CMV pneumonitis
- blindness caused by CMV retinitis
- the appearance of painful ulcers in the mouth, resulting in difficulty eating.

5.9.4.1. Diagnosis

- The most frequent localization is the retina and is diagnosed by a specialized ophthalmologist.
- Other localizations require sophisticated equipment and costly tests, such as tissue biopsies and deoxyribonucleic acid (DNA) hybridization studies.

5.9.4.2. Treatment

Treatments for CMV GI disease, neurological disease and retinitis are found in Tables 22–24.

Table 22. First-line treatment of CMV GI disease, neurological disease and retinitis

Antiviral agent	Dose	Frequency	Route	Duration
Ganciclovir	5 mg/kg	BID	IV	2–3 weeks

Source: *Whitley et al., AIDS Research Group, Martin et al., Jacobson et al., Martin et al. (49–53).*

For secondary prophylaxis, long-term treatment with ganciclovir 5 mg/kg given IV daily may be necessary.

Table 23. Second-line treatment of CMV GI disease, neurological disease and retinitis

Antiviral agent	Dose	Frequency	Route	Duration
Foscarnet	90 mg/kg	BID	IV	3 weeks

Source: *Whitley et al., AIDS Research Group, Martin et al., Jacobson et al., Martin et al. (49–53).*

For secondary prophylaxis, long-term treatment with foscarnet 90 mg/kg given IV daily may be necessary.

Table 24. Secondary prophylaxis of CMV retinitis

Antiviral agent	Dose	Frequency	Route	Duration
Ganciclovir eye implant + Valganciclovir (to prevent infection in the other eye)	900 mg	OD	PO	Until CD4 count is over 100-150 cells/ mm^3 for minimum 3 months

Source: *Whitley et al., AIDS Research Group, Martin et al., Jacobson et al., Martin et al. (49–53).*

Secondary prophylaxis can be stopped after six months and immune reconstitution to 100–150 CD4 cells/mm^3.

5.9.5. Epstein-Barr-virus-related conditions

- Infection with EBV, a herpesvirus, is common in PLHIV and others.
- PLHIV have increased amounts of EBV in their oropharyngeal secretions and higher EBV antibody titres than HIV-negative people.
- EBV is thought to cause a number of conditions including:
  - oral hairy leukoplakia
  - lymphocytic interstitial pneumonitis (LIP)
  - non-Hodgkin lymphoma (see section II.5.8.1 above)
  - Burkitt-type lymphoma (see section II.5.8.2 above)
  - nasopharyngeal carcinoma.

5.9.5.1. Oral hairy leukoplakia

- Oral hairy leukoplakia occurs in PLHIV as well as some immunosuppressed transplant recipients.
- It is a non-malignant lesion of epithelial cells, presenting as raised, white, corrugated lesions of the oral mucosa, especially on the lateral aspect of the tongue.
- It is commonly mistaken for oral candidiasis, as they are frequently found together.
- No specific treatment is available for the condition. Patients are generally advised on good oral hygiene.

5.9.5.2. Lymphocytic interstitial pneumonitis (LIP)

- LIP occurs primarily in children, but it also occurs in adult PLHIV.
- It is characterized by diffused interstitial pulmonary infiltrates that may be confused with TB or PCP. However, patients with LIP often do not have signs of severe respiratory illness.
- No specific treatment is available for LIP.

III. General symptoms

1. Persistent generalized lymphadenopathy (PGL) in adults

- The most common clinical manifestation of HIV infection is symmetric generalized lymph node enlargement.
- Enlarged lymph nodes are generally painless, firm, mobile and rubbery and are most easily palpated in the neck, submental area, axillae and the groin.
- The patient may or may not have other associated symptoms of HIV infection.
- PGL is defined as the presence for more than one month of lymph nodes measuring more than 1 cm in diameter in more than one area of the body other than the groin.
- PGL is a very common feature of HIV infection. In most cases a lymph node histology only reveals “reactive hyperplasia” or “follicular hyperplasia”. A lymph node biopsy is necessary to establish a cause.

