

# **Clinical Tract**

**Module on**

## **Opportunistic infections and cancers**

## **LEARNING OUTCOMES FOR COUNSELLORS, DATA CAPTURERS, SOCIAL WORKERS AND DIETICIANS**

After completion of this module the learner should be able to:

- Explain to a patient the importance of taking treatment correctly.
- Explain different infections in layman's terminology.
- Refer a patient when necessary to a doctor or nurse.

Counsellors, data capturers, social workers and dieticians should only read this module after the Module on Medical Terminology is fully understood.

All the abovementioned team members may not make a diagnosis, but must be aware of signs and symptoms associated with opportunistic infections, so that a patient with complaints can be promptly referred for evaluation. Treatment is also not in the scope of above mentioned team members. These team members should be aware of the treatment used frequently, but is not expected to know dosages.

## **LEARNING OUTCOMES FOR LABORATORY TECHNICIANS**

After completion of this module the learner should:

- Know the spectrum of organisms associated with HIV disease and AIDS specifically.
- Understand the important role the laboratory plays in the management of the HIV infected patient.

This module covers the types of tests requested to confirm a diagnosis on a patient, but does not teach a technician how to perform the test itself.

## **LEARNING OUTCOMES FOR DOCTORS, NURSES AND PHARMACISTS**

After completion of this module the learner should be able to:

- Diagnose and treat the common opportunistic infections seen in HIV positive patients.
- Know when to refer a patient with an opportunistic infection to a specialised facility.
- Know what prophylaxis to offer a patient infected with HIV.
- Know the cancers associated with HIV and the treatment thereof.

## **TABLES WITH DOSAGES OF DRUGS**

For ease of reading of the text in the module, only the generic names of the drugs are given in the text. The three tables following the text provide the treating physician with drug dosages for adults.

Drug dosages for paediatric opportunistic infections will follow in the Module on Management of HIV disease in children.

# 1. INTRODUCTION

Although Human Immunodeficiency virus (HIV) is a virological infection, it progresses to an immunological disease. This results in progressive and insidious destruction of the immune system. Ultimately the resulting profound immune suppression renders patients vulnerable to opportunistic infections (OIs).

OIs are the cause of considerable morbidity in HIV-infected individuals. Some of the OIs decrease quality of life, without being life threatening, while others are immediately life threatening. Multiple OIs can occur concurrently in individuals with advanced disease. All should be treated as quickly and effectively as possible.

The diagnosis and treatment of intercurrent illnesses is the first concern in the medical management of HIV. Thereafter the need for prophylactic therapy needs to be assessed.

The CD4 count remains the most reliable indicator for the occurrence of OIs. Patients are vulnerable to some of the OIs even at relatively preserved CD4 counts (>500 cells/ $\mu$ L), while other OIs are associated with very low CD4 counts (<50 cells/ $\mu$ L).

It is important to distinguish between the concepts of primary prophylaxis and secondary prophylaxis. Primary prophylaxis is initiated at a stage when the patient is at risk of the particular infection. Primary prophylaxis can be initiated in the form of chemoprophylaxis for a defined period or by means of vaccination.

Secondary prophylaxis (also called maintenance therapy) is initiated after appropriate treatment of the initial infection, since relapses of some infections are common as long as the patient is severely immune suppressed.

Prophylaxis in the form of medication and vaccination is readily available and can be given to individual patients with ease.

The timely use of highly active antiretroviral therapy (HAART) with concomitant reconstitution of the immune system is the most effective way to prevent opportunistic infections. Unfortunately many patients are only diagnosed with HIV once they are severely immune compromised and need prophylactic therapy until immune reconstitution takes place. Other patients have such profound damage to the immune system that very little immune reconstitution takes place after initiation of HAART and the prophylaxis of OIs need to be continued indefinitely.

## 2. ORAL CANDIDIASIS

### Clinical presentation

HIV infection is associated with a variety of oral lesions and oral manifestations are often the first clinical expression of HIV infection in an individual.

Oral candidiasis is a useful marker for immune deterioration and is a predictor of full-blown Acquired Immunodeficiency Syndrome (AIDS) in adults. The infection is recurrent and becomes progressively severe as the immune system deteriorates.

One of the earliest symptoms is loss of taste sensation, which has to be elicited in the history. Following that are symptoms of a burning sensation, pain and later

difficulty in swallowing. Oral and oesophageal Candidiasis is not life threatening, but can be severely debilitating.

**The clinical classification of oral candidiasis is as follows:**

Erythematous	Red patches most often on dorsum of tongue and hard palate, often asymptomatic
Pseudomembranous	Cottage cheese-like semi-adherent plaques, can be confluent. Red or bleeding surface underneath when scraped off.
Hyperplastic	Adherent whitish-yellow patches.
Angular cheilitis	Bilateral deep fissures at the labial commissures

The diagnosis is made on clinical appearance.

To an inexperienced eye, oral hairy leukoplakia and pseudomembranous candidiasis can look alike. The plaques of candidiasis can be scraped off.

**Causative organism**

The causative organism is most often *Candida albicans*, although other candida species can cause the same clinical picture. It is not important to culture the organism routinely.

**Special investigations**

Refractory cases of oral candidiasis can be cultured, but this need not be done routinely.

**Treatment**

Topical treatment, and *not* systemic, is the route of choice. Since the drugs work topically, the target is to allow adequate contact time between the drug and the mucous surface, thus necessitating 5 times a day dosing. Treatment should continue at least 7-14 days.

The drugs of choice are either a polyene (nystatin solution or amphotericin B lozenges) or an imidazole (e.g. miconazole gel). The drugs can be unpalatable. Systemic antifungal therapy is reserved for nonresponsive cases and maintenance therapy should be avoided. Chlorhexidine gluconate 0.2% as mouthwash can be used as a prophylactic agent in cases of recurrent candidiasis.

### **3. ORAL HAIRY LEUKOPLAKIA**

**Clinical presentation**

Hairy leukoplakia predicts a rapid progression from HIV to AIDS. It occurs on the lateral borders of the tongue and is a white keratotic lesion that cannot be scraped off with a spatula. Often there are vertical striations, giving it the characteristic “hairy” appearance. Although mostly asymptomatic, the lesions can sometimes cause discomfort.

