Treatment and Prevention of Opportunistic Infections

Referral Hospitals in Resource-limited Settings

ITM 2004
Lut Lynen
FOREWORD

World wide, more than 40 million people are infected with HIV and rely on knowledgeable compassionate providers of care to help them understand a complicated illness, to assist them in coping with HIV-related diseases, and to provide them with comfort and treatment needed to improve the quality and length of their life.

In order to meet these goals, it is essential to mobilize all available health care providers and resources in order to ensure that the burden of care is distributed across a continuum extending from homes and community settings to health centres and hospitals.

Humane care and timely referral of patients requires informed health staff working closely with families, both in health facilities and communities. Health care workers need skills in recognition, diagnosis and treatment of HIV-related conditions, including tuberculosis and sexually transmitted infections. People living with HIV and their families need counselling and education about care and prevention in order to psychologically cope with their diagnosis and to live positively.

In order to achieve the goal of “3x5” WHO has developed IMAAI guidelines, to take care of HIV patients at health centre and health station level.

This manual presents background information about HIV epidemiology and transmission, an overview of AIDS care and the management of opportunistic infections at the hospital level. Also the importance of palliative care and symptom relief is highlighted.

Chronic HIV care and palliative care and counselling are covered by the WHO IMAAI guidelines. Home based care, counselling and training of home caregivers is dealt within the care giver booklet (WHO 2003).

HIV/AIDS is a dynamic epidemic requiring strategic care and support responses that are flexible, in order to fit the evolving needs for comprehensive care across the continuum. Thus, this manual is based on the existing knowledge and practices, but will be updated in order to guide health staff in their important roles in HIV/AIDS prevention and care.

The aim of this manual is to provide doctors at the referral hospital with tools to provide specialty care for people living with HIV.

Resource documents used to write this manual:
- Eritrean HIV/AIDS Care Manual 2001
- MSF-B/L 2001: Clinical AIDS Care Guidelines for Resource-poor settings

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<tr>
<td>ABV</td>
<td>Adriamycine, Bleomycine and Vincristine</td>
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<tr>
<td>AFB</td>
<td>Acid Fast Bacilli</td>
</tr>
<tr>
<td>AIDP</td>
<td>Acute inflammatory demyelinating polyneuropathy</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
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<tr>
<td>ARC</td>
<td>AIDS Related Complex</td>
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<tr>
<td>ARV</td>
<td>Antiretroviral therapy (or drugs)</td>
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<tr>
<td>AZT</td>
<td>Zidovudine</td>
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<tr>
<td>BAL</td>
<td>Broncho-Alveolar Lavage</td>
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<tr>
<td>BID</td>
<td>Twice Daily</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
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<tr>
<td>BV</td>
<td>bleomycine, vincristine</td>
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<tr>
<td>BW</td>
<td>Body Weight</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
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<tr>
<td>CDC</td>
<td>Centre for Disease Control</td>
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<tr>
<td>CIDP</td>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
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<tr>
<td>CL</td>
<td>Cutaneous Leishmaniosis</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>CrAg</td>
<td>Cryptococcal antigen</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CVA</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>d4T</td>
<td>Stavudine</td>
</tr>
<tr>
<td>D5W</td>
<td>Dextrose 5% in water</td>
</tr>
<tr>
<td>DC</td>
<td>Developing Countries</td>
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<tr>
<td>ddl</td>
<td>Didanosine</td>
</tr>
<tr>
<td>DRESS</td>
<td>Diarrhoea, Rash, Eosinophilia, Systemic Symptoms</td>
</tr>
<tr>
<td>DSP</td>
<td>Distal, symmetrical polyneuropathy</td>
</tr>
<tr>
<td>EEG</td>
<td>Electro Encephalogram</td>
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<tr>
<td>EFV</td>
<td>Efavirenz</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
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<tr>
<td>EPO</td>
<td>erythropoietin</td>
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<tr>
<td>ESR</td>
<td>Sedimentation Rate</td>
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<tr>
<td>Fe</td>
<td>Serum Iron</td>
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<tr>
<td>GBS</td>
<td>Guillain Barré Syndrome</td>
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<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
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<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<tr>
<td>HHV8</td>
<td>(Sexually Transmitted) Human Herpes Virus 8</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HSV</td>
<td>Herpes Simplex Virus</td>
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<tr>
<td>HTLV-1</td>
<td>Human T Lymphotropic virus - 1</td>
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<tr>
<td>ICP</td>
<td>Intracranial Pressure</td>
</tr>
<tr>
<td>IM</td>
<td>Intra-muscular</td>
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<tr>
<td>IMAAI</td>
<td>Integrated Management of Adult and Adolescents Illnesses</td>
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<tr>
<td>INH</td>
<td>isoniazid</td>
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<tr>
<td>IPT</td>
<td>INH preventive therapy</td>
</tr>
<tr>
<td>IR</td>
<td>Intrarectal</td>
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<tr>
<td>IRIS</td>
<td>Immune Reconstitution Inflammatory Syndrome</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>IRU</td>
<td>Immune Recovery Uveitis</td>
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<tr>
<td>ITP</td>
<td>Immune Thrombocytopenia</td>
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<tr>
<td>IU</td>
<td>International Units</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IVDU</td>
<td>IV Drug Use</td>
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<tr>
<td>IVIG</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>KCL</td>
<td>Potassium Chloride</td>
</tr>
<tr>
<td>KOH</td>
<td>Potassium Hydroxide</td>
</tr>
<tr>
<td>KS</td>
<td>Kaposi's sarcoma</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<tr>
<td>LIP</td>
<td>Lymphoid interstitial pneumonitis</td>
</tr>
<tr>
<td>LN</td>
<td>Lymph Node</td>
</tr>
<tr>
<td>LP</td>
<td>Lumbar Puncture</td>
</tr>
<tr>
<td>MAC</td>
<td>Mycobacterium Avium Complex</td>
</tr>
<tr>
<td>MAI</td>
<td>Mycobacterium Avium Intracellulare</td>
</tr>
<tr>
<td>MEDL</td>
<td>Model Essential Drug List</td>
</tr>
<tr>
<td>Mg</td>
<td>Magnesium</td>
</tr>
<tr>
<td>MM</td>
<td>Mononeuropathy Multiplex</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTCT</td>
<td>Mother-to-Child Transmission</td>
</tr>
<tr>
<td>NA</td>
<td>Not Available</td>
</tr>
<tr>
<td>NHL</td>
<td>Non-Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside reverse transcriptase inhibitors</td>
</tr>
<tr>
<td>NSAID</td>
<td>non steroidal anti-inflammatory drugs</td>
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<tr>
<td>NVP</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>OC</td>
<td>Oesophageal Candidiasis</td>
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<tr>
<td>OD</td>
<td>Once Daily</td>
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<tr>
<td>OI</td>
<td>Opportunistic Infection</td>
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<td>ORS</td>
<td>Oral rehydration salts</td>
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<tr>
<td>PCP</td>
<td>Pneumocystis carinii pneumonia</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PEP</td>
<td>Progressive encephalopathy</td>
</tr>
<tr>
<td>PGL</td>
<td>Persistent Generalized Lymphadenopathy</td>
</tr>
<tr>
<td>PI</td>
<td>Protease inhibitors</td>
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<tr>
<td>PLHA</td>
<td>People living with HIV/AIDS</td>
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<tr>
<td>PML</td>
<td>Progressive Multifocal Leukoencephalopathy</td>
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<tr>
<td>PMN</td>
<td>Polymorphonuclear leukocytosis</td>
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<tr>
<td>PMTCT</td>
<td>Prevention of Mother-To-Child Transmission of HIV</td>
</tr>
<tr>
<td>PRN</td>
<td>as needed</td>
</tr>
<tr>
<td>PO</td>
<td>per os</td>
</tr>
<tr>
<td>PP</td>
<td>Progressive Polyradiculopathy</td>
</tr>
<tr>
<td>PPE</td>
<td>Papular Pruritic Eruption</td>
</tr>
<tr>
<td>PT</td>
<td>Preventive therapy</td>
</tr>
<tr>
<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RPR</td>
<td>Syphilis tests (Rapid Plasma Reagin)</td>
</tr>
<tr>
<td>RTV</td>
<td>Ritonavir</td>
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<tr>
<td>SC</td>
<td>Subcutaneous</td>
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<tr>
<td>SCrAg</td>
<td>Serum Cryptococcal Antigen</td>
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<tr>
<td>STD</td>
<td>Sexually Transmitted Disease</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually Transmitted Infection</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TB DOTS</td>
<td>Tuberculosis Directly Observed Treatment – Short course</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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</tr>
<tr>
<td>TCA’s</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>TIBC</td>
<td>Total Iron Binding Capacity</td>
</tr>
<tr>
<td>TLC</td>
<td>Total Lymphocyte Count</td>
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<tr>
<td>TMP/SMX</td>
<td>Trimetroprim/sulphamethoxazole</td>
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<tr>
<td>TPHA</td>
<td>Treponema Pallidum hemaglutination</td>
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<tr>
<td>TST</td>
<td>Tuberculin Skin Test</td>
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<tr>
<td>UNAIDS</td>
<td>United Nations Joint Programme on AIDS</td>
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<td>UTI</td>
<td>Urinary Tract infections</td>
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<tr>
<td>VCT</td>
<td>Voluntary Counseling and Testing</td>
</tr>
<tr>
<td>VL</td>
<td>Viral load</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1 Introduction to HIV/AIDS

1.1 HIV Epidemiology

At the end of 2003 an estimated number of 40 million people are living with HIV/AIDS worldwide. In 2003 there were 5 million new HIV infections estimated and 3 million people died because of AIDS. While in sub-Saharan Africa, with an estimated number of 28 million HIV positives, the HIV epidemic has taken devastating proportions, more recent epidemics like in Asia and Eastern Europe, continue to grow.

1.2 HIV Transmission

The major mode of transmission of HIV in the world is through sexual intercourse. Mother to child transmission (MTCT) and blood exchange are the next two highest modes of transmission of HIV, although blood transfusion is now relatively rare, with the launching of HIV blood screening programs. In most Sub-Saharan African Nations the number of men and women infected is equal. Other sexually transmitted diseases, particularly those causing genital ulceration, increase the risk of HIV transmission dramatically. The risk of HIV transmission through receptive vaginal intercourse is from 8-20 per 10,000 exposures, for insertive vaginal sex it is 3-9 per 10,000 exposures. However, in the presence of genital ulcer disease or during menstruation the risk is much higher. Blood-borne HIV transmission usually occurs through HIV contaminated blood transfusions, injections with contaminated needles and syringes, and the use of non-sterile skin-piercing instruments. About 25-35% of children born to HIV infected mothers will remain HIV infected if nothing is done to prevent transmission. This percentage will increase to 50% in case the mother is breastfeeding the infant, as is recommended in most developing countries.

There is no evidence of HIV transmission through the day-to-day contact, such as hugging, kissing, eating together or bites through mosquitoes or other insects.

1.3 Immunopathogenesis of HIV Infection

The HIV virus attacks the CD4 cells. The CD4 T-cells are the helper subset of T-lymphocytes (white blood cells) and are central to cell-mediated immunity. These cells carry the CD4 antigen on their surface (CD4 + lymphocytes). HIV recognizes the CD4 antigen, and enters and infects CD4 + lymphocytes. The result is the destruction of many CD4 + lymphocytes, resulting in progressive immune deficiency and the occurrence of opportunistic infections, leading to death.
1.4 Natural History of HIV Infection (Stages of Infection)

1.4.1 Primary Infection or Acute Retroviral Syndrome
The initial event after HIV transmission is the acute retroviral syndrome. Signs and symptoms of acute retroviral syndrome include fever, myalgia (muscle pain), headache, nausea, vomiting, diarrhea, night sweats, weight loss, and rash. These signs and symptoms usually occur two to four weeks after infection, subside after a few days, and often are misdiagnosed as influenza or infectious mononucleosis. This stage is characterized by a very high viral load, and is a time of great risk for HIV transmission due to lack of awareness of HIV positive status, because the HIV test can still be negative at this stage. The HIV serologic test can remain negative up to 3 months, while the infected person is highly contagious.

1.4.2 Latent infection (CDC clinical category A)
Subsequently, most people infected with HIV have no symptoms for months or years; this period of silent infection is called the latency period. The latency period may vary from 4 months to greater than 10 years, but the average is a period of 5 years without symptoms. The HIV antibody test is positive. There is continued viral replication and gradual decrease of CD4 count. This is when all the infections are transmitted, unknowingly, unless serostatus is known and behaviour change accepted through voluntary counseling and testing (VCT).
In the early latent infection the CD4 count is usually above 500. In this stage, which may last eight to ten years, the HIV-infected individual will not have signs and symptoms of HIV infection. The rate at which the CD4 count will decline is mainly influenced by the viral set point = the total body viral load established early in the course of HIV, after the decline of viral load as a result of the immune response. High viral load (>100,000 copies/ml) predicts a more rapid decline in CD4. Low viral load (< 1000 copies/ml) predicts a favorable course. This type of patient may become a long-term non–progressor, which is generally defined as a patient whose CD4 count remains above 200 for more than 10-20 years without treatment. On average the set point is 30,000-80,000 copies/ml and the average CD4 decline of 30-70 cells/mm³ per year.

1.4.3 Early Signs and Symptoms of HIV (CDC Clinical Category B)
The HIV-infected person may appear to be healthy for years and then minor signs and symptoms of HIV infection begin to appear. The person may experience candidiasis, lymphadenopathy, cervical carcinoma, herpes zoster, and/or peripheral neuropathy. Once the person develops a Category B condition, he or she remains in Category B. He or she can be reassigned to Category C if a condition from this category occurs, but the person cannot be reassigned to Category A if he or she becomes asymptomatic. The CD4 count has declined and is situated between 200 and 500.

1.4.4 AIDS (Clinical Category C)
The viral load continues to increase and the CD4 count falls to < 200. The individual has met the definition of AIDS. AIDS is defined as the presence of an AIDS defining complication (see Table 1: AIDS-defining diagnoses) or as the presence of a significant immune deficiency (CD4 count < 200). The HIV-infected person develops life-threatening infections and malignancies. The development of Pneumocystis carinii pneumonia, toxoplasmosis, cryptosporidiosis, and other opportunistic infections is common. The person may be wasting or losing weight. Without treatment, the median
survival, once the CD4 count has dropped < 200, is 3.7 years. The median CD4 count at the time of the first AIDS-defining event is 60-70. The median survival after an AIDS defining-event is 1.3 years. Once a Category C condition has occurred, the person remains in Category C even if the condition resolves.

**Table 1: AIDS-defining diagnoses**

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis: oesophagus*</td>
</tr>
<tr>
<td>Cervical cancer: invasive</td>
</tr>
<tr>
<td>Cryptococcosis-extrapulmonary</td>
</tr>
<tr>
<td>Cryptosporidiosis with diarrhoea &gt; 1 month</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV): any organ except spleen, liver, or lymph nodes</td>
</tr>
<tr>
<td>Herpes simplex with mucocutaneous ulcer &gt; 1 month or with bronchitis, pneumonia, esophagitis</td>
</tr>
<tr>
<td>Histoplasmosis-extrapulmonary*</td>
</tr>
<tr>
<td>HIV-associated dementia</td>
</tr>
<tr>
<td>HIV-associated wasting with involuntary loss of &gt; 10% body weight + chronic (&gt;30 days) diarrhoea or chronic fever</td>
</tr>
<tr>
<td>Isosporiasis with diarrhoea &gt; 1 month</td>
</tr>
<tr>
<td>Kaposi's sarcoma &lt; 60 years age, or &gt; 60 years*</td>
</tr>
<tr>
<td>Lymphoma of brain &lt; 60 years age, or &gt; 60 years</td>
</tr>
<tr>
<td>Lymphoma-non-Hodgkin’s</td>
</tr>
<tr>
<td>M. avium or M. kansasii disseminated</td>
</tr>
<tr>
<td>M. tuberculosis-disseminated* or pulmonary*</td>
</tr>
<tr>
<td>Nocardia</td>
</tr>
<tr>
<td>P. carinii pneumonia*</td>
</tr>
<tr>
<td>Pneumonia, recurrent*</td>
</tr>
<tr>
<td>Progressive multifocal encephalopathy</td>
</tr>
<tr>
<td>Salmonella septicemia*</td>
</tr>
<tr>
<td>Strongyloides extraintestinal</td>
</tr>
<tr>
<td>Toxoplasmosis of internal organ</td>
</tr>
<tr>
<td>* requires positive HIV serology</td>
</tr>
</tbody>
</table>

**1.4.5 Advanced AIDS (Clinical Category C)**

There is no official definition for advanced AIDS. However, experienced HIV/AIDS-treating physicians will consider advanced AIDS if an HIV-infected individual continues to develop new opportunistic infections such as cytomegalovirus infection, Mycobacterium avium complex, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and other infections that commonly occur, secondary to a severely depressed immune system. The viral load is very high and the CD4 count is < 50 cells/mm. Death is imminent.

Critical predictors of disease progression are viral load and absolute CD4 count. Also a history of a previous preventable opportunistic infection is an independent risk factor for chronic mortality.
Figure 1: Natural Course of HIV infection

Natural Course of HIV Infection and Common Complications

- **CD4+ T cells**
- **VL**

**Months** | **Years After HIV Infection**
--- | ---
0 | 0
1 | 1
2 | 2
3 | 3
4 | 4
5 | 5
6 | 6
7 | 7
8 | 8
9 | 9
10 | 10
11 | 11

**Acute seroconversion syndrome**
HIV test may be negative

**Latency period**
Asymptomatic HIV test positive

**Early HIV related disease**
HIV test positive

**AIDS defining events**
Low CD4 and high viral load (the serologic test can become negative = rare)
1.5 Laboratory Diagnosis of HIV Infection

Diagnosis of HIV is an important component of HIV/AIDS care. It should be preceded by appropriate counselling and it is very important that test results are dealt with in a correct way. Especially in infants it can be complicated to diagnose HIV. It is very important that we understand the meaning of a positive and negative HIV test to give correct information to our patients.

**A diagnosis of HIV should be based on a positive HIV test.**

### 1.5.1 Diagnosis in adults

In the past, case definitions were developed for AIDS surveillance in countries with limited clinical and laboratory diagnostic facilities. These definitions took into account that in some situations no HIV tests were available. With the introduction of simple/rapid tests, it should be possible, at least in adults, to base an *HIV diagnosis* on a positive HIV test.

The *diagnosis of AIDS* should be based on the combination of a positive HIV test and certain clinical signs or diagnoses.

HIV-antibody tests become positive 3-12 weeks after the infection. The number of tests to be done depends on the objectives for HIV testing:
- Screening of donated blood;
- Surveillance of HIV prevalence or trends over time in a given population;
- Diagnosis of infection in individuals.

For the purpose of this document, we will concentrate on a testing system for the *Diagnosis of infection in individuals*. Today's standards require that HIV tests have a sensitivity of >99% and a specificity >98%.

**ELISA** has both high specificity and sensitivity. They do require skilled technical staff and steady power. Regular maintenance of the ELISA equipment is crucial to obtaining reliable results.

Currently, the procedure in case finding includes screening first with a *simple/rapid test* which is then confirmed by a second rapid test. Only in case of discordant results between the two rapid tests, the sample will be sent for a conformation in a well equipped laboratory.

The ultimate diagnostic "gold standard" for HIV is viral isolation from a body fluid or tissue - this is not available in most of the resource limited settings. Other tests that are usually not available are Western Blot (immunoblot assay) and viral PCR.

### 1.5.2 Diagnosis in children

The golden standard for the diagnosis of HIV is detecting antibodies against HIV (serologic test).

For children <18 months it is impossible to use a serologic test, because of the persistence of maternal antibodies up to 18 months. The antibodies of the mother gradually decrease and are usually unmeasurable by 7 up to 10 months of age, but can sometimes persist as long as 18 months: the antibody test can thus be positive until 18 months, whether the infant is infected or not. So the method of diagnosis is age-dependent as well.

**Children < 18 months:**

Diagnosis is possible by detecting the virus directly by PCR, HIV DNA and HIV culture. HIV DNA PCR is the preferred method and HIV culture is acceptable but technically demanding and time consuming. The heat-denaturated p24Ag detection test (Schüpbach) is a reliable sensitive assay. A child is considered positive if results are
positive on 2 separate specimens (one of those being performed at the age of ≥ 4
months). But the child can always get infected after performing the diagnostic test because of
breastfeeding.

**Children > 18 months:**
At that age the same testing strategies as in adults can be used. A child is considered
HIV + in case of a positive result by two different simple/rapid tests.

### 1.6 The WHO Clinical Staging System\(^a\)

The clinical staging of WHO provides us with a prognostic indicator and has therapeutic
consequences. A performance scale has also been incorporated into the system.