1.1. Diagnosis

It is important to palpate lymph nodes specifically in the following areas:

- anterior and posterior triangles of the neck
- submental area
- suboccipital area
- anterior and posterior auricular areas
- both axillae
- epitrochlear areas
- both inguinal regions.

Patients with PGL caused by HIV infection may have other features of HIV infection, including:

- oral thrush
- oral hairy leukoplakia
- pruritic skin rash
- hyperpigmented nails
- oral or genital herpes
- involuntary weight loss
- unexplained fever.

PGL may be caused by a number of conditions other than HIV infection, including TB, leukaemia, lymphoma, KS, syphilis, *Chlamydia trachomatis* (lymphogranuloma venereum), CMV, toxoplasmosis, EBV, cryptococcosis, histoplasmosis and septic skin conditions, bubonic plague and hepatitis B.

1.2. Criteria for performing a lymph node biopsy

A patient with PGL should be referred for a lymph node biopsy if presenting with any of the following:

- asymmetrical lymph node enlargement
- massive lymph node enlargement (at least one lymph node >3 cm in diameter)
- lymph node enlargement over a period of observation
- evidence of TB on a chest X-ray
- evidence of hilar lymph node enlargement on a chest X-ray
- evidence of KS elsewhere
- fever, night sweats and weight loss for more than one week.

A diagnosis of HIV-related lymphadenopathy does not rule out other serious diseases like lymphoma in unbiopsied lymph nodes. Therefore, with any change in condition, persistent fever or other suspicious circumstance, a biopsy or lymphadenectomy should be repeated.

2. Fever

- Fever can occur as a result of infection, inflammation or malignancy. Persistent fever in adults is defined as a body temperature of more than 38°C lasting for more than two weeks.
- In PLHIV, the only clinical presentation of HIV infection may be fever. Thus, it is important to keep in mind a possible diagnosis of HIV infection when managing a patient who presents with a persistent fever and no obvious cause.
- In PLHIV, persistent fever may be accompanied by features of the possible underlying cause, for example pneumonia, TB, gastrointestinal infection or lymphoma. In adults with persistent fever, the following factors may suggest the presence of HIV infection:
  - a history of unsafe sexual behaviour
  - a partner or child known to be HIV-infected
  - other features suggestive of HIV infection, such as:
    - PGL
    - oral or genital thrush
    - oral hairy leukoplakia
    - pruritic skin rash
    - oral or genital herpes
    - involuntary weight loss
    - darkening of the nails (melanonychia)
    - hypopigmentation of the lips
    - thinning and straightening of the hair.

3. Weight loss in adults

- HIV infection is a common cause of weight loss.
- Severe weight loss is defined as involuntary loss of more than 10% of one's body weight.
- Severe involuntary weight loss in PLHIV is known as HIV-associated wasting syndrome or "slim disease".
- The cause of such wasting is not fully understood. Possible unsubstantiated causes include:
  - chronic and recurrent infections
  - chronic diarrhoea
  - malabsorption
  - HIV-induced myopathy
  - HIV-induced poor appetite.

3.1. Clinical features

- The patient may complain of involuntary weight loss or loss of appetite, with or without fever and diarrhoea.
- Patients with HIV-associated wasting disease are ill and emaciated and may be feverish and dehydrated.
- Oral candidiasis is commonly found in such patients.
- The patient may have other features of AIDS, including features of neurological involvement such as encephalopathy and AIDS dementia complex.

4. Chronic diarrhoea in adults

- Adults with chronic diarrhoea complain of frequently passing three or more consecutive loose stools over 28 days. During the course of the illness the patient may also have episodes of acute diarrhoea.
- The stool does not usually contain blood, except if there is concomitant dysentery.
- The patient usually also has a poor appetite and weight loss.
- The patient may also be dehydrated, anaemic and wasted.

- Adults with chronic diarrhoea often have:
  - skin and hair changes typically associated with malnutrition
  - hypopigmentation of the lips
  - darkly pigmented nails
  - oral thrush, hairy leukoplakia or lymph node enlargement.