## **Treatment**

Acyclovir can be used for severe cases, but this treatment is usually not indicated. These lesions do improve when the patient starts HAART.

## **4. HIV-ASSOCIATED PERIODONTAL DISEASE**

### **Clinical presentation**

Periodontitis and gingivitis are observed in all stages of HIV. Acute necrotizing ulcerative gingivitis (ANUG) is a severe form of gingivitis. The patient usually complains of painful or bleeding gums.

### **Causative organisms**

The organisms generally responsible are *Borrelia vincenti* and *Fusobacterium nucleatum*. Culture is not routinely done.

### **Treatment**

Amoxicillin and metronidazole is used for 5 days. Chlorhexidine gluconate 0.2% mouthwash is not only indicated, but can be used long-term. Oral hygiene is important. Cleaning and scaling of teeth should also be done to remove plaque and calculus after the antibiotic course is completed.

## **5. CANDIDA OESOPHAGITIS**

### **Clinical presentation**

The patient experiences dysphagia, first for solid foods, and as the disease progresses, also for fluids. Presenting symptoms may also be vomiting, dehydration and loss of weight. The clinical diagnosis is suggested by the clinical features. In most cases the patient also has oral candidiasis. The CD4 count is usually less than 100 cells/ $\mu$ L.

### **Diagnosis**

The diagnosis is clinical and made on the history that the patient provides. Oral candidiasis, if present, can also guide a clinician towards a diagnosis. An endoscopy is only indicated if empiric treatment fails or in the case of an atypical presentation.

The differential diagnosis of dysphagia in HIV includes:

- Candida oesophagitis
- Cytomegalovirus ulceration
- Herpes simplex ulceration

### **Treatment**

Systemic treatment with an azole is indicated. Itraconazole or fluconazole is effective when given for 14-21 days. Analgesics should not be forgotten in the first few days of treatment. Although relapses are common, prophylactic therapy is not indicated, since it can lead to resistance.

## **Diflucan partnership programme**

Pfizer entered into a partnership with the Ministry of Health for South Africa in April 2001 to make available fluconazole (Diflucan) to patients with Cryptococcal meningitis and Candida oesophagitis who cannot afford treatment. The programme started June 2001 when Pfizer decided to donate Diflucan™ for above indications to government and NGO's in a selected range of countries (Least developed countries and sub-Saharan countries with HIV prevalence of > 1%). As part of the package Pfizer also offers training on the use of the product.

The drug is available in 200mg tablets, 200mg intravenous formulation and powder for oral suspension. The packaging is different from what is available in the private sector. In South African state hospital handled as Schedule 5 drugs to control movement of stock and monitor for theft.

## **6. COMMUNITY ACQUIRED LOBAR PNEUMONIA**

### **Clinical presentation**

People with HIV have a higher risk for community-acquired pneumonia (CAP). HIV positive patients are at risk for pneumonia with any CD4 count. The clinical features are acute onset fever, chest pain productive coughing and pleuritic chest pain. The onset may however be slower.

Chest X-ray would show unilateral or bilateral infiltrates. Sputum must be sent away for gram stain and culture.

The common causative organisms are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Less common organisms are *Staphylococcus aureus* and *Klebsiella pneumoniae*.

### **Treatment**

The drug of choice is penicillin or erythromycin if the suspected organism is *S. pneumoniae*. If the gram stain suggests *H. influenzae*, then ampicillin/amoxicillin or second-generation cephalosporin would be indicated. Treatment will be adjusted according to sensitivity when the culture result is available.

### **Prophylaxis**

The risk of invasive pneumococcal infection is 50-100 times higher in HIV-positive individuals than in the general population. The use of the 23 polyvalent pneumococcal vaccine was until recently recommended as standard of care in the Western world, but a review of available data found no evidence of efficacy in the target population. One large clinical trial in Uganda showed increased risk of pneumococcal disease in vaccine recipients and also a higher mortality rate. Thus pneumococcal vaccine is currently not recommended for HIV-positive individuals.

## 7. PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP)

The organism was previously known as *Pneumocystis carinii*.

### Clinical presentation

The onset of the infection is insidious. The main clinical features are progressive dyspnoea and a dry cough developing over 2-3 weeks. Often, the chest examination is unremarkable, except for tachypnoea. This infection is usually associated with a CD4 count below 100 cells/ $\mu$ L.

### Special investigations

In early cases, up to 20% of chest x-rays can be normal. The classical chest X-ray shows a symmetrical perihilar interstitial infiltrate. It is also described as "ground glass".

The differential diagnosis of a diffuse reticulonodular infiltrate is:

- *Pneumocystis jiroveci*
- Miliary tuberculosis
- Lymphocytic interstitial pneumonia
- Kaposi's sarcoma
- Sarcoidosis
- *Toxoplasma gondii*
- Cytomegalovirus

The arterial blood gases would show varying degrees of hypoxia. Early disease shows only desaturation during exercise. Lactate dehydrogenase (LDH) is significantly increased in 90% of cases, but it is a nonspecific finding.

Diagnosis is made on sputum induced with nebulised hypertonic saline (positive yield in 60-95%) or bronchoscopy with lavage fluid or transbronchial biopsy (positive yield in 95%). Special stains, silver or immunofluorescence is done on the fluids collected.

### Treatment

The treatment choice is high dose co-trimoxazole for 3 weeks. The alveolar inflammatory response to the infection causes the observed hypoxia. The hypoxia is worsened by initiation of treatment. High dose corticosteroids suppresses the body's inflammatory response and is an essential part of the treatment in any hypoxic patient.

In patients allergic to co-trimoxazole, dapsone in combination with trimethoprim can be used, or clindamycin in combination with primaquine.

### Indications for co-trimoxazole prophylaxis

Co-trimoxazole prophylaxis is primarily used for the prevention of PCP. This infection is usually associated with a CD4 count below 100 cells/ $\mu$ L. The risk of PCP infection without prophylaxis is 60-70% per year in those patients with previous PCP and 40-50% in those without previous PCP, but a CD4 count below 100 cells/ $\mu$ L. PCP prophylaxis reduces the risk of PCP 9-fold. Patients who get PCP while on prophylaxis have a lower mortality rate.

