WHO MODEL PRESCRIBING INFORMATION

DRUGS USED IN HIV-RELATED INFECTIONS

WORLD HEALTH ORGANIZATION, GENEVA
WHO Model Prescribing Information

Drugs used in HIV-related infections

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WHO’s revised drug strategy, as adopted in resolution WHA39.27 of the Thirty-ninth World Health Assembly in 1986, calls for the preparation of model prescribing information, which is being developed to complement WHO’s Model List of Essential Drugs. The objective is to provide source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, drug compendia and similar material.

The information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug that is appropriate to circumstances prevailing in each of WHO’s Member States and that some countries have already formally adopted texts of their own that have a statutory connotation.

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Infectious diseases constitute the immediate cause of death in up to 90% of patients with advanced HIV. Some are caused by common pathogens, but many are opportunistic, meaning that they are caused by microbes which usually do not cause disease in the immunocompetent host. Knowledge of these is incomplete and new forms of opportunistic infections attributed to previously unrecognized and uncharacterized microbes are still being discovered.

The incidence and spectrum of these infections differ in important respects from those associated with other immunosuppressive disorders. Whereas all immunocompromised patients are vulnerable to Toxoplasma encephalitis, oral candidiasis and pulmonary tuberculosis, many opportunistic diseases including *Pneumocystis carinii* pneumonia (PCP), and systemic infections due to Cryptococcus neoformans, cytomegalovirus (CMV), the Mycobacterium avium complex and Cryptosporidium species have occurred more frequently in people infected with HIV.

The pattern of infection varies between different socio-ecological settings. In some African countries as many as 50% of patients with advanced HIV disease will develop tuberculosis. In contrast, *Pneumocystis carinii* pneumonia is less frequent in these countries. This may be because many patients die before their immune defences are severely attenuated or because of under-reporting. In the immunocompromised patient infections often present atypically; disseminated disease is common and two or more infections may occur concurrently. The systems commonly involved in manifestations of the opportunistic infections are given below

**Other infections** such as those due to *M. tuberculosis*, *Shigella*, and *Salmonella* species occur in people with normal immunity and are not classified as “opportunistic infections”. They are, however, included as they occur with increased frequency in people with HIV.
<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Potential Opportunistic Organism or Disease</th>
</tr>
</thead>
</table>
| **Lung**       | Bacterial infection: *Streptococcus pneumoniae*, and other common bacteria.  
                 Mycobacterial infection: *M. tuberculosis*, *M. avium-intracellulare* and other mycobacterial species.  
                 Fungal infection: *Pneumocystis carinii* pneumonia *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Aspergillus* species, *Penicillium marneffii*.  
                 Viral infection: Cytomegalovirus.  
| **Central nervous system** | Protozoal infection: *Toxoplasma gondii*  
                             Mycobacterial infection: *M. tuberculosis*  
                             Fungal infection: *Cryptococcus neoformans*, *Candida* species.  
                             Viral infection: Cytomegalovirus, herpes simplex virus, varicella zoster virus, JC virus (progressive multifocal leukoencephalopathy)  
                             Non-infectious disorders: Primary CNS lymphoma, Kaposi’s sarcoma. |
| **Eye**        | Protozoal infection: *Toxoplasma gondii*  
                 Fungal infection: *Candida* species  
                 Viral infection: Cytomegalovirus, varicella zoster virus  
                 Non-infectious disorders: Primary CNS lymphoma, Kaposi’s sarcoma. |
| **Gastro-intestinal Tract** | Bacterial infection: *Shigella*, and *Salmonella* species.  
                              Mycobacterial infection: *M. avium* complex  
                              Fungal infection: *Candida* species  
                              Viral infection: Cytomegalovirus, herpes simplex virus.  
                              Non-infectious disorders: Kaposi’s sarcoma, lymphoma. |
| **Skin and Mucus membranes** | Bacterial infection: *Staphylococcus aureus*, *Streptococcal* species  
                                  Mycobacterial disease: *M. tuberculosis*  
                                  Fungal infection: oral and oesophageal candidiasis, penicillinosis, *Cryptococcus neoformans*, *Histoplasma capsulatum*  
                                  Viral infection: Herpes simplex and zoster virus, cytomegalovirus  
                                  Non-infectious disorders: Kaposi’s sarcoma, drug-induced eruptions, infestations: Scabies |
From the early stage of HIV infection, patients are particularly vulnerable to common pathogens of the respiratory tract. As the immune system continues to deteriorate, they become increasingly susceptible to tuberculosis, non-specific mycobacterial infections, and systemic mycoses. Pneumonia due to *Pneumocystis carinii* is relatively common, in industrialized countries. Pulmonary tuberculosis is particularly common in developing countries.

**Bacterial infection:** *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus*

**Mycobacterial infection:** *M. tuberculosis, M. avium-intracellulare, M. kansasii, M. xenopi.*

**Fungal infection:** *Pneumocystis carinii pneumonia Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Aspergillus species Penicillium marneffii.*

**Viral infection:** Cytomegalovirus.

**Non-infectious disorders:** Non-Hodgkin’s lymphoma, Kaposi’s sarcoma, lymphoid interstitial pneumonitis, non-specific interstitial pneumonitis.

### Summary of main respiratory infections

<table>
<thead>
<tr>
<th></th>
<th>Symptoms &amp; signs</th>
<th>Laboratory investigations</th>
<th>Radiological changes</th>
<th>1st line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial pneumonia</strong></td>
<td>fever</td>
<td>leucocytosis</td>
<td>consolidation (may be lobar)</td>
<td>amoxicillin or according to national guidelines &amp; local sensitivities</td>
</tr>
<tr>
<td></td>
<td>cough</td>
<td>blood cultures may be positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dyspnoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>respiratory rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCP</strong></td>
<td></td>
<td>haemo-gas analysis:</td>
<td>peri-hilar</td>
<td>high dose SMZ/TMP 2–3 weeks then continual maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypoxia</td>
<td>shadowing (ground glass haze)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>bronchial lavage</td>
<td>interstitial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(if available)</td>
<td>infiltrates</td>
<td></td>
</tr>
<tr>
<td><strong>Tuberculosis</strong></td>
<td></td>
<td>sputum examination for AFBs</td>
<td>upper lobe</td>
<td>according to national TB guidelines or 2RHEZ/4RH* (for new cases, recurrences require longer and more aggressive treatment**)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lymph node</td>
<td>consolidation +/-cavities</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>aspiration for AFBs</td>
<td>mediastinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>culture, where possible</td>
<td>lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pleural effusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Xray often atypical)</td>
<td></td>
</tr>
</tbody>
</table>

*Rifampicin and isoniazid for 6 months supplemented in the first 2 months by pyrazinamide and ethambutol

**Treatment is based on a five drug regime
Pneumonia due to *Pneumocystis carinii* (PCP)

The frequency of PCP varies world-wide, ranging from 64% in the US to <5% in reports from some areas in Africa, although some African studies suggest higher rates. The reason for this variability is uncertain, but may in part be due to under-reporting and under-diagnosis in developing countries or perhaps geographic variability. The most typical presenting symptoms of PCP in HIV-positive patients are a non-productive cough, dyspnoea on exertion and fever. The onset of illness is often subtle and many of these symptoms can develop slowly over a number of weeks. Chest X-rays may reveal extensive interstitial infiltration, a mild peri-hilar haze or may be normal. Whenever practicable, attempts should be made to identify the organism using induced sputum or broncho-alveolar washings. Mortality has been reduced significantly due to early recognition of disease, use of the most effective drug regimes and the inclusion of primary and secondary prophylaxis.

**Treatment of PCP**

Sulfamethoxazole (SMZ)/ trimethoprim (TMP) has been shown to be the best regimen for both the treatment and prevention of PCP.

<table>
<thead>
<tr>
<th>1st choice</th>
<th>2nd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>sulfamethoxazole/ trimethoprim oral or sulfamethoxazole/ trimethoprim IV</td>
<td>clindamycin IV/oral and primaquine oral or dapsone (oral) and trimethoprim (IV/oral)</td>
</tr>
</tbody>
</table>

| dose | SMZ 75 mg/kg |
|      | TMP 15 mg/kg |
|      | divided doses daily for 2–3 weeks |

| dose | 600 mg 4 x day |
|      | 15 mg OD |
|      | 100 mg OD |
|      | 20 mg/kg OD (divided doses) daily for 2–3 weeks |

If the patient is unable to tolerate these regimens, pentamidine given intravenously can be used.

Signs of improvement may not be evident for 4–8 days, and treatment should be maintained for 2–3 weeks. For mild to moderate disease oral drugs can be used throughout the treatment (2 week course); in severe disease, treatment is normally administered intravenously during the first 7–10 days (total 3 weeks course). However, if the patient is receiving second line treatment, components that are not available in the intravenous formulation are administered orally.
When no improvement is evident after 7–10 days, clinicians often resort to switching to one of the other regimens. The severe toxicity of pentamidine compared to the other regimens has limited its use. This drug is now used only as a last resort. If switching to pentamidine is being considered, an overlap of two to three days should occur to allow pentamidine to accumulate in the body.

The first few days of antimicrobial treatment are critical since the decomposition of many dead parasites exacerbates the pre-existing inflammatory process and aggravates hypoxia. However, the risk of death at this stage can be substantially reduced especially in patients whose arterial oxygen tension (pO₂) is less than 70 mmHg (9.33kPa) if a corticosteroid - oral prednisolone or, when necessary intravenous methylprednisolone - is administered as soon as antimicrobial therapy is started. Prednisolone given orally at a dose of 40 mg twice daily for 5 days, followed by 40 mg daily for 5 days, and then 20 mg daily for 10 days is a regimen that has been used. It has not demonstrably increased the vulnerability of patients to other opportunistic infections, with the possible exception of candidiasis, herpes virus disease and cytomegalovirus disease.

**Prophylaxis**

In industrialised countries, every patient who has a CD4+ lymphocyte count of less than 200/mm³, or symptomatic disease (oral candida, fevers, weight loss etc.) or another AIDS-defining illness such as Kaposi’s sarcoma, or has been successfully treated for pneumonia due to *Pneumocystis carinii*, should receive continuous prophylaxis. Various estimates place the 3–month relapse rate among patients not receiving prophylaxis following a course of treatment for PCP at 10% – 40%; about one in five such episodes is fatal. In developing countries, where PCP is much less common, there have been no efficacy trials for the use of sulfamethoxazole/trimethoprim as PCP prophylaxis, though early results indicate it may be of benefit in reducing other HIV-associated infections.
# Prophylaxis for PCP

<table>
<thead>
<tr>
<th>1st choice</th>
<th>drug</th>
<th>dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sulfamethoxazole/trimethoprim oral</td>
<td>SMZ 800 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMP 160 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OD</td>
</tr>
<tr>
<td>2nd choice</td>
<td>dapsone oral</td>
<td>50–100 mg OD*</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dapsone oral</td>
<td>100 mg 3 x week</td>
</tr>
<tr>
<td></td>
<td>and pyrimethamine** oral</td>
<td>25 mg 3 x week</td>
</tr>
<tr>
<td>3rd choice</td>
<td>sulfadoxine/pyrimethamine (Fansidar)</td>
<td>1–2 tablets weekly</td>
</tr>
<tr>
<td>4th choice</td>
<td>pentamidine (nebulised)</td>
<td>300 mg every 2–4 weeks</td>
</tr>
</tbody>
</table>

*The higher dose should be used if the patient is taking concurrent enzyme inducers e.g. rifampicin and/or drugs which increase gastric pH e.g. antacids, didanosine (ddI)

**When pyrimethamine is used if the patient is borderline neutropenic i.e. neutrophil count <1.0 x10^9/L folinic acid 15mg orally should be given in conjunction

Sulfamethoxazole/trimethoprim has been shown to be the best form of PCP prophylaxis and also provides protection against *Toxoplasma* encephalitis; therefore, every effort should be made to ensure that where possible patients receive it. A recent trial showed that patients were more likely to tolerate sulfamethoxazole/trimethoprim if a low dose was used (800 mg/160 mg three times a week), and it was as effective as the higher doses, although a higher dose daily may be preferable if the patient has a CD4+ count less than 100/mm^3 and is *Toxoplasma gondii* antibody positive. In patients that have experienced reactions to sulfamethoxazole/trimethoprim that are not considered serious (i.e. rash, fever, or mild elevations of liver function tests), either rechallenge or desensitisation should be attempted. It has been shown that in about 50% of patients this will allow continuation of sulfamethoxazole/trimethoprim.

### Desensitisation schedule for sulfamethoxazole/trimethoprim

Sulfamethoxazole/trimethoprim has been shown to be the best agent for both the treatment and prophylaxis of PCP. It is therefore important that, where indicated, as many patients as possible receive sulfamethoxazole/trimethoprim and not other less

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3 Dapsone and pyrimethamine should be used in patients that cannot tolerate sulfamethoxazole/trimethoprim with a CD4 count less than 100/mm^3 and *Toxoplasma gondii* antibody positive.
effective medications. Desensitisation has been used as a method of increasing the number of patients able to tolerate sulfamethoxazole/trimethoprim.

**Indications:** Patients who have a documented allergy, e.g. rash or itching due to sulfamethoxazole/trimethoprim and have failed rechallenge

**Contraindications:** Patients who have had a serious reaction to sulfamethoxazole/trimethoprim e.g. Stevens-Johnsons, anaphylaxis, hepatitis or pancreatitis.

Desensitisation of sulfamethoxazole/trimethoprim carried be done over a day as an inpatient or over 10 days as an outpatient.

**In patient desensitisation of sulfamethoxazole/trimethoprim**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>dose sulfamethoxazole (TMP)/trimethoprim (SMZ)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.004/0.02mg*</td>
</tr>
<tr>
<td>1</td>
<td>0.04/0.2mg*</td>
</tr>
<tr>
<td>2</td>
<td>0.4/2mg*</td>
</tr>
<tr>
<td>3</td>
<td>4/20mg*</td>
</tr>
<tr>
<td>4</td>
<td>40/200mg*</td>
</tr>
<tr>
<td>5</td>
<td>160/800mg*</td>
</tr>
</tbody>
</table>

* Dilute a solution containing 40 mg of TMP and 200 mg of SMZ per 5 ml.

**Out patient desensitisation of sulfamethoxazole/trimethoprim**

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose of Sulfamethoxazole (mg)</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.4</td>
<td>1 ml in 20 paediatric suspension</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
<td>2 ml in 20 paediatric suspension</td>
</tr>
<tr>
<td>3</td>
<td>9.6</td>
<td>4 ml in 20 paediatric suspension</td>
</tr>
<tr>
<td>4</td>
<td>19.2</td>
<td>8 ml in 20 paediatric suspension</td>
</tr>
<tr>
<td>5</td>
<td>28.8</td>
<td>0.6 ml paediatric suspension</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>1.25 ml paediatric suspension</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>2.5 ml paediatric suspension</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
<td>5 ml paediatric suspension</td>
</tr>
<tr>
<td>9</td>
<td>480</td>
<td>10 ml paediatric suspension</td>
</tr>
<tr>
<td>10</td>
<td>480</td>
<td>One 480 mg tablet or half a 960 mg tablet</td>
</tr>
<tr>
<td>11</td>
<td>960</td>
<td>One 480 mg tablet or half a 960 mg tablet twice a day</td>
</tr>
</tbody>
</table>

Then continue with the regimen or *Pneumocystis carinii* pneumonia prophylaxis. If the regimen, to be used is sulfamethoxazole/trimethoprim (cotrimoxazole) 480 mg daily, stop at day 10 and continue at this dose.
If sulfamethoxazole/trimethoprim cannot be continued due to intolerance or severe side effects dapsone may be given although a small percentage of patients may show cross intolerance.

