The management of opportunistic infections and cancer in HIV disease

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Highlights

- The diagnosis and treatment of common opportunistic infections influencing quality of life in HIV disease.
- The diagnosis and treatment of some life-threatening opportunistic infections in HIV disease.
- The management of the side effects of some of the drugs used.

Introduction

The diagnosis and treatment of intercurrent illnesses is the first concern in the medical management of the Human Immunodeficiency Virus (HIV). Thereafter the need for prophylactic therapy needs to be assessed. The latter is dealt with in the next issue.

Only the opportunistic infections (OIs) seen most commonly will be dealt with. The medication dosages and expected response times are summarised in **Table I**. Only drugs available in South Africa, are suggested. Some of the OIs decrease quality of life, without being life-threatening, while others are immediately life-threatening. All should be treated as quickly and effectively as possible. Treatment with highly active antiretrovirals (HAART) is the best method to prevent OIs in persons with immune suppression due to HIV.

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. [1,2]

Oral candidiasis is a useful marker for immune deterioration and is a predictor of full-blown Acquired Immunodeficiency Syndrome (AIDS) in adults.[3] 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. Thereafter follows a burning sensation, pain and later difficulty in eating. Oral and oesophageal candidiasis is not life threatening, but can be severely debilitating. The clinical classification of oral candidiasis appears in **Table II** and the diagnosis is made on clinical appearance (**Figure 1a-c**).

Special investigations

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

Treatment

Topical treatment, and *not* systemic,

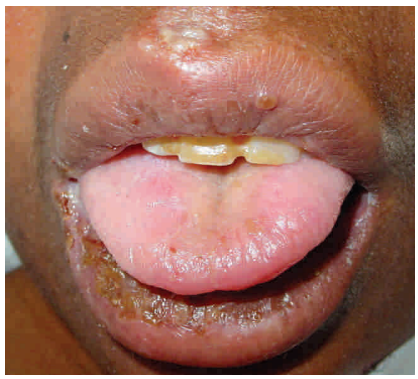

Figure 1a: Erythrematous oral candidiasis.

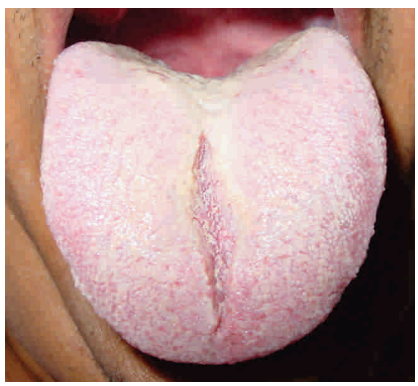

Figure 1b: Pseudomembranous oral candidiasis

is the route of choice.[4] Since the drugs work topically, the target is to allow adequate contact time between the drug and the mucous

Table I: Common opportunistic infections: their treatment and response to therapy.