As additional benefit co-trimoxazole prophylaxis also decreases the incidence of toxoplasmosis and some bacterial infections targeting the urinary tract, respiratory tract or skin. Some bacterial organisms covered by co-trimoxazole include *H. influenzae*, *S. pneumoniae*, gram-negative bacilli, *Salmonella sp.*, methicillin-sensitive *S. aureus*, *Legionella* and *Nocardia*.

Primary co-trimoxazole prophylaxis should be initiated when:

- WHO Stage 2 disease (where no laboratory monitoring facilities)
- the CD4 count decreases to below 200 cells/ $\mu$ L

Secondary prophylaxis (maintenance therapy) should be initiated directly after the three-week treatment of the acute PCP or three month treatment for acute toxoplasma infection has been completed.

Both primary and secondary prophylaxis for PCP and toxoplasmosis continue lifelong or until the CD4 count is sustained above 200 cells/ $\mu$ L for more than three months while on HAART. Prophylaxis should be restarted should the CD4 count declines again below 200 cells/ $\mu$ L.

The regimen for prophylaxis is co-trimoxazole 960mg/day (that is 2 tablets of 480mg). A single 480mg tablet per day is equally effective as prophylaxis for PCP, but the lower dose is not effective against toxoplasma and bacterial infections and thus not recommended.

### **Co-trimoxazole intolerance**

Side effects due to co-trimoxazole are frequent in HIV positive individuals. A maculopapular rash is the most common. However, many of the patients developing itching or a maculopapular rash can continue with co-trimoxazole under antihistamine cover.

Patients with a history of an adverse reaction to co-trimoxazole can either be rechallenged or desensitised. Rechallenging can be done with a single dosage of 480mg and observation for a few hours. However, patients who had skin rash with systemic systems (e.g. fever) or mucocutaneous involvement (oral or urogenital) should not be rechallenged. Patients with a history of allergy and/or skin reaction to co-trimoxazole can, in most cases, be desensitised safely. It should be preferably be done in hospital under at least 24-hour prior antihistamine cover.

A simple desensitisation regimen that can be used:

Day 1	1.25 ml syrup daily (240mg/5ml)
Day 2	1.25 ml syrup bd (240mg/5ml)
Day 3	1.25 ml syrup tds (240mg/5ml)
Day 4	2.5ml syrup bd (240mg/5ml)
Day 5	2.5ml syrup tds (240mg/5ml)
Day 6	480mg tablet once daily

Dapsone is as effective as co-trimoxazole as prophylaxis against PCP, but offers no proven protection against toxoplasmosis and bacterial infections.

## **8. MYCOBACTERIUM TUBERCULOSIS (TB)**

### **The interaction between tuberculosis and HIV**

The incidence of active TB is substantially increased by HIV co-infection. TB is most often the sentinel illness in HIV (that is, the infection that leads a clinician to suspect HIV disease in the patient). TB is the most common cause of morbidity and mortality associated with HIV in Sub-Saharan Africa. An acute TB infection may be due to the flare up of a dormant infection (reactivation) or a reinfection with the organism.

The increased risk for TB accompanied by immune suppression in HIV is due to the decrease in cell-mediated immunity. Conversely, the immune stimulation induced by the TB leads to more rapid HIV disease progression.

### **Clinical presentation**

One has to differentiate between latent TB infection and TB disease. Latent TB infection is where a person has been exposed to TB and the immune system is unable to destroy all the organisms, but still controls the TB. Such a person would have a positive tuberculin skin test. TB disease develops when the immune system cannot control the organisms anymore and the organisms start multiplying.

The diagnosis of TB in HIV-infected patients can be challenging. Pulmonary tuberculosis (PTB) can appear in patients with well-preserved to very low CD4 counts and is the most common presentation of *M. tuberculosis* disease. PTB presents more typically in patients with well-preserved CD4 counts. In patients with very low CD4 counts the normal immune response cannot be mounted and it can be extremely difficult to confirm a diagnosis of PTB because of the atypical presentation of the disease. Lung examination can be deceptively normal.

Extrapulmonary TB presents most commonly as a large pleural effusion, thereafter TB lymphadenitis, miliary TB and TB meningitis. Renal, bone and synovial fluid TB are less frequent. Tuberculous meningitis is a chronic meningitis with a slow onset. With tuberculous lymphadenitis the lymph nodes are usually asymmetrically enlarged, matted and painful.

Regardless of these facts, TB should be considered in almost all clinical situations. In turn, a diagnosis must be made and often this will require invasive and extensive laboratory investigations.

### **Special investigations and diagnosis**

A chest x-ray can be suggestive of TB, but the diagnosis still needs to be confirmed by acid-fast bacilli on sputum. The X-ray picture is dependent on the level of immune function present in the host. With well-preserved CD4 counts the PTB may present on chest X-ray as typical upper lobe cavities, but with lower CD4 counts one can find patchy infiltrates, a miliary picture or even a normal chest X-ray. Cardiomegaly is present on chest x-ray with TB pericarditis.

Diagnosis of pulmonary TB is confirmed by collecting sputa, nasogastric aspirations or doing bronchoscopy with alveolar lavage. In miliary TB, sputum can be positive in 25% of cases. Staining for acid-fast bacilli (AFB) is done on sputum. Culture for TB should be done in HIV positive individuals where AFB's are negative.

and TB is suspected. AFB's are often negative in HIV positive individuals with advanced disease, but then the culture for TB can still be positive.

If lymphadenopathy is thought to be due to TB, a wide needle lymph node aspiration is done. A lymph node excision is sometimes necessary to come to a diagnosis.

Polymerase chain reaction (PCR) for *M. tuberculosis* can yield quick results, but is much more expensive. Culture takes up to a few weeks to yield results. In cases of systemic spread of TB, blood, bone marrow and liver biopsy tissue can be examined for AFB and PCR and culture done on the fluid.

## **Treatment**

South African National Treatment Guidelines should be followed. The treatment duration for both pulmonary TB and extrapulmonary TB is 6 months. The intensive phase of treatment consists of isoniazid, pyrazinamide, rifampicin and ethambutol, usually as a combination pill. In the maintenance phase isoniazid and rifampicin are used. Direct observed treatment (DOTs) is strongly recommended and offers the patient the best chance of treatment success. Pyridoxine 25mg 2 tabs/day should be added to avoid treatment-induced peripheral neuropathy.