Nebulized pentamidine at the dosage of 300 mg every two weeks should be used in patients with a CD4+ count less than 100/mm³ if systemic therapy cannot be tolerated. Sulfadoxine/pyrimethamine (Fansidar), one tablet given once or twice a week, is useful in patients in whom compliance is considered to be a problem. However, it has been associated with hepatotoxicity, Stevens–Johnson syndrome and toxic epidermal necrolysis.

**Pulmonary tuberculosis**

Tuberculosis is the commonest cause of death in people with HIV infection world-wide. There are indications of a resurgence of tuberculosis almost everywhere where HIV is prevalent. HIV infection increases a person’s susceptibility to infection with *M. tuberculosis* and is the most potent factor known to increase the risk of progression from *M. tuberculosis* infection to disease. In an individual infected with HIV the presence of other infections including TB allows HIV to multiply more quickly. This may result in more rapid progression of HIV infection.

The initial signs of disease may become apparent at any time during the evolution of HIV infection. In HIV-infected patients TB may be pulmonary or extra-pulmonary. Pulmonary TB is still the most common form of TB. The presentation depends on the degree of immunosuppression. In advanced HIV disease the immune system is less able to prevent the growth and local spread of *M tuberculosis*; Thus, disseminated and extrapulmonary disease is more common, and unilateral or bilateral infiltrates in the lower lobes are seen more often than upper lobe lesions and cavities. The commonest forms of extrapulmonary disease are lymphadenitis, pleural effusion, pericarditis, miliary disease and meningitis.

The essential elements of tuberculosis control are the same in populations where HIV is common and where it is rare. The objectives are to decrease morbidity, mortality, and transmission of tuberculosis, while avoiding the emergence of drug resistance. One of the essential elements of the WHO strategy is to provide short course chemotherapy under direct observation to at least all identified smear positive cases. The central strategy recommended by WHO is one of the most cost-effective of all health interventions.

Treatment regimens have an initial (intensive) phase and a continuation phase. The initial phase lasts for 2 months and utilises three or four drugs. During this phase there

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3 For further information in the treatment of TB in patients with HIV infection see
is rapid killing of TB bacilli, infectious patients become non-infectious within about two weeks and symptoms improve. The vast majority of patients with smear-positive TB become sputum smear negative within 2 months. Directly observed therapy is recommended in the initial phase to ensure that the patient takes every single prescribed dose. This protects against the development of drug resistance. The risk of drug resistance is higher during the early stages of anti-TB drug treatment when the number of TB bacilli is very high.

The continuation phase lasts for four to six months depending on the combination of medications used\textsuperscript{2}. During this phase the drugs eliminate the remaining TB bacilli. Killing the persistent bacilli prevents relapse after completion of therapy.

There is little evidence, as yet, of atypical patterns of antibiotic resistance in \textit{M. tuberculosis} isolates from patients with HIV. However, reports from the USA describe clusters in which isolates shared multi-drug resistance. This is the result of the spread of TB infection with rapid progression of disease in this population. The limited data on treatment failure in TB/HIV dually infected patients and relapse rates following antituberculosis therapy are comparable to those prevailing in the population at large. Mortality is, however, considerably higher in HIV seropositive than HIV seronegative TB patients. Furthermore, the incidence of adverse reactions may be substantially higher in TB patients with HIV infection. In particular, thiacetazone is associated with a high risk of severe, and sometimes fatal, skin reactions in HIV-infected individuals.

\textbf{TB preventive therapy}

There is evidence showing the efficacy of TB preventive therapy among HIV-infected people. TB preventive therapy can be given to people with HIV who have been screened to exclude active TB and who are PPD positive. Isoniazid is the recommended drug. A dose of 5 mg/kg (maximum 300 mg) may be given daily as self administered therapy for 6 months\textsuperscript{4}.

\textbf{Histoplasmosis and coccidioidomycosis}

In regions where the fungi \textit{Histoplasma capsulatum} (var. \textit{capsulatum} and \textit{duboisii}) and \textit{Coccidioides immitis} are endemic (Histoplasmosis - Ohio and Mississippi River valleys, Puerto Rico, the Caribbean islands and Central America. Coccidioidomycosis - south-western USA and northern Mexico), patients with HIV infection are at risk of developing disseminated histoplasmosis and coccidioidomycosis. In otherwise healthy people such infections are usually subclinical, or self-limiting within the lungs.

The initial symptoms are often non-specific, but pulmonary involvement characterized by cough, fever, malaise and weight loss - and confirmed by radiological evidence of pulmonary interstitial infiltrates - can be prominent. Nausea, vomiting and diarrhoea are

common. Haematogenous dissemination ultimately results in terminal septic shock. Diagnosis is dependent upon demonstration of the organism in bronchoalveolar washings, biopsy material, or cultures from blood or bone marrow. In severely ill patients, initiation of treatment is warranted on the basis of clinical findings and a positive test for serum antibody.

**Treatment**

1st choice  Amphotericin B (0.5 mg – 1 mg/kg/day for 6 weeks)
2nd choice  Histoplasmosis - Itraconazole (200 mg 3 x day, 3–4 days, then 200 mg 2 x day) 6 weeks
           Coccidioidomycosis - Fluconazole (400 mg/day) 6 weeks

Initial treatment for histoplasmosis is amphotericin B for moderate-to-severe cases, and oral itraconazole for mild cases. Maintenance therapy is then required. Itraconazole is the preferred lifelong maintenance therapy, although amphotericin can be given weekly or biweekly. The bioavailability of itraconazole should be improved by ensuring that it is taken with food or the liquid formulation is used. Fluconazole is not as effective as itraconazole for the treatment and maintenance of histoplasmosis. Fluconazole has been used with some success for the treatment of coccidioidomycosis in patients that have been unable to tolerate amphotericin B.

**Aspergillosis**

Infections with various species of the fungus *Aspergillus* are increasingly observed in patients with late stage HIV disease, especially those that have developed neutropenia from underlying HIV infection or myelosuppressive medication. The organism is ubiquitous, being found in soil and water and enters the body through the lungs. The fungal hyphae germinate in the alveoli and invade pulmonary tissue and blood vessels, leading to tissue necrosis and dissemination. Infection has been reported in the brain, heart, liver, spleen, kidneys, pancreas, sinuses and skin.

Diagnosis is by culture and histopathology. Culture positivity alone may reflect environmental contamination; fewer than 10% of patients with positive sputum cultures may have invasive disease, although among neutropenic patients this rises to 23%.

**Treatment**

1st choice  Amphotericin B (1 mg/kg/day for 14 days)
2nd choice  Itraconazole (200 mg 3 x day for 3–4 days. Then 200 mg twice a day maintenance)

Aspergillosis responds best to treatment when it is diagnosed early and treated aggressively. Intravenous amphotericin B is generally used as induction therapy and itraconazole as maintenance or in patients unable to tolerate amphotericin. The bioavailability of itraconazole should be improved by ensuring that it is taken with food or the liquid formulation is used.
Neurological disorders

As many as 20% of HIV-infected patients develop neurological complications. Some of these result from a direct encephalitic effect of HIV, and others are due to neoplastic lesions, notably lymphomas. *Toxoplasma* encephalitis accounts for most focal lesions while cytomegalovirus and herpes simplex viruses are more rarely implicated. Life-threatening meningitis is often due to *Cryptococcus neoformans* and occasionally due to coccidioidomycosis or tuberculosis.

### Summary of CNS infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
<th>Laboratory investigations/imaging</th>
<th>1st line treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>focal neurology fever evolution over days</td>
<td>space occupying lesion on CT, possible ring enhancement (if available)</td>
<td>sulfadiazine and pyrimethamine and calcium folinate</td>
<td>75% response to treatment prophylaxis needed after treatment</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>fever headache meningeal symptoms often absent evolution over weeks</td>
<td>advanced immuno-suppression India ink or specific stain of CSF (lumbar puncture) antigen detection test (from serum or CSF)</td>
<td>amphotericin B (IV) and flucytosine (2 weeks) followed by fluconazole</td>
<td>65% response to treatment fluconazole prophylaxis needed after treatment</td>
</tr>
<tr>
<td>CMV encephalitis</td>
<td>confusion lethargy cranial nerve palsies nystagmus</td>
<td>advanced immuno-suppression</td>
<td>symptomatic or foscarnet or ganciclovir if available</td>
<td>very poor prognosis</td>
</tr>
<tr>
<td>HIV encephalopathy</td>
<td>cognitive and motor impairment</td>
<td>symptomatric or antiretrovirals with CNS penetration, if available</td>
<td></td>
<td>deterioration over months</td>
</tr>
</tbody>
</table>
Protozoal infection: *Toxoplasma gondii*
Mycobacterial infection: *Mycobacterium tuberculosis*
Fungal infection: *Cryptococcus neoformans, Candida species.*
Viral infection: Cytomegalovirus, herpes simplex virus, varicella zoster virus, JC virus (progressive multifocal leukoencephalopathy)
Non infectious disorders: Primary CNS lymphoma, Kaposi’s sarcoma, direct HIV disease

**Toxoplasmosis**

*Toxoplasma gondii*, a protozoan parasite of mammals, is transmitted when oocytes excreted by cats or present in undercooked meat are ingested. Invasive forms enter the bloodstream to reach the brain, heart and lungs, where they form cystic aggregates that remain latent, but are subject to reactivation throughout the life of the host. In many communities most people have been infected by early childhood, but otherwise healthy persons do not develop clinically evident disease. In HIV-infected patients, however, toxoplasmosis holds serious implications:

- Primary infection may result in focal necrotizing encephalitis and occasionally retinochoroiditis and pneumonitis as a result of the unrestrained multiplication of tachyzoites.

- Reactivation of latent bradyzoites produces focal neurological signs mainly in patients with a CD4+ count of less than 100/mm³. Hemiparesis, cognitive disorders, seizures and other signs suggestive of an intracerebral space occupying lesion tend to develop subacutely over several weeks, and they are sometimes accompanied by symptoms of a diffuse encephalopathy. Fever and headache can be prominent, but meningeal irritation is infrequent. Changes in the cerebrospinal fluid are usually non-specific.

- Congenital transmission of *T. gondii* can occur as a consequence of either a latent infection or a new primary infection in the mother. In many instances the parasite induces spontaneous abortion or foetal death. Children born with signs of infection are generally severely ill, often with a potentially fatal syndrome characterized by hydrocephalus, hepatosplenomegaly with jaundice, mental retardation and chorioretinitis. Congenital disease that becomes apparent only later in life is usually less severe, but ocular or neurological impairment is common.5

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Prophylaxis

The risk of transmission can be reduced if meat is adequately cooked and if vegetables and fruit are washed carefully before they are eaten.

In HIV positive patients with a CD4+ count less than 100/mm3 and T. gondii antibody positive, prophylaxis with either sulfamethoxazole/trimethoprim or dapsone and pyrimethamine at doses used for the prevention of PCP, have been shown to reduce the incidence of toxoplasmosis.

Treatment

1st choice Sulfadiazine (6–8 mg in 4 divided doses for 4–6 weeks) and pyrimethamine (200 mg first day then 75–100 mg for 6 weeks then 25–50 mg maintenance) and calcium folinate (3–5 mg every 3rd day)

2nd choice Clindamycin (600 mg 4 x day for 6 weeks then 450 mg 3 x day maintenance) and pyrimethamine (as above) and calcium folinate (as above)

Treatment is often started empirically, sometimes on the basis of computerised tomography showing multiple discrete lesions within the brain. However, a histopathological diagnosis of toxoplasmosis encephalitis should be established, if the diagnosis is in doubt or the patient is not responding to treatment, since non-infective conditions including lymphoma, Kaposi’s sarcoma, and progressive multifocal leukoencephalopathy (PML) may also cause focal neurological lesions. Serological tests are of limited value.

Sulfadiazine and pyrimethamine is the treatment of choice for HIV - positive patients suspected of having acute toxoplasmosis (including children and seriously ill pregnant women). Both drugs penetrate into the cerebrospinal fluid in therapeutically active concentrations. The relatively high doses used can, however, lead to toxicities, so careful monitoring is important. Leukopenia, thrombocytopenia and rash are common. Calcium folinate, which counteracts the blockade of folate metabolism in mammalian cells without affecting antiprotezoal activity should be administered daily to reduce the risk of myelosuppression. Patients should be advised to maintain a high fluid intake and urine output to prevent the development of sulfadiazine induced crystalluria, and to watch for signs of ‘gravel’ (sulfadiazine crystals) in their urine.

If patients develop toxicity to sulfadiazine, clindamycin either orally or intravenously is a good second choice. If toxicity develops to clindamycin (normally a rash or diarrhoea) the options are very limited. The macrolide antibiotic, clarithromycin in combination with either minocycline or pyrimethamine has been shown to have some activity.
Treatment should be continued for six to eight weeks; the doses of the agents used to
treat the acute toxoplasmosis are then reduced and patients should remain on these for
life.

Cryptococcal meningitis

_Cryptococcus neoformans_ is a yeast-like fungus widely present in soil and in greater
centration in bird excreta. It causes disseminated disease ultimately in about 5% of
persons with advanced HIV infection. It readily spreads from the lungs to the meninges
and, less commonly to the bone marrow, genitourinary tract and skin. It is the most
common life threatening AIDS related fungal infection and occurs most often in HIV-
positive patients with CD4+ counts < 50/mm3. In this group of patients its most
common manifestation is cryptococcal meningitis. Early diagnosis is usually dependent
upon demonstration of cryptococcal antigen in the serum, India ink staining of the CSF,
or culture of cryptococci from the cerebrospinal fluid.

The onset of cryptococcal meningitis is generally insidious. Fever and headache are
often the only presenting signs. Nausea, vomiting and neck stiffness may be absent and
focal neurological signs are uncommon. Patients with high initial CSF pressure,
decreased CSF glucose, low leukocyte count, no cryptococcal antibody or high
cryptococcal antigen titres tend to have a poor prognosis. Typical extraneural
manifestations include skin lesions, pneumonitis, pleural effusions and retinitis. Untreated, the disease runs a slowly progressive and ultimately fatal course.

**Treatment**

<table>
<thead>
<tr>
<th>Choice</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st choice</td>
<td>Amphotericin B (IV) (0.5–1.0 mg/kg IV for 6 weeks) + flucytosine (100 mg/kg in divided doses for 2 weeks) followed by fluconazole (200 mg daily maintenance)</td>
</tr>
<tr>
<td>2nd choice</td>
<td>Amphotericin B (IV) + flucytosine (100 mg/kg in divided doses for 2 weeks) followed by itraconazole (200 mg 2 x day maintenance)</td>
</tr>
<tr>
<td>3rd choice</td>
<td>fluconazole (oral) throughout (400 mg daily for 12 weeks then 200 mg daily maintenance)</td>
</tr>
<tr>
<td>4th choice</td>
<td>Amphotericin B IV throughout (as above)</td>
</tr>
</tbody>
</table>

All patients from whom cryptococci are isolated should be treated, even if they have no
signs of infection, because of the high risk of meningitis and disseminated disease.
Treatment with amphotericin B infused intravenously plus or minus flucytosine for two
weeks followed by oral fluconazole is the treatment of choice. In mild disease (i.e. if
there is no demonstrable CNS involvement) oral fluconazole may be used throughout.
Itraconazole may be a suitable alternative in patients unable to take fluconazole. If
azoles are unavailable, treatment with intravenous amphotericin B should continue for 6
weeks, followed by maintenance with intravenous amphotericin B once or twice a week.
Patients should remain on maintenance therapy for life.
HIV itself may occasionally induce retinal haemorrhage and optic neuropathy and Kaposi sarcoma may spread to involve the conjunctivae, eyelids and orbit. However, vision is more frequently compromised by infections with cytomegalovirus and sometimes with *Toxoplasma gondii*. Primary varicella and herpes zoster involving the ophthalmic division of the trigeminal nerve can also affect the eye.