Disease	Treatment	Response
Candida Oral (thrush)	Drugs of choice: Nystatin 1ml gargled 5x/day Miconazole gel (pea size) applied 5x/day Amphotericin B lozenges Alternative for severe/persistent infection Fluconazole 100 mg/day Itraconaczole 100 mg/day	Most respond within 5 days Symptoms resolve within 10-14 days Generally relapses in 3/12
Oesophagal	Drugs of choice: Fluconozole 200 mg/day for 14-21 days Itraconoczole 200 mg/day Resistant infection: Amphotericin B 0.3-0.6 mg/kg IV for 10-14 days	Most within 5-7 days If no response do endoscopy to establish diagnosis Many relapse unless therapy with HAART is initiated
Pneumocystis jiroveci Pneumonia	Drug of choice: Co-trimoxazole 1 tab for every 4kg body weight/day, divided in 3-4 doses for 21 day (ex. 4 tabs qid) Prednisone 40 mg bd 5 days, 40 mg daily for 5 days, then 20 mg/day till completion of treatment. Alternative options: Trimethopim 300mg/day *plus* dapsone 100mg/day Clindamycin 450-600mg/day *plus* primaquine 15mg/day	Slow: usually 5-7 days In 20% of cases no response with in-hospital mortality
Toxoplasma gondii	Drug of choice: Co-trimoxazole 1 tab for every 8kg of body weight/day divided into 2 doses for 4 weeks, followed by half the dose for another 8 weeks (ex. 2 tabs bd for 4 weeks, then 2 tabs bd for 8 weeks). Alternative options: Pyrimethamine 50mg/day plus Clindamycin 600mg tds	Clinical improvement within 1 week (60-80%), MRI imrovement within 2 weeks
Cyptococcus Neoformans Meningitis	Drug of choice: Amphotericin-B 0.7 mg/kg/day IV for 10-14 days Then fluconozole 800 mg/day for 8 weeks Daily CSF taps to decrease pressures	Poor: 40% in hospital death (state) Relapse is inevitable without prophylaxis or immune reconsititution
Cytomegalovirus Retinitis	Drug of choice: Intraocular ganciclovir every 6 months. Alternative options: Ganciclovir IV Foscarnet IV	Vision loss is irreversible. Poor, most relapse, requiring 6 monthly replacement of implants in the absence of immune reconsititution.
Oesophagal Colitis Pneumonitis	Drug of choice: Ganciclovir 5 mg/kg IV q12 hrly for 14- 21 days Alternative: Foscarnet 60 mg/kg q8hrly IV 14-21 days	Oesophagitis: responds well. Colitis: poor response with high mortality rate. Pneumonitis: > 60% of patients responds to therapy
Neurological	Drug of choice: Ganciclovir 5 mg/kg IV q12 hrly for 3-6 weeks Alternative: Foscarnet 90 mg/kg q12hrly IV 3-6 weeks	Encephalitis: median survival with therapy 3 months. Radiculopathy improves in 2-3 weeks.
Mycobacterium Tuberculosis Pulmonary	Standard national treatment regimen Drugs of choice: INH/rifampicin/PZA/ethambutol for induction x 8 weeks INH/rifampicin maintenance x18 weeks	Fever usually abates within 1-2 weeks. Sputa usually become culture negative within 2 months.
Extrapulmonary	Miliary, bone and meningeal TB should be treated for 9-12 months. Do not initiate HAART and antituberculous therapy together.	Be aware of the immune reconstitution inflammatory syndrome.
Mycobacterium avium complex	Drugs of choice: Clarithromycin 500 mg bd *plus* ethambutol 15 mg/kg/day Severe: Add rifabutin to above regimen. Alternative options: Azithromycin instead of Clarithromycin. Ciprofloxacin 500-750 mg bd and Amikacin. Treatment is for 18 months at least.	Prognosis is poor and response is slow: 2-4 weeks. Mortality at 6 months is 60%.
Herpes Zoster Dermatomal	Drugs of choice: Acyclovir 30 mg/kg/ day IV 7-10 days Famcyclovir 500 mg tds Pain: tricyclics, carbamazepine, antiinflammatories	Good, provided that treatment is started early. Postherpetic pain may continue months.
Disseminated	Drug of choice: Acycolvir 30-36 mg/kg/ day IV 7-10 days Foscarnet 40 mg/kg q8hrly IV	
Chickenpox	Drug of choice: Aycolvir 10 mg/kg q8hrly IV or 800 mg qid	
Herpes Simplex Labialis	Drug of choice: Acyclovir 400 mg tds 7-10 days. If severe acyclovir 5-10 mg/kg q8hrly IV	Good, provided that treatment is started early (within 24 hours of onset).
Genital	Drug of choice: Acyclovir 5-10 mg/kg q8hrly IV 2-7 days, then complete 10 day course with oral acyclovir	
Pneumonitis Oesophagitis Disseminated Encephalitis	Drug of choice: Acyclovir 5-10 mg/kg q8hrly IV for 14-21 days	
Chronic infective diarrhoea *Cryptosporidium parvum*	HAART with immune reconstitution (only proven effective therapy) Symptomatic therapy and palliative care.	Poor, high mortality. Usually resolves spontaneously if CD4 > 100
Isospora belli	Drug of choice: Co-trimoxazole 4 tabs bd for2-4 weeks	Responds usually within several days
Microsporidia	Drug of choice: Symptomatic therapy and albendazole. Trial of metronidazole	Response in 4 weeks
Salmonella typhi	Drug of choice: Ciprofloxacin 500mg bd for 6 weeks.	Quick response

Table II: The clinical classification of oral Candidiasis

Type	Physical appearance
Erythrematous	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