The National TB Control Programme strongly recommends FIVE times weekly regimens for the continuation phase of treatment. All patients on three times weekly regimens should be on clinic DOT. Streptomycin should not be given during pregnancy and to those over 65 years.

## **Prophylaxis**

The most effective way of preventing TB infection in an HIV-positive individual is to control HIV in the general population through an effective TB treatment programme. An effective TB programme will ensure high cure rates of TB through DOTs (directly observed treatment, short course).

The risk of active TB for HIV-positive individuals with a positive tuberculin skin test is approximately 10% per annum. The incidence of active TB in those with a positive tuberculin skin test is magnified 7-80-fold by HIV co-infection. It also appears that TB accelerates the rate of HIV progression.

HIV-positive individuals in Sub-Saharan Africa are at significant risk of TB even at relatively preserved CD4 counts. Thus preventative therapy should be offered irrespective of the CD4 count. With the use of TB prophylaxis, the reduction of TB incidence amongst HIV-positive individuals with a positive tuberculin skin test is 60%. However, other categories of patient can also be offered prophylactic therapy.

The objective of TB prophylaxis is to treat latent TB disease.

Indications for the use of TB prophylaxis include:

- Positive PPD (>5 mm)
- TB contact
- Staying in high risk dormitory conditions (e.g. mines, prisons)
- Active TB excluded
- No TB treatment in past 2 years

Tuberculin reading in HIV positive individuals is interpreted differently from non-HIV positive individuals. In HIV-positive individuals a positive reading would be regarded as 5mm or above.

Since drug resistance can occur if a patient with active TB is given a single antituberculous drug, it is essential to exclude active TB before initiating prophylaxis. Signs or symptoms that could fit in with TB (e.g. weight loss, fever, night sweats and coughing) should actively be sought and fully investigated. In any patient with respiratory symptoms, a chest x-ray should be done and sputum samples sent for TB microscopy and culture.

A prerequisite for TB prophylaxis is patient compliance. Without that, drug resistance might emerge. Compliance with 6 months of TB prophylaxis might predict a patient's future compliance with antiretroviral drugs. Patients should only be supplied with one month of preventative therapy at a time and monitored for symptoms and signs of active TB or side effects such as peripheral neuropathy and liver toxicity. It is not necessary to do routine liver functions, unless the patient has underlying liver disease.

Patients with a history of active alcohol abuse or liver disease should not be offered TB prophylaxis, because of possible hepatotoxicity due to antituberculostatics.

Current data seem to suggest that the benefit of TB prophylaxis is lost 18 months after completing therapy.

In Southern Africa 6 months of preventative therapy is regarded as sufficient and also easier for patient compliance. The recommended regimen for primary prophylaxis is isoniazid (INH) plus pyridoxine for 6 months. Alternative regimens exist, but do not have significantly better effectiveness. TB differs from other OIs with regard to secondary prophylaxis. Short course (6 months) treatment of the acute infection is not recommended as a general policy. It may have some indications in special settings with high TB prevalence rates such as mines.

## **9. MYCOBACTERIUM AVIUM COMPLEX (MAC) INFECTION**

### **Clinical presentation**

Disseminated *M. avium* disease is usually a very late opportunistic infection with a CD4 count of less than 50 cells/ $\mu$ L. The symptoms (severe fatigue, chronic malaise, weight loss and diffuse abdominal pain) are quite nonspecific. The clinical impression is that of wasting. Fever might be low grade initially, but eventually increases above 39°C and can be accompanied by rigors. The patient can experience drenching sweats. Clinical examination of the abdomen may reveal organomegaly.

### **Diagnosis**

The treating physician must have a high index of suspicion. A distinction must be made between colonization and infection with MAC. Isolation of MAC from a sterile site (blood, bone marrow, liver tissue and lymph nodes) is diagnostic. Recovery of MAC from sputum or bronchial washing, duodenal aspirates or stool may reflect either colonization or infection.

Special mycobacterial blood culture bottles are used to diagnose disseminated MAC. Cultures may take from one to four weeks to yield positive results. A 24-hour diagnosis may be possible by performing PCR on aspirate or tissue.

### **Treatment**

Combination therapy is used with a macrolide as backbone. The preferred first drug is clarithromycin. The second agent is usually ethambutol, because it is cheap and easy to administer. Critically ill patients may benefit from a third agent, such as rifabutin.

If oral absorption of drugs is a problem, or hepatitis develops, intravenous amikacin can be used. Ciprofloxacin is another drug to be considered as part of an alternative regimen.

Duration of treatment is indefinite in the absence of HAART and immune reconstitution. However, in patients on antiretrovirals, MAC treatment may be discontinued after one year if the patient is asymptomatic, the CD4 count is above 100 cells/ $\mu$ L for more than 3-6 months and bone marrow and blood cultures are negative.

### **Prophylaxis**

The 2002 UPSHDS/IDSA Guidelines for the Prevention of opportunistic Infections in Persons with Human Immunodeficiency Virus strongly recommends a macrolide (clarithromycin 500mg bd or azithromycin 1200mg weekly) as primary prophylaxis against *M. avium* disease when the CD4 count is less than 50 cells/ $\mu$ L. *M. avium* prophylaxis does not form part of any Southern African guideline. This is a yet unobtainable goal in Sub-Saharan Africa, since these drugs are financially out of reach for most of the population.

Should primary prophylaxis be instituted, it can be discontinued once the CD4 count is above 100 cells/ $\mu$ L for more than 3 months. However, in patients on HAART, MAC maintenance treatment can be discontinued after one year, provided that the patient remains asymptomatic, the CD4 count is above 100 cells/ $\mu$ L for more than 3-6 months and bone marrow and blood cultures are negative.

## **10. TOXOPLASMA GONDII**

### **Clinical presentation**

Toxoplasmosis causes focal neurological signs with a slow onset that can include focal weakness and paresis. It leads to hemiparesis/hemiplegia and confusion follows later with a suppressed consciousness. Patients can also present with severely impaired mental and motor functioning without focal neurological signs.

Toxoplasma must be considered in any patient with a CD4 count below 100 cells/ $\mu$ L. A patient may also present with Toxoplasma or other neurological infections as first manifestation of HIV disease.