<table>
<thead>
<tr>
<th>Protozoal infection:</th>
<th><em>Toxoplasma gondii</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infection:</td>
<td><em>Candida species</em></td>
</tr>
<tr>
<td>Viral infection:</td>
<td>Cytomegalovirus, varicella zoster virus</td>
</tr>
<tr>
<td>Non infectious disorders:</td>
<td>Primary CNS lymphoma, Kaposi's sarcoma</td>
</tr>
</tbody>
</table>

**Cytomegalovirus**

Asymptomatic cytomegalovirus infections, which are widespread in most communities, are transmitted congenitally, by sexual contact or by blood transfusion. The primary infection may present as a mononucleosis-like syndrome which soon resolves. Most people then remain latently infected but asymptomatic for life. Primary infection is thought to be rare in HIV as most have been exposed to CMV prior to their HIV infection. CMV disease occurs when a previously latent CMV infection is activated, usually when a patient becomes profoundly immunosuppressed such as in advanced HIV disease. It then causes clinical ‘end organ’ disease, most commonly CMV retinitis, but also, oesophagitis, encephalitis, myelitis, radiculopathy, colitis and rarely a pneumonitis.

The main symptoms of CMV retinitis include; floaters, blurred vision, reduced visual field, and flashing lights/sparks. Even subtle changes, such as minor loss of peripheral vision, can indicate the development of CMV retinitis. There is usually no pain involved. Clinical manifestation of progressive CMV retinitis include flame-shaped intraretinal haemorrhages superimposed on white granular necrotic patches in the fundi. If treatment is not given CMV retinitis results in loss of vision.

CMV disease of other organs is diagnosed by biopsy where histology will reveal typical round intranuclear inclusions, in swollen cells.

**Treatment**

1st choice  Ganciclovir IV (5 mg/kg daily for 14–21 days)
2nd choice  Foscarnet IV (90 mg/kg daily for 14–21 days)

**Maintenance (for CMV retinitis)**

1st choice  Ganciclovir PO (1 g 3 x day)
2nd choice  Ganciclovir IV (5 mg/kg daily)
3rd choice  Foscarnet IV (90 mg/kg daily)
Treatment is required following detection of CMV end organ disease, otherwise it will progress rapidly. In CMV retinitis, treatment for 14 to 21 days is required followed by lifelong maintenance therapy to prevent relapse. With other forms of CMV disease treatment can be for either a specified course (CMV colitis) or until symptoms have resolved or ulcers have healed (CMV oesphagitis). Maintenance therapy is not routinely given. Despite being on maintenance therapy, most patients with CMV retinitis will relapse and reinduction with intravenous therapy will be required.

Both ganciclovir and foscarnet are extremely toxic and close monitoring is required. Oral ganciclovir achieves lower plasma levels than the IV formulation, which has the advantage that toxicity is reduced, but can fail to control the CMV retinitis. Patients should be told to take the ganciclovir capsules with food to obtain maximal bioavailability.
Unexplained fever occurs frequently in HIV-infected patients. Diagnosis should be directed primarily to identifying pathogens causing illness that can be treated effectively.

<table>
<thead>
<tr>
<th>Bacterial infection:</th>
<th>Salmonella species, Pneumococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infection:</td>
<td>Pneumocystis carinii, Cryptococcus</td>
</tr>
<tr>
<td>Mycobacterial infection:</td>
<td>M. tuberculosis, M. avium-intracellulare</td>
</tr>
<tr>
<td>Viral infection:</td>
<td>Cytomegalovirus.</td>
</tr>
<tr>
<td>Non-infectious disorders:</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
</tbody>
</table>

**Bacterial infections**

Hospital based studies have shown that HIV positive patients have a 3–4 fold increased risk for bacteraemia. The highest rate being found in patients with the lowest total lymphocyte count. In HIV-infected patients in East and West Africa infection with different species of *Salmonella* has been shown to be frequent and in Kenya, high rates of *Streptococcus pneumoniae* have been reported. Patients with pneumococcal infection most often have signs of pneumonia but extrapulmonary manifestations may also occur including meningitis. Bacterial infections are particularly common in HIV-infected IV drug users. *Haemophilus influenzae* and *Streptococcus pneumoniae* are the most commonly isolated organisms. *Pseudomonas aeruginosa* induced chest infections are associated with very advanced disease and a prior history of sinusitis. The risk of death is greatly elevated in HIV-positive patients with septicaemia.

**Treatment**

Treat with antibiotics according to local sensitivities.

**Mycobacterial disease**

Any of the known pathogenic mycobacteria can cause febrile illnesses in HIV-infected patients. In North America *Mycobacterium avium-intracellulare* is most commonly implicated, while in Africa *M. tuberculosis* is more common.

**Mycobacterium tuberculosis** (see page 8)

**Mycobacterium avium complex (MAC)**

*Mycobacterium avium* complex organisms which cause disease in HIV-positive patients consist primarily of *M. avium* and *M. intracellulare*. They are ubiquitous organisms found in water, soil foods and a variety of animal species. For most patients there does not seem to be a consistent relationship between specific environmental exposure and the risk of developing MAC disease.

Presenting symptoms and signs are non-specific and frequently difficult to distinguish from HIV constitutional symptoms. They include fever, night sweats, anorexia and
malaise, weight loss, chronic diarrhoea and non-specific abdominal pain, hepatomegaly and anaemia are common. In the chest mediastinal lymphadenopathy is relatively common and focal consolidation can occur.

A diagnosis of disseminated MAC is made by culturing the organism from blood or from an aspirate or biopsy from bone marrow, liver, lymph node or skin. Culture from sputum, bronchoalveolar lavage and urine is often positive, but identification of MAC from these sites alone is not diagnostic of disseminated infection. An acid-fast smear can be used to detect quickly the presence of mycobacteria. However it cannot distinguish between MAC and M. tuberculosis. Mycobacterium avium can take up to six weeks to be recovered on solid media before a definitive diagnosis can be made. In patients with a low CD4+ count, a treatment regimen covering both of these organisms should be introduced until this time.

**Treatment**
The aim of treatment is to alleviate symptoms and this has been associated with reductions in MAC bacteraemia. Unfortunately, MAC is not cleared from the body, and therefore patients must stay on therapy for life.

1st choice: Clarithromycin (500 mg 2 x day) and ethambutol (800–1200 mg 4 x day)

*Severe symptomatic disease:* Add rifabutin (300 mg {<50 kg} or 450 mg {>50 kg} daily to the above.

**Prophylaxis**
1st choice: Azithromycin (1.2 –1.25 mg daily)
2nd choice: Clarithromycin (500 mg 2 x day maintenance)

In countries with a high incidence of MAC, MAC prophylaxis in patients with a CD4+ count less than 50/mm3 has been shown to delay disseminated MAC infection and increase survival. Recent studies have shown that azithromycin once a week or clarithromycin twice a day are more effective than rifabutin. In addition azithromycin was shown to reduce the risk of patients developing PCP by almost one half and reduce the incidence of bacterial infections. There is concern that use of monotherapy will encourage the emergence of resistance, but in one trial, although the combination of azithromycin and rifabutin was found to be superior to both monotherapies, it was less well tolerated and increased the complexity of potential drug interactions and cost.

**Penicillnosis**
*Penicillium marneffii* is a common cause of opportunistic infection in HIV-infected patients in Southeast Asia and Southern China in late stage disease (CD4+ < 50 cells/m3). The exact route of infection in humans is not known. The organism
proliferates in macrophages and is disseminated throughout the body, especially to the endothelial system.

The most common clinical presentations are fever, anaemia, and weight loss. Respiratory complaints (cough, shortness of breath) are also common. In these patients the chest radiograph shows diffuse nodular pulmonary infiltrates or cavity disease. Less commonly, local or generalized lymphadenopathy, hepatomegaly or splenomegaly also occur. Skin involvement occurs in patients with disseminated disease. The typical appearance is one of multiple papular lesions, often with a centralized umbilication or ulceration. The lesions are typically on the head and upper trunk.

The organism may be seen by microscopic examination of skin scrapings, or bone marrow or lymph node aspirates, and has been described as being evident on direct smears of peripheral blood in some patients. The diagnosis is confirmed by culturing the fungus from clinical specimens.

**Treatment**

Initial treatment should be with amphotericin B (for one or two weeks) followed by itraconazole; in mild cases itraconazole can be used throughout.

Long-term suppressive therapy with itraconazole should be given to prevent relapse.
Symptoms of colitis or small-bowel watery diarrhoea are common among HIV-infected patients. When they are severe they constitute the most distressing manifestations of HIV infection. Small-bowel diarrhoea can result from extensive Kaposi lesions and possibly from the cytopathic effect of HIV. However, many cases result from bacterial, protozoal or helminthic colonisation.

Whenever possible, the cause of the diarrhoea should be established and specific treatment provided. Failing this, management is symptomatic. A high energy and protein intake reduces the degree of muscle wasting. The use of anti-diarrhoeal agents such as codeine phosphate is justified when symptomatic relief is a major consideration.

| Bacterial infection: Shigella, and Salmonella species |
| Protozoal infection: Cryptosporidium species, Giardia lamblia, Isospora belli, Entamoeba histolytica, Microsporidium species. |
| Mycobacterial infection: M. avium complex |
| Fungal infection: Candida species |
| Viral infection: Cytomegalovirus, herpes simplex virus. |
| Non infectious disorders: Kaposi’s sarcoma, lymphoma, cytopathic effect of HIV disease |

**Summary of treatment of gastro intestinal tract/diarrhoeal disease**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Treatement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidiosis</td>
<td>Symptomatic treatment</td>
</tr>
<tr>
<td><em>Isospora belli</em> infection</td>
<td>Sulfamethoxazole/trimethoprim (960 mg 4 x day for 10 days)</td>
</tr>
<tr>
<td><em>Microsporidiosis (Microspora)</em></td>
<td>Albendazole 400 mg bd. for 4 weeks</td>
</tr>
<tr>
<td><em>Shigella sp.</em></td>
<td>Local sensitivities (or ciprofloxacin 500 mg bd. for 7 days)</td>
</tr>
<tr>
<td><em>Salmonella sp.</em></td>
<td>Local sensitivities (or ciprofloxacin 500 mg bd. for 7 days)</td>
</tr>
<tr>
<td><em>Campylobacter sp.</em></td>
<td>Erythromycin 500 mg 3 x day for 5 days</td>
</tr>
</tbody>
</table>
Cryptosporidiosis

*Cryptosporidium parvum* is a small, obligate, intracellular protozoan that occurs widely in nature and causes disease in animals and humans. Cryptosporidia are highly infectious and can be transmitted through water, food, animal-to-human and human-to-human contact. Because of cryptosporidia’s ubiquity and ease of transmission, people with compromised immune systems should take special precautions to avoid exposure. It is recommended that people with HIV and a CD4+ count of less than 200/mm3 should boil tap water for at least one minute to reduce the risk of ingestion of the oocytes in potentially contaminated public drinking water.

*Cryptosporidium* is an important cause of debilitating watery diarrhoea and weight loss in HIV-infected patients. The small bowel is extensively colonised and invasion of the biliary tree occasionally results in stenosis and cholecystitis. In HIV-positive patients with a CD4+ count above 200/mm3 cryptosporidiosis manifests as an acute self-limiting disease which does not require treatment. In patients with lower CD4+ counts it may present as chronic diarrhoea or as fulminant disease with greater than or equal to 20 stools a day. The organism can be detected in the stool by immunoflorescence and by acid-fast staining of smears.

**Treatment**
There is no specific curative treatment for cryptosporidiosis and symptomatic control with antidiarrhoeal agents is often the only recourse.

Isospora belli infection

*Isospora belli* infection presents in a manner that is clinically indistinguishable from disease caused by *Cryptosporidium*. It may be demonstrated in the stools by the techniques developed for *Cryptosporidium* species.

**Treatment**
Most cases are readily treated with sulfamethoxazole/trimethoprim (960 mg 4 x day for 10 days) or high dose pyrimethamine with calcium folinate to prevent myelosuppression (see under toxoplasmosis). Long-term maintenance therapy may be required to prevent relapse.

Microsporidiosis (Microspora)

The two most important species are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. The most common manifestation of intestinal microsporidiosis in HIV-positive patients is profuse, watery, non-bloody diarrhoea, sometimes accompanied by abdominal pain and cramping, nausea, vomiting and weight loss. Species of microsporidia have been linked with disseminated disease: cholangitis, keratoconjunctivitis, hepatitis, peritonitis and infections of the lungs, muscles and brain. However, presence of microsporidia does not always correlate with symptomatic disease.

**Treatment** Albendazole is the treatment of choice for microsporidial disease.
Many patients with HIV infection develop dermatological conditions at some point in the course of the disease.

**Bacterial infection**: *Staphylococcus aureus*, *Streptococcal* species
**Mycobacterial disease**: *M. tuberculosis*
**Fungal infection**: oral and oesophageal candidiasis, penicilliosis, *Cryptococcus neoformans*.
**Viral infection**: Herpes simplex and varicella zoster virus, cytomegalovirus, molluscum
**Infestations**: Scabies (Norwegian variant)
**Non infectious disorders**: Kaposi’s sarcoma, drug eruptions, folliculitis

### Summary of treatment for oral and oesophageal infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>1st line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>gingivitis</td>
<td>oral hygiene</td>
</tr>
<tr>
<td></td>
<td>metronidazole 400 mg bd.</td>
</tr>
<tr>
<td>oral candidiasis</td>
<td>1% gentian violet</td>
</tr>
<tr>
<td></td>
<td>topical antifungals</td>
</tr>
<tr>
<td></td>
<td>(e.g. nystatin oral suspension)</td>
</tr>
<tr>
<td>oesophageal candidiasis</td>
<td>nystatin oral suspension 5 x day</td>
</tr>
<tr>
<td></td>
<td>then</td>
</tr>
<tr>
<td></td>
<td>ketaconazole 200 mg for 14 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>fluconazole 400 mg stat</td>
</tr>
<tr>
<td>herpes simplex mouth ulcers</td>
<td>1% gentian violet</td>
</tr>
<tr>
<td></td>
<td>aciclovir 400–800 mg 5 x day</td>
</tr>
</tbody>
</table>
Oral and oesophageal candidiasis

*Candida albicans* is an endogenous yeast which in healthy individuals dwells predominately in the gastrointestinal tract, and sometimes in the respiratory tract. It can be pathogenic in immunocompromised patients. Though *C. albicans* is the most prevalent form, a number of other species can cause disease. Candida may cause infections of the oesophageal, oral, anorectal and vaginal mucosa, the eyes, the skin, and nails as well as life threatening fungaemia.