#### 1.6.1 Adults

**Clinical stage 1**
1. Asymptomatic infection
2. Persistent generalised lymphadenopathy (PGL)

**Clinical stage 2**
3. Unexplained weight loss, <10% of presumed body weight
4. Papular pruritic eruptions
5. Seborrheic dermatitis
6. Angular cheilitis
7. Recurrent oral ulcerations (2 or > episodes in 6 months)
8. Herpes zoster (2 or > episodes in 6 months)
9. Recurrent upper respiratory tract infections (2 or > episodes in any 6 month period
   of sinusitis, bronchitis, otitis media, tracheitis, pharyngitis)
10. Fungal nail infections

**Clinical stage 3**
11. Unexplained weight loss, >10% of presumed body weight.
12. Unexplained chronic diarrhoea, >1 month
13. Unexplained prolonged fever (intermittent or constant for >1 month)
14. Oral candidiasis
15. Oral hairy leukoplakia
16. Pulmonary tuberculosis (including pleural involvement)
17. Tuberculous lymphadenopathy (axillary, inguinal or cervical)
18. Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis,
bone or joint infection, meningitis, bacteremia)
19. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

---

\(^a\) Newly proposed WHO staging (Draft October 2004)
Clinical stage 4

**Conditions where clinical diagnosis is accepted:**
20. HIV wasting syndrome\(^{b}\)
21. *Pneumocystis* pneumonia
22. Recurrent severe or radiological bacterial pneumonia (2 or > episodes within 1 year)
23. Chronic orolabial, genital, or anorectal Herpes simplex infection (of > 1 month duration)
24. Candidiasis of the oesophagus
25. Extrapulmonary tuberculosis (excluding lymphadenopathy)
26. Kaposi's sarcoma
27. Cytomegalovirus retinitis
28. CNS toxoplasmosis
29. Cryptococcal meningitis

**Conditions where confirmatory diagnosis is recommended:**
30. HIV encephalopathy\(^{c}\)
31. Progressive multifocal leukoencephalopathy (PML)
32. Candidiasis of trachea, bronchi, or lungs
33. Cryptosporidiosis, Isosporiasis (with diarrhoea > 1 month)
34. Cytomegalovirus infection (of an organ other than liver, spleen, or lymph nodes)
35. Any disseminated endemic mycosis (e.g. Histoplasmosis, Cryptococcosis, Coccioidiomycosis, Penicilliosis)
36. Disseminated Mycobacterial diseases other than tuberculosis
37. Recurrent non-typhoidal salmonella septicaemia (2 or > episodes in one year)
38. Lymphoma (Cerebral or B cell non-Hodgkin's)
39. Invasive cervical carcinoma
40. Leishmaniasis, visceral
41. American trypanosomiasis reactivation

A further refinement of the WHO clinical staging system includes a laboratory axis. The laboratory axis subdivides each category into 3 strata (A, B, C) depending on the number of CD4 cells. If this is not available, total lymphocytes can be used as an alternative marker. **The substitution of CD4 by TLC has only been evaluated for adults! For children up to 6 years the only immunological test validated is CD4\(^{\%}\).**

<table>
<thead>
<tr>
<th>Laboratory axis</th>
<th>Clinical axis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphocytes</strong></td>
<td><strong>CD4</strong></td>
</tr>
<tr>
<td><strong>Stage 1</strong></td>
<td><strong>Stage 2</strong></td>
</tr>
<tr>
<td><strong>Asympt.</strong></td>
<td><strong>Early</strong></td>
</tr>
<tr>
<td><strong>PGL</strong></td>
<td><strong>HIV</strong></td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td><strong>Intermediate</strong></td>
</tr>
<tr>
<td><strong>(ARC)</strong></td>
<td><strong>Late AIDS</strong></td>
</tr>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>1000-2000</td>
</tr>
<tr>
<td>&gt;500</td>
<td>200-500</td>
</tr>
<tr>
<td>1A</td>
<td>1B</td>
</tr>
<tr>
<td>2A</td>
<td>2B</td>
</tr>
<tr>
<td>3A</td>
<td>3B</td>
</tr>
<tr>
<td>4A</td>
<td>4B</td>
</tr>
</tbody>
</table>

Grey area refers to progression to AIDS.

---

\(^{b}\) Weight loss of > 10% of BW, plus unexplained chronic diarrhoea (> 1 month) or chronic weakness and unexplained prolonged fever (> 1 month).

\(^{c}\) HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.
1.6.2 Children

Clinical stage 1
1. Asymptomatic
2. Persistent generalised lymphadenopathy (PGL)
3. Hepatoslenomeagly

Clinical stage 2
4. Papular pruritic eruptions
5. Seborrhoeic dermatitis
6. Fungal nail infections
7. Angular cheilitis
8. Lineal gingival erythema (LGE)
9. Extensive Human papilloma virus infection or Molluscum contagiosum infection (>5% body area)
10. Recurrent oral ulcerations (2 or >episodes in 6 months)
11. Parotid enlargement
12. Herpes zoster (2 or > episodes in 6 months)
13. Recurrent or chronic upper respiratory tract infections (otitis media, sinusitis 2 or > episodes in any 6 month period)

Clinical stage 3

Conditions where presumptive diagnosis is accepted
14. Unexplained low weight for age/low height for age/low weight for height
15. Unexplained persistent diarrhoea (>14 days)
16. Unexplained persistent fever (intermittent or constant, for longer than >1 month)
17. Oral candidiasis (outside neonatal period)
18. Oral hairy leukoplakia
19. Pulmonary tuberculosis
20. Tuberculous lymphadenopathy (axillary, cervical or inguinal)
21. Severe recurrent presumed bacterial pneumonia (2 or > episodes in 6 months)
22. Acute necrotizing ulcerative gingivitis/periodontitis

Conditions where confirmatory diagnosis is recommended
23. LIP
24. Unexplained Anaemia (>8gm/dl), neutropenia (>1,000/mm3) or thrombocytopenia (<30,000/mm3) for >1 month
25. HIV related cardiomyopathy
26. HIV related nephropathy
STAGE 4

Conditions where clinical diagnosis is accepted
27. Unexplained severe wasting or severe malnutrition
28. Pneumocystis pneumonia
29. Recurrent severe presumed bacterial infections (2 or > episodes within one year e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
30. Chronic orolabial or cutaneous Herpes simplex infection (of > 1 month duration)
31. Extrapulmonary tuberculosis
32. Kaposi's sarcoma
33. Oesophageal candida
34. CMV retinitis
35. CNS Toxoplasmosis
36. Cryptococcal meningitis

Conditions where confirmatory diagnosis is recommended
37. Any disseminated endemic mycosis (e.g. extra-pulmonary cryptococcosis Histoplasmosis, Coccidiomycosis, Penicilliosis)
38. Cryptosporidiosis or Isosporiasis (with diarrhoea > 1 month)
39. Cytomegalovirus infection (onset at age >1 month of organ other than liver, spleen, or lymph nodes)
40. Disseminated mycobacterial disease other than tuberculous
41. Candida of tracheal, bronchi or lungs
42. Recurrent non-typhoidal salmonella septicaemia
43. Cerebral or B cell non-Hodgkin's Lymphoma
44. Progressive multifocal leukoencephalopathy (PML)
45. HIV encephalopathy

1.7 WHO Case Definitions for AIDS Surveillance in Countries with Limited Clinical and Laboratory Diagnostic Facilities

1.7.1 Adults and adolescents
The case definition for AIDS is fulfilled if the HIV test is positive and one or more of the following conditions are met:

- weight loss >10 % body weight or cachexia, with diarrhoea or fever, or both, for at least one month, not known to be due to a condition unrelated to HIV infection
- cryptococcal meningitis
- tuberculosis (pulmonary or extrapulmonary)
- Kaposi's sarcoma
- HIV encephalopathy: neurological impairment which prevents independent daily activities, not known to be due to a condition unrelated to HIV infection
- oesophageal candidiasis
- life-threatening, or recurrent episodes of, pneumonias
- invasive cervical cancer
1.7.2 Children, born from HIV-positive mothers
Diagnosis of AIDS in children is different according to the age.

**Children ≥ 18 months:**
Positive HIV antibody test **and** Stage 3 disease (irrespective of CD4 %)
or
Positive HIV antibody test **and** Stage 1 or 2 disease **and** CD4% < 15%

**Children < 18 months:**
Any confirmed AIDS-defining opportunistic infection (irrespective of CD4%)
or
Any other stage 3 disease **and** CD4 % < 20%
or
Stage 1 or 2 disease **and** CD4 % < 20% **and** Positive PCR
2 Follow up of patients after HIV diagnosis

It is important that patients benefit from medical follow up after the diagnosis of HIV. They need reassurance and correct information on HIV, their prognosis and the possible interventions that can be offered. The stage of the disease and the CD4 count will determine the need for prophylaxis, and the need for ARV. Regular medical follow-up of asymptomatic patients will provide an opportunity for the healthcare worker to address various questions with the patient, such as the prevention of transmission, how to maintain good nutritional status, how to prevent healthcare problems, and opportunistic infections.

2.1 History and physical

As a medical doctor ask about:

- Diagnosis of HIV: when and where was HIV infection diagnosed and were there any previous negative HIV tests. This gives you an idea of the duration of the infection, possible route and risk behaviour.
- Previous HIV care including CD4 counts and ARV use?
- Past medical history and current symptoms (See Table 3: Symptoms and signs suggestive of HIV infection)
- Medications
- Social and financial situation

Perform a complete physical exam and look for signs suggestive for HIV (See Table 3 page 23)
Determine HIV clinical stage (See page 16)
Perform additional laboratory tests and chest X ray (as a baseline and to exclude active tuberculosis; See Table 2 page 21).

<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Blood Count</td>
<td>To detect anaemia, thrombocytopenia</td>
</tr>
<tr>
<td>CD4 or TLC</td>
<td>To assess stage of disease and need for ARV, repeat every 3-6 months</td>
</tr>
<tr>
<td>ESR</td>
<td>Usually elevated in HIV patients but when &gt;100 suspect TB</td>
</tr>
<tr>
<td>VDRL/TPHA</td>
<td>Check for other STD, if VDRL (+) confirm with TPHA. Treat if (+)</td>
</tr>
<tr>
<td>Hepatitis B serology</td>
<td>Chronic active hepatitis B may give problems during ARV treatment, if negative consider vaccination</td>
</tr>
<tr>
<td>Hepatitis C serology</td>
<td>Chronic hepatitis C can give problems during ARV, progression of hepatitis C is accelerated through HIV</td>
</tr>
<tr>
<td>Toxoplasmosis serology</td>
<td>Identifies patients at risk for toxoplasmosis encephalitis or brain abscess</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Useful in the initial check up because it serves as a comparison to later chest X-rays when pulmonary problems appear. Sometimes, it allows for early detection of TB. Where INH-prophylaxis is possible, chest X-ray is recommended to exclude active TB, prior to starting the prophylaxis.</td>
</tr>
</tbody>
</table>
Provide information (See Table 4 page 24)
Assess understanding: the patient should have received post test counselling, but
make sure that he understood the messages. (See Health Education page 24)
Provide supportive counselling: the patient will have many questions and anxieties.
Psychological support is needed.
Depending on the stage of the disease, the medical team should, together with other
institutions, address social and financial problems. It is essential that PLHA are offered
the opportunity to take part in AIDS support groups.
Table 3: Symptoms and signs suggestive of HIV infection

<table>
<thead>
<tr>
<th>Stages of HIV infection</th>
<th>Ask about (History)</th>
<th>Look for (Examination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>No symptoms</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>Weight loss</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Mild weight loss (less than about 5kg)</td>
<td>Weight loss</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Skin, mouth and nail diseases*</td>
<td>Skin, mouth and nail problems</td>
<td>Skin, mouth and nail problems</td>
</tr>
<tr>
<td>Shingles</td>
<td>Painful blistering rash on one side of the body</td>
<td>Shingles</td>
</tr>
<tr>
<td>Repeated upper respiratory tract infections</td>
<td>Colds, sore throats, sinusitis</td>
<td></td>
</tr>
<tr>
<td>Serious symptoms</td>
<td>Weight loss</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Serious weight loss (more than about 5kg)</td>
<td>Weight loss</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Diarrhoea for more than one month</td>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Fever for more than one month</td>
<td>Fever and/or sweats</td>
<td>Fever</td>
</tr>
<tr>
<td>Thrush in the mouth†</td>
<td>Sores, bad taste or white spots in mouth</td>
<td>White spots in mouth</td>
</tr>
<tr>
<td>Chronic vaginal thrush</td>
<td>Chronic vaginal itch and white discharge</td>
<td>White vaginal discharge</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>Chronic cough, weight loss, fever, sweats</td>
<td>Weight loss, signs of pneumonia</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Acute cough, fever, shortness of breath</td>
<td>Signs of pneumonia</td>
</tr>
<tr>
<td>Very serious symptoms‡</td>
<td>Weight loss, diarrhoea, fever, sweats</td>
<td>Weight loss and fever</td>
</tr>
<tr>
<td>Serious weight loss plus either diarrhoea or fever for more than a month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrush in the oesophagus</td>
<td>Pain when swallowing</td>
<td></td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> pneumonia (PCP)</td>
<td>Shortness of breath and fever getting worse over a few weeks</td>
<td>Dyspnoea and fever</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis</td>
<td>Abdominal pain, swollen lymph nodes, weight loss</td>
<td>Abdominal tenderness, swollen lymph nodes</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Headache, fever</td>
<td>Fever</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Focal weakness, headache, seizures, fever</td>
<td>Altered mental state, focal neurological signs, fever</td>
</tr>
<tr>
<td>HIV encephalopathy§</td>
<td>Declining mental function</td>
<td>Decreased mental function</td>
</tr>
<tr>
<td>CMV retinitis</td>
<td>“Floaters”</td>
<td>Decreased vision</td>
</tr>
<tr>
<td>Chronic herpes genital ulcer</td>
<td>Genital ulcer</td>
<td>Genital ulcer</td>
</tr>
</tbody>
</table>

* seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis
† also oral hairy leukoplakia
‡ Other illnesses not included here include penicilliosis, atypical mycobacteria, non-typhoid salmonella septicemia, lymphoma and Kaposi sarcoma.
§ also progressive multifocal leukoencephalopathy
Table 4: Basic HIV facts

| HIV is a virus that weakens the body’s ability to protect itself against other illnesses. |
| AIDS is the syndrome that occurs when the body’s defences have been weakened by HIV. |
| HIV can be spread by sexual intercourse via blood, semen or vaginal fluids. |
| HIV can also be transmitted by blood transfusion, reusing needles or from mother to child during pregnancy, labour or breast feeding. |
| HIV cannot be transmitted by normal social contact, kissing, sharing food or insects |
| Someone can be infected with HIV and be well for many years. |
| Treatment can control HIV infection, but cannot cure it. |

2.2 Health education

2.2.1 Information on HIV transmission

2.2.1.1 How to prevent the transmission of HIV to others
Give information about how HIV is transmitted, about risk behaviour. Discuss points such as safe sex (condom use) and prevention of transmission.

Give reassurance that they do not pose a risk for other family members in normal daily life.

Body fluids that may transmit HIV through contact with abrasive skin are semen, vaginal secretions, and blood. Other risk fluids are peritoneal, pleural, pericardial, amniotic, CSF and synovial fluids, although contact with those fluids is less likely in household environment.

Urine, stools, sputum, saliva, tears, vomit, and nasal secretion do not transmit HIV unless they are contaminated with blood.

Care providers are advised to protect their hands whenever handling body fluids (including soiled bedding and clothes, or cleaning up vomit), or when coming into contact with open wounds. If gloves are not available, plastic bags can be used instead.

2.2.1.2 Prevention of vertical transmission
Contraceptive use in women: if pregnancy is desired, discuss the risk of HIV in the offspring (30%) and discuss possible interventions to prevent this (according to the setting).

2.2.1.3 Prevention of transmission by exposure to blood
Needles, razor blades, and used condoms should be thrown away in such a way that their re-use is not possible. Do not share syringes or tattoo equipment.

For professionally-acquired exposure to blood, refer to the PEP section in the ARV guideline.
2.2.1.4 **Transfusion**
HIV patients should know that they cannot give blood.

2.2.2 **Hygiene**
Good hygiene is necessary for everybody, not only HIV patients. The importance of good personal hygiene should be stressed.

2.2.2.1 **Environment**
Wounds and skin lesions should be kept dry and clean. Contact with infectious people or places like hospitals should be avoided when possible, but in a way that ensures that stigmatisation is not increased.
Some professions bring about risks of opportunistic infection. Of particular relevance in the hospitals is the issue of healthcare workers who are HIV positive, and who are at risk of exposure to infections such as TB, entero-pathogens, etc. It is therefore recommended that cotrimoxazole and INH prophylaxis be offered to health workers if possible. Avoid swimming in lakes and rivers.

Hand washing is the most effective way of preventing transmission of infections. Laundry, especially soiled bedding and clothes should be washed with hot water. Clothes stained with blood or body fluid stains should be washed with bleach solution (one part bleach (70%) to ten parts water).

2.2.2.2 **Animals**
Animals are a reservoir for *Salmonella*, *Cryptosporidium*, and *Campylobacter*. Avoid any contact with animal excrement; use gloves to clean up the environment around the house if necessary.

2.2.2.3 **Nutritional advice**
Water for consumption should be boiled or bottled water should be used instead. Good nutrition means balanced food (cereals, fruits, vegetables, oil, meat/fish) prepared in a clean way. Avoid raw foods as much as possible. Meat and eggs should be thoroughly cooked. Fruit and vegetables should always be washed with clean water; vegetables should be cooked before eating. When re-heating food, make sure it is very hot throughout. Do not reheat more than once.

2.2.2.4 **Medical advice**
Explain to patients that whenever they develop signs of infection they should present themselves to a doctor or healthcare worker.

2.2.3 **Regular physical exercise**
This favours digestion and appetite, helps to maintain physical fitness and improves emotional wellbeing.
2.2.4 Adequate rest

2.2.5 Emotional well-being

The medical care-provider has to take into account the emotional wellbeing of the patient. People who are sad and depressed will not take care of their physical wellbeing. Important social and communication skills are required, but are often neglected because of time constraints. This is a mistake: patients will not feel understood and will stay away, even when they have medical problems. Therefore, it is difficult to imagine AIDS care without a multidisciplinary team that supports the medical care-provider.

It is essential to:
- listen carefully to the patient.
- try to understand their feelings.
- ask questions in an empathic way.
- respect their feelings.
- encourage patients when they express emotions.
- offer care that helps to maintain self esteem and self confidence.
- give correct information; do not give false hope.
- help the family to deal with the emotions (the patient's and their own).

Patients should continue to do their daily routine work, and continue to attend the usual religious and community meetings. Families should be mobilised to take an active part in the care of the patient. Some traditional practices or religious rituals can be helpful. Certain traditional healers, priests, can play a role in guiding the patient and the family through the process of shock, denial, anger, fear, sadness, hope and acceptance. Patients should be gently encouraged to think about death and express their feelings. Patients should participate in the decision making process when dealing with their health problems. This will help them to understand their medical problems and increase self-esteem.
3  CLINICAL AIDS CARE AND MANAGEMENT

3.1 General Principles of AIDS Care

3.1.1 Comprehensive care or Continuum of Care
AIDS, like many other conditions such as cancer, tuberculosis, hypertension, and congestive heart disease is a long-term illness, requiring a long-term maintenance plan to meet clinical, emotional and social needs. Most people suffering from long-term illness live at home with their families. Consultation at the clinic, health center or hospital may lead to admission and care for stabilization or intensive care where indicated. However, as soon as the patient's condition is stable and based on the judgement of the physician and care team, he or she is discharged home where the family continues with the nursing care and additional palliative care & support may be provided by a community based home care person(s). Various arrangements exist for the home-based care of patients, but it must be recognized that the families play the most important role in any such arrangement.

The patient's discharge plan, originated by the hospital, must clearly define the responsibilities of all parties involved in the follow-up care of the patient. A holistic approach to the care of long-term illness gives the best results. It usually involves many participating partners, whose interventions result in a range of comprehensive care and social support across a continuum extending from the hospital to the community and the patient's home. AIDS care should follow this pattern if it is to be effective and result in a better quality of life for those affected (see Figure 2).

Service providers from whichever sector must be linked together in the discharge planning and referral networks, so that any of them can function as an entry point into the continuum of care scheme for the patient. The needs of persons suffering from AIDS or any chronic illness are varied and are not limited to drugs for treatment alone. Very often, needs related to food and nutrition, accommodation, employment, finance, social and family relationships, status and self-esteem, and the avoidance of stigma and discrimination are often expressed by persons suffering from incurable chronic diseases and long-term illness. Hospital in-patient care of an AIDS patient must therefore be seen as only a part of the wide-ranging care and support required by the patient.
3.1.2 Care of the HIV Positive pregnant women

As soon as the diagnosis of HIV infection is made in a pregnant woman, she must be referred to the trained counsellor or social worker for care and advice. The counsellor should invite the pregnant woman to bring her husband to share the information with the pregnant woman and her spouse, including messages on how to reduce the risk of transmission to the newborn.

Pregnant women may receive the diagnosis of HIV early in the pregnancy, some may already know since a while that they are HIV-infected, some will need HAART for their own health, others do not yet need treatment but need information on how to reduce the transmission of HIV to the newborn.

A good coordination between gynaecologists, midwives doing antenatal care and physicians or health care workers caring for HIV patients, is essential.
3.1.3 Care for the tuberculosis patients

50% of the HIV patients will develop active tuberculosis. Tuberculosis can occur in an early stage of disease, when the immunity is still preserved. TB/HIV co-infected patients who develop active TB benefit from cotrimoxazole prophylaxis. It is important to offer VCT to TB patients in order to give them correct care for HIV. This may increase the uptake of VCT and contribute to prevention of HIV. On the other hand, patients diagnosed at VCT, may have undiagnosed tuberculosis. It is important that they are seen by a medical doctor and that in case of symptoms a sputum examination, a chest X-ray and/or an abdominal ultrasound is done to diagnose and treat TB. Asymptomatic patients can be started on INH prophylaxis (see chapter Prevention of OI). This will decrease the number of new active tuberculosis cases. Again an operational link between TB and HIV services is essential in care for HIV patients (see Figure 3).

Figure 3: Operational links between VCT and TB services (PROTEST initiative)
3.2 Prevention of opportunistic infections

3.2.1 Prevention of bacterial infections, PCP and toxoplasmosis, using cotrimoxazole

3.2.1.1 Background on cotrimoxazole prophylaxis
Cotrimoxazole is a combination of two antibiotics, trimethoprim and sulphamethoxazole, that has been used extensively throughout the world for more than two decades. It is formulated as tablets of ‘single’ or ‘double’ strength tablets with 80mg and 400mg or 160mg and 800mg of trimethoprim and sulphamethoxazole respectively. There are numerous indications for its use, particularly in the treatment of common infections such as urinary tract infections, upper and lower respiratory tract infections, enteritis and dysentery. It is also useful for the prevention and treatment of infections in immunosuppressed individuals, particularly Pneumocystis carinii pneumonia (PCP) and Toxoplasma gondii encephalitis. Usage and rates of resistance have varied widely around the world.

In PLHA cotrimoxazole is potentially useful for the prevention and treatment of a wide range of infections. This includes PCP and toxoplasmosis, but also the most important causes of serious bacterial infections such as pneumonia, bacteraemia and bacterial enteritis: Streptococcus pneumoniae, Salmonella species, Shigella species, Eschericia coli, Staphylococcus aureus and Haemophilus influenzae. Cotrimoxazole also has activity against Plasmodium species (malaria), Isospora belli (cause of diarrhoea) and Nocardia asteroides (respiratory and generalized infections).

Benefit of cotrimoxazole prophylaxis in high income countries was established since the late 1980s, primarily for the prevention and treatment of PCP. Several controlled trials and meta-analyses have shown that PCP prophylaxis reduces the risk of PCP and that cotrimoxazole is the most effective prophylactic agent with virtually no failures. It also reduces the risk of toxoplasmosis.

Benefit of cotrimoxazole prophylaxis in developing countries has been proven in a randomized trial conducted in Abidjan, Cote d’Ivoire. This study compared the efficacy of daily double strength cotrimoxazole to placebo in PLHA in WHO clinical stage 2 and 3. It found a significant reduction in severe events defined as either death or hospitalization, but not a significant reduction in mortality alone. The use of cotrimoxazole prophylaxis in a subgroup of PLHA with smear positive pulmonary TB was investigated by a second randomized study conducted in Abidjan. This showed more marked benefits with significant reductions in OIs and hospital admissions and a 50% reduction in mortality.