The differential diagnosis of this clinical picture includes:

- Lymphoma
- Tuberculoma
- Cryptococcoma

- Neurosyphilis

### **Special investigations**

A brain scan with contrast will reveal multiple ring enhancing lesions with surrounding oedema. Toxoplasma IgG antibodies will be positive. This clinical picture is due to the reactivation of a previous toxoplasma infection. In South Africa, 30-40% of adults in the general population are Toxoplasma IgG positive.

Should the facilities for a brain scan not be available in a patient with focal neurological signs, the patient should be treated as for toxoplasmosis

### **Treatment**

The active infection should be treated with co-trimoxazole for a period of three months. Clindamycin and pyrimethamine is the second-line treatment for patients who cannot tolerate co-trimoxazole. Folinic acid (not folic acid) should be added if pyrimethamine is used, to treat or prevent bone marrow suppression. The patient's response is monitored clinically.

Response to treatment for toxoplasmosis is within a week and most patients recover well.

Thereafter co-trimoxazole should be used as secondary prophylaxis, lifelong or until the CD4 count increases to above 200 cells/ $\mu$ L on HAART.

## **11. CRYPTOCOCCUS MENINGITIS**

### **Clinical presentation**

The most prominent clinical symptom is severe headache. Thereafter the cognitive functioning may change. Confusion follows later. The neurological examination may be normal in a patient presenting early in the disease. The patient will only have meningism late in the disease, and much later, severe neck stiffness and papilloedema. The patient may also be vomiting.

Differential diagnosis includes:

- TB meningitis
- Bacterial meningitis (can sometimes have a slow onset)
- Cytomegalovirus meningitis
- Primary CNS lymphoma

### **Special examinations**

A lumbar puncture is immediately indicated. A high cerebrospinal fluid (CSF) pressure is usually found.

Sensitivity of the different tests is as follows:

- CSF culture (>95%)
- CSF Cryptococcus latex antigen (>99%)
- CSF Indian ink (>95%)
- Serum Cryptococcus latex antigen (>95%)

## **Treatment**

Amphotericin-B is the drug of choice for the first 14 days of treatment. Thereafter fluconazole is given for the remainder of 8 weeks at a high dosage. In mild cases of cryptococcus meningitis, an earlier switch will be made to fluconazole.

Adverse effects to IV administration can be alleviated by a one-day lead in dose of Amphotericin-B, and by giving an antihistamine and paracetamol in advance. The infusion should run in over four hours. Renal function should be monitored and hydration maintained during treatment. Treatment should be interrupted if kidney function decreases. Potassium levels should be monitored and hypokalemia corrected. Thrombophlebitis occurs frequently due to the corrosive nature of the drug.

Repeated lumbar puncture to remove large volumes of CSF (up to 20ml) might be necessary to relieve the raised intracranial pressure.

## **Prophylaxis**

Fluconazole at 200mg/day is used for secondary prophylaxis of cryptococcus meningitis after treatment of the acute infection. This continues lifelong or until sufficient immune reconstitution has taken place. Although international data suggest that prophylaxis in patients on HAART may be discontinued at a CD4 count of 100 cells/ $\mu$ L, it might be safer to continue until the CD4 count is above 200 cells/ $\mu$ L since no data exist for our patient population.

Primary prophylaxis does not form part of any Southern African Guidelines, but can be considered for selected patients.

## **12. CYTOMEGALOVIRUS (CMV)**

### **Clinical presentation**

CMV may present as retinitis, encephalitis, pneumonitis or colitis in patients with CD4 count below 50 cells/ $\mu$ L. With retinitis the patient presents with floaters, blurring and painless vision loss. CMV retinitis can be diagnosed clinically with fundoscopy (fluffy white lesions and haemorrhages). CMV colitis may cause chronic, often severe and bloody diarrhoea.

### **Diagnosis**

CMV Polymerase Chain Reaction (PCR) can be done on the CSF or pulmonary secretions in cases of encephalitis or pneumonitis. Typical inclusion bodies can be seen on biopsy of the affected organ.

### **Treatment**

Without treatment, CMV retinitis destroys the retina in six months with blindness as outcome. Intravitreal ganciclovir is the drug of choice. The aim of treatment would be to protect the vision since damage cannot be reversed. Intravenous treatment of the infection is for 14-21 days, but life-long maintenance therapy is required. Ganciclovir is nephrotoxic. The patient must preferably be referred to an expert for treatment.

## **13. HERPES ZOSTER**

### **Clinical picture**

The diagnosis of shingles is made on clinical grounds – the severe pain and the unilateral vesicular eruption corresponding to a dermatome innervated by a sensory nerve.

### **Treatment**

An antiviral such as acyclovir, valacyclovir and famcyclovir should be used, as long as treatment is initiated within 72 hours of blisters starting. Therapy shortens the duration of the disease and decreases the incidence and severity of post-herpetic pain.

The short-term management of the pain itself is with a non-steroidal inflammatory such as ibuprofen or indomethacin for a short period (1 week). Amytriptiline, sometimes in combination with carbamazepine is used for long-term management. Amytriptiline is started at 10mg in the evening for a week, and can then be increased to 25mg/day for another week and then to 50mg/day. The clinically important side effects of amytriptiline are a dry mouth and drowsiness. This is managed by starting with a low dosage. Carbamazepine is added if pain is not controlled on maximum dosage of amytriptiline.

If herpes zoster is treated early, post herpetic pain usually clears up within a month. There are, however, some patients who are debilitated by post herpetic pain for months afterwards and in whom treatment will continue. Tramahexadol or codeine can be added in patients such as these.

For pain management, also read the Module on Palliative Care.

## **14. HERPES SIMPLEX**

### **Clinical picture**

Herpes simplex causes mucocutaneous ulceration of the mouth, oesophagus, anus and genital area, starting as numerous fluid-filled vesicles that coalesce and progress into ulcers before they heal. These ulcers are usually extremely painful. Recurrence is common. Oesophageal or genito-anal ulcers that persist longer than one month constitutes an AIDS defining condition. The diagnosis is made on clinical grounds.

### **Treatment**

Systemic antivirals such as acyclovir, valacyclovir and famcyclovir should be used for 7 days. Treatment can continue for 14 days should the response after 7 days not be sufficient. These drugs are virostatics, thus infections would most likely recur. Each episode should be treated, and maintenance therapy should only be reserved for extreme cases.