Oral candidiasis is frequently the first indication of immune impairment in HIV-infected patients. It is characterized by white sloughs covering areas of superficial ulceration on the gums, palate and tongue, which contain many yeast organisms and are readily detached. In severe cases these lesions extend into the lower pharynx and oesophagus to cause dysphagia, nausea and epigastric pain. Since Candida is the most common oesophageal infection in HIV-positive patients, oesophageal symptoms are usually treated empirically with oral systemic antifungal agents. However, other pathogens such as CMV, HSV and bacteria can also affect the oesophagus. Definitive diagnosis of oesophageal candidiasis requires endoscopic biopsy and histopathology.

**Treatment of oral Candida**

**Step 1** Topical antifungals
- Nystatin (1 tablet 4 x day)
- Amphotericin B (10 mg lozenges 4 x day)
- Miconazole gel (4 x day)

**Step 2** Systemic therapy
- 1st choice: Ketoconazole (200–400 mg daily)
- 2nd choice: Fluconazole (200 mg loading close then 100 mg day)
  or Itraconazole (100 mg 2 x day)
- 3rd choice: Amphotericin B (Intravenous) (0.5–1.5 mg/kg per day)

Initially localised lesions in the mouth responds to topical antifungals. However, after a time these agents often become ineffective and systemic agents are required. For as long as possible intermittent therapy should be used in an attempt to delay the emergence of resistant Candida. Ketoconazole and itraconazole have good spectrums of activity against Candida species but both have limited bioavailability. This can be increased by taking the solid formulations with food or acidic drinks. Use of the liquid formulations can further increase bioavailability and by asking the patient to swill them around the mouth for as long as possible before swallowing can have an additional topical action. Fluconazole is well absorbed but has limited activity against *C. glabrata* and *C. krusei*. Therefore, long-term low dose prophylaxis should be avoided as it can select for these inherently resistant species.
Due to the toxicity of amphotericin B it is only used as a last resort in patients with azole resistant oral/oesophageal Candida. However it is first choice in patients with serious Candida infections at other sites.

**Herpes simplex**

Herpes simplex virus 1 and 2 (HSV) are common in HIV positive patients, often appearing among the earlier infections associated with AIDS. For some, HSV remains asymptomatic or causes only occasional outbreaks. For others, HSV mucosal or cutaneous lesions may persist or continue to enlarge, exposing the patient to the extreme pain and the risk of secondary infection. In severe cases, HSV may spread through the blood or cerebral spinal system to the oesophagus, lung, eye or brain. Though it occurs rarely, HSV associated encephalitis is a debilitating and life threatening condition. HSV lesions presenting for longer than a month, or the occurrence of HSV-related pneumonitis, bronchitis or oesophagitis in a person with HIV (or no other apparent cause for immunodeficiency) is considered an AIDS-defining condition.

**Treatment**

Severe primary genital lesions, oesophagitis, and proctitis may be treated with oral aciclovir. Suspected HIV encephalitis or pneumonitis should be treated with intravenous aciclovir. Herpes simplex infections of the eye include keratitis, keratoconjunctivitis, uveitis, and keratouveitis. Serious cases can result in damage to the cornea. Ophthalmic diagnosis requires differentiation from varicella zoster virus. Herpetic keratitis may be treated with ophthalmic antiviral formulations of aciclovir or trifluridine. Systemic therapy may be required to prevent recurrences.

Herpes ‘resistant’ to aciclovir has been reported. Sometimes this can have been caused by lack of absorption of oral aciclovir. This can be overcome by increasing the oral dose to aciclovir 800 mg five times a day, or if there is still no response, giving intravenous aciclovir. Lack of response to intravenous aciclovir denotes a truly resistant virus which can be treated using intravenous foscarnet.

**Herpes zoster**

Varicella zoster virus (VZV), a member of the human herpes virus family, is the cause of both chicken pox (varicella) and shingles (herpes zoster). While most HIV positive people with zoster experience only one self-limiting course, some will experience repeated episodes. In the later stages of HIV disease dissemination may occur.

Primary varicella and herpes zoster involving the ophthalmic division of the trigeminal nerve can affect the eye. The eye infection may or may not occur in conjunction with a cutaneous outbreak. Symptoms include, floating spots, loss of vision, and a high incidence of retinal detachment. VZV-associated progressive outer retinal necrosis is a sight-threatening condition which is difficult to treat. Patients may also develop
keratitis, anterior uveitis or corneal scarring which can lead to permanent visual loss. VZV encephalitis is very rare. It tends to occur in conjunction with ocular or viscerally disseminated VZV. Symptoms include headache, vomiting, lethargy, tremors and dizziness. Diagnosis is often aided by the presence of cutaneous lesions. A brain scan often reveals a multifocal infection on white matter or vasculitis.

**Treatment**

Treatment should be reserved for debilitating disease and when there is a high risk of serious complications such as in advanced HIV disease.

Aciclovir is the treatment of choice. It can be administered at a high oral dose, or in the cases of lack of response to oral therapy or ocular or CNS involvement it should be given intravenously.

**Pyomyositis**

Pyomyositis, caused most commonly by *Staphylococcus aureus*, has emerged as an unusual complication of HIV in Africa. In Tanzania 62% of a series of patients with pyomyositis were HIV-infected. In the northern hemisphere individual case have been reported but the condition is rare.
Drugs

**Aciclovir**

*Group: antiviral agent*

**Tablet, 200 mg [EDL], 400 mg, 800 mg**

**Suspension, 200 mg/5ml**

**Powder for injection 250 mg [EDL], 500 mg**

**General information**

Aciclovir, which is derived from guanine, is a synthetic purine nucleoside analogue with antiviral properties. It acts against herpes viruses by disrupting DNA synthesis and thus inhibiting viral replication. However, in immunocompromised patients, alpha herpes viruses are sometimes resistant to aciclovir.

Absorption from the gastrointestinal tract is variable and incomplete. Aciclovir is widely distributed in tissues and body fluids and is excreted in the urine primarily unchanged.

**Clinical information**

**Uses**

- severe primary genital herpes
- herpes viral encephalitis
- disseminated zoster.

**Dosage and administration**

Intravenous infusions should be administered slowly over a period of at least one hour to reduce the risk of acute impairment of renal function.

**Primary genital herpes**

5 mg/kg intravenously three times daily for 5 days.

200 mg – 400 mg orally five times a day for 5–7 days.

Occasionally, higher doses i.e. 800 mg orally five times a day may be required.

In patients that relapse frequently (i.e. more than 6 times/year) maintenance therapy may be required. The most commonly used dose is aciclovir 400 mg twice a day.

**Herpes viral encephalitis**

10 mg/kg intravenously three times daily for 10 days

**Disseminated zoster**

10 mg/kg intravenously three times daily for 7 days

**Contraindications**

Known hypersensitivity to purine nucleoside analogues.

**Precautions**

Reduce the dose in renal impairment

**Use in pregnancy**

Aciclovir is mutagenic in animal models. Its use in pregnancy must be determined by the physical state of the mother.

**Adverse effects**

Headache, nausea and vomiting occur commonly after oral administration. Transient renal impairment may occur during intravenous therapy, possibly as a result of crystallisation in the renal tubules. This usually responds rapidly to dosage reduction or withdrawal of the drug. Acute renal failure has responded to haemodialysis.
Overdosage
Since aciclovir is incompletely absorbed from the gastrointestinal tract, oral overdosage is unlikely to have serious sequelae. Blood concentrations can be lowered by haemodialysis.

Storage
Tablets should be stored in tightly closed containers below 25°C. Suspension and powder for injection should be stored below 25°C.

ALBENDAZOLE
Group: anthelmintic/antiparasitic
Tablet, 200 mg, 400 mg [EDL] chewable tablet

General information
Albendazole is a benzimidazole carbamate anthelmintic which is also active against various protozoa. Albendazole is poorly and variably absorbed from the GI tract but absorption is increased when administered with a fatty meal. It undergoes extensive first pass metabolism. The active principal metabolite has a plasma half-life of about 8.5 hours. It is excreted in the urine.

Clinical information
Uses
Treatment and suppression of microsporidial infections

Dosage and administration
Treatment and suppression of microsporidial infections: 400 mg twice a day for four weeks. If the patient relapses after therapy is stopped, it should be assumed that the microsporidia has not been completely cleared and suppressive therapy of 400 mg once a day will be required after the infection has been brought under control with the original treatment dose.

To increase absorption albendazole should be taken with a fatty meal.

Contraindications
Known hypersensitivity; pregnancy

Precautions
Monitor liver function tests, and full blood count during therapy.

Use in pregnancy
In animal studies albendazole has been found to be teratogenic and therefore should not be used.

Adverse effects
Elevations in liver function tests, and reversible reductions in total white cell counts and pancytopenia have been reported. Mild gastrointestinal disturbances, headaches, dizziness, alopecia (limited to thinning of the hair) have also been reported.

Drug interactions
Albendazole has been shown to induce liver enzymes of the cytochrome P450 system responsible for its own metabolism. Therefore, there is a theoretical risk of interaction with theophylline, anticonvulsants, oral contraceptives, and oral hypoglycaemic agents.

Overdosage
There is no experience of overdosage. Gastric lavage may be performed in the first two to three hours after ingestion. No specific antidote is known.
Storage
Tablets should be stored in tightly closed containers protected from light.

AMPHOTERICIN B
Group: antifungal agent
Powder for injection, 50 mg in vial [EDL]
Lozenge, 10 mg [non-EDL]

General information
Amphotericin B is a lipophilic polyene antibiotic that is active against protozoa and certain fungi. Since it is poorly absorbed from the gastrointestinal tract it must be administered parenterally.

It is extensively bound to lipoproteins, but it enters serous cavities and crosses the placental barrier. It is excreted unchanged in the urine over a period of several weeks.

Clinical information
Uses
- oesophageal and oral candidiasis resistant to azole derivatives
- cryptococcal meningitis
- histoplasmosis and coccidiodomycosis
- aspergillosis

Dosage and administration
Oral candidiasis
Amphotericin 10 mg lozenge four times daily after food. Lozenges should be retained as close to major lesions as possible.

All other indications
Intravenous amphotericin B is a highly toxic substance that should only be used under experienced medical supervision. The dosages should be administered as a slow intravenous infusion over 2-4 hours. The administration of hydrocortisone sodium succinate 100 mg iv, paracetamol and an antihistamine prior to the infusion may reduce the incidence of fever and chills. Inclusion of 500IU-1000IU heparin in the infusion bag reduces the incidence of thrombophlebitis, and prehydration with 1 litre normal saline helps reduce the incidence of nephrotoxicity.

Infusion fluids should be freshly prepared by dissolving 50 mg in 10 ml water for injection and adding to the appropriate amount of fluid to give a maximum concentration of 1 mg/10 ml. Amphotericin B is incompatible with electrolytes (i.e. sodium chloride) and preservatives. Therefore glucose 5% + buffer should be used as the infusion fluid. If buffer is not available glucose 5% with the longest expiry date should be used as the pH of glucose decreases with time and amphotericin B will precipitate at a pH less than 4.2. NB: cannulae, lines etc. should be flushed with glucose 5% not sodium chloride.

Amphotericin B can cause anaphylaxis. Prior to the first dose, a 1 mg test dose should be given over 20 minutes; then, if after a further 30 minutes anaphylaxis has not occurred, the rest of the dose may be given. The dose for all indications should be started at 0.25 mg/kg/day and increased in increments of 0.25 mg daily until the target dose is obtained, or as high a dose as can be tolerated.

Cryptococcal meningitis
0.7–1 mg/kg/day for either 2 or 6 weeks (until the condition has stabilised or improved) followed by maintenance therapy with either oral fluconazole or amphotericin B IV 50 mg once or twice a week.
Oesophageal candidiasis (resistant to azole antifungals)
0.5 mg–1 mg/kg/day until symptoms have resolved.
Maintenance: Amphotericin B IV 50 mg on a minimum number of days of the week to keep symptoms at bay.

Histoplasmosis and coccidioidomycosis
0.5 mg–1 mg/kg/day for at least 6 weeks.
The cumulative dose of amphotericin B is recommended as 10–15 mg/kg for histoplasmosis and 1000 mg–2000 mg for coccidioidomycosis. Patients should be maintained on oral antifungals. If these are unavailable, amphotericin 50 mg may be administered weekly or biweekly for life.

Aspergillosis
1 mg/kg/day for 14 days or until symptoms have resolved followed by maintenance with itraconazole.

Penicillinosis
0.6–1 mg/kg/day for 7–14 days or until there is clinical resolution followed by maintenance with itraconazole.

Contraindications
Known hypersensitivity to amphotericin B.

Precautions
Close medical supervision is required throughout treatment.
A high fluid intake should be maintained. Potassium and magnesium supplements may be required to compensate for urinary losses. Prehydration with 1 litre normal saline can help reduce the incidence of nephrotoxicity. Dosage must be reduced if renal function deteriorates substantially.
The blood count should be monitored at regular intervals. Occasionally blood transfusions may be required.

Use in pregnancy
Safe use in pregnancy has not been established. Amphotericin B should be used only when the need of the mother outweighs the risk of harm to the foetus.

Adverse effects
Chills, fever and vomiting are frequent during infusion. Anaphylaxis, flushing, muscle and joint pains, headache and anorexia may also occur. These effects are often most marked in the first days of treatment.

Deterioration of renal function, which may be only partially reversible, must be anticipated.

Progressive normochromic anaemia is indicative of bone-marrow suppression. Selective leukopenia and thrombocytopenia are less common.

Nerve palsy, impaired vision, tinnitus and difficult micturition have also been reported.

Drug interactions
Concomitant administration of other nephrotoxic drugs should be avoided.

Overdosage
Large doses may result in anuria, dysrhythmias, cardiac arrest, hypotension, visual disturbances and convulsions. Treatment is symptomatic. Amphotericin B cannot be removed by haemodialysis.

Storage
Vials of powder for injection should be kept in tightly closed containers, protected from light. Lozenges should be stored in tightly closed containers.
Azithromycin

Group: antimicrobial (macrolide) agent
Capsule, 250 mg [nonEDL]
Powder for oral suspension, 200 mg/ml [nonEDL]

General information
Azithromycin is an azalide antibiotic derived from macrolides. Its mode of action is that it inhibits protein synthesis by binding to the 50S ribosomal subunit. Following oral administration it is widely distributed throughout the body; its bioavailability is approximately 37% and is reduced by food. Small amounts are demethylated in the liver but most is excreted unchanged in the bile. The plasma elimination half-life is 2 to 4 days.

Clinical information
Uses
Prophylaxis against Mycobacterium avium complex

Dosage and administration
Prophylaxis against Mycobacterium avium complex
1.2 g/1.25 g (depending on tablet strength availability) once a day indefinitely
Azithromycin should be taken one hour before or two hours after food.

Contraindications
• known hypersensitivity macrolide antibiotics
• severe liver impairment
• concomitant administration of ergotamine or dihydroergotamine (see under drug interactions)

Precautions
Monitor liver function tests during therapy.

No dosage adjustment is needed in patients with renal impairment.

Use in pregnancy
There are no adequate well controlled studies in pregnant women, and azithromycin should be used in pregnancy only if adequate alternatives are not available.

Adverse effects
The majority of side effects are gastrointestinal in origin, including nausea, abdominal discomfort (pain and cramps), vomiting, flatulence, diarrhoea, and loose stools. Allergic reactions such as rash or photosensitivity have occurred and there have also been rare reports of serious hypersensitivity reactions - angioneurotic oedema and anaphylaxis. Reversible elevations in liver transaminases and rarely cholestatic jaundice have been observed. Ototoxicity has been reported in patients on high doses for prolonged periods of time. Transient reductions in neutrophil count have been seen especially when azithromycin is used in conjunction with rifabutin (see under drug interactions).