Risks of cotrimoxazole prophylaxis
Side effects from cotrimoxazole prophylaxis in PLHA are very common, occurring in up to 50%. The most common side effect is rash, which is often mild, but can be severe or life threatening. The other major side effects are hepatitis, anaemia and neutropenia.
3.2.1.2 Recommendations on cotrimoxazole prophylaxis

When to give cotrimoxazole prophylaxis? See Table 5 and Table 6
Cotrimoxazole prophylaxis should be offered as an integrated part of comprehensive care for PLHA. The primary aim of cotrimoxazole prophylaxis is to prevent major bacterial illness and PCP, with the prevention of toxoplasmosis as secondary aim. It can be commenced as either primary prophylaxis (given to PLHA who have never had these infections) or secondary prophylaxis (given to PLHA who have had an episode of these illnesses to prevent recurrence) using the criteria detailed below.

Table 5: When to stop and when to start cotrimoxazole prophylaxis in adults?

<table>
<thead>
<tr>
<th>ADULTS</th>
<th>DOSE</th>
<th>WHEN TO START</th>
<th>WHEN TO STOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>800 mg SMX/160 TMP (1 double strength) OD</td>
<td>Symptomatic HIV disease (WHO clinical stage 2, 3 or 4) or CD4 &lt; 200/mm³ or TLC &lt; 1200/mm³</td>
<td>Patient on HAART for at least 6 months and sustained increase† of CD4 &gt;200/mm³</td>
</tr>
<tr>
<td></td>
<td>1DS* OD</td>
<td>All patients after an event of PCP, Isospora belli, toxoplasmosis</td>
<td>Patient on HAART for at least 6 months with treatment success evidenced by a sustained increase of CD4 count &gt; 200/mm³</td>
</tr>
</tbody>
</table>

* Double Strength tablet containing 800 mg sulphamethoxazole and 160 mg trimetroprim once daily (OD)
† If the CD4 count drops below 200 then cotrimoxazole prophylaxis should recommence until the CD4 count is again consistently above 200 for at least 6 months. If ARV are stopped for more than a few weeks cotrimoxazole should be restarted.
‡ For pregnant women start only after the first trimester of pregnancy
Table 6: When to stop and when to start cotrimoxazole prophylaxis in children?

<table>
<thead>
<tr>
<th>DOSE</th>
<th>WHEN TO START</th>
<th>WHEN TO STOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY PROPHYLAXIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 kg</td>
<td>All children born to an HIV infected woman from 6 weeks of life on</td>
<td>At 12 months if the HIV test is negative or if the child is asymptomatic</td>
</tr>
<tr>
<td>2.5 ml OD (once daily):‡</td>
<td>Child HIV (+) and symptomatic</td>
<td>At 18 months if HIV negative</td>
</tr>
<tr>
<td>5-9kg: ½ tab* OD or 5mL OD</td>
<td>Child HIV (+), asymptomatic but CD4 &lt; 15%</td>
<td>At 18 months in HIV positive child if CD4 &gt; 15% and asymptomatic</td>
</tr>
<tr>
<td>10-14kg: 1 tab OD or 10mL OD</td>
<td></td>
<td>After the start of HAART and sustained increase of CD4 &gt; 15% for 6 months†</td>
</tr>
<tr>
<td>15-24kg: 1tab OD or 15mL OD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25kg: 2tab OD 6 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SECONDARY PROPHYLAXIS</td>
<td>All children who have been treated for PCP</td>
<td>No data available on the safety of discontinuation of cotrimoxazole for secondary prophylaxis in children</td>
</tr>
<tr>
<td>Same as above</td>
<td></td>
<td>➔ Lifelong</td>
</tr>
</tbody>
</table>

* Single Strength Tablet (SS) containing 400 mg sulphametoxazole and 80 mg trimetroprim
† If the CD4 percentage drops below 15 then cotrimoxazole prophylaxis should recommence until the CD4 percentage is again consistently above 15 for at least 6 months. If ARV are stopped for more than a few weeks cotrimoxazole should be restarted.
‡ Or divided into two doses; every day or three days/week (consecutive or alternating).

PCP prophylaxis is recommended for all exposed children in the first year of life, from the age of 6 weeks. From the age of one year (12 months) prophylaxis can be discontinued if the HIV test of the child is negative or if the child has no symptoms at all. From the age of 18 months, when a definite serologic diagnosis of HIV infection is made, prophylaxis is reserved for symptomatic children and asymptomatic children with CD4<15%. Prophylaxis can be discontinued in children receiving HAART with CD4>15% for 3 months.

**Side effect management**

The main side effects of cotrimoxazole are rash, bone marrow suppression and hepatitis. They are more likely to occur soon after initiation of cotrimoxazole. Minor rashes are common and can usually be managed with careful observation and continuing cotrimoxazole. More severe rashes including Stevens Johnson syndrome and clinical hepatitis are possible and must lead to immediate cessation of cotrimoxazole. Supportive management including hospital admission is sometimes necessary. Reductions in haemoglobin or white cell count can be managed by dose reduction if not severe.
If cotrimoxazole has been ceased for non-life threatening indications, it can be recommenced following 'desensitisation', for example using a cotrimoxazole suspension of 40mg TMP + 200mg SMX per 5ml and use one of the following:

- **Inpatient:** Over 6 hours, give hourly doses (TMP/SXT in mg): 0.004/0.02, 0.04/0.2, 0.4/2.0, 4.0/20, 40/200 and 160/800.
- **Outpatient:** Give 1ml daily for 3 days; 2ml for 3 days and so forth until the dose can be administered as 1 SS daily and the next day 1 DS daily.
- If desensitization fails dapsone 100 mg daily should be given for the prevention of PCP (children 2mg/kg daily).
- NEVER try desensitisation in a patient who had severe side effects (life-threatening hepatitis or Stevens Johnson’s syndrome).

**Initiation and monitoring**

Cotrimoxazole prophylaxis should be initiated by health care workers at all levels. Home care teams and peer support members of associations of PLHA should include the benefits of cotrimoxazole prophylaxis in their counselling. All PLHA commencing cotrimoxazole should be given the opportunity to learn about cotrimoxazole and counselled about possible benefits, side effects and the importance of regular administration. The use of cotrimoxazole should be monitored within a continuum of care. Ongoing support, explanation, encouragement as well as monitoring for side effects and provision of medicine should be coordinated between care services.

**Program implementation**

Integration of cotrimoxazole prophylaxis into a HIV comprehensive care program should include training of all involved in HIV continuum of care. A social marketing approach should be used to rapidly increase awareness and understanding of PLHA.

### 3.2.2 Prevention of active tuberculosis using isoniazid

**3.2.2.1 Background on INH prophylaxis**

**TB/HIV interaction**

Tuberculosis (TB) is the most common opportunistic infection and cause of death among people living with HIV/AIDS (PLHA). It is estimated that half of all PLHA in developing countries will develop active TB at some time. Once TB becomes active it increases HIV replication resulting in increased HIV viral load and may accelerate HIV disease progression. PLHA with active TB can be treated with standard regimens, but their survival is lower than others with TB due to the occurrence of other opportunistic infections. Relapse and re-infection is commoner in PLHA than others with TB.

HIV is the strongest risk factor for progression from latent to active TB. It is estimated that this risk is approximately 5-10% lifetime risk for individuals negative for HIV compared to 2.4% to 7.5% per year for PLHA living in high TB prevalence countries. This has resulted in dramatic increases in TB prevalence in areas of high HIV prevalence, particularly sub-Saharan Africa.

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*a Do not start desensitisation before the rash has disappeared. In 70% of the patients this process is successful and cotrimoxazole can be used again

*b Dapsone alone is not enough to prevent toxoplasmosis. If a patient has CD4< 100 and Toxoplasma serology positive you need to add pyrimethamine (see p 57)*
Efficacy of INH preventive therapy (IPT) in PLHA

A number of large randomized trials have shown the efficacy of drug therapy in the prevention of active TB in PLHA. Randomized trials administering isoniazid for 6 months and 12 months duration have shown a significant decrease in TB incidence in tuberculin skin test (TST) positive persons compared to those who took placebo. In TST positive PLHA living in areas of high TB prevalence, isoniazid therapy will reduce the short-term risk of TB by 60%.

In PLHA who are TST negative, including those who are anergic, no statistically significant effect of preventive therapy has been found, either in a randomized trial or meta-analysis. In a meta-analysis of studies that included both TST positive and negative PLHA preventive therapy reduced the risk of active TB by 40%. Using these data it can be estimated that approximately 36 PLHA would need to be treated with preventive therapy in order to prevent 1 case of active TB over 3 years.

Effect on mortality

Effect on mortality has not been demonstrated in any study, although none were powered to demonstrate this. Meta-analyses have shown non-statistically significant reductions in mortality in TST positive PLHA to 68-77% of what it would otherwise have been. No trial or meta-analysis has demonstrated an effect on mortality of TST negative or combined TST positive and negative PLHA. It therefore remains unknown whether preventive therapy given to populations of PLHA with unknown TST status would have an effect on survival.

Efficacy in PLHA with advanced HIV disease

Anecdotal reports suggest that the efficacy of preventive therapy in PLHA with advanced HIV disease is reduced, but this has not been proven. Certainly the management of this group is more complicated. Active TB is more difficult to exclude as smear negative pulmonary and extra-pulmonary disease is more common and other OIs that mimic active TB are more common. Also tolerance for drug therapy is reduced in this group.

Choice of regimen

Regimens other than isoniazid that have been investigated include rifampicin plus either isoniazid or pyrazinamide or both given over two to four months. The trend in these studies was for isoniazid to be slightly more effective, perhaps related to the longer duration of therapy.

Exactly how long isoniazid therapy should be is unknown. Extrapolation from the use of isoniazid in HIV negative individuals would suggest 9 months.

Duration of benefit

The duration of the efficacy of PT for tuberculosis depends on the regimen used. INH alone has an efficacy during 18 months, while a two-month regimen with rifampicin and pyrazinamide has an efficacy during 3 years. However with the latter regimen there are reports of severe fatal liver injury in non HIV-infected patients treated for latent TB.

The duration of benefit is in part related to the risk of re-infection. Some indication of this can be gained from studies of relapse following treatment for active TB. Studies to date would support re-infection as the major cause of relapse in PLHA living in high TB prevalence areas, providing further support to the suggestion that the efficacy of preventive therapy may not be long term.

Isoniazid resistance

There is concern that rates of isoniazid resistance could increase with expanded isoniazid preventive therapy programs. No increase in isoniazid resistance was seen in the studies in PLHA who developed active TB despite isoniazid, but this may change
when large scale programs are implemented. The efficacy of IPT is also dependent on the rate of isoniazid resistant TB infection.

Secondary prophylaxis
To explore ways to reduce rates of relapse following treatment for active TB secondary prophylaxis has been investigated. In a study in Haiti it was found that the rate of relapse following treatment for active TB was approximately ten times higher in PLHA than in HIV negative participants. Twelve months of isoniazid commenced soon after completion of treatment for active TB reduced the risk of recurrent TB in PLHA by 80%, to 20% of the risk if no isoniazid had been given. All relapses were in PLHA who had symptomatic HIV disease prior to active TB.

Additional ways to prevent active TB
PLHA should be aware of the risks associated with contact with people with pulmonary TB, for example in health care environments. Restoration of immune function using antiretroviral medication is a powerful intervention for reducing the risk of active TB, particularly in PLHA with advanced immunosuppression.

3.2.2.2 Recommendations on Prevention of active tuberculosis using isoniazid

Isoniazid prophylaxis
Isoniazid can be an integrated part of a package of comprehensive care for PLHA. All PLHA should have access to information and educational materials regarding TB and preventive therapy. IPT can be offered to PLHA who agree, who do not have active TB at screening and who can be adequately monitored for isoniazid side effects and active TB.

Recommended regimen
Isoniazid at a dose of 5 mg/kg to a maximum of 300 mg/day should be used. Pyridoxine (vitamin B6) 50 mg/day should be given at the same time to reduce the risk of peripheral neuropathy. The duration of IPT should be 9 months, on the condition that there are adequate systems for monitoring and support of adherence. Chronic suppressive therapy or secondary prophylaxis is not widely recommended.

When to start?
PLHA should be offered IPT as early as possible because active TB can occur at any CD4 count and once present leads to further weakening of the immune system and increased risk of other opportunistic infections. PLHA with symptoms of TB such as cough or fever should not commence IPT until a cause for these symptoms is found. IPT should not be given to PLHA with known active hepatitis. IPT should be delayed until after the first trimester of pregnancy.

Screening for active TB
Adequate systems must be in place to screen for active TB prior to commencement of an IPT program. This must include the capacity to diagnose all forms of TB, including smear negative pulmonary TB and extrapulmonary TB, using history taking, careful physical examination, chest X-rays, abdominal ultrasounds and sputum examination. In advanced HIV disease it is very difficult to exclude an active TB. The decision to start IPT should be made at the level of the referral hospitals.
Monitoring
PLHA taking IPT should meet with a specifically trained health care worker at least monthly and medication dispensed monthly. This could be at an outpatient department or a health center.
They should be evaluated for any clinical evidence of isoniazid toxicity. The main side effects of isoniazid are gastro-intestinal including nausea and vomiting, hepatitis and peripheral neuropathy. The risk of hepatitis is approximately 0.3% in young healthy adults and increases to 2.6% in the elderly. The risk of neuropathy is largely prevented with the use of pyridoxine. PLHA taking IPT should be warned of the symptoms of hepatitis: nausea, vomiting, abdominal pain, lethargy, jaundice and dark urine. They should be advised that if any of these symptoms occur to cease isoniazid and consult their health care provider. No routine baseline or follow up laboratory investigations for side effects are recommended. Liver function tests should be considered for those who have symptoms or signs of hepatitis and IPT ceased if there is evidence of severe hepatitis.

Program implementation
Despite the evidence of efficacy, the success of implementation of IPT on a large scale is dependent on overcoming a number of operational issues. Steps necessary in delivery of IPT are:

- Identification of PLHA, for example through VCT.
- Screening to exclude active TB.
- Regular delivery of medicines and monitoring for treatment side effects and active TB.
- Adherence support leading to completion of IPT.

To minimize the risk that implementation of IPT programs will harm existing TB control efforts, the following are minimum criteria for establishment of IPT programs:

- Commitment to establishment of IPT program by key decision makers in province/district including TB and HIV program leaders
- Effective TB DOTS program e.g. combined defaulter and failure rate of less than 10%. IPT is not a substitute for TB DOTS and implementation of IPT should never be allowed to undermine case detection and treatment of active TB.
- Adequate facilities and capacity for excluding active TB. One of the main risks of IPT is that isoniazid monotherapy will be given to PLHA with active TB. This is a very real risk given that many PLHA are diagnosed at a late stage of HIV disease and are therefore more likely to present with smear negative pulmonary or extrapulmonary TB.
- Integration into comprehensive care for PLHA. This is essential for cost-effectiveness as it will ensure that benefits are available for those PLHA who enter the program regardless of whether they are eligible or able to complete IPT. This is particularly true for health services that are developing both TB/HIV activities and HIV continuum of care.
- Referral, monitoring and reporting systems. Systems for managing the flow of PLHA between services and adequately assessing the efficacy of the IPT program are essential.

Rigorous systems for evaluation of IPT programs are essential for assessing the ability of each program to reduce drop-outs and to ensure comprehensive HIV care is provided, and thus demonstrate cost-effectiveness.

IPT for children should only be provided in specialized centres with access to TST and ability to exclude active TB in children.
The regimen depends on the weight of the child:

**TB Prophylaxis in HIV infected children**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dosage of INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 kg</td>
<td>50 mg</td>
</tr>
<tr>
<td>11-20 kg</td>
<td>100 mg</td>
</tr>
<tr>
<td>21-30 kg</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

INH prophylaxis should not be given to symptomatic children because of the difficulty to exclude the diagnosis of TB in infants and children. Pyridoxine 25 mg per day should be added to the prophylaxis due to the high frequency of HIV associated peripheral neuropathy.

### 3.2.3 Prevention of fungal infections

Fungal infections are important causes of morbidity and mortality in PLHA throughout the world. They include oral, oesophageal and vulvo-vaginal candidiasis, cryptococcal disease especially meningitis and various endemic mycoses such as penicilliosis in south-east Asia. Oral candidiasis is an important contributor to wasting in PLHA. In some regions with an unusual high incidence of cryptococcal meningitis or *P. marneffei*, primary prophylaxis with fluconazole or itraconazole might be considered. Fluconazole is not recommended for primary prophylaxis of fungal infections in general because of the relative infrequency of deep fungal infection, potential development of drug resistance and cost.

Patients who have been treated with fluconazole for cryptococcal meningitis should receive secondary prophylaxis (200 mg daily). Discontinuation of fluconazole as secondary prophylaxis of cryptococcal meningitis following immune reconstitution with ARV has been investigated in several studies. There is increasing evidence from these studies that cessation of fluconazole secondary prophylaxis is safe if PLHA have no signs or symptoms of cryptococcal disease and have had a sustained increase in CD4 count above 100 cells/m³ for at least 6 months.

### 3.2.4 Mucocutaneous Herpes simplex

If frequent and severe recurrences of genital or mucocutaneous herpes preventive doses of acyclovir (200 mg 3 x daily or 400 mg 2 x daily) can be given.

### 3.2.5 Helminthic infections

Treatment of helminthic infections with albendazole or mebendazole once a year has a positive effect on HIV progression because of decreased immune activation.

### 3.2.6 Vaccination

HIV-infected patients have a suboptimal antibody response in comparison to healthy controls, especially when CD4 counts are < 100. This response improves again after the administration of HAART.

#### 3.2.6.1 23-valent pneumococcal vaccine

This vaccine, while effective in the US, had a negative effect on the incidence of pneumococcal disease in Kenya. Therefore it is not recommended in Africa.
3.2.6.2 **Hepatitis B vaccination**
HIV-infected patients have a higher risk of hepatitis B because of common risk factors. Patients who are HIV-positive are more likely to develop chronic hepatitis. In the industrialised world, hepatitis B vaccination is recommended for certain risk groups, such as IV drug users, homosexuals, household contacts of hepatitis B carriers, healthcare workers and sex workers.

In developing countries, although some EPI programmes include vaccination against hepatitis B, it is not routinely recommended in adult HIV patients, because very few countries are able to purchase the vaccine.

3.2.6.3 **Childhood immunisation**
At birth all vaccinations should be given according to the regular vaccination scheme. All asymptomatic children should receive all vaccinations as prescribed by the national immunisation schedule. It is recommended in HIV infected children to give an extra dose of measles vaccine at 6 months, followed by a second dose at 9 months. Only BCG should not be administered in case of HIV symptomatic children.
4 Management of Specific HIV/AIDS Related Conditions

4.1 Gastrointestinal Disease Conditions

4.1.1 Chronic diarrhoea

Epidemiology
Chronic diarrhoea is defined as liquid stools three or more times a day, continuously or episodically for more than one month. Chronic diarrhoea is a common problem in HIV infected individuals affecting up to 60% of HIV-positives at some time in their illness. Chronic diarrhoea has a significant impact on quality of life. It is often accompanied by nausea, weight loss, abdominal cramps and dehydration. There is often intermittent watery diarrhoea, without blood or mucus. In one-third to two-thirds of cases, no cause is identified.

An infectious agent can be identified in about 50% of patients with AIDS-associated diarrhoea. Other non-infectious causes are malignancies and drugs, especially antibiotics and antiviral therapy.

<table>
<thead>
<tr>
<th>INFECTIONS</th>
<th>Non infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidiosis</td>
<td>MALIGNANCIES</td>
</tr>
<tr>
<td>Isospora belli</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Giardia Lamblia</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td></td>
</tr>
<tr>
<td>Shigella flexneri</td>
<td>DRUGS</td>
</tr>
<tr>
<td>TB or MAC enteritis</td>
<td></td>
</tr>
<tr>
<td>Campylobacter spp</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td></td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus colitis</td>
<td></td>
</tr>
<tr>
<td>Toxin induced diarrhoea</td>
<td>(Clostridium difficile)</td>
</tr>
<tr>
<td>Microsporidiosis</td>
<td></td>
</tr>
</tbody>
</table>

Clinical presentation
This depends on the causative organism. Invasive bacterial pathogens such as *Campylobacter, Shigella* and *Salmonella* species can cause severe and prolonged illness in PLHA. They are however not a frequent cause of chronic diarrhoea. They usually present with fever and diarrhoea.

It is clinically impossible to distinguish the different agents without stool culture. Protozoan infections like cryptosporidium, *Isospora belli* and *Microsporidium* present with debilitating watery diarrhoea and weight loss in HIV-infected patients. These infections usually occur in patients with low CD4 count (CD4 <100). MAC and TB enteritis usually present with high fever and abdominal pain, accompanied with
diarrhoea. In TB enteritis, the presence of abdominal lymph nodes on ultrasound is very suggestive. *Clostridium difficile* may be underestimated as a cause of diarrhoea in AIDS patients in the tropics because of difficulty in making the diagnosis. Frequent hospitalisation and exposure to antibiotics puts AIDS patients at high risk of infection with the toxin-producing strain of *C. difficile*. They present with fever and bloody diarrhoea. *S. stercoralis* can complete its life cycle entirely within the human host. As a result, the burden of adult worms in infected humans can increase substantially through a cycle of auto-infection. In immunocompromised patients, it can cause overwhelming infection, especially when cell-mediated immunity is impaired. This serious complication is called Strongyloides hyper-infection syndrome and has a high case-fatality rate. Patients present with diarrhoea, abdominal pain, skin lesions, cough and fever. The full blown hyperinfection syndrome is not frequent in HIV. CMV colitis will present with rectal bleeding, tenesme and fever. MAC associated diarrhoea is usually accompanied by fever and anaemia.

Diarrhoea due to drugs is suggested by the history. Antibiotics and ARV can cause diarrhoea, especially DDI, lopinavir/rtv and nelfinavir.

**Diagnosis**

Stool culture is the only way to distinguish between Campylobacter, Shigella and Salmonella infections. In patients who have been taking antibiotics the result will often be negative. In a resource-poor setting the diagnosis and treatment of MAC is difficult to realise. Blood cultures are needed for MAC, but will be positive only 3-4 weeks later and therefore do not help in the immediate management. Most common findings at diagnosis are fever and severe anaemia (denoted by a haematocrit of <26 percent). Cryptosporidiosis can be easily detected in the stool by using a modified acid-fast stain. *Isospora belli* can be detected in stools by the same techniques as those developed for Cryptosporidium species. *Isospora belli* oocysts are relatively big (20-30 µm) and can be easily identified in unstained wet preparations. *Clostridium difficile* is a toxin induced diarrhoea. Special assays to detect this toxin exist but are usually not available. The presence of faecal leukocytes and blood supports the diagnosis. Diagnosis of microsporidiosis is made by modified trichrome stain to identify the spores in stool specimens. In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, broncho-alveolar lavage fluid, pleural fluid, peritoneal fluid and surgical drainage fluid. CMV colitis can be suspected by sigmoidoscopy with ulcerations. Often patients will also have CMV retinitis.