Details on the management of chronic diarrhoea and assessment of dehydration in adults are provided in Protocol 3, *Palliative care for people living with HIV*.

5. Oral lesions

Besides candidiadis (see section II.5.3 above), a large number of other oral lesions may be found in patients with HIV infection. Some of these are described in Table 25.

Table 25. Description and treatment of oral lesions common in PLHIV

Condition	Description	Treatment
Gingivitis	Swollen and red gums that tend to bleed easily	Metronidazole 400 mg PO BID for 7 days or erythromycin 500 mg PO QID for 7 days
Pyorrhoea	An accumulation of pus in the gingival margin around the teeth	Gargling with warm salty water after every meal and brushing the teeth BID
Periodontitis	A painful condition with rapid loss of the bone and soft tissue supporting the teeth, bleeding of the gums, tooth loss and possible ulceration	Local debridement, chlorhexidine mouth washes Amoxycillin 500 mg PO TID or metronidazole 200 mg PO TID for 5 days
Aphthous ulcers	Painful punched-out ulcers on the mucosal surface, usually covered in a purulent exudate and tending to bleed when touched	Oral hygiene and treatment with topical steroids
Stomatitis	Inflammation of the mucosa in the oral cavity, often associated with poor oral hygiene and invasion of anaerobic bacteria	Gargling with warm salty water after every meal and brushing the teeth BID
Cheilitis	Inflammation, redness and eventual pallor of the lips, common in patients with advanced immunosuppression	No specific treatment available; vitamins A, B and C and advice on oral hygiene
Secondary syphilis	Lesions on the buccal mucosa, including moist papules, "snail track" ulcers and condylomata lata at the angles of the mouth and around the nostrils. (In secondary syphilis, all serological tests for syphilis are positive.)	Benzathine penicillin 2.4 milliunits IM QW for three weeks *or* doxycycline 100 mg PO BID for 28 days *or* erythromycin 500 mg PO QID for 28 days

6. Skin and nail conditions

6.1. Dermatomycosis

- Fungal skin rashes (dermatomycoses) occur commonly in PLHIV and others.
- Rashes are usually itchy and dry, with visible scales of dead skin.
- The lesions may be found anywhere on the body.

6.1.1. Diagnosis

Fungal elements may be found on microscopic examination of skin scrapes.

6.1.2. Treatment

Topical applications of antifungal ointments and creams will usually clear the lesions. The following may be used for treating dermatomycoses.

Table 26. Treatment of dermatomycosis

Antifungal preparation	Dose	Frequency	Route	Duration
First-line treatment				
Topical miconazole		TID	Topical	21 days
or:				
Topical clotrimazole		TID	Topical	21 days
Second-line treatment				
Ketoconazole	200 mg	OD	PO	1–3 months
or:				
Itraconazole	100 mg	OD	PO	1–3 months

6.2. Onychomycosis

Nails may also become infected with fungi (onychomycosis). The infection can result in discoloration, distortion or destruction of the nails.

6.2.1. Diagnosis

- Diagnosis is usually made on clinical findings.
- Microscopic examination of potassium hydroxide (KOH) preparations of subungual material may reveal fungal elements.

6.2.2. Treatment

Table 27. Treatment of onychomycosis

Antifungal preparation	Dose	Frequency	Route	Duration
First-line treatment				
Terbinafine	250 mg	OD	PO	6 weeks for fingers 12 weeks for toes
or:				
Itraconazole	200 mg	BID	PO	For fingers, 1 week each month for 2 months For toes, 1 week each month for 3–4 months

6.3. Seborrhoeic dermatitis

- Seborrhoeic dermatitis is a common presenting feature in PLHIV. It is probably caused by a fungus known as *Pityrosporum ovale* (also known as *Malasezia furfur*).
- The rash is erythematous and scaly. In persons with HIV infection it may be extensive, persistent and recurrent.

6.3.1. Diagnosis

- Diagnosis is made on clinical grounds. The rash appears commonly on the:
  - face
  - area around nostrils
  - nasolabial folds
  - eyebrows

- scalp
- chest
- axillae
- upper trunk
- genital area.