Drug interactions
Azithromycin should be taken at least one hour before or two hours after antacids.
Azithromycin may increase plasma levels of cyclosporin, digoxin and warfarin these should be monitored.
An increased incidence of neutropenia has been reported in patients on concurrent azithromycin and rifabutin.
Concomitant administration of ergotamine or dihydroergotamine has been associated with acute ergot toxicity, characterized by severe peripheral vasospasm and dysesthesia.
Overdosage
There is no data on overdosage with azithromycin. Treatment is supportive.

Storage
Azithromycin should be stored in well closed containers.

BENZYL PenicillINS
Group: antimicrobial (penicillin) agent
Benzylpenicillin: powder for injection 600 mg (=1 million IU), 3 g (=5 million IU) (as sodium or potassium salt) in 5 ml vial [EDL]
Benzathine benzylpenicillin: powder for injection, 1.44 g of benzylpenicillin (=2.4 million IU) in 5 ml vial [EDL]
Procaine benzylpenicillin: powder for injection, 1g (=1 million IU), 3 g (=3 million IU) in vial [EDL]

General information
Benzylpenicillin is a natural substance derived from Penicillium notatum. It consists of a thiazolidine ring connected to a beta-lactam ring. It is bactericidal against Streptococci, Neisseriae, many anaerobes and spirochaetes.
After intramuscular injection, peak plasma concentrations are reached within 15–30 minutes. It is widely distributed throughout the body, has a plasma half-life of 30 minutes and is excreted mainly in the urine.
Repository preparations of benzylpenicillin are available for parenteral use. They are designed to provide a tissue depot from which the drug is slowly absorbed over a period of 12 hours to several days. Procaine benzylpenicillin produces a peak plasma concentration within 1–3 hours and is excreted over a period of several days and benzathine benzylpenicillin over a period of about 14 days.

Uses
Benzylpenicillin:
Pneumonia in adults, group B Streptococcus infections, Clostridium perfringens, septicaemia
Procaine benzylpenicillin:
Cervical adenitis, gingival infection, dental abscess.
Benzathine benzylpenicillin:
Streptococcal pharyngitis.

Dosage and Administration
Benzylpenicillin and its repository formulations must be administered parenterally. The repository formulations must always be administered intramuscularly.
The powder for injection should be diluted in 'water for injection' in accordance with the manufacturer's directions.
Benzylpenicillin:
0.6–1.2 g i.m. or i.v. four times daily in mild to moderate infections; in more severe disease doses up to 1.8 g eight times daily may be necessary.
Procaine benzylpenicillin:
1 g i.m. in a single dose for five days.
Benzathine benzylpenicillin:
0.9 g i.m. as a single dose.

Contraindications
Known hypersensitivity to penicillin or cefalosporins.

Precautions
Facilities should be available for treating anaphylaxis whenever penicillin is used.
A careful history should be taken with regard to previous allergic reactions.
If skin rashes develop, the patient should be given another antimicrobial.
Rapid intravenous administration of large doses of sodium benzylpenicillin may cause hypokalaemia, dysrhythmias and cardiac arrest, particularly in patients with impaired renal function.

**Use in pregnancy**
There is no evidence of teratogenicity with benzylpenicillin or its repository formulations. They can be used during pregnancy.

**Adverse reactions**
The most common adverse effects of these substances are hypersensitivity reactions that range in severity from skin rashes to immediate anaphylaxis.
Pain and sterile inflammation can occur at the site of intramuscular injection and phlebitis or thrombophlebitis is sometimes seen when these drugs are administered intravenously.

Accidental injection into a peripheral nerve causes pain and dysfunction. High concentrations of benzylpenicillin in the central nervous system may cause confusion, convulsions, coma and fatal encephalopathy.
Nephropathy manifested as interstitial nephritis has been reported.
Neutropenia and thrombocytopenia have occurred rarely.

**Overdosage**
Overdosage with large intravenous doses can cause convulsions, paralysis and may be fatal. Excessive blood levels can be corrected by haemodialysis.

**Storage**
Powder for injection should be stored at temperatures between 2 and 8°C.

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**Calcium Folate**

*Group: antidote to folic acid antagonists*

*Tablet, 5 mg, 15 mg [EDL]*

**General information**
Calcium folinate is a metabolically active, reduced form of folic acid that is rapidly absorbed and extensively metabolized in the liver to other folic acid derivatives.

**Clinical information**
**Uses**
To decrease the haematopoetic toxicity of pyrimethamine and other inhibitors of folic acid metabolism in patients with HIV infection.

**Dosage and administration**
Adults and children: 5–50 mg/day dose adjusted according to patients blood counts.

**Precautions**
The possibility of pernicious anaemia should always be excluded before starting treatment with calcium folinate. Its use obscures the diagnosis by rectifying the characteristic megaloblastic anaemia but it does not prevent neurological damage.

**Use in pregnancy**
Calcium folinate should always be used when pyrimethamine and sulfonamides are administered during pregnancy.

**Adverse effects**
Calcium folinate is generally well-tolerated. Rarely, hypersensitivity reactions occur, including urticaria, rash and pruritus.

**Storage**
Tablets should be stored in tightly closed containers protected from light.
**Ceftriaxone**

*Group: antimicrobial (cefalosporin) agent powder for injection 250 mg in vial [EDL]*

**General information**

Ceftriaxone is a third-generation cefalosporin derived from *Cephalosporium acremonium* which is highly active against Gram-negative cocci and Gram-negative bacilli. Like benzylpenicillin, it has a beta-lactam ring.

After intramuscular administration, the drug is distributed widely throughout the body. It has a relatively long plasma half-life of about eight hours and is excreted as an unchanged drug both in the urine and bile.

**Clinical information**

**Uses**

- *Haemophilus influenzae* meningitis, pneumococcal meningitis.
- Hospital acquired pneumonia.
- Bone and joint infections due to resistant *H. influenzae*.

**Dosage and administration**

Ceftriaxone must be administered parenterally.

2–4 g i.m. daily for 10–14 days, or for up to six weeks in resistant bone infections.

**Contraindications**

Known hypersensitivity to other beta-lactamase antimicrobials.

**Precautions**

Transient increases in liver enzymes may develop.

**Use in pregnancy**

There is no evidence of teratogenicity with the use of ceftriaxone. It may be used during pregnancy.

**Adverse effects**

Hypersensitivity reactions are the most common adverse effects. These are most frequently manifested by skin rashes. Urticaria, bronchospasm and anaphylaxis are uncommon. Nausea, vomiting and diarrhoea have been reported.

Rarely, antimicrobial-associated pseudomembranous colitis due to *Clostridium difficile* occurs. The drug should be immediately discontinued.

Reversible cholestatic jaundice has been reported.

**Storage**

Powder for injection should be stored in tightly closed containers, protected from light.

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**Ciprofloxacin**

*Group: antimicrobial (quinolone) agent tablet 250 mg (as hydrochloride) [EDL]*

**General information**

Ciprofloxacin is a synthetic fluoroquinolone which acts as a specific inhibitor of bacterial DNA gyrase. It has a broad spectrum of antibacterial efficacy against both Gram-negative and Gram-positive aerobic organisms. Reports of chromosome resistance have been reported but as yet are of relatively little clinical significance.

It is rapidly absorbed from the gastrointestinal tract. Peak plasma levels
occur 0.5–1.5 hours after dosing. It is widely distributed in body tissues and is concentrated in the bile. It has a plasma half-life of 3–5 hours and is excreted in the urine mainly as unchanged drug.

**Clinical information**

**Uses**
- Typhoid fever
- Shigellosis due to resistant strains
- Infections due to susceptible organisms resistant to other antimicrobials.

**Dosage and administration**
250 mg two times daily for five days.

**Contraindications**
- Hypersensitivity to any quinolone.
- Pregnancy.

**Precautions**
Patients with hepatic or renal impairment may require reduced dosage. Ciprofloxacin should be administered cautiously to patients with epilepsy since seizures may be precipitated. Ensure adequate fluid intake since crystalluria may occur.

**Adverse effects**
Ciprofloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, rash, dizziness and pruritus.

**Drug interactions**
Plasma levels of theophylline may be increased. Prolongation of bleeding time has been reported in patients receiving anticoagulants concurrently.

**Overdosage**
Supportive therapy including gastric lavage and maintaining electrolyte balance should be performed. Serum levels of ciprofloxacin are reduced by dialysis.

**Storage**
Tablets should be stored in well closed containers.

**General information**
Clarithromycin is a semisynthetic macrolide antibiotic, structurally very similar to erythromycin. It inhibits protein synthesis by penetrating the cell wall and binding to the 50S ribosomal subunit. The absolute bioavailability of clarithromycin after oral administration is 50–55%, which probably underestimates its systemic activity, as it undergoes extensive first pass metabolism to its active metabolite, 14-hydroxyclarithromycin. Limited data are available on the distribution of clarithromycin in humans. It appears to be distributed into most body tissues and fluids. However, no data is available on CSF penetration of clarithromycin. Elimination of clarithromycin follows non-linear kinetics. It is extensively metabolized in the liver and excreted as parent drug and metabolites in urine, and faeces.

**Clinical information**

**Uses**
Treatment of *Mycobacterium avium* complex.
Prophylaxis of *Mycobacterium avium* complex
Treatment and maintenance of toxoplasmosis

**Dosage and administration**

*Treatment of Mycobacterium avium complex*
500 mg twice a day in combination with ethambutol or ethambutol and rifabutin indefinitely.

*Prophylaxis of Mycobacterium avium complex*
500 mg twice a day indefinitely

*Treatment and maintenance of toxoplasmosis*
1 g twice a day for 6–8 weeks in combination with either pyrimethamine and calcium folinate or minocycline then reduced to 500 mg twice a day indefinitely.

The oral formulations may be given with food to reduce the incidence of GI side effects.

The powder for injection is reconstituted with water for injection and administered in sodium chloride 0.9% or glucose 5% at a final concentration of 2 mg/ml at a rate of 500 mg over one hour.

**Contraindications**
Known hypersensitivity, to clarithromycin, erythromycin or any other macrolide.
Severe liver impairment

Concomitant administration of terfenadine, astemizole or cisapride (see under drug interactions).

Concomitant administration of ergotamine or dihydroergotamine (see under drug interactions).

**Precautions**
Reduce dose by 50% if renal function falls below 30 ml/min. Monitor liver function tests during therapy. If the patient develops diarrhoea during therapy, test for *Clostridium difficile* toxin.

**Use in pregnancy**
While the potential risk to the foetus has not been elucidated to date, clarithromycin should only be used in pregnancy if the benefits outweigh the risks to the foetus.

**Adverse effects**
Nausea, vomiting, diarrhoea and abdominal pain, headache, ototoxicity and skin rash. Taste perversion may occur. There have been reports of transient central nervous system side effects including anxiety, dizziness, insomnia, hallucinations, bad dreams and confusion, however, a cause and effect relationship has not been established.

**Drug interactions**
Concomitant administration of terfenadine, astemizole or cisapride should be avoided as potentially fatal cardiac irregularities including prolonged Q-T intervals and ventricular fibrillation may occur.

Concomitant administration of ergotamine or dihydroergotamine has been associated with acute ergot toxicity, characterized by severe peripheral vasospasm and dysesthesia.

Clarithromycin may produce clinically significant increases in serum levels of the following drugs: carbamazepine, corticosteroids, digoxin, rifabutin, theophylline and warfarin.

Reduced serum levels of clarithromycin have been reported with rifampicin and to a lesser extent rifabutin. The clinical significance of this is unknown, but might lead to treatment failure. The concomitant use of rifabutin and clarithromycin has been reported to cause an increased incidence of neutropenia and uveitis.
Overdosage
Reports indicate that ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Allergic reactions accompanying overdosage should be treated by gastric lavage and supportive measures. Clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

Storage
Tablets and granules for oral suspension should be stored in tight containers at 15–30°C and protected from light. Following reconstitution, oral suspensions should be stored at 15–30°C in tightly closed containers; the reconstituted solution should not be refrigerated. Any unused solution should be discarded after 14 days.

CLINDAMYCIN
Group: antimicrobial agent
Capsule, 75 mg, 150 mg [EDL]
Solution for injection, 150 mg/ml 2 ml, 4 ml ampoules [EDL]

General information
Clindamycin is a semisynthetic derivative of lincomycin, an antibiotic derived from cultures of *Streptomyces lincolnensis*. Clindamycin inhibits protein synthesis in susceptible organisms by binding to the 50S ribosomal subunits. Clindamycin is rapidly absorbed from the GI tract. It is partially metabolized to bioactive and inactive metabolites which are excreted in urine, bile and faeces. The serum half life of clindamycin is 2–3 hours.

Clinical information
Uses
- Treatment of *Pneumocystis carinii* pneumonia
- Treatment and maintenance of toxoplasmosis.
- Treatment of Gram-positive cocci, some anaerobic and microaerobic gram negative and gram positive organisms.

Dosage and administration
*Treatment of Pneumocystis carinii pneumonia*
600 mg four times a day oral/IV for 21 days or to complete a course of 21 days of PCP therapy.
*Treatment and maintenance of toxoplasmosis*
(in combination with pyrimethamine)
600 mg four times a day oral/IV for 6 to 8 weeks, then reduced to 450 mg three times a day and continued indefinitely.
Intravenous doses are diluted in 100 ml sodium chloride 0.9% or dextrose 5% water and administered over at least 20 minutes.

Contraindications
Known hypersensitivity to clindamycin or lincomycin. Diarrhoeal states.

Precautions
If clinically important persistent diarrhoea occurs during clindamycin therapy, the drug should be discontinued, and the diarrhoea should be tested for *Clostridium difficile* toxin.
Severe rash associated with clindamycin commonly occurs after 10 to 14 days of therapy, clindamycin should be stopped.
Use in pregnancy
Safety in pregnancy has not been established. Because of the need to treat either PCP or toxoplasmosis therapy should not be withheld.

Adverse effects
In the doses given above there is a high incidence of GI side effects including nausea, vomiting, abdominal pain and diarrhoea (see under precautions). Other adverse effects include rash (see under precautions), abnormal liver function tests, and rarely; neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia.

Drug interactions
Antagonism has been demonstrated in vitro between clindamycin and erythromycin. Because of possible clinical significance the to drugs should not be administered concurrently.

Overdosage
In cases of overdosage no specific treatment is recommended. It is not readily removable from the blood by dialysis or peritoneal dialysis.

Storage
Avoid refrigeration. All formulations should be stored below 25°C.

CODEINE
Group: antidiarrhoeal and analgesic agent
Tablet, 30 mg of codeine phosphate[EDL]

General Information
Codeine is a semisynthetic methyl derivative of morphine. It is less likely to cause dependence than morphine; none the less, its supply is controlled under Schedule 1 of the Single Convention on Narcotic Drugs, 1961. It exerts its effect mainly on the central nervous system and by an antimitotility effect on the bowel.

Codeine is readily absorbed after oral administration and is metabolized in the liver. The plasma half-life is 2–3 hours and it is excreted in the urine largely as inactive metabolites.

Clinical information
Uses
• treatment of mild to moderate pain
• symptomatic relief of diarrhoea.