**Treatment**

Usually patients are started empirically on cotrimoxazole 480 mg two tablets twice daily for 5 days. If in Eritrea there is a high resistance rate for *Salmonella or Shigella* to cotrimoxazole, initial treatment with fluoroquinolones can be considered. Because of the frequency of antibiotic associated diarrhoea and *Clostridium difficile* it is recommended to give metronidazole 500mg three times daily for 7 days in the same time. If this is not effective do a stool exam (fresh and modified acid fast stain) to exclude strongyloides or cryptosporidiosis or *Isospora belli*. If the stool exam shows only many white and red blood cells, treat the patient for bacillary dysentery, resistant to cotrimoxazole, with fluoroquinolones. If this fails try erythromycin if symptoms of bloody diarrhoea persist to cover for quinolone resistant *Campylobacter*. If oocysts of *Isospora belli* are seen treat with a high dose of cotrimoxazole 480 mg two tablets 4 x daily for 10 days, followed by two tablets 2 x daily for 3 weeks, then chronic suppression with the same dose of cotrimoxazole as used for PCP prophylaxis (two tablets daily or two tablets 3 x weekly as tolerated). In case the stool exam reveals *cryptosporidium* oocysts, there is no proven effective treatment. ARV is the most
Effective therapy for this protozoan infection. **Strongyloidiasis** can be successfully treated with ivermectin 12 mg daily for 3 days, and this drug is also considered by some as the drug of choice for the treatment of systemic strongyloidiasis. An alternative treatment is albendazole 400 mg 2 x daily for 5 days. A maintenance therapy once a month is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once monthly).

**Microsporidiosis, AIDS enteropathy** and cryptosporidium related diarrhoea will respond to ARV.

The treatment of **MAC** consists of Clarithromycin 500 mg 2 x daily or Azithromycin 500 mg daily and ethambutol 15 mg/kg daily with or without rifabutin 300 mg daily. Rifabutin is not readily available in a resource-poor setting. Some experts say that in case of doubt between tuberculosis and MAC one could add clarithromycin to the tuberculosis treatment, awaiting the results of the culture. However MAC is rare compared to TB. In settings where TB culture is not available, the choice should be to treat tuberculosis as this has a significant impact on survival.

In case of severe **antiretroviral – induced** diarrhoea, switch of treatment regimen should be considered. Studies have shown benefit with Oat Bran 1500 mg twice daily, increase in dietary fibre intake and CaCO₃ 500 mg three times daily in PI-induced diarrhoea.

**Other measures:**
- Correct hydration with oral rehydration salt or parenteral fluids (normal saline).
- Consider supplemental feeding as tolerated
- Consider potassium supplements
- Loperamide (Imodium®) 4 mg PO first dose followed by 2 mg-4 mg after each unformed stool (max 16 mg daily).
- Codeine 30-60 mg 3-6 x daily. Maximum dose = 200-300 mg in a day.
- Avoid constipating agents with bloody diarrhoea because of the risk of inducing toxic megacolon.

**4.1.2 Oropharyngeal Candidiasis (thrush) and Oesophageal Candidiasis (OC)**

The most frequent cause of oral and oesophageal lesions in PLHA is candidiasis.

**Definition:** the presence of white plaques on the oral mucosa (thrush) or on the oesophageal mucosa (OC).

**Clinical manifestations**
These plaques, usually located on the palatal or buccal mucosa, can be removed and then often reveal a bleeding surface. It is cause by **Candida albicans**.

The risk factors for invasive candidiasis include cellular immunodeficiency, prolonged neutropenia, diabetes mellitus, and broad-spectrum antibiotic therapy. When no underlying cause is found, persistent oropharyngeal candidiasis should arouse a suspicion of HIV infection.

Oesophageal candidiasis will present with dysphagia and odynophagia (retrosternal pain when swallowing).
Diagnosis

- History & physical examination reveal oral candidiasis
- Microscopy of oropharyngeal scraping demonstrates pseudohyphae and/or blastospores of Candida albicans.
- Radiography or endoscopy is not necessary for oesophageal candidiasis. It is the most common cause of dysphagia in PLHA and empirical antifungal therapy is justified, especially because most patients will present with oral candidiasis.

Differential diagnosis

Oral hairy leukoplakia
Herpes and CMV oesophagitis
Aphthous stomatitis

Treatment

For oesophageal candidiasis always use a systemic treatment!

4.1.2.1 Topical antifungal therapy

Nystatin: one tablet 500,000 IU 4 x daily; tablets should be sucked and retained in the mouth for as long as possible. Therapy should be continued for at least 48 hours after symptoms have resolved. Suspension is less effective because of shorter contact time with the oral mucosa.

Children: Nystatin 100,000 units /ml suspension. Give 1-2 ml into the mouth 4-6 times daily for 7 days. Using cotton wool or a piece of cloth to paint the mouth with nystatin may even be better.

Gentian violet: local application of Gentian Violet 1% aqueous solution 2 x daily for 1 week is effective. However the acceptability of this treatment may be low in adults. If these are not effective, and give the following if available:

4.1.2.2 Systemic therapy

Where no improvement is seen after 7 days of a topical treatment, a switch should be made to a systemic antifungal therapy. In case of suspicion of oesophageal candidiasis, a systemic antifungal therapy should be first line.

First choice treatment:

Fluconazole: 100 – 200 mg daily during 14 days. Doses of up to 400 mg daily have been used in resistant cases. Fluconazole is preferred to ketoconazole and itraconazole, because they are hepato-toxic and have interactions with some ARV’s. Moreover, itraconazole is very expensive in many countries. Both ketoconazole and itraconazole are also contra-indicated in patients on TB treatment (INH, rifampicin).
Children: Fluconazole, 3 mg/kg daily orally for 7 days.
If fluconazole is not available:

Ketoconazole\(^a\): 200 mg - 400 mg daily during 14 days. Concurrent rifampicin therapy should be avoided: rifampicin induces the metabolism of ketoconazole, and ketoconazole is thought to inhibit the absorption of rifampicin. Treatment should be withdrawn in case of evidence of severe hepatocellular damage.

**Children:** Ketoconazole 3-6 mg/kg daily for 7 days

### 4.2 Respiratory Disease Conditions

There are various HIV related conditions of respiratory diseases. Persistence or worsening of cough, chest pain or dyspnoea in a patient with symptomatic HIV infection is known to be caused by:

**Infections:**
- Pyogenic bacteria
- Mycobacterium tuberculosis
- Pneumocystis carinii pneumonia
- Cryptococcus
- Atypical bacteria
- Others: Cytomegalovirus infection, Toxoplasmosis

**Malignancies as:**
- Kaposi sarcoma
- Lymphoma

**Others:**
- Lymphoid interstitial pneumonitis (mainly in children).

#### 4.2.1 Pulmonary Tuberculosis

HIV increases a person's susceptibility to infection with *M. tuberculosis*. About one third of HIV infected people worldwide are also co-infected with *M. tuberculosis*. HIV is the strongest risk factor for progression from latent to active TB. It is estimated that this risk is approximately 5-10% *lifetime* risk for individuals negative for HIV compared to 2.4% to 7.5% *per year* for PLHA living in high TB prevalence countries. An individual infected with HIV has 10 times increased risk of developing TB. This has resulted in dramatic increases in TB prevalence in areas of high HIV prevalence, particularly sub-Saharan Africa. Studies show in some parts of sub-Saharan Africa, HIV sero-prevalence among TB patients is as high as 70%.

**Clinical Presentation**
The presentation of PTB depends on the degree of immunosuppression.

\(^a\) In the 1999 WHO MEDL (Model Essential Drug List), ketoconazole was replaced by fluconazole, which has a better therapeutic profile and less hepatotoxicity.
Table 7: Characteristics of TB in different stages of immune deficiency

<table>
<thead>
<tr>
<th>Features of PTB</th>
<th>Stage of HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
</tr>
<tr>
<td>Clinical picture</td>
<td>Often resembles post-primary PTB</td>
</tr>
<tr>
<td>Sputum smear result</td>
<td>Often positive</td>
</tr>
<tr>
<td>Chest X-ray appearance</td>
<td>Often cavities</td>
</tr>
</tbody>
</table>

TB can appear at a level of immunity that is still relatively good, and in that case will present as typical cavitary TB or upper lobe consolidation (post-primary pattern). At lower CD4 levels more atypical presentations are likely: extra-pulmonary TB, disseminated TB, diffuse pulmonary or miliary presentations with usually negative TST. Diagnosis of these cases is more difficult.

In up to 35% of patients, signs of primary infection (recent infection) are evident: lower lobe infiltrate, pleural effusion, intra-thoracic adenopathy. Patients with suspected intrathoracic tuberculosis frequently have cervical and axillary palpable lymph nodes.

The most important symptoms in diagnosis of pulmonary tuberculosis are cough more than three weeks, weight loss, haemoptysis, chest pain, breathlessness, fever with night sweats and loss of appetite. Weight loss and fever are more common in HIV positive pulmonary TB patients, than in those who are negative. Conversely cough and haemoptysis are less common in HIV positive patients than in those who are HIV negative. This difference is probably because there is less cavitation, inflammation and endobronchial irritation in HIV positive patients. Physical signs are non-specific. They do not help to distinguish from other chest conditions.

**Note: Extrapulmonary TB**

In PLHA the proportion of extrapulmonary TB and smear-negative PTB is increased. This makes the diagnosis difficult. Patients may present with lymphadenopathy (cervical, intrathoracic, abdominal), pleural effusion, pericardial effusion, miliary TB and meningitis. Patients usually present with constitutional features and local symptoms related to the site of disease.

**Diagnosis**

**History and physical Examination:** suggestive symptoms.  
**Sputum microscopy** is the best initial test. AFB staining of expectorated sputum is positive in around 50% of patients with pulmonary TB. PTB suspects should submit three sputum samples for acid fast staining. Sputum induction is only useful in patients who cannot cough up sputum.

Smear positivity rates in HIV patients depend on immune status. For severely immunocompromised patients, the likelihood for positive sputum smears is low.

**X-ray:** Chest x-ray changes patients reflect the degree of immunosuppression (see Table 7 page 44).

**Fine needle aspiration of extra-thoracic lymph nodes** and AFB stain on the aspirate can confirm the diagnosis of smear-negative pulmonary, pleural or pericardial TB.  
**Aspiration of pleural or pericardial fluid is not necessary,** unless it is indicated for clinical reasons (Cardiac tamponade or dyspnoea). Pleural and pericardial effusion in a PLHA is in 90% of the cases due to tuberculosis.
Bronchoscopy is helpful in taking specimens: bronchus aspirate for TB, broncho-alveolar lavage (BAL) for PCP.

Treatment
Standard therapy for tuberculosis is generally as successful in HIV infected patients as in the HIV negative patient. Follow the national TB protocol as in HIV negative patients. Given the plethora of gastrointestinal problems in patients with HIV infection, malabsorption should be considered in any patient in whom a tuberculosis infection fails to clear despite appropriate therapy. To ensure the best possible treatment outcomes, daily therapy should be observed directly by a health care professional. Because of malabsorption problems the thrice weekly DOT regimens are not recommended in PLHA.

Table 8: Recommended drugs, dosages and common reactions for the initial treatment of tuberculosis in Adults

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DAILY DOSE</th>
<th>ADVERSE REACTION</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg PO</td>
<td>Elevated hepatic enzymes, peripheral neuropathy, Hepatitis, hypersensitivity</td>
<td>Peripheral neuropathy is common but pyridoxine 50 mg/d is suggested for patients with AIDS. Higher risk when combined with d4T</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 mg/kg max 600 mg PO</td>
<td>Discoloration urine &amp; nausea vomiting, fever, hepatitis</td>
<td>Accelerated clearance of methadone and other drugs Do not use together with nevirapine</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>15-30 mg/kg max-2mg PO</td>
<td>Hepatitis hyperuricemia, arthralgias, rash, glucose intolerance.</td>
<td>Hyperuricemia, but clinical gout is rare.</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-25 mg/kg max-2.5 gm PO</td>
<td>Optic neuritis, skin rash</td>
<td>25 mg/kg /day first 1-2 months or if strains resistant to anti TB are suspected.</td>
</tr>
</tbody>
</table>

Testing for HIV in a TUBERCULOSIS PATIENT:
Tuberculosis is an AIDS defining condition. Every TB patient should be offered the opportunity to get an HIV test done. All HIV positive TB patients should receive cotrimoxazole prophylaxis because this will increase survival.

4.2.2 Bacterial Pneumonia
Bacterial pulmonary infections are common and severe in HIV disease. The most common causes are Streptococcus pneumoniae or Haemophilus influenzae. The shorter history usually differentiates pneumonia from TB. Pneumonia in HIV-positive patients is more frequently associated with bloodstream infections and they represent a
not uncommon cause of early death in HIV patients in developing countries. An acute respiratory illness in a patient known to be HIV-positive, accompanied by high fever and chills, should therefore be treated as an emergency.

Other causes of bacterial pulmonary infection are staphylococcal infections, nocardiosis and *Mycoplasma pneumoniae*.

**Clinical Presentation**
The onset is frequently abrupt. There is a sudden shaking chill in more than 80% of the cases and a rapid rise in temperature, with corresponding tachycardia and an increase in respiratory rate. About 75% of patients develop severe pleuritic pain and cough. Untreated patients may have fever sustained up to 40°C. Herpes labialis is a common complication. Death is associated in a few patients with empyema or suppurative complications like meningitis or endocarditis. Nocardiosis is usually associated with multiple abscesses (lung, brain, skin). Physical examination reveals restricted motion of the affected hemi-thorax, decreased tactile fremitus and later signs of consolidation may develop. In complicated cases, signs of pleural effusion or empyema may be detected.

**Diagnosis**

**History and physical examination**

**Sputum for microscopy**
*Gram stain:* Gram stain of sputum and culture yields the diagnosis in 75% of cases. It shows polymorphonuclear leukocytes, and depending on the underlying pathogen Gram positive cocci in clusters (staphylococcus) or in pairs (streptococcus), gram negative rods (*Haemophilus influenza*) or in the case of nocardiosis a Gram stain will show Gram-positive thin branching (mycelium-like) filaments. *AFB stains:* if patient had cough for 3 weeks or more. *Wet mount:* (at x 10) can show strongyloides stercoralis larvae in the case of hyperinfection.

**Blood examination**
White blood count usually shows a polymorphonuclear leukocytosis (PMNs). A normal white count or leukopenia is some times observed in patients with overwhelming infection and bacteremia.

**X-ray of the chest** usually reveals homogeneous density in the affected area of the lung. Atypical patterns of consolidation may be seen in-patients with underlying chronic pulmonary disease. Infiltrates that are localised to one lobe, especially when an air-bronchogram is present, are suggestive of bacterial pneumonia, most likely *S.pneumoniae*. More diffuse infiltrates are more likely to be due to *H.influenzae*. Bilateral patchy consolidations in a critically ill patient suggest staphylococcal pneumonia. Patients with staphylococcal pneumonia often have other signs of staphylococcal infection: pyomyositis, abscess. A Gram stain of aspirated pus (Gram-positive cocci in clusters) can help in the diagnosis. Upper lobe consolidation with cavitation has been observed in pulmonary nocardiosis, which can mimic tuberculosis.

**Treatment**
Regardless of HIV status acute bacterial pneumonia usually responds well to standard treatment with penicillin, cotrimoxazole or ampicillin.
Second-generation cephalosporines (cefuroxime, cefaclor) and amoxy-clavulanic acid (Augmentin®) have very good respiratory coverage because they are active against *S.pneumoniae*, *Moraxella catharalis* and *H.influenzae*. The antibiotic of choice for staphylococcal infections is (flu)cloxacillin 1-2 g 4 x daily IV or 500 mg 4 x daily PO. The recommended treatment for Nocardia is cotrimoxazole 10/50 mg/kg 2 x daily. This usually corresponds with 4-6 tablets (480 mg) 2 x daily. The duration of the treatment varies from 6 weeks (for localised disease) to 6 months (for disseminated disease). Critically ill patients with a respiratory infection should receive a combination that contains a quinolone or chloramphenicol (or ceftiraxone if available) to cover for Gram-negative infections.

4.2.3 Pneumocystis Carinii Pneumonia

**Epidemiology**

Pneumocystis Carinii (PCP) is an opportunistic pathogen whose natural habitat is the lung. The organism is an important cause of pneumonia in the immunocompromised host. **PCP** occurs in the following hosts: premature, malnourished infants, children with a primary immunodeficiency disease, patients receiving immunosuppressive therapy and patients with AIDS. AIDS is currently the most common underlying disease for **PCP**.

**Clinical Features**

Patients with **PCP** complain of dyspnoea, fever, and non-productive cough gradually getting worse. The duration of illness until diagnosis is typically 1 to 2 weeks, although considerable variation exists.

**Diagnosis**

In general the diagnosis is based on the history and physical exam, combined with a suggestive chest X-ray and hypoxia. It would be good to confirm the diagnosis in the laboratory if possible.

**History and physical examination**

Sub-acute onset of symptoms, gradually getting worse. Physical findings include tachypnoea, tachycardia, and cyanosis. Dyspnoea on exertion is always present. Lung auscultation reveals course dry crackles, but can be normal. If oxygen saturation measurement is possible, it will always show a decrease in O₂ saturation during physical effort in patients with **PCP**.

**Blood Examination**

Complete blood count (CBC) - the white blood count is variable and usually governed by the patient's underlying disease. Arterial blood gases demonstrate hypoxemia, increased alveolar-arterial oxygen gradient and respiratory alkalosis. A lactate dehydrogenase (LDH) level of >1000 U/l is suggestive of **PCP**.

**Chest X- ray**

The classic findings on chest X-ray consist of bilateral diffuse infiltrates beginning in the perihilar regions. Sometimes there are nodules or cavities, but the X-ray can be (at first presentation) misleadingly normal (25%). More than 80% of cases of pneumothorax in HIV-infected patients are due to **PCP**. Therefore all patients with pneumothorax should be given empirical **PCP** treatment.
Laboratory diagnosis

*P. Carinii oocysts* is rarely present in sputum. *P. Carinii oocysts* can be demonstrated in specially prepared *induced sputum* smears (sens. 60%) or in bronchoalveolar lavage (BAL: sens. 90%). In patients who are not taking PCP prophylaxis, the sensitivity of induced sputum may be as high as 90%. Measurement of serum lactate dehydrogenase (LDH) can be helpful. A normal LDH makes PCP unlikely. A strongly elevated LDH (>2 times the normal value) suggests that PCP is likely. Two methods can be used to identify the parasite: one is based on classical staining of cell walls (e.g. Toluoidine-blue-O-stain or Gram-Weigert) and a staining for the parasite (e.g. May-Grünwald-Giemsa or methanol Giemsa). The other is based on immunochemical methods using the immunefluorescence microscope\(^b\).

Treatment

**Supportive:**
General supportive measures include:
- Maintenance of adequate oxygenation
- Maintenance of fluid and electrolyte balance
- Nutritional support

**Drug Treatment**

The two major drugs used in the treatment of *PCP* have been cotrimoxazole and pentamidine. These drugs are equally effective, with success rates of 50 to 80%. Pentamidine has more side effects (renal failure, hypoglycaemia, hypotension) and therefore the first choice treatment is:

1. **Cotrimoxazole (TMP/SMX)** IV or PO: TMP 20 mg/kg daily and SMX 100 mg/kg daily divided over 4 doses for 21 days.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose in mg</th>
<th>Dose in tablets of 400/80 mg (SS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-45 kg</td>
<td>800/160 mg x 4/day</td>
<td>2SS x 4/day</td>
</tr>
<tr>
<td>45-60 kg</td>
<td>1600/320 mg x 3/day</td>
<td>4SS x 3/day</td>
</tr>
<tr>
<td>&gt; 60 kg</td>
<td>1600/320 mg x 4/day</td>
<td>4 SS x 4/day</td>
</tr>
</tbody>
</table>

Any patient who is hypoxic (pO2<70 mmHg) should receive prednisolone.

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 is less than 70 mmHg, if a corticosteroid (oral prednisolone or intravenous methylprednisolone) is administered as soon as antimicrobial therapy is started.

<table>
<thead>
<tr>
<th></th>
<th>ADULTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1-5</td>
<td>40 mg x 2/day</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>D6-10</td>
<td>40 mg x 1/day</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>D11-D21</td>
<td>20 mg x 1/ ay</td>
<td>0.25 mg/kg</td>
</tr>
</tbody>
</table>

\(^b\) In some laboratories a fluorescence microscope is used for the diagnosis of TB. The same microscope could be used for immunefluorescence diagnosis of PCP.
In case there is no response after 7-10 days repeat the bronchoscopy and do a transbronchial biopsy. The patient may have tuberculosis as well. 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 (renal failure, hypotension, hypoglycaemia) compared to the other regimens has limited its use and it is now used only as a last resort. If a switch to pentamidine is being considered, there should be an overlap of 2-3 days to allow pentamidine to accumulate in the body.

2. **Pentamidine** given by slow intravenous infusion 4 mg/kg per day for 14-21 days. The infusion should be given over 2 hours while the patient is lying down. In case the patient becomes unconscious during infusion, suspect hypoglycaemia and give glucose 30% IV. Do not give it intramuscular because of the risk of sterile abscesses.

3. **Trimethoprim,** 15mg/kg/d + **dapsone,** 100 mg/d once daily for 14-21 days

4. **Primaquine,** 15-30mg daily and **clindamycin** 300-900 mg every 6 hours 14-21 days

**Prophylaxis** (see also Prevention of bacterial infections, PCP and toxoplasmosis, using cotrimoxazole page 30)

Every HIV-positive patient who 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 of such episodes is fatal.

First choice:   **TMP/SMX** 1DS daily  
Second choice:    **dapsone** 100 mg daily  
Third choice:    **pentamidine (nebulised)** 300 mg once a month  
Fourth choice: **sulfadoxine/pyrimethamine (Fansidar ®)** 1-2 tablets weekly.