## 15. CHRONIC DIARRHOEA

### What is chronic diarrhoea?

The bowel habits of healthy persons vary widely. The complaint of diarrhoea should be evaluated in terms of degree of change from an individual's customary pattern. Questions should be asked about an estimate of the volume, consistency, as well as frequency of stools. It is best to directly examine a stool sample for consistency, blood and malodour.

### Clinical picture

Chronic diarrhoea is debilitating to the patient. It is usually accompanied by loss of weight. *Cryptosporidium parvum* is the cause of chronic to fulminant diarrhoea in some cases.

### Special investigations

Chronic diarrhoea has many possible causes (which can be related to the level of immune suppression) and should be investigated for other possible infective pathogens before ascribing it to HIV. Stool microscopy and culture should be done on three occasions, as well as microscopy for parasites. A modified acid-fast stain on the stool is required to diagnose *cryptosporidium* and *Isospora belli*.

### Treatment

The best practical approach would be to treat empirically for ten days with co-trimoxazole and metronidazole. Should there be no response to treatment, further investigations should be initiated and treatment tailored to the causative organisms isolated.

*Salmonella typhi* responds to ciprofloxacin for six weeks. *Isospora belli* would respond to co-trimoxazole, but a course of 4 weeks is indicated. Unfortunately no effective treatment exists for *cryptosporidium* infection. Here, antimotility drugs are used in conjunction with palliative care. Microsporidiosis responds to albendazole. In severe diarrhoea, attention should be paid to fluid maintenance, as well as possible potassium depletion.

## 16. INFLUENZA

### Clinical picture

Influenza is more severe and prolonged in HIV-infected individuals.

### Treatment

Symptomatic management.

### Prophylaxis

HIV-infected individuals form a prime target group for influenza vaccine. Influenza vaccine should be administered annually, preferably March to May, due to the antigenic shift in strains from year to year. Influenza vaccines currently used are inactive subunits or split-product vaccines and are safe to use. CD4 cells govern the

humoral response (IgG and IgA) stimulated by the vaccination. In HIV positive individuals with CD4 counts less than 200 cells/ $\mu$ L, the antigenic response tends to be poor.

A transient increase in viral load can occur. Thus viral load monitoring should not be done within two weeks of vaccination. This however, does not have any clinical implications.

## **17. HEPATITIS B AND C**

Hepatitis B and hepatitis C are not opportunistic infections, but co-infections of HIV that can be prevented. These co-infections can complicate the management of HIV. Hepatitis B and C are both transmitted through blood and sexual contact. Hepatitis B is more easily transmitted than HIV. Hepatitis C is still a relatively scarce infection, but has a high rate of transmission.

Hepatitis B has an incubation period of 45-160 days, while hepatitis C has an incubation period of 15-50 days. The acute infection presents like many viral infections with flu-like symptoms. Upper abdominal pain, nausea, vomiting and jaundice follow. Hepatitis B is fulminant and fatal in 1% of cases; while 6% of patients go on to develop chronic hepatitis. With hepatitis C infection 85% of patients develop chronic hepatitis and 10% develop liver cirrhosis.

### **Diagnosis**

Liver functions tests are done to determine whether there is liver damage. Protein and albumin reflect the synthetic function of the liver. Bilirubin is increased in a patient with jaundice. Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) is increased with obstruction or granulomatous disease. The transaminases (AST and ALT) are increased with liver cell damage or inflammation.

The cause of hepatitis needs to be determined by further blood tests.

A person that is vaccinated against hepatitis B will only have HbsAb positive. In acute hepatitis B, the HBsAg will be positive and antiHBc IgM will be positive. With chronic hepatitis B the HBsAg will stay positive more than six months and antiHob IgG will be positive.

In acute hepatitis C the Hepatitis C antibody will be positive. Then an HCV RNA (hepatitis C viral load) needs to be done.

### **Prophylaxis**

Hepatitis B vaccine can be administered to patients who are antiHBs and antiHBc antibody negative. It is given as 3 doses intramuscularly, spaced over a period of 6 months.

There is no prophylaxis against hepatitis C infection.

## Treatment

Treatment for hepatitis B infection is indicated if:

- HbsAg positive > 6 months
- Evidence of acute viral replication (HbeAg and HBV DNA positive)
- Active liver disease (elevated ALT and AST and hepatitis on liver biopsy)

Possible treatment options include interferon alpha and lamivudine.

Treatment for hepatitis C is indicated if:

HCV RNA >50 IU/mL

Liver biopsy shows moderate inflammation and necrosis or portal or bridging fibrosis

Treatment options for hepatitis C include interferon and ribavirin.

Treatment for hepatitis B and C should be referred to a specialist physician.

## 18. KAPOSI'S SARCOMA

### Clinical picture

Kaposi's sarcoma presents as discrete purple to brown-black patches on the skin that can infiltrate any mucocutaneous surface, including the gastrointestinal tract and lungs. The skin lesions can be very unsightly and embarrassing for the patient. Larger lesions often ulcerate. Infiltration of lymph glands causes lymph oedema. Kaposi's sarcoma is regarded as AIDS defining, even if the CD4 count is above 200 cells/ $\mu$ L.

Poor prognostic features include:

- Visceral involvement
- Lymph node involvement
- Lymph oedema
- Systemic symptoms
- Low CD4 cell count

### Diagnosis

Kaposi's sarcoma can be suspected clinically, but must be confirmed by histology. Severe HIV pruritis and other skin conditions may be confused with Kaposi's sarcoma. Chemotherapy can only be considered after histological proof of Kaposi's sarcoma.

### Treatment

Kaposi's sarcoma is an AIDS defining condition and the patient should start antiretrovirals, irrespective of the CD4 count. Kaposi's sarcoma can never be cured. The goal with therapy is to reduce symptoms and prevent progression.

Local radiotherapy often gives excellent results.

Chemotherapy should be considered in combination with antiretrovirals if there is no response on antiretrovirals and bad prognostic features are present. Chemotherapy should be left to an oncologist. For patients with Kaposi's sarcoma limited to the skin and for patients with low CD4 counts only vinblastin is used. For full treatment of

Kaposi's sarcoma the abbreviation ABC is used, that is adriamycin, bleomycin and vinblastin is used. Liposomal anthracyclines are also used, but very expensive.