Dosage and administration
A dose of 30–60 mg should be taken three or four times daily, as necessary.

Contraindications
Exacerbations of bronchial asthma.

Precautions
Prolonged use can result in tolerance. However, the risk of dependence is less than with other opioids.

Use in pregnancy
Codeine should be used during pregnancy only when the need outweighs any possible risk to the foetus. Its use during labour can produce respiratory depression in the infant sufficient to necessitate administration of naloxone, 10 mg/kg i.m., upon delivery.

Adverse effects
Dose-related adverse effects include nausea, dizziness and sedation. Prolonged use can result in intractable constipation and, rarely in paralytic ileus or toxic megacolon.

Drug interactions
Codeine potentiates the effects of other cerebral depressants.
Overdosage
Serious overdose is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, and pinpoint pupils. Cardiovascular collapse and cardiac arrest are terminal events.

Supportive therapy includes mechanically assisted ventilation and administration of pressor drugs and fluids to maintain the circulating blood volume. Naloxone should be administered, as necessary, at 2–minute intervals.

Storage
Codeine tablets should be kept in tightly closed containers.

Dapsone
Group: antiparasitic agent
Tablet, 25 mg, 50 mg, 100 mg [EDL]

General information
Dapsone is a synthetic sulfone anti-infective. It is usually bacteriostatic in action. The mechanism of action has not been fully elucidated but is thought to be similar to that of sulfonamides which involves inhibition of folic acid synthesis in susceptible organisms. Dapsone is well absorbed from the GI tract, and distributes into most body tissues. The plasma half-life may vary from 10–83 hours and averages 20–30 hours. Dapsone is metabolised in the liver and excreted in the urine.

Clinical information
Uses
- Treatment of *Pneumocystis carinii* pneumonia (PCP)
- Prophylaxis of *Pneumocystis carinii* pneumonia

Dosage and administration
*Treatment of Pneumocystis carinii pneumonia*
100 mg daily for 21 days or to complete a 21 day course of therapy for PCP in combination with trimethoprim.

*Prophylaxis of Pneumocystis carinii pneumonia*
50 mg – 100 mg* daily (in combination with pyrimethamine if the patient is *Toxoplasma gondii* antibody positive and has a CD4+ count < 100/mm3).
*Higher doses may be more effective but also more toxic.*
Taking dapsone with food may reduce the incidence of GI side effects.

Contraindications
Known hypersensitivity to dapsone. Liver failure. Severe G–6–PD deficiency. Severe anaemia prior to therapy.

Precautions
The most common side effects of dapsone are dose-related anaemia and methaemoglobinemia and should be monitored for throughout therapy. Haemolysis and Heinz body formation may be exaggerated in patients with G–6–PD deficiency, methaemoglobin reductase deficiency or haemoglobin M. Toxic hepatitis and cholestatic jaundice have been reported with dapsone. Liver function test should be monitored before and during therapy.

Use in pregnancy
Although dapsone has been used in pregnant women without evidence of foetal abnormalities, the drug should only be used in pregnancy when benefits outweigh the risk.
Adverse effects
Nausea, vomiting, anorexia, headache, hepatitis, psychosis, haemolysis, methaemoglobinenaemia, and aplastic anaemia. Rash, pruritus, and serious cutaneous hypersensitivity reactions including Stevens-Johnson syndrome, peripheral neuropathy with motor loss.

Drug interactions
Dapsone requires an acidic environment for absorption. Drugs which increase the pH of the stomach (i.e. antacids, H2 blockers) can lead to decreased dapsone absorption. Rifampicin increases dapsone metabolism. The higher doses i.e. 100 mg/day should be used for PCP prophylaxis in patients receiving this combination. Care should be taken when dapsone is used with other drugs that may induce anaemia (e.g. zidovudine), haemolysis or methaemoglobinenaemia. Didanosine (ddl) significantly reduces serum dapsone levels.

Overdosage
Overdosage of dapsone generally results in nausea, vomiting, and hyperexcitability within a few minutes to up to 24 hours later. Methaemoglobin-induced depression, seizures, and severe cyanosis may occur and require prompt treatment with methylene blue (in non G-6-PD deficient patients). Haemolysis may occur 7–14 days after an acute ingestion. Orally administered activated charcoal and haemodialysis have been shown to substantially enhance the elimination of dapsone and its main metabolite.

Storage
Dapsone may discolor following exposure to light; however, no chemical change is detectable. Dapsone tablets should be stored in well-closed, light resistant containers, at a temperature less than 40°C, preferably between 15–30°C.

FLUCONAZOLE
Group: antifungal agent
Suspension, 50 mg/5ml, 200 mg/5ml
Solution for infusion, 2 mg/ml in 25 ml and 100 ml ampoule [non-EDL]
Tablet, 50 mg, 100 mg, 200 mg [non-EDL]

General information
Fluconazole is a fungistatic triazole derivative that is particularly effective against Cryptococcus neoformans. It is well absorbed and passes readily across the blood-brain barrier into the cerebrospinal fluid. It is slowly eliminated unchanged in the urine.

Clinical information
Uses
- treatment and prophylaxis of cryptococcal meningitis
- treatment of oesophageal and resistant oropharyngeal candidiasis, and vaginal candidiasis.
- treatment and maintenance of coccidioidomycosis

Dosage and administration:
Cryptococcal meningitis
Following treatment with amphotericin B For either two weeks or until the condition has stabilised or improved: fluconazole 800 mg either orally or intravenously for two days followed by 400 mg once a day for 8 weeks, reduced to fluconazole 200 mg oral once a day thereafter.

Oesophageal and resistant oropharyngeal candidiasis
200 mg as an initial loading dose followed by 100 mg daily until symptoms have
resolved. Doses of up to 400 mg daily have been used in very resistant cases.  
**Vaginal candidiasis**  
150 mg as a single oral dose.  
**Coccidioidomycosis**  
400 mg orally or intravenously daily in patients unable to tolerate amphotericin B.

**Contraindications**  
Hypersensitivity toazole derivatives.

**Precautions**  
Dosage should be reduced in accordance with the creatinine clearance rate in patients with renal impairment.

**Use in pregnancy**  
Safe use in pregnancy has not been established. The need for treatment must be determined by the condition of the mother.

**Adverse effects**  
Fluconazole is generally well-tolerated. Nausea is the most frequently reported adverse effect. Vomiting and abdominal distension and discomfort are also reported.

Elevation of hepatic enzyme levels, which occurs in a small percentage of individuals, is readily reversible in the early stages. Treatment should be discontinued if signs develop that are suggestive of hepatic disease. Exfoliative skin disorders have been reported, but a casual association has not been established.

**Drug interactions**  
Concomitant administration of terfenadine, astemizole or cisapride should be avoided as potentially fatal cardiac irregularities including prolonged Q-T intervals and ventricular fibrillation may occur.

The hepatic metabolism of lipid soluble drugs such as ciclosporin, phenytoin, sulfonylureas, warfarin and rarely theophylline is inhibited. Rifampicin and rifabutin accelerate the clearance of fluconazole, the dose of fluconazole should be increased by one half to allow for this.

**Overdosage**  
No experience has been gained with overdosage of fluconazole. Induction of emesis and gastric lavage may be tried in the case of accidental overdosage.

**Storage**  
Tablets should be kept in well-closed containers, protected from light. Intravenous preparations should be stored in well-closed containers and should not be allowed to freeze.

![Flucytosine](https://example.com/flucytosine.png)  
**Group:** antifungal  
**Capsule, 250 mg [EDL]**  
**Solution for injection, 2.5 g in 250 ml [EDL]**

**General information**  
Flucytosine is a fluorinated pyrimidine, non-antibiotic antifungal agent. Flucytosine is deamminated to fluorouracil in fungal cells. It is believed to act as an antimetabolite by competing with uracil, thereby interfering with pyrimidine metabolism and ultimately RNA and protein synthesis. It is readily absorbed from the gut and is widely distributed through body tissues and fluids including the CSF. It is excreted mainly unchanged via the kidneys. The plasma half-life is 2.5–6 hours in people with normal renal function.
Clinical information

Uses
Treatment of cryptococcal disease in conjunction with amphotericin B

Dosage and administration
Treatment of cryptocoecal disease in conjunction with amphotericin B
100mg/kg/day in 3–4 divided doses
Intravenous flucytosine may be administered via a peripheral or central vein over 20 minutes.

Contraindications
Known hypersensitivity (anaphylaxis has been reported)
Pre-existing bone marrow depression

Precautions
Flucytosine may effect rapidly proliferating tissues, particularly the bone marrow and lining of the GI tract. The risk of bone marrow suppression appears to be increased if high serum concentration of flucytosine occur. The dose should be reduced if the patient’s renal function is impaired and serum concentrations of the drug should not exceed 80 micrograms/ml (levels of 25–50 micrograms/ml are normally effective). Reduce the dose in patients with renal impairment.

Use in pregnancy
Flucytosine should only be used during pregnancy when the potential benefits justify the possible risks to the foetus.

Adverse effects
Moderate hypoplasia of the bone marrow resulting in anaemia, leukopenia, pancytopenia, thrombocytopenia, or rarely agranulocytosis may occur. Death from aplastic anaemia has been reported. Nausea, vomiting, anorexia, abdominal bloating, diarrhoea, and rarely bowel perforation, and rash have also been reported. Confusion, hallucinations, headaches, sedation, vertigo, and liver enlargement have been reported more rarely.

Drug interactions
Possible additive toxicity with other myelosuppressive drugs e.g. zidovudine, ganciclovir, pyrimethamine, sulphonamides etc.
The dose of flucytosine needs to reduced in renal failure. Therefore caution with nephrotoxic drugs e.g. amphotericin B, foscarnet and pentamidine.

Overdosage
In the event of flucytosine overdosage the manufacturer recommends prompt use of gastric lavage or an emetic. Because flucytosine is eliminated essentially unchanged in urine, adequate fluid intake should be maintained and IV fluids given if necessary. Haematological parameters should be assessed frequently and liver and kidney function carefully monitored. Consideration should be given to the use of haemodialysis, which readily removes the drug in anuric patients.

Storage
Flucytosine capsules should be stored in tight, light resistant containers at a temperature less than 40°C. The solution for injection should not be allowed to freeze as precipitation will occur.

FOSCARNET

Group: antiviral

Solution for injection, 24 mg/ml 250 ml, 500 ml [non-EDL]
General information
Foscarnet is a non-nucleoside pyrophosphate analogue given by intravenous infusion. It is excreted mainly by the kidneys, the pharmacokinetics are complicated by the high incidence of renal function impairment during therapy, and deposition into and subsequent release of foscarnet from bone. Terminal half-lives of up to 87 hours have been reported. Foscarnet crossed the blood brain barrier in variable amounts.

Clinical information
Uses
Treatment of cytomegalovirus end organ disease and maintenance of CMV retinitis.
Treatment of resistant herpes or varicella virus infection

Dosage and administration
Treatment of cytomegalovirus end organ disease and maintenance of CMV retinitis.
A dose of 90 mg/kg (adjusted for renal function) should be given over 2 hours twice a day for 14-21 days or until symptoms have abated or healing has been confirmed (CMV oesophagitis). In CMV retinitis, if ganciclovir cannot be tolerated: foscarnet is administered at a dose of 90 mg/kg once a day (adjusted for renal function) over two hours indefinitely.

Treatment of resistant herpes or varicella virus infection
A dose of 60 mg/kg (adjusted for renal function) should be given twice (or 40 mg/kg three times) a day until healing has occurred. If no response is seen the dose should be increased to the CMV dose given above.
If foscarnet is being administered peripherally it is important that foscarnet is diluted by at least 50% to reduce the risk of local irritation. One litre of sodium chloride 0.9% should be administered either prior to or with each dose of foscarnet during the treatment phase to reduce the risk of nephrotoxicity. This is not necessary after the patient has been reduced to maintenance doses.

Contraindications
- known hypersensitivity
- concomitant administration of other nephrotoxic drugs
- pre-existing renal failure (<0.4 ml/min/kg)

Precautions
Foscarnet is extremely nephrotoxic, regular monitoring of renal function should occur during treatment (twice a week) and maintenance (once every two weeks), and the dose adjusted accordingly. 24 hour creatinine clearances should be carried periodically to confirm the dose being used. There is a high incidence of hypocalcaemia, hypokalaemia, hypophosphataemia and hypomagnesaemia: electrolytes should be monitored as above. Foscarnet concentrates in the urine and can cause genital ulceration especially in men with foreskins. At the start of therapy all patients should be told to wash the genital area with soap and water after they have urinated.

Use in pregnancy
Skeletal abnormalities have been seen in animal studies. However, the data was insufficient to define the potential teratogenicity of foscarnet in humans at the dosages used. Therefore, foscarnet should only be used in pregnancy if the potential benefits outweigh the risks to the foetus.
Adverse effects
Nephrotoxicity, hypomagnesaemia, hypocalcaemia, hypokalaemia, hyperphosphataemia, hypercalcaemia (accompanied by perioral tingling, numbness in the extremities, paraesthesia), hyperphosphataemia, headache, nausea, vomiting, rash, convulsions (though to be associated with hypocalcaemia), genital ulceration, and anaemia.

Drug interactions
Concurrent administration of other nephrotoxic drugs during treatment with foscarnet i.e. pentamidine, amphotericin B and aminoglycosides is contraindicated. During the maintenance phase, if there are no alternative therapies, they should be used with extreme caution.

Overdosage
Overdose has been reported in 33 patients, the highest dose being about 10 times the prescribed dose. Twenty-eight of the patients experienced adverse events and five patients suffered no ill effects in connection with foscarnet overdosing. Four patients died, one from respiratory/cardiac arrest 3 days after stop of foscarnet, one from progressive AIDS and renal failure approximately 2 months after the last foscarnet dose, one from end stage AIDS and bacteraemia 2 weeks after overdosing and one from multi-organ failure 11 days after stopping foscarnet. The pattern of adverse events reported in connection with overdose was in correspondence with the symptoms previously observed during foscarnet therapy. Haemodialysis increases foscarnet elimination and may be of value in severe overdose.

Storage
Store below 30°C, do not freeze.

GANCICLOVIR

Group: antiviral agent
Powder for injection, 500 mg in vial [non EDL]
Capsules, 250 mg [non-EDL]

General information
Ganciclovir is an acyclic nucleoside analogue of guanine that acts by disrupting DNA synthesis and inhibiting viral replication. The intravenous formulation is used to treat cytomegalovirus end organ disease, and the oral formulation as maintenance therapy for patients with CMV retinitis. Ganciclovir also has activity against herpes viruses.

After intravenous infusion ganciclovir readily penetrates into the brain and subretinal fluids. It has a plasma half-life of 3–4 hours and is excreted primarily in the urine.

Clinical information
Uses
Treatment of cytomegalovirus end organ disease and maintenance of CMV retinitis.

Dosage and administration
A dose of 5 mg/kg should be given by slow intravenous infusion over 1 hour twice a day for 14–21 days or until symptoms have abated or healing has been confirmed (CMV oesophagitis). In CMV retinitis this should be followed by oral ganciclovir 1g three times a day with food thereafter. If this has failed or the patient cannot tolerate oral medication,
intravenous ganciclovir should be given at a dose of 5 mg/kg daily thereafter.

Contraindications
Known hypersensitivity to purine nucleoside analogues.