**4.2.4 Deep fungal infections**

Several deep fungal infections can cause pulmonary symptoms in HIV patients, but they are less frequent. *Histoplasmosis, Coccidioidomycosis, Aspergillosis:* these infections are rare in HIV-infected persons in developing countries. They occur only with profound immune suppression and with severe neutropenia. Diagnosis is made by blood and sputum culture.

Treatment consists of amphotericin B 0.7 mg/kg during 14 days, followed by maintenance therapy with itraconazole 200 mgx2/day during 10 weeks, followed by secondary prophylaxis with itraconazole 200 mg/day.

**4.3 Neurological complications of HIV infection**

HIV infected patients are at markedly increased risk for neurological disease or dysfunction, where as up to two-third of patients with HIV disease has neurological complications. This is either due to primary HIV infection, since HIV itself is a neurotropic virus and secondary to opportunistic CNS infectious diseases and

\[c\] Pyrimethamine should be added in patients with a CD4 count lower than 100/mm3 and *Toxoplasma gondii* antibody positive, if they do not tolerate TMP/SMX.
malignancies. In post-mortem examination of patients with AIDS, CNS abnormalities occur in 70-80%.

4.3.1 Pathogenesis of Neurological abnormalities

Neurological abnormalities are commonly found in HIV infected individuals. It has been well established that HIV is present in the brain and cerebrospinal fluid of infected individuals at all stages of the infection.

A. Direct HIV-1 infection
- Acute meningo-encephalitis
- Aseptic Meningitis
- AIDS Dementia complex (HIV encephalopathy)
- HIV encephalitis
- Vacuolar myelopathy
- Peripheral Neuropathy
- Acute demyelinating polyneuropathy
- Mono neuritis multiplex
- Distal symmetric polyneuropathy
- Myopathy

B. Opportunistic infections
- Cryptococcal meningitis
- Cerebral toxoplasmosis
- Tuberculous Meningitis
- Cytomegalovirus encephalitis
- Progressive multifocal leucoencephalopathy (PML)
- Neurosyphilis

C. Opportunistic Neoplasms
- Primary brain lymphoma
- Metastatic lymphoma

4.3.2 Primary involvement of the CNS by HIV

4.3.2.1 AIDS Dementia Complex or HIV Encephalopathy

An infection with HIV is frequently complicated in its late stages by the AIDS dementia complex, a neurological syndrome characterized by abnormalities in cognition, motor performance and behaviour. Approximately 7-9% of patients with AIDS become demented.

Progressive AIDS dementia may precede the development of opportunistic infection. AIDS dementia begins insidiously and progresses over months or years. Occasionally the disorder may be acute or sub acute in onset. Poor concentration and memory, slowing of thought process, behavioural abnormalities, social withdrawal and apathy characterize AIDS dementia complex. Few patients become agitated, confused or paranoid or develop hallucination. Motor abnormalities are common including impaired rapidly alternating movements, impaired ocular motility, and mild gait ataxia. As the disease progresses, patients become more and more demented and may develop a
myelopathy characterized by spastic weakness of the lower extremities and incontinence. Sometimes the myelopathy precedes signs of intellectual impairment. The patient eventually becomes completely withdrawn and bedridden before death from an opportunistic infection or tumor occurs. Cranial computed tomography (CT) scan usually shows increased ventricular and sulcal size suggestive of cerebral atrophy and may show generally hypodense white matter. On MRI, patchy white abnormalities are frequently seen. The CSF is usually normal, although 20% of cases may have a mild mononuclear pleocytosis (<50 WBC/mm³) with slightly increased protein content (<200 mg/dl).

NOTE:

AIDS dementia complex is a diagnosis of exclusion. It is important to rule out opportunistic infections of the brain first. Also severe depression may mimic dementia.

When available, an AZT or D4T-containing HAART regimen is an effective treatment for HIV-associated dementia. There is not enough evidence to promote adding a PI rather than a NNRTI to the 2 NRTIs.

4.3.2.2 HIV Meningo - Encephalitis

Early-stage symptomatic meningitis occurs in a minority of patients, but when present indicates an increased risk for more rapid disease progression. Acute aseptic meningitis is associated with a high viral load in the CSF. The result of the CSF exam is usually normal. This condition resolves spontaneously and does not require treatment. Acute inflammatory demyelinating polyneuropathy (AIDP) can be seen during acute seroconversion and resembles Guillain Barré Syndrome (GBS). In this case there is lymphocytic pleocytosis in CSF in contrast to the non-HIV associated GBS. Steroids may help.

4.3.2.3 Vacuolar Myelopathy

HIV-related spinal cord involvement is rare. It presents as spastic paresis with bowel and bladder dysfunction, gait ataxia and variable sensory loss. Clinical feature includes gait ataxia, leg weakness, upper motor neurological signs, incontinence and posterior column deficit. Ninety percent of cases also have dementia. This condition can respond to HAART. Differential diagnosis has to be made with cord-compression (epidural abscess, tumor), vitamin B12 deficiency or other viral infections (varicella, CMV, HTLV-1).

4.3.2.4 Mononeuropathy and polyneuropathy

Neuropathy is one of the most common neurological manifestations in AIDS patients, occurring in as many as 30% of the patients. At every level of the peripheral nervous system, abnormalities in patients have been described with HIV infection. Nearly every patient has one of four readily distinguishable syndromes: Mononeuropathy Multiplex, Distal Symmetrical Peripheral Neuropathy, Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Progressive Polyradiculopathy (see Table 11 page 52).
### Table 11: The major peripheral neuropathy syndromes in HIV infected patients

<table>
<thead>
<tr>
<th></th>
<th>Distal symmetrical peripheral neuropathy</th>
<th>Inflammatory demyelinating neuropathy</th>
<th>Mono neuropathy multiplex</th>
<th>Progressive Poly radiculoneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AIDS</td>
<td>AIDS related complex</td>
<td>AIDS related complex</td>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td>Motor</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Sensory</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>Late</td>
</tr>
<tr>
<td>Urinary retentions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>CSF WBC Protein Glucose</td>
<td>Normal high</td>
<td>Mononuclears high normal</td>
<td>Mononuclears high normal</td>
<td>PMN high</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

PMN = polymorphonuclears

#### 4.3.2.4.1 Mononeuropathy multiplex (MM)
This neuropathy may occur during latent or early symptomatic stages. Facial palsy (Bell’s palsy) is a common presentation. Clinically they present with patchy, asymmetric sensory and motor deficits. It can be due to immune dysfunction or to vasculitis. In the latter, pain is usually the first symptom, and in that case steroids may help.

#### 4.3.2.4.2 Distal, symmetrical polyneuropathy (DSP)
This is the most common type of neuropathy seen. It is associated with lower CD4 counts and high viral load and causes painful paresthesias and numbness of fingertips and toes, which progresses proximally. Symptoms are usually worse at night and are aggravated by contact with bed sheets or wearing shoes. In severe forms, the painful paresthesias and burning can prevent patients from walking despite intact motor function. On physical examination there is a decreased sensation to pinprick, light touch and vibration, and the ankle reflexes are diminished. Sensory function is usually more affected than motor. There is evidence of autonomic dysfunction in about 10% of AIDS cases.

It can be caused by HIV itself or by other viral infections such as Herpes zoster and CMV. CMV is an unlikely cause of neuropathy if vision and fundoscopy are normal. Nutritional deficiencies (vitB6, vitB12) and syphilis can also cause DSP. Drug-associated neurotoxicity as is the case with isoniazid (INH) is a well-known phenomenon, and is more frequent in HIV-infected patients. INH should always be given together with pyridoxine to prevent neuropathy (10-50 mg daily). Once INH induced neuropathy is established the dose of pyridoxine should be increased to 100-200 mg daily.

In case of positive VDRL the patients need treatment for neurosyphilis (see below). Also antiretroviral drugs, especially nucleoside analogues are frequently responsible for peripheral neuropathy (D4T 23%, ddI 13%). The onset can be as early as one week after the start of the treatment. Ritonavir can give peri-oral paresthesias, and in rare cases distal sensory neuropathy. The patients should be carefully monitored and when
the neuropathy is extending above the level of ankles and/or hands, or if the neuropathy prevents the patient from sleeping, one should consider switching to another non-neurotoxic drug. Waiting too long before switching can cause irreversible damage. Symptoms continue to worsen after interruption of the offending drug, but usually improve over a period of months. Treatment is symptomatic and includes amitriptyline and non-steroidal agents for pain.

4.3.2.4.3 Chronic inflammatory demyelinating polyneuropathy (CIDP)
CIDP is another type of polyneuropathy, which can be the presenting illness in HIV. It occurs at a CD4 count of 200-500. It is considered a chronic Guillain-Barré Syndrome (GBS). It usually produces more severe motor than sensory symptoms. Tendon reflexes are usually absent or markedly hypo-active throughout and there is progressive symmetrical loss of sensation or pain in fingers and hands and/or feet and legs. Unlike in GBS, the autonomic symptoms are usually absent. Treatment with steroids may help, but is potentially problematic in the setting of immune suppression due to HIV. When these patients are started on HAART it is better to avoid potential neurotoxic drugs.

4.3.2.4.4 Progressive Polyradiculopathy (PP)
Usually develops in patients with low CD4 count (<50). Patients present with sub-acute low back pain and radicular pain over a period of a few days, evolving in flaccid paralysis, sphincter dysfunction and areflexia. Usually only the lower extremities are involved. The most common cause is CMV. In the absence of anti-CMV therapy, treatment is supportive.

4.3.2.4.5 Acute neuromyopathia syndrome
This syndrome is characterized by ascending paresis, areflexia and cranial nerve lesions, compatible with Guillain-Barré syndrome, sometimes with severe neuropathic pain and muscle weakness. The differential diagnosis has to be made with myelitis and botulism. It often occurs in association with lactic acidosis in patients with prolonged use of stavudine.

4.3.2.4.6 Generalised motor weakness
Extreme muscle weakness with inability to walk can be due to severe hypokalemia. Low potassium is frequently encountered in AIDS patients with chronic diarrhoea and during treatment with amphotericin B.

4.3.2.4.7 Treatment of neuropathies in HIV
Treatment of sensory neuropathy is largely symptomatic. Offending drugs should be discontinued. Vitamin B complex should be given to replace possible nutritional deficiencies. Amitriptyline at bed time, starting from a low dose (25 mg) and then gradually increasing till 75 mg if needed. In case of lancinating pain, carbamazepine seems to be more effective (100 mg twice daily, can be increased to a maximum dose of 400 mg twice daily) (see neuropathic pain page 86).
4.3.3 Opportunistic infections involving the brain

The differential diagnosis includes the following pathogens:
- Protozoal infection: *Toxoplasma gondii*
- Mycobacterial infection: *M. tuberculosis, M. Avium (in immune reconstitution syndrome)*
- Fungal infection: *Cryptococcus neoformans, Histoplasmosis, Coccidioidomycosis, Candida* species (rare)
- Viral infection: Cytomegalovirus, Herpes simplex virus, Varicella zoster virus, JC virus (slow virus causing progressive multifocal leuko-encephalopathy - PML).

Since neurological involvement in AIDS patients can present in many different ways and since some of the conditions can be treated, early diagnosis is important. This is true for TB meningitis, Toxoplasma brain abscess and fungal meningitis. The threshold for performing an LP should therefore be kept very low in AIDS patients who have headache.

**Even in the presence of papiloedema, an LP seems to carry no excessive risk in TB meningitis or toxoplasmosis, and is even indicated for treating intracranial hypertension in the case of cryptococcal meningitis.**

4.3.3.1 Cryptococcal Meningitis

*Cryptococcus neoformans* is the most common life-threatening fungal infection in patients with AIDS. Meningo-encephalitis due to Cryptococcal Neoformans occurs in approximately 6-12% of AIDS patients. Typically, it is a sub-acute illness and its symptoms include headache, alteration in consciousness or cognition, fever, nausea, vomiting, neck stiffness and sometimes seizure. Focal findings other than cranial neuropathy are uncommon. Neck stiffness can be absent!! Thus prolonged headache and fever, behavioural changes and confusion justify a lumbar puncture in PLHA.

**Diagnosis**

Lumbar puncture is the diagnostic procedure of choice. Cerebrospinal fluid cell counts; glucose and protein levels may be only minimally abnormal. Examination with **Indian ink** staining is frequently positive in 70-80%. **Cryptococcal antigen (CrAg)** is nearly always detected in the serum and cerebrospinal fluid in 95-100% of cases. 

Note: A positive India ink staining in a patient, who completed treatment and has no symptoms anymore, does not prove active infection or failure of therapy. A positive culture always proves active infection.

**Treatment**

The recommended treatment option for Cryptococcal meningitis includes:

**1st choice**

Amphotericin B (IV) (0.7 mg/kg daily by I.V injection for 2 weeks) followed by fluconazole 400 mg daily for 8 weeks, followed by fluconazole 200 mg daily as secondary prophylaxis.

**Children:** Amphotericin B, 0.7-1mg/kg/d IV diluted in 5% glucose infused by slow drip over 4 hrs, during 2 weeks, followed by maintenance therapy of fluconazole 10-12 mg/kg during 8 weeks.

Secondary prophylaxis: fluconazole 5mg/kg/day lifelong, or until immune restoration after HAART (CD4 > 100 during 3-6 months)
2nd choice
In patients with less severe disease, oral fluconazole treatment alone (400 mg once daily during 10 weeks, after an initial loading dose of 800 mg during 3 days) may be sufficient. This should be used in patients with less severe headache who have a negative CSF exam, but cryptococcal antigen (CrAg) is positive on CSF.

**Children**: fluconazole 10-12/mg/kg once daily during 10 weeks always followed by secondary prophylaxis.

### 4.3.3.1.1 How to safely administer amphotericin B?

Infuse amphotericin B over 4-6 hours. Rapid infusion is associated with hypotension, hypokalemia, shock, arrhythmias and should be avoided.

Infusion-related reactions such as nausea and vomiting are common with amphotericin B. They usually occur between 15 minutes and 3 hours following the start of the infusion. Drug-induced fever, chills and headache are also seen. These symptoms can be prevented by premedication with 1 g of paracetamol and 25 mg of promethazine.

For severe chills and rigors, pethidine 25 mg IM or IV is frequently prescribed. The severity of the reactions tends to decrease with subsequent doses of amphotericin B. Some clinicians prefer to start with a lower dose (0.3 mg/kg) the first day. Severe hypokalemia can occur during treatment with amphotericin B due to a potassium wasting nephropathy. In some patients, this leads to severe muscle weakness, muscle cramps, chest pain, palpitations, drowsiness and mental status changes.

Replacement with oral potassium and magnesium supplements is indicated. Prehydration with 1 litre normal saline can help reduce the incidence of nephrotoxicity. Close medical supervision is required throughout treatment. Check the renal function once a week if possible or monitor the urine output. When renal failure develops interrupt the treatment or increase the dosing interval of amphotericin B. Thrombocytopenia and hypoglycaemia are other possible side effects. Patients may become hypotensive or hypertensive, in which case the rate of the infusion needs to be slowed down, after a temporary interruption of 30 minutes.
Table 12: Close medical supervision is required throughout treatment with amphotericin B.

**Example of treatment protocol**

<table>
<thead>
<tr>
<th>Daily procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take history:</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhoea, anorexia, severe muscle cramping, weakness, chest pain, palpitations, CNS disturbance (lethargy, sleepiness), decreased urination, black stool or easy bruising/bleeding, pain at previous IV site.</td>
</tr>
<tr>
<td>2) Laboratory if indicated:</td>
</tr>
<tr>
<td>• Routine monitoring: K, creatinine, BUN, CBC, glucose (day 1, 7, 14) If you do not have this, the most important is to observe well your patient. Give him enough food, and supplement of potassium and magnesium.</td>
</tr>
<tr>
<td>• More frequently as indicated (in case of bleeding, decreased urination, mental changes to evaluate symptoms elicited in the history.</td>
</tr>
<tr>
<td>3) Pre-medication 30-60 minutes before infusion:</td>
</tr>
<tr>
<td>• Paracetamol 1 gm PO, Promethazine 25 mg PO.</td>
</tr>
<tr>
<td>• Hydrocortisone 50 mg IV if severe rigor/chills occurred on previous infusion.</td>
</tr>
<tr>
<td>4) Record vital signs:</td>
</tr>
<tr>
<td>T, P, R, BP initially and every 30 minutes during infusion.</td>
</tr>
<tr>
<td>5) Hydrate NS 500 -1000 ml IV (over 2 hours) to avoid nephrotoxicity</td>
</tr>
<tr>
<td>6) Infuse Amphotericin B over 4-6 hours</td>
</tr>
<tr>
<td>• Starting dose: Day 1 :0.3 mg/kg in 250 D5W.</td>
</tr>
<tr>
<td>• Full dose: Day 2-14 :0.7 mg/kg in 250 D5W.</td>
</tr>
<tr>
<td>• Adjusted dose: if decline in renal function during therapy, or significant adverse reactions may cut full dose in half.</td>
</tr>
<tr>
<td>• The total cumulative dose should remain the same when dose is adjusted.</td>
</tr>
<tr>
<td>• If chills/rigor develop give Pethidine 25 mg IV, hydrocortisone 50 mg IV.</td>
</tr>
<tr>
<td>7) LP if patient has known or suspected increased intracranial pressure – (&gt;25 cm of H2O)</td>
</tr>
<tr>
<td>• Measure and record OP at each LP.</td>
</tr>
<tr>
<td>• If &gt; 25 cm H2O drain 30cc of CSF.</td>
</tr>
<tr>
<td>• Repeat daily until OP &lt; 25 cm.</td>
</tr>
<tr>
<td>• Repeat later on if patient’s headache increases again</td>
</tr>
<tr>
<td>8) Review instructions to patient:</td>
</tr>
<tr>
<td>• Drink 2-3 litres of fluids per day.</td>
</tr>
<tr>
<td>• Small frequent meals</td>
</tr>
<tr>
<td>• Replace with oral Magnesium, one tablet daily and KCL 600 mg twice daily (caution with K replacement if significant pre-existing renal failure).</td>
</tr>
<tr>
<td>9) For seizures:</td>
</tr>
<tr>
<td>Benzodiazepines IV or IR, then load with phenytoin. If seizures do not recur, the phenytoin may be interrupted during the maintenance phase.</td>
</tr>
<tr>
<td>10) Begin Fluconazole 400 mg per day for 8 weeks upon completion of the 14 day Amphotericin B regimen.</td>
</tr>
</tbody>
</table>

### 4.3.3.1.2 Treatment of increased CSF pressure

The management of high intracranial pressure (ICP) is considered one of the most important factors influencing early mortality. High ICP is present in more than 50% of patients with cryptococcal meningitis. Even in the US with the current treatment regimens, there was a high rate of acute mortality during initial therapy (10%-25%). Often there is a sudden deterioration and catastrophic visual loss in patients with elevated intracranial pressure. The only effective therapy to reduce the severe headache is to lower intracranial pressure by...
repeated spinal taps. Most patients declare dramatic relief of headache within minutes of the procedure. There is no place for corticosteroids\textsuperscript{d} as adjuvant therapy in cryptococcal meningitis. If the initial opening pressure was normal, perform a follow-up LP at 1 and 2 weeks or if any worsening of headache, visual or hearing problems. If the initial opening pressure was >250 mmH\textsubscript{2}O, perform a spinal tap sufficient to achieve pressure < 200 mmH\textsubscript{2}O or 50\% of initial opening pressure. You can tap up to 30 ml each time. Daily taps should be performed until opening pressure is below 200 mm H\textsubscript{2}O. For the first diagnostic LP, use a 20-22 G spinal needle. For therapeutic tapping: an 18G spinal needle can be used.

4.3.3.2 Cerebral Toxoplasmosis

Cerebral Toxoplasmosis is a common non-viral opportunistic pathogen in the CNS of AIDS patients, occurring in 5\% to 47\% of HIV-infected patients with serologic evidence of \textit{Toxoplasma gondii} infection. In some countries it occurs infrequently. It would be interesting to have an idea of the seroprevalence of toxoplasmosis among the general population in Eritrea. Hemiparesis, cognitive disorders, fever, seizures and other signs suggestive of an intracerebral space-occupying lesion tend to develop sub-acutely over several weeks, and they are sometimes accompanied by symptoms of a diffuse encephalopathy. Less frequent presentations include ataxia incontinence, hemi sensory deficit, cranial nerve paresis, aphasia, anisocoria, hemi-anopsia, diplopia, dysarthria and photophobia. In contrast to AIDS dementia complex, the loss of consciousness occurs early in the evolution.

\textbf{Pathogenesis}

Reactivation of latent bradyzoites produces focal neurological signs mainly in patients with CD4<100. Primary infection may result in focal necrotizing encephalitis and occasionally chorioretinitis and pneumonitis.

\textbf{Symptoms}

Symptoms are variable, but typically subacute over several weeks. Fever is present in about 50\% of patients and headache, which may be very prominent, is present in 50\%-70\% of patients. 50\% of patients have hemiplegia or hemiparesis. 30\% have seizures. Meningeal irritation is infrequent.

\textbf{Diagnosis}

The most useful diagnostic test has been the CT scan. Lesions are usually multiple, ring enhancing with contrast, associated with oedema and located in cortical or sub cortical regions of the brain such as basal ganglia. CSF findings are non-specific or normal. In many countries, \textit{Toxoplasma gondii} is the most common cause of focal brain disease in HIV patients. It is therefore worth treating any HIV-positive patient presenting with headache, fever and focal neurological signs, and who has normal CSF findings, for toxoplasmosis. If the diagnosis of toxoplasmosis is correct, 74\% of patients will have responded to treatment by day 7 and 91\% by day 14. The median time to response is 5 days. Response to empirical therapy is currently being considered as a diagnostic criterion. If possible, toxoplasma antibody (IgG) can be useful, because the negative predictive value is high (94-97\%) In other words, toxoplasma brain abscess is less likely if the toxoplasma serology is negative. If there is no response to empirical therapy after 2 weeks an alternative diagnosis needs to be considered.

\footnote{\textsuperscript{d} except in IRIS?}
Treatment

First choice: sulfadiazine and pyrimethamine and folinic acid for 6-8 wks.
- pyrimethamine 100 mg loading dose, followed by 50 mg daily
- sulfadiazine 1-2g 4 x daily (100 mg/kg daily)
- folinic acid 10 mg daily.

Overall 45-70% of patients will develop side effects of treatment and 33% of patients will require a change in therapy. The side effects of therapy are anaemia and leucocytopenia, thrombocytopenia which may be ameliorated by the concomitant use of folinic acid. Another side effect is renal failure due to sulfadiazine crystaluria. Administering fluids and alkalining the urine without discontinuing the medication can manage crystaluria.