## **19. NON-HODGKIN'S LYMPHOMA (NHL)**

### **Clinical picture**

The patient may present with unilateral lymphadenopathy. The disease, however, is often atypical with extranodal or central nervous system involvement and the patient may present with systemic features (e.g. fever or malaise) or central nervous system abnormalities (e.g. confusion or localizing signs).

### **Diagnosis**

Excision biopsy of a suspected lymph node must be done. Aspiration of a lymph node cannot confirm the diagnosis. Stereotatic brain biopsy should only be undertaken for possible NHL of the central nervous system if treatment can be offered to the patient.

### **Treatment**

Patients with lymphoma must be referred to an oncologist together with starting antiretrovirals. This is not a condition to be managed by a peripheral hospital or clinic.

Histologically, NHL is usually a high-grade lesion and they require intensive chemotherapy regimens. Since this is an aggressive cancer, not all patients will benefit from the chemotherapy, and only candidates with a better possible outcome, should be offered chemotherapy. Chemotherapy should be used in conjunction with antiretrovirals. The chemotherapy drugs used are abbreviated by CHOP; that is a combination of cyclophosphamide, adriamycin, prednisone and vincristine.

## 20. TABLES WITH ADULT MEDICATION DOSAGES FOR TREATMENT OF OPPORTUNISTIC INFECTIONS

Table 1. Treatment of common opportunistic infections.

Disease	Treatment
Oral candidiasis	<p><b>Drugs of choice</b> Nystatin 1 ml swished and swallowed 5x/day for 7-14 days. Miconazole gel (pea size application) 5x/day for 7-14 days. Amphotericin B 1 lozenge 5x/day for 7-14 days.</p> <p><b>Alternative for severe/persistent infection</b> Fluconazole 150-200 mg/day Itraconazole 100-200 mg/day</p>
Oesophageal Candidiasis	<p><b>Drugs of choice</b> Fluconazole 150-200 mg/day for 14-21 days. Itraconazole 200 mg/day.</p> <p><b>Alternative for resistant infection</b> Amphotericin B 0.3-0.6 mg/kg IV for 10-14 days.</p>
<i>Pneumocystis jiroveci</i> pneumonia	<p><b>Drug of choice</b> Combination drug co-trimoxazole, that is 80mg trimethoprim and sulphamethoxazole 400mg in a single strength (SS) pill. Use co-trimoxazole 20/100 mg/kg/day PO or IV in 3-4 divided dosages. Treat for 21 days.</p> <p><b>Plus (for inflammation)</b> Prednisone 40 mg bd 5 days, 40 mg daily for 5 days, then 20 mg/day till completion of treatment.</p> <p><b>Alternative for co-trimoxazole allergy:</b> Trimethoprim 300mg/day plus dapsone 100mg/day for 21 days. Clindamycin 450-600mg/day plus primaquine 15mg/day for 21 days.</p>
<i>Toxoplasma gondii</i>	<p><b>Drug of choice</b> Combination drug co-trimoxazole, that is 80mg trimethoprim and sulphamethoxazole 400mg in a single strength pill. Use co-trimoxazole 320/1600 mg twice daily for 4 weeks, followed by 160/800mg twice daily for another 8 weeks.</p> <p><b>Alternative for co-trimoxazole allergy</b> Pyrimethamine 50mg/day plus Clindamycin 600mg tds for 8 weeks.</p>
<i>Cryptococcus neoformans</i> meningitis	<p><b>Drug of choice</b> Amphotericin-B 0.7 mg/kg/day IV for 10-14 days, then fluconazole 800 mg/day for 8 weeks. Daily CSF taps to decrease pressures.</p>
CMV Retinitis	<p><b>Initial treatment</b> Intraocular ganciclovir implant every 6 months plus ganciclovir 1000-1500mg tds PO. Ganciclovir 5mg/kg bd IV for 21 days. Foscarnet 60mg/kg tds IV for 21 days.</p> <p><b>Maintenance treatment</b> Ganciclovir 5mg/kg/day IV for 5 days/week or 1000mg tds PO. Foscarnet 90-120mg/kg/day IV.</p>
CMV oesophagitis, colitis, pneumonitis	<p><b>Drug of choice</b> Ganciclovir 5 mg/kg IV bd for 14- 21 days.</p> <p><b>Alternative</b> Foscarnet 60 mg/kg IV tds for 14-21 days</p>

**Table 1. Treatment of common opportunistic infections continues**

<b>Disease</b>	<b>Treatment</b>
<i>M. tuberculosis</i>	Standard national treatment regimen: Isoniazid/rifampicin/pyrazinamide/ethambutol as combination pill for induction treatment of 8 weeks. Isoniazid/rifampicin as combination pill as maintenance of 16 weeks. Do not initiate HAART and antituberculous therapy together.
<i>M. avium</i> disease	<b>Drugs of choice</b> Clarithromycin 500 mg bd <i>plus</i> ethambutol 15 mg/kg/day Severe: Add rifabutin 450-600mg/day to above regimen. <b>Alternative</b> Azithromycin instead of Clarithromycin. Ciprofloxacin 500-750 mg bd <i>or plus</i> Amikacin 15mg/kg/day IV. Treatment is for 9 months at least.
<i>Herpes zoster</i> shingles	Drugs of choice Acyclovir 800mg tds PO for 7 days If severe: Acyclovir 5mg/kg tds IV, then switch to oral. Famcyclovir 500 mg tds Acute pain: ibuprofen or indomethacin Pain: amitriptyline start at 10mg/day and increase over a month to 75mg/day if necessary. Add carbamazepine 200mg bd if amitriptyline at max dosage.
Herpes simplex Labial or genital	Drug of choice Acyclovir 400 mg tds 7-10 days. If severe: acyclovir 5mg/kg tds IV, then switch to oral.
<i>Cryptosporidium parvum</i>	HAART with immune reconstitution (only proven effective therapy) Symptomatic therapy and palliative care.
<i>Isospora belli</i>	Co-trimoxazole 4 tabs bd for 2-4 weeks.
<i>Microsporidia</i>	Symptomatic therapy and albendazole. Trial of metronidazole 400mg bd for 4 weeks.
<i>Salmonella typhi</i>	Ciprofloxacin 500mg bd for 6 weeks.