Precautions
The dose should be adjusted in accordance with the creatinine clearance rate in patients with impaired renal function. The dose should be halved for patients receiving maintenance therapy.
The blood count should be monitored twice a week and every two days during the treatment period. Particular vigilance is required when ganciclovir is administered with other myelosuppressive therapy such as zidovudine (full dose is not usually tolerated and it may have to be stopped during the treatment period), trimethoprim/sulphamethoxazole, pyrimethamine and flucytosine.

Use in pregnancy
There is a high potential that ganciclovir will cause foetal malformations during pregnancy.

Adverse effects
The most common severe adverse effects are anaemia, leukopenias (especially neutropenia) and thrombocytopenia. Fever, rash, abnormal liver function tests, raised blood urea concentrations, behavioural changes, psychosis, convulsions and coma sometimes occur.

Drug interactions
Concomitant administration of zidovudine and other myelosuppressive drugs has been associated with severe haematological abnormalities.

As ganciclovir has activity against herpes viruses suppressive aciclovir therapy can be stopped. Occasionally herpes will relapse, this should then be treated using aciclovir in the usual doses.
Didanosine (ddl) significantly reduces absorption of ganciclovir.

Overdosage
Overdosage causes bone-marrow depression. Management is largely supportive; haemodialysis may be of value.

Storage
Capsules should be stored in well-closed containers. Vials of powder for injection should be stored below 25°C. Infusion solutions may be stored for up to 24 hours at 4°C.

ITRACONAZOLE
Group: antifungal
Capsules, 100 mg [non-EDL]
Solution, 10 mg/ml [non-EDL]

General information
Itraconazole is a synthetic triazole derivative antifungal agent.

Clinical information
Uses
- Treatment of resistant oral and oesophageal Candida
- Maintenance of cryptococcosis
- Treatment and maintenance of histoplasmosis
- Treatment and maintenance of aspergillosis
- Treatment and maintenance of penicillinosis
Dosage and administration

Treatment of resistant oral and oesophageal Candida
Doses start at 100 mg twice a day and can be increased to a maximum of 400 mg/day. To get a maximal topical effect, the solution should be swilled around the mouth for as long as possible before swallowing.

Maintenance of cryptococcosis following amphotericin therapy
200 mg three times a day for 3–4 days followed by 200 mg twice a day.

Treatment and maintenance of histoplasmosis, and aspergillosis.
200 mg three times a day for 3–4 days followed by 200 mg twice a day long-term.

Treatment and maintenance of penicillinosis
200 mg three times a day for 3–4 days followed by 200 mg twice a day.
Long-term suppressive therapy is continued at a dose of 200 mg once a day for life.

Contraindications
Known hypersensitivity
Concomitant administration of terfenadine, astemizole or cisapride (see under drug interactions).

Precautions
Itraconazole is an cytochrome P450 enzyme inhibitor, and will increase serum levels of drugs metabolised by this enzyme. Serum levels of itraconazole are reduced by concurrent use of enzyme inducers (see under drug interactions). Liver function tests should be monitored throughout therapy.
The capsules should be taken with food or an acidic drink to increase their bioavailability.
The solution contains a buffer and maximal absorption is achieved when it is taken on an empty stomach.

Use in pregnancy
Itraconazole should be used for the treatment of systemic fungal infections in pregnancy only when the potential benefits justify the possible risks to the foetus.

Adverse effects
Increased liver function tests, rarely idiosyncratic hepatitis, hypokalaemia leading to ventricular fibrillation, nausea, abdominal pain, dyspepsia, flatulence and headache. Rash and pruritis have been reported, in addition, urticaria, angiodema, and toxic epidermal necrolysis have been reported with anaphylaxis and Stevens-Johnson syndrome occurring rarely.

Drug interactions
Concomitant administration of terfenadine, astemizole or cisapride should be avoided as potentially fatal cardiac irregularities including prolonged Q-T intervals and ventricular fibrillation may occur.
Itraconazole requires an acidic environment for absorption. Drugs which increase the pH of the stomach (i.e. antacids, H2 blockers) can lead to decreased itraconazole absorption.
Itraconazole produces clinically significant increases in serum levels of the following drugs: midazolam, triazolam, digoxin, phenytoin, ciclosporin, sulphonylureas, saquinavir and indinavir. Clinically significant decreases in itraconazole serum levels are produced by rifampicin, rifabutin, phenobarbitone and phenytoin.
Overdosage
Patients should be treated symptomatically, with supportive measures and gastric lavage as necessary. No specific antidote is available. Itraconazole cannot be removed by haemodialysis.

Storage
Capsules: protect from light, store in a dry place between 15–30°C. Solution: store at 25°C or below.

**KETOCONAZOLE**
*Group: antifungal agent*
*Tablet, 200 mg [EDL]*
*Oral suspension, 100 mg/5 ml [EDL]*

**General information**
Ketoconazole is a synthetic imidazole derivative with fungistatic activity against a wide range of organisms. It is rapidly absorbed from the gastrointestinal tract and is partially metabolized in the liver. It is largely excreted in the faeces via the bile.

**Clinical information**
**Uses**
Treatment of oesophageal and resistant oropharyngeal candidiasis.

**Dosage and administration**
**Oral and oesophageal candidiasis**
200mg–400mg daily until remission is obtained. Ketoconazole should be taken with food or an acidic drink to increase its bioavailability.

The suspension can be used when the tablets have failed. Patients should be told to swill it around the mouth for as long as possible before swallowing to have an additional topical action.

**Contraindications**
- hypersensitivity toazole derivatives
- impaired hepatic function
- chronic alcohol dependence
- age less than 2 years
- concurrent rifampicin therapy

**Adverse effects**
Anaphylactic reactions have been reported following the first dose. Hypersensitivity may also present as pruritus, purpura or urticaria. Nausea and vomiting, abdominal pain, constipation, diarrhoea and transient increases in plasma concentrations of hepatic enzymes are common. Treatment should be withdrawn immediately if there is evidence of more severe hepatocellular damage. Gynaecomastia and menstrual irregularities have been reported. Adrenal suppression may occur at doses higher than 400 mg a day.

**Drug interactions**
Concomitant administration of terfenadine, astemizole or cisapride should be avoided as potentially fatal cardiac irregularities including prolonged Q-T intervals and ventricular fibrillation may occur.

Absorption of ketoconazole from the gastrointestinal tract is pH dependent. Concomitant administration of drugs that reduce gastric acid secretion, such as histamine H₂-receptor antagonists, and of other antacids should be avoided whenever possible.
Ketoconazole’s extensive binding to plasma proteins and inhibition of hepatic enzymes are responsible for certain drug interactions. The hepatic metabolism of lipid soluble drugs such as cyclosporin, phenytoin, sulfonylureas, warfarin and, rarely
theophylline, is inhibited. Rifampicin induces the metabolism of ketoconazole, and ketoconazole is thought to inhibit the absorption of rifampicin; therefore the two should not be used together. Protease inhibitors and ketoconazole should not be given together as ketoconazole increases serum levels of protease inhibitors.

**Overdosage**
Induction of emesis or gastric lavage should be undertaken in the event of overdose.

**Storage**
Ketoconazole tablets should be kept in well-closed containers.

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**Nystatin**

*Group: antifungal agent*

*Tablet, 500 000 IU [EDL]*

*Pessary, 100 000 IU [EDL]*

**General information**
Nystatin is an antifungal polyene antibiotic derived from *Streptomyces noursei*. It is effective against infections caused by a wide range of yeasts and yeast-like fungi.

**Clinical information**

**Uses**
Treatment of oral and vaginal candidiasis.

**Dosage and administration**

**Vaginal candidiasis:**
100 000 – 1000 000 IU as pessaries inserted high into the vagina nightly for at least 2 weeks.
Administration should be continued for 48 hours after clinical cure. Higher doses and longer period of treatment may be necessary in immunocompromised patients.

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**Oral candidiasis:**
One tablet four times daily; tablets should be sucked, not swallowed, and retained in the mouth for as long as possible. Therapy should be continued for at least 48 hours after symptoms have resolved.

**Contraindications and precautions**
Treatment should be discontinued if symptoms of irritation or sensitization occur.

**Use in pregnancy**
Nystatin is poorly absorbed, if at all. It has been shown to be safe in pregnancy.

**Adverse effects**
Mild and transient nausea, vomiting and diarrhoea may occur after oral administration. Irritation rarely occurs after topical application.

**Storage**
Tablets should be stored in well-closed containers. Pessaries should be stored below 15°C in well-closed containers, protected from light.

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**Pentamidine**

*Group: antiprotozoal agent*

*Powder for injection, 200 mg pentamidine isethionate in a vial [EDL]*

*Solution for nebulisation, 300 mg pentamidine in a nebul [non-EDL]*

**General information**
Pentamidine is a stable diamidine compound with antiprotozoal activity that is administered parenterally because it is absorbed unreliably from the gastrointestinal tract. It does not enter the cerebrospinal fluid. Detectable amounts remain in the liver and kidney for many
months as a result of selective binding. Excretion occurs mainly in the bile; a small fraction is excreted unchanged in the urine within 24 hours.

**Clinical information**

**Uses**
- Prophylaxis of *Pneumocystis carinii* pneumonia
- Treatment of *Pneumocystis carinii* pneumonia in patients unable to tolerate first-line treatment

**Dosage and administration**

**Prophylaxis Pneumocystis carinii** pneumonia:
300 mg (in solution for nebulisation or dissolve powder for injection in 6ml water for injection) by oral inhalation as a single dose every four weeks if CD4+ >100/mm³ or every 2 weeks if CD4+ count <100/mm³. The nebulizer should provide a particle size of less than 5 μm.

**Treatment of Pneumocystis carinii** pneumonia:
4 mg/kg by intravenous infusion over at least 60 minutes, daily for at least 3 weeks. For patients with renal failure, infusions should be administered on alternate days.

**Contraindications**
Known hypersensitivity to pentamidine.

**Precautions**
Because of the risk of hypotension and syncope all patients should remain supine and under observation for at least 30 minutes after each injection. Blood pressure, blood count and serum creatinine and blood glucose concentrations should be monitored regularly throughout treatment.

**Use in pregnancy**
Use in pregnancy can induce abortion.

**Adverse effects**
Nephrotoxicity is common, often necessitating dosage reduction or change in therapy. Rapid intravenous infusion can induce acute hypotension and syncope. Oral inhalation can precipitate bronchospasm. Pancreatic damage firstly induces hypoglycaemia due to excessive insulin release. Hyperglycaemia due to insulin insufficiency and pancreatitis may occur subsequently. Other adverse effects include hypocalcaemia, gastrointestinal effects, confusion, hallucinations and cardiac dysfunction. Local induration and sterile abscess formation can result from intramuscular administration. Rarely, thrombocytopenia, leukopenia, abnormal hepatic function tests and erythema multiforme (Stevens-Johnson syndrome) have been reported.

**PRIMAQUINE Group: antiprotozoal agent**
Tablet, 7.5 mg, 15 mg [EDL]

**General information**
Primaquine is a synthetic antimalarial agent that is a 8-aminoquinoline derivative. It is well absorbed from the GI tract, and widely distributed into body fluids. The plasma half-life is reported as 3.7–9.6 hours in healthy adults. It is rapidly metabolised in
the liver and only a small amount of the drug is excreted unchanged in urine.

Clinical information
Uses
Treatment of *Pneumocystis carinii* pneumonia

Dosage and administration
*Treatment of Pneumocystis carinii pneumonia*
15 mg daily for 21 days or to complete a course of 21 days of PCP therapy.

Contraindications
Patients with severe G–6–PD deficiency.

Precautions
Primquine should be discontinued immediately if evidence of haemolytic anaemia occurs especially in patients with G–6–PD deficiency or other defects of the erythrocytic pentose phosphate pathway of glucose metabolism or in patients with certain haemoglobinopathies. Methaemoglobinemia and leukopenia occur occasionally. Regular monitoring of the full blood count should occur throughout therapy.

Use in pregnancy
Safe use of primquine during pregnancy has not been established, but transplacental transfer of drug to a G–6–PD deficient foetus potentially could result in life-threatening haemolytic anaemia in utero. Primquine should only be used in pregnancy when the benefits outweigh the risks.

Adverse effects
Haemolytic anaemia, methaemoglobinemia and leukopenia (see under precautions). Nausea, vomiting, epigastric discomfort and mild to moderate abdominal cramps. GI side effects can be reduced by administering the primaquine with food. Other side effects include headache, interference with visual accommodation and pruritis, rarely hypotension and arrhythmias have also been reported.

Drug interactions
Concurrent administration of primaquine with quinacrine is contraindicated because of its ability to potentiate primaquine toxicity.

Overdosage
Symptoms include abdominal cramps, vomiting, dyspepsia, CNS and cardiovascular disturbances, cyanosis, methaemoglobinemia, moderate leukocytosis or leukopenia, and anaemia. The most striking symptoms are granulocytopenia and acute haemolytic anaemia in sensitive individuals. Acute haemolysis occurs but patients recover completely if the drug is discontinued.

Storage
Primquine phosphate tablets should be stored in well-closed, light resistant containers, at a temperature less than 40°C, preferably between 15–30°C.

**PYRIMETHAMINE**
*Group: antiprotozoal agent*
*Tablet, 25 mg, 50 mg [EDL]*

General information
Pyrimethamine is an inhibitor of folic acid metabolism that acts synergistically with sulfonamides to kill *Toxoplasma gondii* tachyzoites. The high doses required may also interfere with folic acid metabolism in the host.
The plasma half-life after oral administration is about 4 days. Pyrimethamine is partially metabolized in the liver and ultimately excreted in the urine.

**Clinical information**
**Uses**
- Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis
- Treatment of isoporidiosis

**Dosage and administration**
**Treatment of toxoplasmosis**
A total of 200 mg on the first day in divided doses followed by 50mg–75mg daily for 6 to 8 weeks. suppressive therapy with a daily dose of 25 mg should then be continued indefinitely.

Pyrimethamine is administered in combination with either sulphadiazine or clindamycin for the treatment and suppression of toxoplasmosis.

**Treatment of Isospora belli infection**
75 mg daily (with calcium folinate) until symptoms have resolved followed by 25 mg daily indefinitely.

**Contraindications**
- Known hypersensitivity to pyrimethamine
- Severe hepatic or renal dysfunction
- Pregnancy during the first trimester, except when the mother’s health is seriously endangered

**Precautions**
All patients should receive calcium folinate concurrently to prevent folinic acid deficiency resulting from high daily doses of pyrimethamine.

**Use in pregnancy**
Pyrimethamine is normally contraindicated during the first trimester, but administration should not be delayed when the mother’s health is seriously endangered. It should always be given thereafter to reduce the risk of congenital transmission.

**Adverse effects**
Anorexia, abdominal cramps, vomiting, ataxia, tremors and seizures have been reported. At the high doses required for the treatment of toxoplasmosis, pyrimethamine may induce thrombocytopenia, granulocytopenia and a megaloblastic anaemia due to folinic acid deficiency.

**Drug interactions**
Various other drugs, including all sulfonamides, trimethoprim and methotrexate act synergistically with pyrimethamine to inhibit folic acid metabolism. Calcium folinate can counteract the competitive blockade of folic acid metabolism and should be used.

**Overdosage**
Excessive doses of pyrimethamine are potentially fatal and induce anorexia, vomiting and seizures. Induction of gastric lavage is of value when undertaken within a few hours of ingestion. Convulsions may be controlled with parenteral diazepam.