Children: See CNS Toxoplasmosis in children page 103

Second choice: high dose TMP/SMX (10/50 mg/kg daily) for 4 weeks.
- Several Italian studies have shown that, high dose TMP/SMX 10/50 mg/kg daily PO or IV, divided over 2 doses for 4 weeks, followed by a lifelong maintenance of 1 DS (960 mg) TMP/SMX daily is effective in the treatment of toxoplasma encephalitis, and has fewer side effects than the combination sulfadiazine/ pyrimethamine.

Third choice: clindamycin and pyrimethamine and folinic acid for 6-8 wks.
- clindamycin 600 mg 3 x daily
- pyrimethamine 100 mg daily loading dose followed by 50 mg daily
- folinic acid 10 mg daily.

- If the response is good (response rate of approximately 90%), life long suppression therapy (maintenance therapy) is advisable. Without maintenance therapy the relapse rate is over 50% at 6 months.

Maintenance therapy
- TMP/SMX: 1DS daily.
- Sulfadiazine 500 mg 2 tablets 2 x daily + pyrimethamine 25 mg daily + (folinic acid 25 mg weekly)
- Dapsone 200 mg daily or 50 mg daily + pyrimethamine 75 mg weekly + (folinic acid 25 mg weekly)

Other measures
- In case of intracranial hypertension: papiloedema, vomiting: corticosteroids: prednisolone 40 mg 4 x daily or dexamethasone 4 mg 4 x daily.
- If there is no sign of mass effect avoid using steroids because it may be difficult to assess the response to empirical treatment.
- Anti-epileptic treatment in case of prolonged or recurrent seizures: phenytoine 100 mg 2-3 x daily (after a loading dose of 15 mg/kg daily the first day).

- It is important to remember that folic acid counteracts the anti-protozoal activity of pyrimethamine and is not a good alternative for the expensive folinic acid.
- Note that of the commercial antimalarial drugs, Maloprim® contains dapsone 100 mg/pyrimethamine 12,5 mg and Daraprim® contains pyrimethamine 25 mg.
Primary prophylaxis and secondary prophylaxis (see also p 30)
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 CD4<100 and T. gondii antibody positive, prophylaxis with either TMP/SMX or dapsone and pyrimethamine at doses used for the prevention of PCP, have been shown to reduce the incidence of toxoplasmosis.
TMP/SMX: 1DS daily.
Dapsone 200 mg weekly or 50 mg daily + pyrimethamine 75 mg weekly + folinic acid 25 mg weekly

Primary and secondary prophylaxis can be stopped if the CD4 is more than 100-200 cells/mm³ for at least 6 months, in patients taking HAART.

4.3.3.3 **Tuberculous Meningitis**

Up to 10% of AIDS patients who present with TB will show involvement of the meninges. This results from rupture of a cerebral tuberculoma or is blood-borne. Be aware of IRIS related TB meningitis, especially in the first 6 weeks after starting HAART.

The presentation is generally one of sub acute meningitis with a neurological syndrome being present for less than two weeks in over half of patients. Headache, low-grade fever, meningismus and altered mental status are characteristic: with papilloedema, cranial nerve palsies (I, II, IV, VI, or VIII) and in severe cases seizure and signs of focal neurological deficit and loss of consciousness may occur. Up to 40% of patients may also have an abnormal chest X-ray.

**Diagnosis**

Examination of the CSF is a useful diagnostic tool. If possible exclude an intracranial mass by brain CT scan in patients who present with headache and focal neurological deficit.

But lumbar puncture is mostly safe in tuberculous meningitis if one uses a 20-22 G needle for diagnostic LP.

Microscopic examination of spinal fluid for acid-fast bacilli is the most important procedure for a definitive early diagnosis. Acid-fast bacilli are identified in the CSF of 10-40% of patients. However, the yield of positive results can increase depending on both the time devoted to searching and the number of specimens examined. CSF cultures to isolate AFB are positive in 45-90% depending upon the quantity of the fluid cultured and laboratory facility. The use of a fluorescence microscope is more sensitive to detect mycobacteria in fluids.

The diagnosis of tuberculous meningitis relies on isolation of *Mycobacterium tuberculosis* from the CSF. Unfortunately this is a slow process, and therefore not helpful in clinical decision making.

CSF in TB meningitis looks clear and colourless, but a pellicle or cobweb clot develops on standing. There is a moderate degree of pleocytosis usually not exceeding 500 cells/mm³. The majority of cells are lymphocytes.

The CSF protein level usually ranges between 100-500 mg per dl. It increases gradually as the disease progresses. Initial values above 300 mg correlate with a poor prognosis. The CSF glucose concentration is below 40-50 % of simultaneously measured blood glucose in 50-85% of patients and it tends to decline steadily in untreated cases.

Always exclude cryptococcal meningitis by CSF microscopy (Indian ink stain).
**Treatment**
The treatment of tuberculous meningitis is according to the National Tuberculosis Control Program.

Prolonged treatment: a **7-month continuation** phase with **daily isoniazid and rifampicin** (7HR) is recommended for category 1 patients with the following forms of TB: TB meningitis, miliary TB, spinal TB with neurological signs. In case of severe neurological signs (cranial nerve lesions, drowsiness, coma) the use of **steroids** (prednisone 1 mg/kg for 2-4 weeks, then tapered off over 4-6 weeks) is good clinical practice. Patients treated with steroids have more rapid symptomatic relief and less neurological sequelae.

Thioacetazone should not be used in persons known to be or suspected of being infected with HIV because of the occurrence of severe hypersensitivity reactions.

**Note:**
There is a higher incidence of paradoxical reactions if patients are started on HAART and TB treatment at the same time. Therefore always start first TB treatment and add HAART when the treatment is tolerated between 2 weeks and 2 months (WHO) or when the intensive phase of 2 months with rifampicin is finished.

TB meningitis during Immune Reconstitution Inflammatory Syndrome (IRIS) can sometimes have a very fulminant course if not recognized. Steroids should always be added to the TB **treatment** in case of IRIS related TB meningitis. HAART can be continued, but in very severe cases, a temporary interruption may be justified. Switch to efavirenz (EFV) if the patient was taking a Nevirapine-containing regimen, but keep in mind that giving EFV to a patient with neurological problems can worsen the clinical picture due to EFV side effects. If efavirenz is not available you can continue nevirapine. Watch out for hepatotoxicity.

**4.3.3.4 Syphilis and HIV Infection, Neurosyphilis**
Tertiary syphilis involving the brain and spinal cord used to be common before the availability of antibiotics. In PLHA, syphilis can occur even in people who had previously a complete course of antibiotics, and it can occur without a rise in VDRL or RPR. If clinical suspicion is high and serology is negative, the VDRL should be rechecked after dilution of the sample (to rule out the prozone effect = false negative tests due to excessive presence of antigen). All the classical presentations of neurosyphilis are seen again: tabes dorsalis, gumma (meningo-vascular disease), etc.

**Diagnosis**
An elevated CSF white blood cells count, elevated protein and positive VDRL on samples of CSF establish the diagnosis of neurosyphilis. Although serum VDRL has a high sensitivity (90%) and low specificity, this trend is reversed on the CSF sample. CSF VDRL has high specificity but low sensitivity. A patient with persistent positive blood VDRL and FTA - ABs with neurologic syndrome consistent with syphilis is a sufficient indication for treatment.
Treatment of neuro-syphilis
The recommended treatment for neuro-syphilis is aqueous penicillin G 20-24 mega units IV daily in divided doses for 10 - 14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks. Check VDRL again at 3, 6, 12 and 24 months. If VDRL fails to decline: repeat treatment. Alternative: penicillin procaine IM 2,4 MIU daily plus probenecid PO 500 mg 4 x daily for 10-14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks. A small proportion (2-3%) of patients with neuro-syphilis may undergo abrupt deterioration following treatment with penicillin. The Jarisch-Herxheimer reaction of uncertain cause may be ameliorated by concomitant treatment with corticosteroids.

4.3.3.5 Cytomegalovirus infection

CMV disease in PLHA is due to reactivation, occurring in patients with CD4<50 and presenting with gastrointestinal disease and retinitis. 50% of PLHA with active CMV disease will have CMV retinitis. Neurological manifestations include myelopathy or progressive polyradiculopathy and encephalitis. Clinically encephalitis presents as a rapidly progressive delirium, cranial nerve deficits, nystagmus and ataxia. The diagnosis is difficult. CSF exam may reveal lymphocytic pleocytosis, low glucose and increased protein, therefore indistinguishable from tuberculous meningitis. In case of radiculomyelitis the CSF shows predominant neutrophils. PCR for CMV on the CSF has a good sensitivity and specificity but is rarely available. Serology has no place in the diagnosis of CMV.

Prognosis is poor for patients with CNS CMV disease. Induction therapy with IV ganciclovir effectively treats retinitis in 70%-90% of patients, but the effect is much less in CNS disease. Lifelong maintenance therapy is necessary. Severe bone marrow suppression can occur. The drug is expensive and beyond the reach of most developing countries. All patients should be treated with HAART, as immune reconstitution will improve survival. However, patients should be informed about the possibility of IRIS after the start of HAART, which in the case of CMV may cause blindness (usually after 1-2 months), due to immune recovery uveitis (IRU) or vitritis. The best way to decrease the risk of blindness is to start early with HAART, before severe immune suppression. It is not clear whether intra-ocular injections with ganciclovir decrease the risk of IRU.
Table 13: Three drugs Ganciclovir, Foscarnet and Cidofovir are currently licensed for systemic treatment of CMV infection.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Induction regimen</th>
<th>Maintenance regimen</th>
<th>Lab tests</th>
<th>Dose-toxicity</th>
<th>Serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ganciclovir</td>
<td>5 mg/kg bid x 14 days</td>
<td>5 mg/kg/day</td>
<td>CBC twice a week during induction; weekly during maintenance; serum creatinine monthly</td>
<td>Neutropenia, thrombocytopenia</td>
<td>Central venous catheter infection</td>
</tr>
<tr>
<td>Oral valganciclovir</td>
<td>900 mg bid x 21 days</td>
<td>900 mg/ day</td>
<td>Same as above</td>
<td>Neutropenia, thrombocytopenia, diarrhoea</td>
<td>/</td>
</tr>
<tr>
<td>Intraocular injection</td>
<td>400 µg twice/week</td>
<td>400 µg/ week</td>
<td>NA</td>
<td>Direct retinal toxicity, if doses are excessively high</td>
<td>Intravitreal bleeding, endophthalmitis</td>
</tr>
<tr>
<td>IV Foscarnet</td>
<td>90 mg/ kg bid x 14 days</td>
<td>90 mg/ kg daily</td>
<td>Serum creatinine, K, Mg, Ca, and phosphorous twice/ week during induction, weekly during maintenance; Hb</td>
<td>Nephrotoxicity, ionised hypocalcemia, genital ulcers, fluid overload</td>
<td>Central venous catheter infection</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>5 mg/ kg/ week x 2 weeks</td>
<td>5 mg/ 2 weeks</td>
<td>Serum creatinine, urinary protein, and CBC before each infusion</td>
<td>Nephrotoxicity, neutropenia, low intraocular pressure, uveitis, neuropathy, nausea, fever, rash</td>
<td>Nephrotoxic effect</td>
</tr>
</tbody>
</table>

**Treatment**

**Treatment of CMV Retinitis**

1st choice:
Ganciclovir IV 5mg/kg twice daily for 14 days has a response rate of 80-90%. Relapse rate is extremely high. Patients must receive long-term maintenance therapy. Side effects are bone marrow suppression. Therefore do not combine with Zidovudine or cotrimoxazole.
4.3.3.6 **Herpes Simplex virus infection (HSV)**

In HIV infected patients Herpes simplex type 1 and 2 are associated with encephalitis and myelitis. The diagnosis of herpes simplex encephalitis is by brain biopsy. Infection with Herpes Simplex Virus (HSV) in HIV infected individuals is associated with recurrent mucocutaneous lesions (orolabial, genital), which often appear as beefy red and are exquisitely painful. Perirectal HSV may be associated with proctitis and anal fissures. It may also cause oesophagitis with multiple small ulcers.

**Treatment:** Acyclovir 200 mg PO five times daily for 10-14 days or Acyclovir 800 mg x 3/day.

4.3.3.7 **Varicella Zoster infections**

The neurological syndromes associated with Varicella - Zoster infection in HIV/AIDS patients are described as radiculitis, myelitis, encephalitis, cranial neuropathies, leukoencephalopathy and cerebral vasculitis. Treatment is with acyclovir 800 mg x 5/day during 7-10 days. In AIDS patients the prognosis is poor and recurrence is more common.

4.3.3.8 **Progressive Multifocal Leucoencephalopathy (PML)**

This is a viral opportunistic brain infection caused by the JC virus. It occurs in up to 4% of patients with advanced AIDS. CSF is typically normal. A positive PCR for JC virus on CSF has a high positive predictive value, but is rarely available in resource-limited settings. The illness often begins with relatively subtle signs of personality changes, memory deficit, mild cognitive impairment, and incomplete or complete transverse myelitis and aphasia, dysarthria and visual field abnormalities. No specific CSF abnormalities are identified.

CT scan shows single or multiple hypo-dense lesions in the white matter without mass effect. Rapid clinical progression is common and death usually occurs within 6 months of diagnosis. Specific antiviral therapy (cytarabine, cidofovir, acyclovir, alpha-interferon) does not alter the prognosis and survival is usually less than three months. HAART is the standard of care for PML. However some patients develop PML while on HAART and also cases of IRIS have been described with PML, in patients responding well to HAART.

4.3.4 **Opportunistic CNS tumours**

4.3.4.1 **Primary Central Nervous system lymphoma**

Primary lymphomas are now recognized to be relatively common in the CNS because of the AIDS epidemic. Lymphomatous involvement of the CNS in patients with AIDS may be due to primary or metastatic lymphoma. The tumour is of the B-cell type. One or a few intraparenchymal lesions are typical, although a diffuse infiltrating tumour occasionally is seen.

Epstein Barr Virus may play a role in the pathogenesis of the disease.
AIDS patients with primary CNS lymphoma usually present with alterations in consciousness or cognition, hemiparesis or aphasia (40%), seizures (10-15%) or cranial neuropathies (5-10%). Thus, primary CNS lymphoma may be difficult to distinguish from cerebral toxoplasmosis. Patients with HIV infection are often treated presumptively for toxoplasmosis, because CT and MRI scan fail to distinguish between the two. When the mass lesion fails to respond to toxoplasmosis treatment, the likely diagnosis is a CNS lymphoma. Concomitant corticosteroid (dexamethasone 6-10 mg four times/day) results in marked reduction or disappearance of lesions after few weeks, and this may give the false impression that the patient is responding to toxoplasmosis treatment. While brain radiation is recommended for patients with CNS lymphoma, the role of adjuvant chemotherapy is undefined. Regression of radiosensitive tumour is the rule. However, prognosis is relatively poor. Survival is usually less than six months.

4.3.4.2 Metastatic Lymphoma

Less commonly, systemic lymphoma (usually Non-Hodgkin's) may lead to neurological dysfunction in AIDS patients. The neurological syndrome usually results from meningeal or skull base involvement rather than intra-parenchymal growth. Cranial neuropathy and headache are common. Epidural compression of the spinal cord or cauda equina may occur. Diagnosis is made by cytological examination of the cerebrospinal fluid. This reveals malignant cells in about 70% of cases.

Treatment
Treatmen: Different standard combination chemotherapy e.g. CHOP + Bleomycin & Methotrexate, or etoposide. Intra-thecal chemotherapeutic agents usually methotrexate, arabinoside-cytosine or both. If compressive myelopathy is present radiation therapy and corticosteroid should be employed.

4.3.4.3 Kaposi sarcoma

Kaposi's sarcoma of the brain occurs rarely and specific diagnosis is difficult. See also page 75.

4.3.5 Cerebrovascular Diseases

It has been documented that cerebrovascular accident (CVA) is a common phenomenon in HIV patients. This complication has been demonstrated clinically and at post mortem examinations. Cerebral infarctions, intra-cranial haemorrhages and vasculitis are the main underlying pathologies in AIDS cases with stroke. In AIDS patients presenting with stroke or transient ischemic attack, potentially treatable causes, such as cerebral co-infection or tumour, should be sought. Cerebral infarction is more common than intra-cranial haemorrhages. Associated conditions include opportunistic CNS conditions, meningovascular syphilis, cerebrovasculitides etc. Intra cerebral haemorrhage could be associated with immune thrombocytopenia, aneurnsm and lymphoma. Diagnostic evaluation should include CT scans or MRI, when available, CSF analysis, echocardiography to exclude endocarditis, platelet count, VDRL etc.
Treatment is directed at specific aetiology found at the basis of pathology of CVA. The prognosis is poor unless a specific aetiology is discovered and treated accordingly. In patients taking protease inhibitors there is a greater incidence or thrombotic events (arterial and venous), probably due to hypercoaguability.

4.4 Skin Manifestations

Many patients with HIV infection (80%-100%) develop dermatological conditions at some point in the course of the disease. Skin conditions may be very disabling, disfiguring and even life-threatening.

4.4.1 Acute HIV infection

The acute retroviral syndrome occurs approximately 1 month after primary infection. It may present as fever and rash. The rash is usually erythematous and maculo-papular. Other symptoms may be: arthralgia, lymphadenopathy, weight loss, meningo-encephalitis and pharyngitis. HIV antibody tests may still be negative. No specific treatment is indicated.

4.4.2 Opportunistic infections and other disorders

4.4.2.1 Bacterial Infections

4.4.2.1.1 Bacterial folliculitis, furunculosis, pyomyositis,

*Folliculitis and furunculosis*, which are usually caused by staphylococci, need careful management in HIV patients because life-threatening disseminated infections occur. *Impetigo and ecthyma* are caused by *S.pyogenes* or *S.Aureus*. *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. One study showed that pyomyositis was often associated with a CD4 count of less than 150 cells/mm³. *Cellulitis and erysipelas* are streptococcal infections of the subcutaneous tissue resulting from contamination of minor wounds. In patients who remain untreated, life-threatening systemic infections may occur.

In general, HIV patients should have a local antiseptic at home to apply to minor wounds after washing. Mild localised infections are effectively treated with a topical antiseptic such as: gentian violet, polyvidone iodine, chlorhexidine or bacitracin 2%, a topical antibiotic.

However, when there is a deep-seated infection or high fever, systemic antibiotics should be prescribed:

(flu)cloxacillin 500 mg PO 4 x daily for 10 days, or
Erythromycin 500 mg PO 4x daily for 10 days, or
(flu)cloxacillin 1-2 g IV 4 x daily for 10 days.

Avoid manipulations of furunculosis in the face: this can cause trombosis of the sinus cavernosus.

In the case of pyomyositis, surgical drainage is necessary together with antibiotics (flu)cloxacillin. Gram stain of pus can confirm the presence of Gram-positive cocci in clusters.
4.4.2.1.2 **Syphilis**

*Primary syphilis*: a painless, indurated genital ulcer (chancre) at the site of inoculation, usually accompanied by inguinal lymphadenopathy. VDRL is still negative.

*Secondary syphilis*: Weeks to months later, about 25% of untreated patients will develop a systemic illness with fever, rash, condyloma lata, lymphadenopathy and oral lesions (mucous patch). The rash typically involves the palms and the soles, and is maculo-papular. Treatment of primary and secondary syphilis is Benzathine penicillin 2.4 MIU IM or erythromycin 4 x 500 mg daily for 4 weeks in case of penicillin allergy. It is important to follow up VDRL after treatment, at 3, 6, 12 and 24 months. If the VDRL fails to decline, the patient must be retreated.

4.4.2.2 **Viral infections**

4.4.2.2.1 **Herpes Zoster**

Herpes Zoster is an extremely common finding in HIV infection and an indicator of at least WHO stage 2. Frequently occurs early in the disease and often is a poor prognostic factor. It is generally localized to two or three dermatomes and tends to recur frequently. Clinical characteristics include clusters of vesicular lesions, which eventually erupt and coalesce to form ulcers with moderate to severe pain. Almost 25% of PLHA experience recurrences of Herpes zoster. Lesions can become necrotic and extensive, taking a long time to heal. If they involve the ophthalmic branch of the trigeminus nerve (V), they can involve the cornea and cause corneal scarring with loss of vision in that eye.

**Diagnosis**

Most often a clinical diagnosis is made based on symptoms and signs. A Tzanck test smear of material scraped from the basis of a lesion will show multinucleated giant cells with inclusion bodies, which are pathognomonic.

**Treatment**

Severe and disseminated Varicella Zoster or involvement of the trigeminus nerve: Acyclovir 10 - 12 mg/kg IV every 8 hours; for 7-14 days

Dermatomal Zoster: Acyclovir 800 mg PO 5 times daily, 7-14 days

**Supportive care**

Analgesics for pain and fever NSAID and/or carbamazepine 200-600 mg daily or clomipramine/amitriptyline 25-75 mg. Clomipramine and carbamazepine are also effective in controlling post-zoster neuralgias.

Topical antiseptics to accelerate drying of the lesions and to prevent secondary bacterial infection.

If secondary bacterial infections occur treat with antibiotics.

**Prevention**

If indicated in severely immunocompromized patients, isolate hospitalized patients to prevent concomitant nosocomial infection. Universal precautions are administered for dressing care.
Note: Up to 4 months after initiating HAART, Herpes Zoster is commonly seen as a manifestation of immune reconstitution. This does not mean treatment failure. HAART must be continued, and the treatment of the lesions and neuralgia is the same as the one described above. There is no place for corticosteroids in this case.

4.4.2.2.2 Herpes Simplex

The usual localisation is anogenital, although orolabial lesions can be seen. Chronic (>3 weeks) ulcers are only seen with advanced immune suppression. If untreated, they can last for months and finally involve most of the genital and peri-anal skin and mucous membranes. High-grade fever and meningitis may also complicate it.

Diagnosis
Most often diagnosis is clinical. Laboratory tests include Tzanck test and viral culture.

Treatment:
Mild mucocutaneous disease - Acyclovir 200-400 mg PO 5 times/day 7-10 days. In disseminated mucocutaneous Herpes simplex infection treatment for 2 weeks is often necessary. Supportive care: Analgesic for associated pain and fever. Antibiotic therapy if secondary bacterial infection occurs.

Note: Recurrences occur frequently (more than 6/year) in some patients. In that case, they may require lifelong suppressive therapy: acyclovir 200 mg 2 x daily or if not successful increase to 400 mg 2 x daily.

Prevention
Primary varicella and herpes zoster is potentially infectious. Risk of nosocomial infection especially in the immunocompromised patient is high. Strict isolation is recommended if patient were hospitalized.