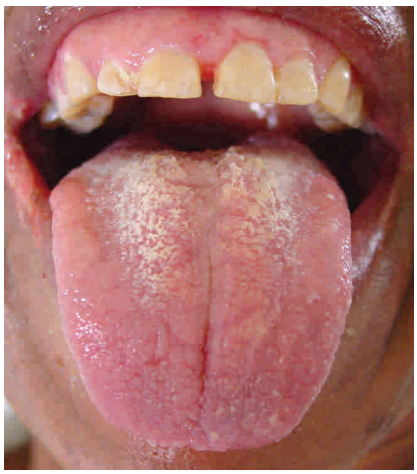

Figure 1c: Hyperplastic oral candidiasis

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 (eg. miconazole gel). The drugs can be unpalatable. Systemic antifungal therapy is reserved for non-responsive cases and maintenance therapy should be avoided. Chlorhexidine gluconate 0.2% mouthwash can be used as a prophylactic agent in cases of recurrent candidiasis.

ORAL HAIRY LEUKOPLAKIA

Clinical presentation

Hairy leukoplakia predicts a rapid progression from HIV to AIDS.[5] It occurs on the lateral borders of the tongue and is a white keratotic lesion that cannot by 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 improve when the patient starts HAART.

HIV-ASSOCIATED PERIODONTAL DISEASE

Clinical presentation

Periodontitis and gingivitis are observed in all stages of HIV.[6] Acute necrotising ulcerative gingivitis (ANUG) is a severe form of gingivitis. The patient usually complains of painful or bleeding gums.

Treatment

For acute cases amoxicillin and metronidazole may be used for 5 days. Chlorhexidine gluconate 0.2% mouthwash is also indicated for long-term use. Oral hygiene is important. Cleaning and scaling of teeth should also be done to remove plaque and calculus.[7]

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 clinical features. In most cases the patient also has oral candidiasis. The CD4 count is usually less than 100 cells/L. Endoscopy is only indicated for an atypical presentation or treatment failure.

The differential diagnoses of dysphagia in HIV include:

- 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 be administered in the first few days of treatment. Although relapses are common, prophylactic therapy is not indicated, since it may lead to resistance.

PNEUMOCYSTIS JEROVECI PNEUMONIA (PCP)

Clinical presentation

This organism was previously known as *Pneumocystis carinii*. 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/L.[8]

Special investigations

In early cases, up to 20% of chest x-rays can be normal. The classical chest X-ray **(Figure 2)** shows a symmetrical perihilar interstitial infiltrate. It is also be described as "ground glass". The differential diagnosis of a diffuse reticulonodular infiltrate is listed in **Table III**.

The arterial blood gasses 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.

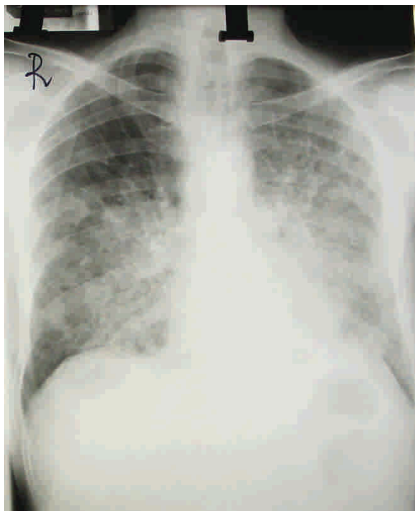

Figure 2: Interstitial infiltrate of *Pneumocystis jeroveci* pneumonia

Table III: The differential diagnosis of a diffuse reticulonodular infiltrate on chest X-ray in an HIV positive patient.

Pneumocystis jeroveci
Miliary tuberculosis
Lymphocytic interstitial pneumonia
Kaposi's sarcoma
Sarcoidosis
Toxoplasma gondii
Cytomegalovirus

Treatment

The treatment choice is high dose co-trimoxazole for three 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.[8]

In patients allergic to co-trimoxazole, dapsone in combination with trimethoprim may be used, or clindamycin in combination with primaquine. Life-long co-trimoxazole prophylaxis must be instituted after the treatment of the acute infection. The prophylaxis may be stopped if the CD count rises above 200 cells/L in a patient on HAART.

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 with a suppressed consciousness. Toxoplasmosis is usually associated with a CD4 count below 100 cells/L.