**Storage**
Tablets should be kept in well-closed containers, protected from light and moisture.

*Group: antimicrobial agent*
*Capsule, 150 mg [non-EDL]*
General information
Rifabutin, a semisynthetic derivative of rifamycin S, is an ansamycin antibiotic similar to rifampicin. It is poorly absorbed from the GI tract, but is widely distributed. Approximately 70% is bound to plasma proteins. Both hepatic and renal elimination occurs. A terminal half-life of 36 hours has been reported.

Clinical information
Use
Treatment of *Mycobacterium avium* complex

Dosage and administration
*Treatment of Mycobacterium avium* complex
300 mg (<50kg) or 450mg >50kg daily in combination with ethambutol and clarithromycin
Rifabutin can be taken without regard to food.

Contraindications
- Known hypersensitivity
- Concomitant administration of ritonavir, or saquinavir

Precautions
Rifabutin may impart a red/orange colour to urine, faeces, tears, sputum and sweat. Patients should be warned of this and the possibility of it staining soft contact lenses
Rifabutin has been reported to cause neutropenia and uveitis especially when used in combination with cytochrome P450 enzyme inhibitors such as fluconazole, clarithromycin and azithromycin. The patient should be monitored regularly for these conditions.

The dose of rifabutin should be reduced by 50% in patients with a creatinine clearance below 30 ml/min.

Use in pregnancy
At high doses skeletal abnormalities were observed in animal studies. However, no studies have been conducted on the use of rifabutin in pregnant women. Therefore it should only be used if the benefits outweigh the potential risks to the foetus.

Adverse effects
Nausea, vomiting, discolouration of skin and urine (orange), increased liver function tests, and leukopenia. At high doses polyarthritis/arthritis, transient aphthous stomatitis and uveitis have been reported.

Drug interactions
Rifabutin should not be used with protease inhibitors ritonavir, or saquinavir or with non-nucleoside reverse transcriptase inhibitor, delavirdine. Use with enzyme inhibitors such as clarithromycin, azithromycin, and fluconazole has been reported to increase the incidence of neutropenia, and uveitis; this could also be expected with other drugs of the same classes e.g.itraconazole, ketoconazole, erythromycin etc.

Rifabutin induces hepatic microsomal enzymes. Patients on concurrent medications including analgesics, azole antifungals, coumarin anticoagulants, cortico-steroids, dapsone, oral hypoglycaemic agents and anti-epileptics should be monitored for decreased therapeutic effect. Women taking oral contraceptives should be advised to take additional precautions. These should be continued for 4–8 weeks if the rifabutin is stopped.
Overdosage
Gastric lavage and diuretic treatment should be carried out.

Storage
No special storage requirements are necessary.

**SULFADIAZINE**
*Group: antimicrobial agent*
*Tablet, 500 mg [EDL]*
*Solution for injection, 250 mg/ml in 4 ml ampoule [EDL]*

**General information**
Sulfadiazine is an inhibitor of folic acid metabolism in bacteria and protozoa that acts synergistically with pyrimethamine. Sulfadiazine is rapidly absorbed from the gastrointestinal tract and widely distributed in the body. The serum half-life is about 10–12 hours. After partial acetylation in the liver it is excreted in the urine.

**Uses**
Toxoplastic encephalitis and other manifestations of active toxoplasmosis.

**Dosage and administration**
100 mg/kg to a maximum of 6 g/day in divided doses for 6 to 8 weeks followed by suppressive dose of 2–4 g daily to be continued indefinitely.
Sulfadiazine is administered in combination with pyrimethamine for the treatment and suppression of toxoplasmosis.

**Contraindications**
- known hypersensitivity to sulfonamides
- pregnancy during the first trimester except when the mother’s health is seriously endangered
- severe hepatic or renal dysfunction

**Precautions**
Patients receiving sulfadiazine and pyrimethamine should be given calcium folinate concurrently to prevent folinic acid deficiency.
The blood count should be monitored twice weekly throughout therapy to detect signs of bone-marrow depression. Administration should be discontinued immediately should presumptive signs of hypersensitivity occur, such as skin rashes, dark urine and purpura.

Sulfadiazine is less soluble in urine than many other sulfonamides. Patients should be advised to maintain a high fluid intake and urine output to prevent the development of sulfadiazine induced crystalluria, and to watch for signs of ‘gravel’ (sulfadiazine crystals) in their urine.
In patients with impaired kidney function (creatinine clearance 20–50 ml/min) the treatment dose of sulfadiazine should be reduced to 1 g four times a day.

**Use in pregnancy**
Administration of sulfonamides during pregnancy can induce severe hypersensitivity reactions in the mother. Their action in displacing bilirubin from protein-binding sites has given rise to concern, based on data derived from premature neonates, that they may promote kernicterus. Although sulfonamides readily cross the placental barrier, there is no conclusive evidence that the foetus is at risk. Nevertheless, sulfadiazine should not be administered during the first trimester, except when the mother’s health is seriously endangered.

**Adverse effects**
Nausea, vomiting, diarrhoea and headache sometimes occur.
Sulphonamide-induced hypersensitivity reactions can be severe. They include rare life-threatening cutaneous reactions such as erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis. Crystalluria may result in dysuria, renal colic, haematuria and acute renal obstruction. Other occasional adverse effects include granulocytopenia, thrombocytopenic purpura, agranulocytosis, aplastic anaemia and toxic hepatitis. Haemolysis occasionally occurs in individuals deficient in glucose-6-phosphate dehydrogenase.

**Overdosage**
Continuous forced diuresis may be beneficial and an alkaline urine should be maintained. Treatment is otherwise symptomatic.

**Storage**
Tablets should be kept in well-closed containers, protected from light. Solution for injection should be kept in ampoules.

**SULFADOXINE:**

**PYRIMETHAMINE**

qryxwr

*Group: antiprotozoal agent*
*Tablet, 500 mg [EDL] and 25 mg [EDL]*

**General information**
The two components of this combination product have antiprotozoal activity. They operate synergistically because they independently inhibit different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process. Sulfadoxine is a long acting sulphonamide. It is well absorbed from the GI tract and widely distributed in the body. The average plasma half-life of sulfadoxine is 170 hours (100–230 hours). It is excreted mainly in the urine. (see under pyrimethamine for additional information)

**Clinical information**

**Use**
Prophylaxis of *Pneumocystis carinii* pneumonia

**Dosage and administration**

*Prophylaxis of Pneumocystis carinii pneumonia*
1 or 2 tablets weekly indefinitely

**Contraindications**
- Known hypersensitivity reactions to sulphonamides or to pyrimethamine
- Liver or renal impairment
- Documented history of megaloblastic anaemia secondary to folate deficiency

**Precautions**
Severe sometimes fatal hypersensitivity reactions have occurred with this combination. In most cases fatalities resulted from severe cutaneous reactions, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Patients should be warned to stop the drug immediately if a rash occurs. Fatal hepatitis has also been reported, liver function test should be routinely monitored and the drug discontinued immediately if they become abnormal. Haemolysis may occur in patients with G-6-PD deficiency.

**Use in pregnancy**
The combination of sulfadoxine and pyrimethamine is best avoided during pregnancy as it may give rise to kernicterus of the new-born. However, the need for PCP prophylaxis should be weighed against the risk to the new-born.
Adverse effects
Severe cutaneous reactions and fatal hepatitis have been reported (see under precautions). Leukopenia, reversible granulocytopenia, and agranulocytosis have been reported. Other hypersensitivity reactions include; serum-sickness reactions, urticaria, pruritis, exfoliative dermatitis and photosensitivity.

Drug interactions
See under pyrimethamine and sulphadiazine

Overdosage
See under pyrimethamine. In addition, overdosage of sulfadoxine/pyrimethamine may result in megaloblastic anaemia, leukopenia, thrombocytopenia, glossitis, and crystalluria.

Storage
Store in well closed light resistant containers.

SULFAMETHOXAZOLE
(TRIMETHOPRIM)
(COTRIMOXAZOLE)
Group: antimicrobial agent
Tablet, 100 mg of sulfamethoxazole + 20 mg of trimethoprim, 400 mg + 80 mg [EDL]
Oral suspension, 200mg+40mg/5ml [EDL]
Injection, 80 mg + 16 mg/ml in 5 and 10 ml ampoule [EDL]

General information
The two components of this combination product have a similar antimicrobial spectrum and both have antiprotozoal activity. They operate synergistically because they independently inhibit different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible organisms. Trimethoprim is absorbed more rapidly, is more widely distributed in tissues, and enters the cerebrospinal fluid more quickly than sulfamethoxazole. Both compounds are moderately bound to plasma proteins, and each is excreted largely unchanged in the urine at a rate that gives a plasma half-life of about 12 hours.

Clinical information
Uses
- Treatment and prophylaxis of pneumonia due to Pneumocystis carinii.
- Treatment of diarrhoea due to Isospora belli infection.

Dosage and administration
Pneumonia due to Pneumocystis carinii pneumonia in patients with HIV infection
Sulfamethoxazole 75 mg/kg + trimethoprim 15 mg/kg oral/IV daily in divided doses for 21 days.
The intravenous dose is routinely administered as 2 infusions/day, and the oral dose three or four times a day to reduce the incidence of nausea.
Intravenous infusions are administered in glucose 5% over at least 90 minutes. Oral dosage forms should be substituted as soon as they can be tolerated.
Pneumocystis carinii pneumonia prophylaxis
Sulfamethoxazole 800 mg + trimethoprim 160 mg once a day on three days of the week.
Diarrhoea due to Isospora belli
Sulfamethoxazole 800 mg + trimethoprim 160 mg four times a day for 10 days followed by twice a day for two weeks.
Isospora bell prophylaxis
Sulfamethoxazole 800 mg + trimethoprim 160 mg once daily on three days of the week.

Contraindications
- known severe hypersensitivity to sulfamethoxazole/trimethoprim
- severe hepatic or renal dysfunction

Precautions
In patients with *Pneumocystis carinii* pneumonia whose arterial oxygen tension is less than 70 mm Hg (9.33kPa), the risk of death during the first few days of treatment can be substantially reduced if a corticosteroid is administered as soon as therapy is started.

Treatment should be suspended immediately should a rash or any other manifestation of sulphonamide hypersensitivity occur.

The risk of sulphonamide crystalluria is decreased by maintaining a daily urinary output of at least 1.5 litres.

Patients should be advised to seek medical advice should they develop a sore throat or fever during treatment. This advice can be of greater value than routine monitoring of the white cell count.

Since elderly patients may more susceptible to severe adverse reactions, especially blood dyscrasias, their treatment should not be unnecessarily prolonged.

The dose of sulfamethoxazole/trimethoprim should be reduced in patients with impaired renal function. If the creatinine clearance (ml/min) is < 25 ml/min give standard dose for 3 days then reduce the dose by 50%. Do not use if creatinine clearance < 13 ml/min.

Patients deficient in folate may require supplementary calcium folinate to prevent myelosuppression.

Use in pregnancy
Treatment of patients with *Pneumocystis carinii* pneumonia, which is life-threatening, should in no circumstances be delayed. Sulfamethoxazole/trimethoprim is the best form of PCP prophylaxis and is recommended in pregnant women.

Adverse effects
Nausea, vomiting, glossitis and skin rashes are common. Recurrent fever, neutropenia, thrombocytopenia and increases in serum levels also occur frequently. Trimethoprim may induce a megaloblastic anaemia responsive to calcium folinate. Sulphonamide-induced hypersensitivity can be severe. They include life-threatening cutaneous reactions such as erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis. Other reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Haemolysis occasionally occurs in individuals deficient in glucose-6-phosphate dehydrogenase.

Drug interactions
Maintenance requirements for sulfonylureas and coumarin anticoagulants are often reduced as a result of their displacement from plasma proteins by sulfamethoxazole.

Concomitant use of other inhibitors of folate metabolism (such as pyrimethamine, methotrexate and certain anticonvulsants) may increase the risk of myelosuppression.
Folic acid can counteract the competitive blockade of folic acid metabolism and should not be used.

Caution when used concurrently with zidovudine. Regular haematological monitoring is advisable.

Overdosage
Symptoms of acute overdosage include vomiting, dizziness and confusion followed by visual disturbances, petechiae, purpura and jaundice. Crystalluria, haematuria and anuria may also occur.

Emesis or gastric lavage may be of value within a few hours of ingestion. Provided urinary output is satisfactory, a high fluid intake should be maintained. Haemodialysis may be of value in eliminating some of the drug. Otherwise, treatment is symptomatic and supportive.

Storage
Tablets, oral suspension and concentrate for infusion should be stored, protected from light, in well-closed containers.

TRIMETHOPRIM
Group: antimicrobial agent
Tablet, 100 mg, 200 mg, [EDL]
Suspension, 50mg/5 ml [EDL]
Solution for injection, 20mg/5ml 5ml ampoule [EDL]

General information
Trimethoprim is a synthetic folate-antagonist anti-infective. By inhibiting the synthesis of tetrahydrofolic acid, the metabolically active form of folic acid, trimethoprim inhibits bacterial thymidine synthesis.

Trimethoprim is readily absorbed from the GI tract. It distributes widely into body tissues and fluids including the CSF. The plasma half-life is 8–11 hours, it is metabolised in the liver and rapidly eliminated via the kidneys by glomerular filtration and tubular secretion.

Clinical information
Uses
Treatment of *Pneumocystis carinii* pneumonia (PCP) (with dapsone)

Dosage and administration
*Treatment of Pneumocystis carinii pneumonia* (PCP) in combination with dapsone
20 mg/kg/day oral/IV in 2–3 divided doses for 21 days or to complete a 21 day course of therapy for the treatment of PCP in combination with dapsone.

Trimethoprim may be administered as a slow IV bolus, or added to 100 ml Glucose 5% or sodium chloride 0.9% and infused over 30 minutes.

Contraindications
- Known hypersensitivity to trimethoprim
- Documented history of megaloblastic anaemia secondary to folate deficiency

Precautions
Reduce the dose in renal failure. If the creatinine clearance is between 10 and 25 ml/min, give the normal dose for three days and then half the normal dose. If the creatinine clearance is less than 10ml/min give half the normal dose and monitor serum levels.

Trimethoprim increases serum levels of phenytoin; monitor for signs of phenytoin
toxicity, and serum levels. The effect of coumarin anticoagulants may be enhanced.

Potentiation of folate deficiency may occur if trimethoprim is given with other anti-folate drugs e.g. phenytoin. Folic acid can counteract the competitive blockade of folic acid metabolism and should not be used.

**Overdosage**

Overdose may produce nausea, vomiting, diarrhoea, mental depression, confusion, facial swelling, headache, bone marrow depression and slight elevation of liver transaminases. Acidification of the urine may enhance elimination of the drug. Haemodialysis may remove only moderate amounts of trimethoprim from the serum, peritoneal is ineffective in enhancing elimination.

**Storage**

Tablets should be stored in a tight, light resistant container at 15–30°C in a dry place.
WHO Model Prescribing Information is being prepared to provide up-to-date and independent clinical information on essential drugs, including details of dosage, uses, contraindications and adverse effects. It is intended as source material for adaptation by national authorities, in particular in developing countries, that wish to produce drug formularies, data sheets and teaching materials.

This update of the volume on HIV-related illnesses covers drugs currently used for the prophylaxis, treatment and palliative care of patients with opportunistic infections and other illnesses related to HIV infection. For further information on the drugs used in the treatment of early HIV infection see The implications of antiretroviral treatments WHO/ASD 97.2 and Guidance Modules on Antiretroviral Treatments WHO/ASD 98.1UNAIDS 98.7.