A worsening of HSV lesions has been described in association with an immune reconstitution inflammatory syndrome, 1-6 months after starting HAART. The lesions were irresponsive to acyclovir which had previously been effective, and there was no resistance found. Steroids are not useful in this case.

4.4.2.2.3 Molluscum contagiosum

This is a viral skin infection, characterised by centrally umbilicated, non-pruritic papules on the face, neck, and ano-genital areas. It is commonly seen in PLHA, especially in children. Lesions in the face tend to proliferate, especially if injured during shaving. Differential diagnosis has to be made with disseminated cryptococcosis, histoplasmosis and penicilliosis. Those systemic mycoses are usually associated with fever, pulmonary or meningeal involvement.
Treatment
- usually does not require treatment.
- It is possible to prick the centre of the lesion with a needle dipped in Phenol or iodine, followed by expression of the central core.
- Alternatively cryotherapy (liquid nitrogen), electrocoagulation or curettage can be proposed.

Note: an exacerbation of existing lesions can occur in patients taking HAART, shortly after initiation, due to immune reconstitution. HAART should not be interrupted, and even giant lesions can reduce spontaneously with HAART alone after some time.

4.4.2.2.4 Genital warts (Condyloma accuminata) and verruca vulgaris

Genital warts, condylomata accuminata, are caused by human papilloma virus. They can be seen as STI in any patient, but they are much more frequent in HIV-infected patients. Patients with small numbers of warts are often asymptomatic. Other patients may have pruritus, bleeding, or pain. Genital warts should only be treated in the case of large lesions.

If the number of lesions is small, treatment is best done by the patient with daily podophyllotoxin 0.5% solution strictly on the lesions. Let it dry. Protect the unaffected skin with vaseline or zinc ointment. Apply twice a day and repeat every day for 3 consecutive days per week for 4 weeks maximum.

Improper treatment can cause painful ulcerations. More extensive lesions (condyloma > 3 cm) should be treated by cryotherapy or cauterisation. Total volume of podophyllotoxin should not exceed 0.5ml per day. Podophyllotoxin should not be used during pregnancy. It is also contra-indicated for cervical, urethral, anorectal and buccal condylomata.

Remission is often only temporary, relapses extremely frequent.

Common warts (verruca vulgaris) are diffuse flat or filiform warts often located in the beard area, extensive plantar warts and confluent peri ungual. It may occur in unusual sites, such as the lips, tongue and oral mucous. Warts can have a temporary exacerbation after initiation of HAART, but will reduce spontaneously later in most cases.

4.4.2.3 Scabies

Pruritic, hypertrophic, crusted plaques that may involve any region of the skin. The interdigital lesions characterize the condition. In the HIV infected host it may progress to an erythroderma.

It can be life-threatening when secondary infection is severe.

Diagnosis
The mites can be seen by microscope on a KOH preparation of skin scales. Histologic examination of scraping or biopsy of the papules reveals the mite and its ova within the cornified layer of the epidermis.

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9 Podophyllotoxin is preferred above Podophyllum resin 10 or 25%, which is much more caustic and has to be applied by the health staff.
Treatment
Treatment is with topical benzyl benzoate 20% (3 consecutive days on whole body except the face.) Itching can be relieved by chlorpheniramine 4 mg, 3-4 tabs daily. Clothing should be thoroughly laundered and ironed to kill the mites. In case there is bacterial surinfection, treat first with local antiseptics and antibiotics and apply the benzyl benzoate only later. After treatment, all clothes and bed linen should be washed and dried. Do not forget to treat family members who have scabies as well. Ivermectin is an effective alternative when available (dose: 12 mg (2 tablets) in a single dose). In case of Norwegian scabies, it is best to combine ivermectin with the topical treatment of benzyl benzoate lotion. Persistent itching after treatment is frequent and can be treated with a steroid cream (hydrocortisone 1%).

Children: Application of 12.5% Benzyl Benzoate emulsion to the affected skin to be washed off after 24 hours. Repeat 3 times.

4.4.2.4 Fungal skin disease

Fungal skin disease is extremely common in HIV-infected patients. It usually responds to topical antifungal drugs (Whitfield's, gentian violet, imidazole cream, ketoconazole cream).

4.4.2.4.1 Seborrheic dermatitis

Seborrheic dermatitis is a very common complaint and is one of the earliest clinical markers of HIV infection. The most common locations are in the hairline, eyebrows, nasolabial folds and chest. This condition responds well to topical antifungals. In general, treatment needs to be continued for 14 days after symptoms have disappeared:
- Whitfield's ointment 2 x daily, or
- ketoconazole ointment 2 x daily, or
- miconazole 2% cream 2 x daily.
For severe inflammation or for refractory cases, a topical steroid cream can be added to the miconazole cream.

4.4.2.4.2 Dermatophytosis

Tinea corporis, tinea pedis, tinea cruris and onychomycosis all occur more frequently in patients with HIV infection. This is usually severe and often widespread characterized by scaly, red, pruritic, papules and plaques. Dermatophytosis in HIV-infected individuals is usually extensive and resistant to topical antifungal agents.

Diagnosis
Skin scraping and KOH stain
Fungal culture
Treatment
In uncomplicated cases, treatment with local imidazole cream (1% clotrimazole, 2% miconazol) or Whitfield’s ointment is sufficient. Treatment is necessary for 4 weeks. In severe cases, oral griseofulvin (10 mg/kg daily for 4 weeks) may be necessary.

Onychomycosis is also frequent in HIV-positive patients. Direct microscopy of KOH preparations of nail scrapings is enough to make the differential diagnosis with dystrophic nails. Griseofulvin 10 mg/kg daily should be given for 12-18 months. If available, pulsed therapy with itraconazole (200 mg 2 x daily for the first 7 days of each month for 4 months) is effective.

4.4.2.4.3 Mucocutaneous Candidiasis

- **Oral and oesophageal** see page 41
- **Vulvovaginal Candidiasis**
  Nystatin 100,000 intravaginal at night during 7 days
  OR
  Miconazole ovules intravaginal at night during 3 days

- Severely immunocompromised patients may have **balanitis, distal urethritis, or paronychia** (nail wall infection).

Topical anti-fungal cream twice a day is usually effective (clotrimazole cream 1%, miconazole cream 2%). This treatment can be combined with local application of gentian violet to keep the lesions and the surrounding skin dry.

In generalised skin infections, oral fluconazole 50 mg 2 x daily for 2 weeks is effective.

**Children:** For severe skin involvement not responding to topical treatment, systemic Ketoconazole, 3 mg/kg/day or Fluconazole, 3 mg/kg/day for 7 days should be considered.

4.4.2.4.4 Deep mycosis

Cryptococcosis can present with pustules, nodules, ulcers and papules. Patients with cryptococcosis may have molluscum contagiosum-like, centrally umbilicated lesions. These are typically located on the trunk and face.

Histoplasma Capsulatum has a varied clinical presentation, ranging from only slightly pink to red 2-6 cm cutaneous papules, to larger reddish plaques and multiple shallow, crusted ulcerations.

**Diagnosis**
Diagnosis is suggested by the clinical picture. Patients usually have high fever and other symptoms such as severe anaemia, cough, lymphadenopathy, hepatomegaly and meningeal signs, which suggest the diagnosis (see: Respiratory Problems page 43 and Neurological Disorders page 49)

The organism may be seen by microscopic examination of skin scrapings, touch preparations of skin biopsy or lymph node aspirate stained with Wright's stain, or Cotton-blue stain. Bone marrow aspirate is diagnostic in 100% of cases of

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(h) Fluconazole is not effective against dermatophytosis
disseminated infections. The diagnosis is confirmed by culturing the fungus from clinical specimens.

**Treatment**
Initial treatment of histoplasmosis should be with amphotericin B 0.7 mg/kg daily IV for 2 weeks, followed by itraconazole 200 mg 2 x daily for 10 weeks. Long-term suppressive therapy with itraconazole 200 mg daily should be given to prevent relapse. The treatment of choice for cryptococcosis is amphotericin B 0.7 mg/kg daily followed by fluconazole 400 mg daily for 8 weeks. Secondary prophylaxis with fluconazole 200 mg daily is necessary to prevent relapse. In non-severely ill patients, oral itraconazole (400 mg daily) or oral fluconazole (400 mg daily) may be sufficient.

### 4.4.3 Itchy skin eruptions

This affects up to 30% of HIV patients.

#### 4.4.3.1 Papular pruritic eruption (PPE)

PPE is a very chronic symmetric papular eruption, predominant at the extensor surface of upper and lower extremities. It may be an allergic reaction to a flea bite. It is very itchy and frequently secondarily infected. Treatment success has been achieved with UV light, antihistamines, and potent topical steroids. Also HAART is effective.

#### 4.4.3.2 Eosinophilic folliculitis

Eosinophilic folliculitis is characterised by urticarial follicular papules above the nipple line: there is mainly truncal involvement, but a significant proportion of patients also has neck and face involved. It is seldom possible to differentiate clinically from other types of folliculitis. Potent topical steroids and antihistamines are the first choice of treatment. An increase in CD4 due to HAART has been associated with a temporary increase in eosinophilic folliculitis.

#### 4.4.3.3 Xerosis

This skin condition is frequently encountered in PLHA. The aetiology is not known. Lesions consist of a diffuse, pruritic, scaly rash, involving mainly the limbs and the back. Treatment is topical with dry skin lotion, or, when important scaling is present, with Whitfield’s ointment, twice a day for 2-4 weeks. For pruritus: chlorpheniramine 4 mg 3 x daily for 1 month. If no improvement a trial with benzyl benzoate to treat scabies may be worthwhile.
4.4.4 Kaposi’s Sarcoma (KS)

This cancer of the skin and the blood vessels is rarely seen in HIV-negative patients and is thus an indicator disease of symptomatic HIV infection. It is caused by a sexually transmitted Herpes virus (HHV8) or Kaposi’s Sarcoma herpes virus (KSHV). Lesions are usually multiple and can involve the skin as well as mucous membranes. Cutaneous lesions occur most commonly on the trunk, the extremities and the face. Initially lesions are papular. Later the papules become nodules and plaques, and the colour changes from violet to dark brown.

Treatment of localised disease
The most easy and acceptable treatment would be a local treatment. This is only indicated in patients with limited lesions (T0) and no systemic signs (S0). Possibilities are intralesional vinblastine, cryotherapy and others. Although these local treatments seem attractive, they do not prevent the appearance of new lesions. In the group T0S0 it is likely that HAART alone is sufficient in the majority of patients.

Treatment of systemic KS
Local therapy is not recommended for treatment of systemic AIDS-related Kaposi’s sarcoma, characterized by at least 10 new lesions in the prior month, symptomatic lymphoedema, pulmonary Kaposi’s sarcoma, or visceral disease. Chemotherapeutic combinations used are ABV (adriamycine, bleomycine and vincristine) or BV (bleomycine, vincristine). These regimens caused important toxicity and response rate varied from 25-88%. However the duration of treatment effect was limited to a median of 4 months (before HAART). Two new formulations, liposomal daunorubicin (40mg/m² IV every 2 weeks) and doxorubicin (20mg/m² IV every three weeks) are now considered first line therapy in western world. However, their cost price is far beyond reach of DC (USD 11,000 per responding patient) and is unacceptably high even in the HAART era. HAART is also effective against systemic KS, but usually not alone without chemotherapy.

4.4.5 Bedsores

This is a frequent problem in bedridden patients. Clean the wound every day with normal saline and keep it as dry as possible. Apply zinc oxide ointment around the wound and iodine in the wound. In case of secondary infection, use antibiotics. Prevention: frequent massages on pressure points by family members (instructed by physiotherapist). Turn the patient over in bed every 3-4 hours. Avoid moist or wet bed sheets. Pain treatment is provided with stepwise analgesia. In case of malodorous wounds, crushed metronidazole tablets can be put on the lesions.

4.4.6 Drug reactions

Drug reactions are common in PLHA and are directly related to the degree of immunosuppression. The drugs that are most frequently involved are TMP/SMX, dapsone and amoxicillin. Antiretroviral drugs can cause skin eruptions as well. Rash is a well-known side effect of nevirapine. A morbilliform rash is most frequently observed. INH also commonly causes skin reactions. Treat with chlorpheniramine 4 mg 3-4 x daily. In case of severe reactions, stop the drug. Nevirapine should be switched to efavirenz or another drug in case systemic symptoms (fever, arthralgia, myalgia, eosinophilia, hepatitis) or a wet rash occur. There is no cross reactivity between NVP and EFV.
Cases of Stevens-Johnson due to nevirapine occur rarely. In this case one should not give efavirenz, but switch to a protease inhibitor (PI).
In case of a rash in patients taking ABC, ABC should be interrupted and never restarted again. Nelfinavir has also been associated with rash. Alopecia and paronychia have been described as a side effect of indinavir. Zidovudine can cause a blue colouration of the nails. If Stevens-Johnson syndrome occurs, the patient needs to be admitted to a hospital for aggressive treatment (rehydration, nasogastric tube feeding, antiseptic treatment of areas of epidermolysis. Early in the course, before extensive skin breakdown, it is useful to give steroids: prednisolone 1 mg/kg daily for 1 week. In case of extensive epidermolysis, do not use steroids because of the risk of infection and bacteraemia. In case of high fever, treat with broad-spectrum antibiotics that cover both Gram-positives and Gram-negatives (ceftriaxone + amikacin or ciprofloxacin). However, do not use the culprit drug!!

4.4.7 Cutaneous Leishmaniosis

Leishmaniasis is a protozoan disease with clinical manifestations which can vary according to the infecting species (over 20 pathogenic species are known) and the immune response of the host. The disease is transmitted by the bite of an infected sandfly. Cutaneous leishmaniosis (CL) is common in South Europe, South-western, central and eastern Asia (India and Pakistan), Africa and Latin America. It can present with ulcers, papules or nodules of the skin. Amastigotes can be detected in Giemsa stained touch preparations of the basis of the ulcers. This form can heal spontaneously after 1 month up to 3 years. Deciding on whether to treat or not depends on the risk for developing mucocutaneous leishmaniosis and the place of the lesions (face and joints involvement favours treatment).
Treatment consists of itraconazole 200 mg x 2/day during 2-3 weeks or amphotericin B.

4.5 Haematological and Neoplastic Manifestations

Besides the suppression of immunity and subsequent development of opportunistic infections and malignancies, HIV-infected patients often manifest clinically significant haematological abnormalities such as bone marrow dysplasia, thrombocytopenia, anaemia and leukopenia.

4.5.1 Anaemia and Red Cell Abnormalities

Anaemia may be present in 70-93% of AIDS patients at presentation. Mean hemoglobin values of 9.7 - 11.7 gr/dl in AIDS patients are the norm and the anaemia is typically normocytic – normochromic. In patients treated with AZT there is macrocytosis in 70% of the patients. Reticulocyte response is inappropriately low in AIDS related anaemia. Low serum B-12 levels may be present, but clinically significant complications are rarely seen. The anaemia is similar to other chronic patients; high ferritin level, decreased serum iron and TIBC (total iron binding capacity). The Coombs test is positive in some HIV infected patients, but auto-immune hemolytic anaemia is rare. Most of the anaemia in HIV patients will be due to an underlying disease: disseminated mycobacterial, CMV or fungal infections.
**Diagnosis**
Exclude other causes of anaemia:
Iron deficiency anaemia: Fe, TIBC, ferritine
Macrocytic anaemia: AZT, vitB12 deficiency, Folate deficiency: serum vitB12 and red blood cell folate
Hemolysis: blood smear
Bleeding (guaiac stool+)
Drugs: AZT, cotrimoxazole, ganciclovir, acyclovir, pyrimethamine

**Treatment**
Ineffective or reduced erythropoiesis is the hallmark of most anaemic HIV - infected patients, thus recombinant human erythropoietin (EPO) is effective. A schedule for EPO is in the John Hopkins HIV manual.
If no other causes of anaemia are found:
Start EPO at 40,000 units SC per week. Give iron supplements if ferritine is less than 100 ng/ml or if transferrine saturation is less than 20%. The effect will only be evident in 2-4 weeks.
At 4 weeks if Hb increase of > 1 g/dl continue at this dose. If increase less than 1 g/dl: increase the dose of EPO to 60,000 units SC/week. When HB approaches 12 à 13 g/dl, decrease the dose of EPO to by 10,000 Units/week. Haemoglobin should be monitored every 2-4 weeks.
If Hb > 15 g/dl hold EPO and start again when Hb < 12 g/dl.
But if AZT is the cause the anaemia is usually reversed after stopping the drug.

In patients who develop significant anaemia under AZT the drug should be replaced by d4T. AZT should never be prescribed again in this patient.
In case no EPO is available, a trial of Folic acid supplements and vit B12 could be done.
Iron supplements are not considered appropriate in HIV patients, unless there are clear arguments for iron deficiency anaemia.
If patients are symptomatic anaemic, a blood transfusion should be considered. There is some concern about a risk of progression of the disease.
Treatment of the underlying infections and other causes.

When patients are started on HAART the increase in haemoglobin is one of the clinical parameters of treatment response.

**4.5.2 Immune Thrombocytopenia (ITP)**
Can be present at the initial presentation, but more frequent in advanced disease. Clinical features are similar to those of ITP. Bone marrow reveals increased numbers of megakaryocytic and the spleen is generally not palpable. Some drugs are also associated with thrombocytopenia (amphotericin B, ganciclovir)
Clinically significant bleeding is rarely seen.

**Treatment**
The optimal treatment of HIV related ITP is not well documented. Therapies include systemic steroids, intravenous immunoglobulin (IVIG) and splenectomy. The long-term benefits of such therapy are not known.
**Steroids** carry the risk of further immunosuppression as doses of 1 mg/kg during 2 weeks are needed and the duration of response is low.
**IVIG** 400 mg/kg/day on Day 1, 2 and 14 and then every 2-4 weeks.
In case of haemorrhage: Fresh whole blood transfusion, but preferably packed cells + platelets transfusions, IVIG 1 g/kg days 1, 2, and 14 and prednisolone 60 mg/day.
The experiences with splenectomy are variable. Some data reflect an increased risk of disease progression others don’t.
Start of HAART will usually resolve the ITP, but not always.

4.5.3 Kaposi’s Sarcoma (KS)

Before the era of HIV, KS was described as a rare vascular tumour manifesting as multiple skin nodules in the lower extremities of elderly men. It occurs in different forms.
Over the past 2 decades some African countries with a high HIV prevalence have seen a 20-fold increase in the incidence of KS, and it has become the most common cancer in men.
It is an AIDS defining event, and is caused by human herpes virus 8 (HHV-8) or KSHV.

Clinical manifestations of AIDS KS may vary from macular skin lesions, evolving to papules and nodular tumours, to life-threatening visceral involvement of lungs and gastrointestinal tract, leading to lymphatic obstruction and respiratory failure.
Sometimes, the oedema (often hard) can precede the skin lesions (legs). Often, hard regional lymph nodes are present.
AIDS KS lesions can wax and wane related to the occurrence of other OI. GI lesions are often asymptomatic, but can cause ulceration and bleeding. Pulmonary KS is rapidly fatal when left untreated. Patients present with dyspnoea without fever, sometimes with haemoptysis. Mostly, there are skin lesions present as well. A chest X-ray may show reticulo-nodular infiltrates, enlargement of the mediastinal shadow and sometimes a pleural effusion.

Diagnosis is made by biopsy (spindle cells), but often lesions are typical in appearance.
In the early stages it may be difficult to differentiate KS from bacillary angiomatosis.
The latter is caused by Bartonella henselae and responds to doxycycline.
Staging is based on size and number of lesions and on the presence of symptoms (see Table 14: staging of KS page 75)

Table 14: staging of KS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>lesions confined to the skin and/or lymph nodes/ and or minimal oral disease*</td>
</tr>
<tr>
<td>T1</td>
<td>tumour-associated oedema or ulceration</td>
</tr>
<tr>
<td>S0</td>
<td>No B† symptoms, no history for OI, no oral thrush</td>
</tr>
<tr>
<td>S1</td>
<td>history of OI and/or oral thrush, B symptoms present</td>
</tr>
</tbody>
</table>

*Minimal oral disease = non-nodular KS confined to the palate
†B-symptoms = unexplained fever, night sweats, >10% involuntary weigh loss or diarrhoea > 2 weeks

Treatment

There is no cure for AIDS KS in the absence of HAART. No local or systemic therapy has proven to increase survival. Therefore the primary goal of treatment is to provide safe and effective palliation.
**Indications**

In order to pursue quality of life, chemotherapy will only be initiated when patients have disfiguring lesions in visible areas of the body, extensive painful skin lesions and oedema, oral lesions that cause obstruction or dysphagia, evidence of rapid tumour progression or visceral involvement.

In HIV care in low-resource settings without access to HAART, we used to advise palliative care, which consisted of effective pain control, or sometimes chemotherapy with vincristin or bleomycin, or a combination of both. When used without HAART, these drugs had high toxicity and very little benefit with relapses shortly after stopping, and therefore did not reach the aim of palliation.

The gold standard in the western world is now liposomal anthracyclines (daunorubicin or doxorubicin). However, they are myelosuppressive and increase the risk for OI due to progressive decrease in CD4 count (except when combined with HAART).

Response to HAART alone for KS is more than 90% in patients with $T_0S_0$ or $T_0S_1$ stage.

In patients who have $T_0S_0$ or $T_0S_1$ it is advised to use **only HAART**. There is no consensus about the preferred regimens, NNRTI based or PI based. However, so far there is no proof that PI based regimens have better results. The response to HAART is probably dependent on the immune reconstitution.

In case there is no response to HAART alone, one can use **intralesional chemotherapy**.

- Intra-lesional injection of Vinblastine 0.1 ml per 0.5 cm$^2$ of a solution containing 0.2 - 0.3 mg/ml saline every 3-4 weeks and maximum 3 injections per lesion.
- Topical application of liquid nitrogen.

In patients who have multiple lesions, big obstructing lesions or visceral lesions, systemic chemotherapy is advised.

**Chemotherapy**

Bleomycin alone at the dose of 15 mg IM every two weeks has a response rate of up to 65% and has the advantage that it is less myelosuppressive. Not more than 20 cycles should be used because of pulmonary toxicity becoming frequent at a cumulative dose of 300 mg.

**Radiotherapy**

Radiotherapy plays a major role in palliation of impaired function, relief of pain and reduction of cosmetically troublesome lesions.

**4.5.4 Non Hodgkin Lymphoma**

There is an increased incidence of lymphomas, especially Non-Hodgkin’s Lymphoma (NHL). They are usually aggressive with high mortality rate. Extra sites are common such as the CNS, bone marrow, and gastrointestinal liver skin and mucous membranes. Despite aggressive chemotherapy the outcome and results are extremely poor.
Treatment
Different standard combination chemotherapy like CHOP + Bleomycin & Methotrexate, or etoposide can be used as in non-AIDS patients. Most hospitals in developing countries are not equipped for chemotherapy. In the case of AIDS patients the survival benefit is also very limited. Therefore it is not considered a priority.