**Table 2. Prophylaxis of common OIs in HIV positive patients.**

Infection	Indication	Prophylaxis	Drug dosages for adults	Duration
<b>M. tuberculosis</b>	PPD > 5mm Tuberculosis contact No active tuberculosis No TB treatment in past two years High risk dormitory conditions	Primary	Isoniazid 5mg/kg/day (max 300mg/day) plus pyridoxine 50mg/dly	6 months  2 months
M. avium complex	CD4 < 50 or previous infection	Primary Secondary	Clarithromycin 500mg bd or azithromycin 1200mg/week	Life long or till CD4 >100 on HAART
<i>Pneumocystis jiroveci</i> pneumonia (PCP)	CD4 < 200 Previous PCP infection	Primary Secondary	Co-trimoxazole 960mg or 480mg/day Alternative: Dapsone 100mg	Life long or till CD4 >200 on HAART
Cerebral toxoplasmosis	CD4 < 100 & positive IgG serology	Primary Secondary	Co-trimoxazole 960mg or 480mg/day	Life long or till CD4 >200 on HAART
Cryptococcal meningitis	Previous cryptococcus meningitis	Secondary	Fluconazole 200mg/day	Life long or till CD4 >200 on HAART

**Table 3. Vaccines used in HIV disease.**

Disease	Indication	Vaccine
Influenza	All patients, but poor response with CD4 <200	Influenza vaccine 0.5ml IMI yearly
Hepatitis B	Negative anti-HBc or anti-HBs serology	Hepatitis B vaccine 3 injections of 1mL IM

**Table 4. Tuberculosis Control Programme, Drug Regimens 2003**

R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol

**Regimen 1 (Newcases, age above 8 years and adults)**

New smear-positive patients, new smear-negative patients and extra-pulmonary TB.

Pretreatment body weight	Two months initial phase given FIVE times a week	Four months continuation phase			
		When given FIVE times a week		When given THREE times a week	
	RHZE (150,75,00,275)	RH (150,75)	RH (300,150)	RH (150,150)	RH (300,150)
30-37 kg	2 tabs	2 tabs		2 tabs	
38-54 kg	3 tabs	3 tabs		3 tabs	
55-70 kg	4 tabs		2 tabs		3 tabs
≥ 71 kg	5 tabs		2 tabs		3 tabs

**Table 2. Retreatment cases**

Previously treated TB patients after cure, after completion, interruption and failure.

Pretreatment body weight	Two months initial phase treatment given FIVE times a week		3 <sup>rd</sup> month initial phase	Five months continuation phase when given FIVE times a week			
	RHZE (150,75,400,275)	Streptomycin (g)		RH (150,75)	E (400)	RH (300,150)	R (400)
30-37 kg	2 tabs	0,5	2 tabs	2 tabs	2 tabs		
38-54 kg	3 tabs	0,75	3 tabs	3 tabs	2 tabs		
55-70 kg	4 tabs	1,0	4 tabs			2 tabs	3 tabs
≥ 71 kg	5 tabs	1,0	5 tabs			2 tabs	3 tabs

Pretreatment body weight	Two months initial phase treatment given FIVE times a week		3 <sup>rd</sup> month initial phase	Five months continuation phase when given THREE times a week			
	RHZE (150,75,400,275)	Streptomycin (g)		RH (150,150)	E (400)	RH (300,150)	R (400)
30-37 kg	2 tabs	0.5	2 tabs	2 tabs	2 tabs		
38-54 kg	3 tabs	0.75	3 tabs	3 tabs	3 tabs		
55-70 kg	4 tabs	1.0	4 tabs			3 tabs	4 tabs
71 kg	5 tabs	1.0	5 tabs			3 tabs	4 tabs

Fixed dose combination tablets available for adults	Recommended dose range in mg/kg	5 times/week	3 times/week
RHZE (150,75,400,275mg)	Isoniazid	4-6 (5)	8-12 (10)
RH (150,75mg)	Rifampicin	8-12 (10)	8-12 (10)
RH (150,75mg)	Pyrazinamide	20-30 (25)	30-40 (35)
RH (150,150mg)	Streptomycin	12-18 (15)	12-18 (15)
	Ethambutol	15-20 (15)	25-35 (30)

**Regimen 3 (children with tuberculosis – up to the age of 8 years)**

Pretreatment body weight	2 months initial phase treatment given FIVE times/week	4 months continuation phase	
		Given 5 times/week	Given 3 times/week
	<b>RHZ (60,30,150)</b>	<b>RH (60,30)</b>	<b>RH (60,60)</b>
3-4 kg	½ tab	½ tab	½ tab
5-7 kg	1 tab	1 tab	1 tab
8-9 kg	1½ tabs	1½ tabs	1½ tabs
10-14 kg	2 tabs	2 tabs	2 tabs
15-19 kg	3 tabs	3 tabs	3 tabs
20-24 kg	4 tabs	4 tabs	4 tabs
25-29 kg	5 tabs	5 tabs	5 tabs
30-35 kg	6 tabs	6 tabs	6 tabs

Fixed dose combination tablets for children RHZ (60,30,150 mg), RH (60,30 mg), RH (60,60 mg)

## 21. FURTHER READING

- Wilson D, Naidoo S, et al. (Eds), *Handbook of HIV Medicine*. Oxford University Press, New York. 2002. 181.
- Clinical Guideline. The prevention and treatment of opportunistic infections in HIV-infected adults. *Southern African Journal of HIV Medicine* 2002;**1**:17-20.
- Southern African HIV Clinicians Society Guidelines for Tuberculosis Preventive Therapy in HIV infection. *SAMJ* 2000;**90**:59-64.
- The 2002 UPSHDS/IDSA Guidelines for the Prevention of opportunistic Infections in Persons with Human Immunodeficiency Virus. *MMWR* 2002;**51**[RR-8:1].
- Brittain D. Management of cancer in patients with HIV. *Southern African Journal of HIV Medicine* 2002;**1**:24-28.
- HIV Clinicians Society of Southern Africa. Guidelines for tuberculosis preventive therapy in HIV infection. *S Afr Med J* 2000;**90**:592-594.
- Ferraz V. Editorial. Diagnosing opportunistic infections in patients with AIDS. *South Afr J Epidemiol Infect* 1998;**13**:102-103.