Diagnosis can be confirmed by finding fungal elements on microscopic examination of skin scrapes.

6.3.2. Treatment

- Frequent skin washing to remove scales is advised.
- Shampooing with selenium sulfide shampoo is effective.
- Topical applications of 1% hydrocortisone are probably the most effective. Ketoconazole 2% cream has also been shown to be effective.

6.4. Scabies

Scabies is caused by the mite *Sarcoptes scabei*. The female mite burrows into the skin, and the burrows appear as raised lines up to several centimetres long.

- When a person is infested with scabies mites for the first time, there is usually little evidence of infestation for the first 2–6 weeks.
- In subsequent infestations, people usually have become sensitized to the mites, and the symptoms generally occur within 1–4 days.
- The burrowing of the mites under the skin causes a rash, most frequently found on the:
  - hands (particularly the web spaces between the fingers)
  - folds of the wrist, elbow or knee
  - ulnar margins of the forearms
  - penis
  - breast
  - shoulder blades
- Burrows and mites may be few in number and difficult to find in some cases.
- Severe itching is common, especially at night and frequently over much of the body, including areas where no mites are living.
- Norwegian scabies, a more severe form more common among immunocompromised patients, is characterized by vesicles and the formation of thick crusts on the skin, accompanied by abundant mites but only slight itching.
- Complications due to infestation are usually caused by secondary bacterial infections from scratching.

6.4.1. Diagnosis

- The diagnosis is usually made on finding the rash and burrows.
- Skin scrapes may reveal mites or mite ova on microscopic examination.

6.4.2. Treatment

- The treatment of choice is the topical use of gammabenzene hexachloride 1%, applied to the whole body from the neck down and washed off after 24 hours in adults and 8 hours in children. A single application is sufficient.
- Permethrin 1% applications are also useful. Both are applied to affected areas and washed off after 8 hours.
- These agents should not be used during pregnancy or lactation or on children until 2 ½ years old.
- Ivermectin in a single oral dose of 200 µg/kg is an alternative that is effective for crusted scabies in immunocompromised people.
- All members of the household and sexual partners should also be treated.
- All clothes, bedding and towels should be washed in hot water, dried and ironed.

6.5. Staphylococcal folliculitis

- Folliculitis is a skin infection that is localized in the hair follicles.
- A pustular perifolliculitis occurs commonly in PLHIV.
- Usually the condition is caused by *Staphylococcus aureus,* though other organisms may also be responsible.

6.5.1. Diagnosis

- Diagnosis is made on clinical findings.
- Lesions are small (less than 5 mm in diameter), and found in multiple erythematous follicles that may have a purulent centre.
- Lesions are itchy and often found in clusters.

6.5.2. Treatment

Treatment is with antibiotics, such as cephalexin or cloxacillin 500 mg PO QID for 7–21 days.

6.6. Molluscum contagiosum

- Molluscum contagiosum is a superficial skin infection caused by the molluscum contagiosum virus.
- The infection is spread through close body contact and may occur through sharing clothing, bedding or towels or through sexual transmission.
- The incubation period varies from several weeks to several months.
- Shaving or scratching may cause the infection to spread.
- The infection occurs more commonly in immunosuppressed PLHIV.
- In comparison to the lesions found on HIV-negative people, those found on PLHIV are:
  - more widespread
  - more persistent
  - much larger
  - more difficult to treat.

6.6.1. Diagnosis

- The diagnosis is based on the characteristic appearance of the bumps.
- The virus invades the skin, causing the appearance of firm, flesh-coloured papules 2–5 mm in diameter. The lesions contain a white sebaceous material.
- The papules can occur anywhere on the body and often remain unchanged for many months, after which they disappear and may or may not reappear.
- No diagnostic test for this virus is available.

6.6.2. Treatment

The goal of treatment is to remove the soft centre, after which the papule resolves. As such, each lesion needs to be treated individually. Various methods are available for the destruction of the lesion, including:

- curettage
- chemical destruction with concentrated phenol
- cryotherapy
- electrocautery.

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