The differential diagnoses of this clinical picture include:[9]

- Lymphoma
- Tuberculoma
- Cryptococcoma

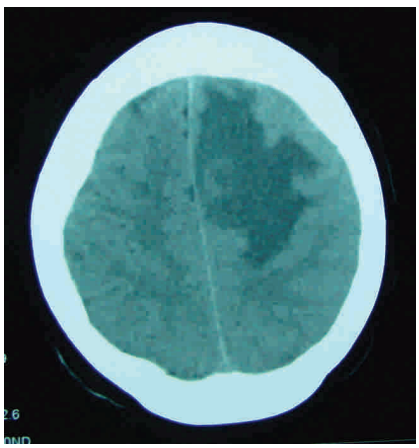

Figure 3a: Mass lesion of *Toxoplasma* on brain scan.

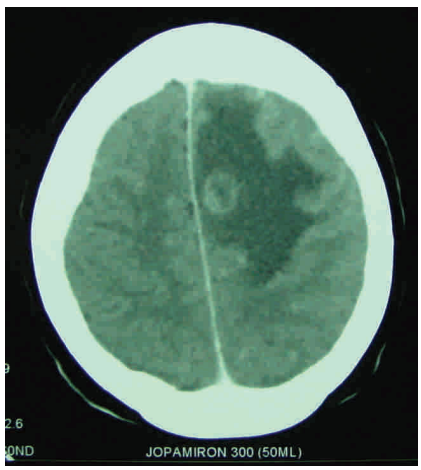

Figure 3b: Mass lesion enhances with contrast.

Special investigations

A brain scan **(Figure 3a,b)** 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.

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

Treatment

The active infection is 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 then monitored clinically.

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

CRYPTOCOCCAL 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 papil oedema. The patient may also be vomiting.

Special examination

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

Sensitivity of the different tests are 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.[10] Thereafter fluconazole is given for 8 weeks at a high dosage. In mild cases of Cryptococcus meningitis, an earlier switch can be made to fluconazole.

Adverse effects to IV administration can be alleviated by a one-day lead in dose of Amphotericin-B, 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 each time) may be necessary to relieve the raised intracranial pressure.

After completion of treatment for the acute infection , the patient should continue prophylactic fluconazole at a lower dosage . This continues lifelong or until the CD4 count increases to above 100 cells/L on HAART.[11]

CYTOMEGALOVIRUS (CMV)

Clinical presentation

CMV may present as retinitis, encephalitis, pneumonitis or colitis in patients with CD4 count below 50 cells/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 resultant blindness . Intravitreal ganciclovir is the drug of choice. The aim of treatment would be to protect the vision; 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.

MYCOBACTERIUM TUBERCULOSIS (TB)

Clinical presentation

Pulmonary tuberculosis (PTB) may present in patients with well preserved to very low CD4 counts and is the most common presentation of *M. tuberculosis* disease. The presentation is more typical in patients with well preserved CD4 counts, while in patients with very low CD4 counts 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, followed by 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 asymetrically enlarged, matted and painful.

Special investigations

Chest x-ray can be suggestive of TB, but the diagnosis still needs to be confirmed. PTB may present on chest X-ray as typical upper lobe cavities, patchy infiltrates, a miliary picture **(Figure 4)** or as a normal chest X-ray. The X-ray picture is dependent on the level of immune function present in the host. With TB pericarditis, cardiomegaly is present on chest x-ray **(Figure 5)**.

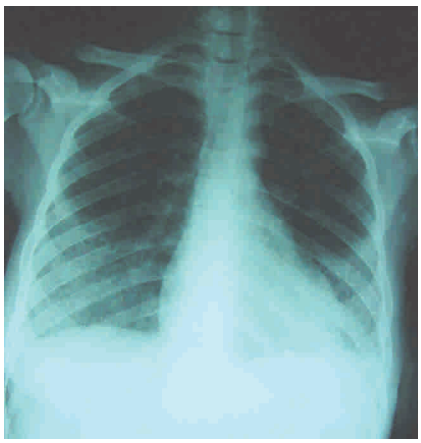

Figure 4: Miliary tuberculosis.

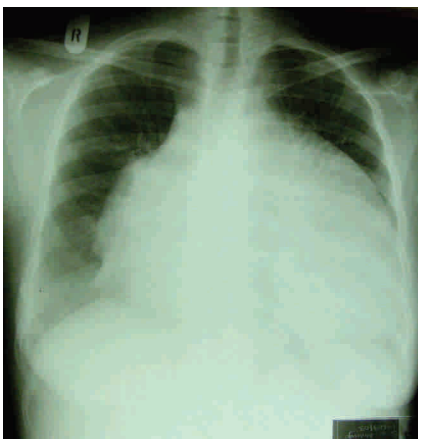

Figure 5: Massive TB pericardial effusion.

Diagnosis

Diagnosis is made on sputa, nasogastric aspirations or bronchoscopy with alveolar lavage. In miliary TB, sputum can be positive in 25% of cases. Staining for acid fast bacilli (AFB) should be done on sputum or

a lymph node aspirate. PCR for *M. tuberculosis* can yield quick results, but is 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 pulmonary TB is the standard short course of 6 months and 9 months for extrapulmonary TB. The intensive phase of treatment consists of isoniazid, pyrazinamide, rifampicin and ethambutol, usually as a combination pill. In the maintenance (continuation) phase isoniazid and rifampicin are used. Direct observed treatment (DOTs) is strongly recommended and offers the patient the best chance of treatment success.

Pyridoxine should be added to avoid treatment-induced peripheral neuropathy.

MYCOBACTERIUM AVIUM COMPLEX (MAC) INFECTION

Clinical presentation

Disseminated *M. avium* disease is usually a very late opportunistic infection with CD4 count of less than 50 cells/mm^3. The symptoms (severe fatigue, chronic malaise, weight loss and diffuse abdominal pain) are nonspecific. The clinical impression is that of "wasting". Fever may be low grade initially, but eventually goes up to above 39°C and can be accompanied by rigors. The patient may experience drenching sweats. Clinical examination of the abdomen may reveal organomegaly.[12]

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 colonisation 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 the aspirate or tissue.

Treatment

Combination therapy is used with a macrolide as backbone. The preferred first drug of choice 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 problematic, or hepatitis develops, intravenous amikacin may be used. Ciprofloxacin is considered 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/mm^3 for more than 3-6 months and bone marrow and blood cultures are negative.[13]

HERPES ZOSTER

Clinical picture

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

Treatment

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

The pain itself can be managed with a nonsteroidal inflammatory for a week, as well as amytriptiline or carbamasepine for a longer period (month or longer).

HERPES SIMPLEX

Clinical picture

Herpes simplex causes mucocutaneous ulceration of the mouth **(Figure 6)**, 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 or famcyclovir should be used for 7 days. Treatment may continue for 14 days if the response after 7 days is not 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.

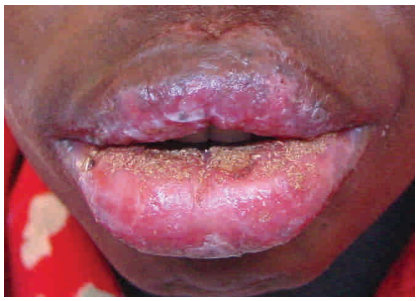

Figure 6: Herpes simplex.

CHRONIC DIARRHOEA

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.[14]

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. Antimotility drugs may be 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.

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. **Figure 7** demonstrated Kaposi's sarcoma of the gums. 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/L. Infiltration beyond the skin, as well as a low CD4 count, would constitute poor prognostic features.

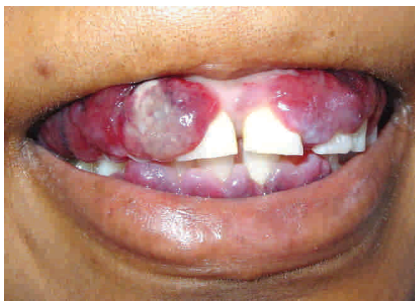

Figure 7: Kaposi's sarcoma.

Diagnosis

A biopsy of the tissue is required for histology.

Treatment

The patient should be commenced on antiretrovirals, irrespective of the CD4 count. Local radiotherapy often gives excellent results.[14] Chemotherapy should be considered in combination with antiretrovirals if there be no response on antiretrovirals and bad prognostic features are present.

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 (eg. fever or malaise) or central nervous system abnormalities (eg. confusion or localizing signs).

Diagnosis

Excision biopsy of a suspected lymph node. Aspiration of a lymph node cannot confirm the diagnosis. Stereotatic brain biopsy should only be undertaken if treatment can be offered to the patient.

Treatment

Histologically, NHL is usually a high-grade lesion and they require intensive chemotherapy regimen. 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.[14]

CPD Questionnaire p.45

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