4.5.5 Carcinoma of the cervix

The rate of squamous intraepithelial lesion (SIL) is increased in young women with HIV (33% to 45% HIV+ vs 7% to 14% HIV-) and the incidence of cervical cancer is almost twice as high as in HIV negative women. A Pap smear should be obtained twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter. In some settings in developing countries pathology laboratories can interpret cytology smears, in other places equipment for telepathology may be available. If the results of the Pap smear are abnormal, care should be provided according to the Interim Guidelines for Management of Abnormal Cervical Cytology published by a National Cancer Institute Consensus Panel and briefly summarized in the following table.

Table 15: Recommendations for Intervention Based on Results of PAP Smear

Table 15: Recommendations for Intervention Based on Results of PAP Smear
(MMWR 2002;51[RR-6]:58), adapted to low-resource setting because Human Papilloma virus (HPV) typing is often not possible.

<table>
<thead>
<tr>
<th>Results</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe inflammation</td>
<td>Evaluate for infection; repeat PAP smear, preferably within 2 to 3 months.</td>
</tr>
<tr>
<td>Atypical squamous cells of undetermined significance (ASCUS)</td>
<td>Follow-up PAP without colposcopy every 4 to 6 months x 2 years until three are negative; if second report of ASCUS, perform colposcopy.</td>
</tr>
<tr>
<td>■ ASC-US (undetermined significance)</td>
<td></td>
</tr>
<tr>
<td>■ ASC-H (cannot exclude HSIL). ASC-H is intermediate between ASC-US and HSIL</td>
<td></td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>Colposcopy ± biopsy or follow with PAP smear every 4 to 6 months, as above, with colposcopy and biopsy if repeat smears are abnormal.*</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (HSIL) (carcinoma in situ)</td>
<td>Referral for colposcopy ± biopsy.</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>Colposcopy with biopsy or conization; treat with surgery or radiation.</td>
</tr>
</tbody>
</table>

* Most gynecologists recommend evaluation with any abnormality due to the high prevalence of underlying SIL.

[No data are available to demonstrate that these guidelines to prevent cervical disease should be modified for women on HAART.]
4.5.6 Anal carcinoma

Evidence from multiple studies demonstrates that HPV-positive men who have sex with men (MSM) and HPV-infected women are at increased risk for anal HSILs and might be at increased risk for anal cancer. The prevalence of HPV in MSM is 60% to 75% and the frequency of anal carcinoma is about 80 times that of the general population. Recent studies suggest that this risk applies to all men with HIV, leading to the recommendation of routine anal cytology every 3 years regardless of a history of receptive anal intercourse, especially those with a low CD4 count.
4.6 Abdominal pain

Abdominal pain is frequent in people with AIDS. One observation from South Africa has shown 45% of outpatients presenting with abdominal pain. Abdominal pain is associated with reduced survival. Very few prospective studies on aetiology of abdominal pain in HIV exist. One retrospective study from Italy showed that CMV, MAI (Mycobacterium Avium Intracellulare) and GI lymphoma were the three most frequent causes of abdominal pain. On the contrary, a prospective study in South Africa in patients presenting with abdominal pain showed that MAI was rare, and that the most frequent cause of abdominal pain was disseminated TB.

4.6.1 Mycobacterium Tuberculosis

Africa and Asia have a high TB/HIV co-infection rate (40-50%) with the highest burden of TB and HIV coinfection in SSA. Disseminated tuberculosis has been described in 50% to 72% of patient with AIDS and tuberculosis. Abdominal TB was the commonest cause of abdominal pain in non white persons with advanced HIV infection (CD4<200) in South Africa reflecting the high prevalence of TB in these communities.

Symptoms & Physical exam

Patients with early AIDS demonstrate features similar to non HIV patients. A big psoas abscess or tuberculous peritonitis can present with abdominal pain in early stages of HIV disease. However, advanced stage AIDS patients show a high incidence (60-70%) of extra pulmonary and disseminated TB. The most common presenting symptoms in abdominal TB in HIV are prolonged high fever and chills (usually >39 °C), night sweats, anorexia, progressive weight loss, abdominal pain, diarrhoea (less common).

The most common physical findings are abdominal tenderness, location depending on site of infection, abdominal swelling and/or mass, and peripheral lymphadenopathy (>1,5cm in diameter). Unlike in non HIV patients ascites and jaundice are rarely seen.

Diagnosis

Common but non specific laboratory findings are anaemia, elevated serum alkaline phosphatase concentration and elevated percentage of mononuclear cells in peritoneal fluid (even small amount available).

Ultrasound of the abdomen often shows multiple enlarged peri-aortic or mesenteric lymph nodes (>1,5cm) or one mass of adherent lymph nodes with central necrosis or multiple hypoechogetic nodules or abscesses in the spleen and in the liver. The diagnostic yield of an abdominal ultrasound is so high in abdominal pain in HIV, that all physicians taking care of HIV patients should develop or have access to skills in ultrasound.

Chest X-rays show evidence of pleuro-pulmonary disease in the majority of patients (pleural effusion, parenchymal infiltrates, miliary pattern, peri-hilar lymphadenopathies). A normal chest X-ray does not exclude the diagnosis of abdominal TB, however.

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1 3 or more non-contiguous sites affected by TB, or blood culture positive, or miliary pattern on chest X-ray.
**Mycobacteriological diagnosis**

Delayed diagnosis of TB may result in early mortality in AIDS patients. As many patients with abdominal TB have disseminated TB (93%), an effort should be made to isolate AFB from one or other site. Blood culture and urine culture were positive in 50-70% of patients with disseminated disease & CD4<100.

**Differential diagnosis**

Abdominal tuberculosis has to be differentiated from *Mycobacterium avium* complex, but this is a rare pathology in developing countries. Lymphoma and Kaposi’s sarcoma can present with abdominal pain and lymph nodes. Some of the deep mycosis (cryptococcosis, histoplasmosis) can present with bulky abdominal lymph nodes causing pain. In patients presenting with splenic abscesses, visceral leishmaniasis has to be excluded. This disease is a frequent cause of fever in HIV patients living in Mediterranean countries, the horn of Africa and India. Nocardiosis can present with multiple abscesses.

**Treatment**

Based on National TB guidelines

### 4.6.2 MAC

MAC infection has not clearly emerged as a problem in the developing world where *Mycobacterium Tuberculosis* appears to be the predominant pathogen. It is speculated that acquired immunity against mycobacteria through previous infection with tuberculosis or through vaccination with BCG provides protection against MAC. Typically MAC presents with prolonged fever, gradual wasting, severe anaemia and neutropenia. The CD4 count is usually less than 50. MAC infection frequently involves gastrointestinal tract, liver, abdominal lymph nodes and spleen. A new clinical syndrome of focal adenitis due to MAC has been recognized in AIDS patients on HAART as an immune restoration phenomenon. Patients may present with fever, abdominal pain and malaise.

**Diagnosis**

Blood cultures are highly sensitive for detection of disseminated MAC in AIDS patients (a single blood culture has a 90 to 95% sensitivity. However, in rare cases, bone marrow & liver biopsy may be useful. Stool cultures are often positive, but not helpful to diagnose MAC disease, as they are also present in 50% of healthy patients. In AIDS patients with a focal lymphadenitis syndrome, blood cultures are often negative and a LN biopsy is required for diagnosis. In a resource-poor setting without possibility to do mycobacterial cultures the diagnosis is often made by exclusion, in a patient with symptoms compatible with disseminated TB or MAC, who fails to respond to TB medicines.

**Differential diagnosis**

See 4.6.1: Tuberculosis

**Prognosis and treatment**

In a resource-poor setting the diagnosis and treatment of MAC is difficult to realize.
Treatment including azithromycin or clarithromycin is effective and well tolerated, but expensive. At least two drugs should be used to avoid emergence of resistance. Clarithromycin 500 mg 2 x daily or Azithromycin 500 mg daily and ethambutol 15 mg/kg daily with or without rifabutin 300 mg daily.

4.6.3 Bacterial infections

In HIV patients the bacterial causes of GI disease are the same as in the general population: S. Typhi and non S. Typhi, Shigella, Campylobacter and Clostridium difficile. Salmonella can lead to peritonitis due to perforation. Secondary bacterial peritonitis may happen in patients with bowel perforation due to CMV, Kaposi’s sarcoma, tuberculosis and lymphoma.

Symptoms
Most of them present with acute diarrhoea, high fever, and diffuse abdominal pain. Patients look toxic.
In the case of acute bloody diarrhoea and tenesme Campylobacter and Shigella are suspected. When there is a history of previous antibiotic intake and hospitalization, Clostridium difficile is possible.

Diagnosis is based on blood and stool culture.
C. difficile requires Clostridium toxin assay on stool.

Treatment depends on the underlying cause.

Campylobacter: Erythromycin 500 mg twice daily for five days, or ciprofloxacin 500 mg twice daily for 5 days.
Shigella: the recommended treatment is ciprofloxacin 500 mg twice daily or norfloxacin 400 mg twice daily for 5 days. In case of recurrence sometimes it is necessary to give ciprofloxacin 500 mg twice daily indefinitely.
Salmonella: Ciprofloxacin 500 mg twice daily for 2 weeks. Continue with cotrimoxazole prevention. In case of recurrent bacteremia, the treatment should be continued indefinitely.

Any peritonitis due to bowel perforation (free air under diaphragm) should receive surgical attention.

4.6.4 Gastrointestinal Parasites and Protozoan infections

Gastrointestinal parasitic infection is a major source of disease in people living with HIV/AIDS, especially in tropical countries. Most of morbidity and mortality of advanced AIDS is associated with GI disease, especially Microsporidia and Cryptosporidia because they are difficult to treat. Parasites commonly involved with abdominal pain are Cryptosporidium parvum, Isospora belli and Strongyloides stercoralis in hyperinfection syndrome.
Both microsporidium and cryptosporidium cause chronic watery diarrhoea and sclerosing cholangitis. Enteric protozoan infections in PLWA cause cramping abdominal pain and often present with diarrhoea, malabsorption and wasting.

Diagnosis of gastrointestinal parasites is done by stool microscopy (see page 39 chronic diarrhoea)
Treatment: see page 39 chronic diarrhoea.
4.6.5 Fungal infections

4.6.5.1 Cryptococcosis

Rarely, cryptococcal infection can give rise to bulky abdominal lymphadenopathy, which may cause abdominal pain. 90% of AIDS patients infected with Cryptococcus neoformans will present with meningitis.

**Diagnosis** of disseminated cryptococcosis is based on serum cryptococcal antigen tests, or isolation of the pathogen from biological material such as CSF, lymph nodes, sputum or skin ulcers.

**Treatment** of disseminated cryptococcosis is with amphotericin B and fluconazole (for details, see page 54 cryptococcal meningitis) Secondary prevention with fluconazole 200 mg/day is necessary to reduce relapse rates.

4.6.5.2 Histoplasmosis

Histoplasma capsulatum is rarely seen in developing countries, but may be underdiagnosed. Gastrointestinal histoplasmosis differs from other forms of disseminated histoplasmosis in that pulmonary symptoms and fever may be absent. An oral ulcer is the most common manifestation, besides splenomegaly, lymphadenopathy (30%) and hepatomegaly (26%).

Diagnosis of disseminated histoplasmosis depends on tests usually not available in resource-poor settings: Antigen testing in urine and serum (sensitivity of 90% and 70% respectively), blood culture (sens 50-70%), bone marrow aspiration or biopsy for fungal stain or culture (positive in 75% of cases). In developing countries the diagnosis will be clinically and suggested by response to treatment.

Treatment: Amphotericin B 0.5-1 mg/kg daily IV for at least 6 weeks. The cumulative dose of amphotericin B is recommended as 10-15 mg/kg for histoplasmosis. Patients should be maintained on oral antifungals (itraconazole 200 mg twice daily) lifelong, or as long as immunosuppression is present.

4.6.6 Cytomegalovirus infection

CMV GI disease is an uncommon but serious complication of AIDS which can cause severe pain or diarrhoea which are difficult to treat.

**Epidemiology**

CMV gastrointestinal disease occurs in up to 5% of patients with AIDS, primarily in those with a CD4 < 50. In the industrialized world the incidence of CMV GI disease has decreased substantially since HAART became available.

**Pathology**

CMV GI disease is characterized histologically by mucosal inflammation and tissue necrosis with vascular endothelial involvement. Cytomegalovirus enterocolitis may result in deep ulcers, fistulas, and bowel perforation.

**Symptoms depend on the localization.** Nearly all patients with gastrointestinal CMV have fever. CMV gastritis presents with substernal and/or epigastric burning pain. CMV
pancreatitis presents with epigastric pain irradiating to the back. CMV small bowel disease is manifested clinically by generalized abdominal pain and sometimes diarrhoea. CMV colitis causes abdominal pain and bloody diarrhoea and rebound tenderness. CMV of small bowel and colon can cause perforation, leading to peritonitis. CMV can rarely cause large, painful ulcers of the mouth, pharynx, or anus. CMV proctitis presents with tenesmus. The other origin of abdominal pain unique to HIV (+) patients is an AIDS related sclerosing cholangitis caused by CMV. Disseminated CMV infection can show multifocal hepatic lesions with increased echogenicity.

**Diagnosis and differential diagnosis**

In practice in a developing country the diagnosis is suspected in patients with AIDS and abdominal pain, bloody diarrhoea and/or mucosal ulcers, which do not respond to common antibacterial and antifungal therapy. A hint towards the diagnosis of CMV disease is the presence of CMV retinitis.

**Treatment**

HAART with immune restoration is one of the most effective methods to control CMV disease. Two antiviral drugs that are recognized for the treatment of CMV are gancyclovir and Foscarnet. Both drugs are very expensive and have serious side effects. They are not available in developing countries because of their exorbitant cost.

**4.6.7 Drug induced abdominal pain/problems**

Many drugs can cause GI upset, a few of them may cause life threatening pancreatitis or hepatitis.

**4.6.7.1 Drug induced pancreatitis**

In general acute pancreatitis is much more common in HIV-infected patients than in the general population. It mostly occurs as a complication of medications taken to combat the virus or treat opportunistic infections (sulphonamides, didanosine, stavudine, pentamidine). Drug induced pancreatitis may not develop until after many months of use. Especially the combination of didanosine and stavudine carries a high risk for pancreatitis.

**Diagnosis**

Acute onset upper abdominal pain reaching maximum intensity in many cases within 10 to 20 minutes. One characteristic of the pain that is present in about one-half of patients and suggests a pancreatic origin is band-like radiation to the back. The pain is relieved by sitting up and leaning forward. The pain of pancreatitis lasts days. Hyper-amylasemia is frequent and 25 % have an abnormal pancreas on abdominal ultrasound.

**Treatment**

Cessation of potential pancreatotoxic medications, cessation of enteral feedings, IV hydration, gastric decompression with nasogastric suction and analgesia. Didanosine should never be restarted again after a drug-induced pancreatitis. Stavudine must be withdrawn but can be re-introduced carefully after symptoms and serum amylase have returned to normal. A dose reduction from 40 mg to 30 mg is indicated.
Prophylactic antibiotics (Amoxycillin, quinolones) are only necessary in case > 30% of the pancreas seems to be affected on US.

4.6.7.2 **Drug induced hepatitis**
Drug related hepatotoxicity can occur in earlier stage HIV infection (CD4 > 200). Patients may experience malaise, jaundice, anorexia, nausea, vomiting, abdominal pain, and weight loss. Drug-induced hepatitis is the most frequent cause of jaundice in HIV patients, most often related to antituberculous medication and carries a high mortality rate.

4.6.7.2.1 **INH induced hepatitis**
The onset of INH-induced hepatotoxicity is observed within the first two months of therapy in approximately 50 percent of patients. Some factors are related with increased risk: patients >35 years old, those receiving concurrent hepatotoxic medication (rifampin, ketoconazole), chronic alcohol use, concurrent liver disease, African-American and Hispanic women, postpartum women, injection drug users.

Patients who are asymptomatic with SGPT elevations less than five times the upper limit of normal can usually be continued on INH therapy. In many such cases, SGPT elevations decline spontaneously.

If transaminases are increased more than 5 times the upper limit, or the patient has developed jaundiced, INH (and also rifampin and pyrazinamide) should be interrupted until the jaundice has disappeared.

In most patients treatment can be restarted without problem. In case of severe TB disease alternative anti-tuberculous treatment is recommended in the meanwhile (streptomycin, ciprofloxacin and ethambutol).

4.6.7.2.2 **ARV and hepatitis**
All antiretroviral drugs are potentially hepatotoxic. The incidence may be higher in patients with underlying hepatic damage. In case of hepatitis stop the drugs. In Thailand in the HIV-NAT Trials cohort the incidence of severe hepatotoxicity was 14% per year in the group of patients taking nevirapine. Usually hepatitis occurs within the first month after the start of the treatment. Patients with hepatitis B or hepatitis C co-infection had a 3-4 times higher risk.

Hypersensitivity syndrome (DRESS = Diarrhoea, Rash, Eosinophilia, Systemic Symptoms: lymph adenopathy, hepatitis, nephritis, myocarditis) is seen with efavirenz, nevirapine and abacavir. Stop the offending drug and treat with prednisolone 1 mg/kg.

4.6.7.3 **Renal colics, nephrolithiasis**
Indinavir and sulfadiazine are eliminated as crystals in the urine. If the patients fail to drink enough or do not get sufficient fluid during treatment, they may develop renal stones and as a consequence present with colicky abdominal pain.
5 Palliative care and symptom management

Palliative care provides physical, psychological, social, emotional and spiritual care in incurable illness and is integral to a comprehensive care strategy for PLHA. Even with HAART becoming available many people will present late with immune suppression and severe symptoms. Palliative care does not mean that the underlying cause should not be treated. As an example, the headache in cryptococcal meningitis will only respond to frequent lumbar taps to release the high intracranial pressure. On the other hand, even if you treat somebody for abdominal tuberculosis, this does not mean that you can add analgesics to relieve his abdominal pain.

In this manual we will focus on symptom management.

5.1 Pain

WHO has written guidelines on the treatment of cancer pain. Those are very useful for symptom relief in HIV/AIDS as well. They follow a stepwise approach to pain control, where one would start with paracetamol or a non steroidal anti-inflammatory drugs (NSAID), if the pain is more severe or the first step is not enough one could add a weak opioid (like codeine) and if this is still not enough the weak opioid would be replaced by a strong opioid like morphine (see Table 16: Stepwise approach to analgesia, page 86)

Dosing
It is important to provide "around-the-clock-dosing" for constant pain at rest. Never provide pain relief only when the patient asks for it (PRN dosing) in palliative care. It takes time before the patient receives the medication and before it is absorbed and effective.

In case of extra nursing care or a specific examination causing extra pain, provide breakthrough dosing for intermittent pain.

If the patient needs all the time breakthrough doses do not hesitate to increase the baseline dose of analgesics. When changing the route of administration from PO to parenteral, decrease the dose by 50%. If a patient is on continuous infusion, provide breakthrough dosing by adding 1/2 of a normal hourly dose every 30 minutes. Respect maximum dosing for NSAID, paracetamol and codeine. There is no maximum standard dose for morphine.

Side effects
Anticipate and educate about potential side effects: constipation, nausea, dry mouth, sedation, confusion, urinary retention, twitches/jerks, myoclonus. Provide stool softener to prevent constipation, unless the patient had diarrhoea.

Adjuvant drugs
1. To treat adverse effects of analgesics: haloperidol, chlorpromazine, metoclopramide, senna tablets against vomiting, nausea and constipation.
2. To enhance pain relief: Corticosteroids: they are useful for relieving pain associated with nerve compression or spinal cord compression, and headache from raised intracranial pressure.
3. To treat concomitant psychological disturbances such as insomnia, depression: psychotropic drugs: some have an analgesic effect (clomipramine for neuropathic
pain); others counteract side effects (haloperidol for opioid induced vomiting). For other patients, an anxiolytic drug such as diazepam is necessary. Diazepam is also useful for muscle spasms.

**Table 16: Stepwise approach to analgesia**

<table>
<thead>
<tr>
<th>step</th>
<th>Type of drug</th>
<th>Recommended drug</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pain</td>
<td>Non-opioid</td>
<td>Aspirin PO, Paracetamol PO, NSAID</td>
<td>4 g daily in 4-6 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indometacin 25 mg 4 x daily (or ibuprofen 400 mg 4 x daily)</td>
<td>4 g daily in 4-6 doses, 200 mg daily, 3 g daily</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>Weak opioid</td>
<td>Add a weak opioid</td>
<td>240 mg daily in 4-6 doses, 400 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Codeine phosphate 30 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tramadol 50-100 mg 2-4 x daily</td>
<td></td>
</tr>
<tr>
<td>Severe pain</td>
<td>Strong opioid</td>
<td>Replace the weak opioid with a strong opioid</td>
<td>No maximum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphine every 4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pethidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Buprenorphine: 0,3 mg 3 x daily</td>
<td>1 mg every 8 hours</td>
</tr>
</tbody>
</table>

**5.2 Neuropathic pain**

There are two types of pain, pain due to nerve compression and pain due to nerve damage.

1. **Pain due to nerve compression**: Sharp pain, stabbing, "shooting electrical feeling", e.g. trigeminus neuralgia. There is usually a normal cutaneous sensation. Provide stepwise analgesia and associate carbamazepine: The starting dose is 100 mg 2 x daily. This can be increased slowly, at a rate of 200 mg every few days. Sometimes nerve compression pain only responds when corticosteroids are added.

2. **Pain due to nerve damage**: infiltration, e.g. tumour invasion, drug induced neuropathy (INH, d4T). Burning, tingling, pins and needles, hyperalgesia (skin is painful on light touch, e.g. patient cannot support bed sheets) or numbness. Provide stepwise analgesia and associate TCA's (tricyclic antidepressants). TCA's enhance the analgesic effect of opioids. Clomipramine: a dose as low as 10 mg may be appropriate for some patients, but most can take 25-50 mg. The dose can be gradually increased (every 3-4 days), as rapidly as can be tolerated in terms of postural hypotension, sedation and dry mouth. The total daily dose should be given at bedtime because of the sedative effect. Maximum dosage: 200 mg daily. In drug induced neuropathy stop the offending drug or add pyridoxine 100 mg daily in case of INH induced neuropathy.
5.3 Cough

Make sure the patient's room is well ventilated. Avoid smoke in the room. Put the patient in a semi-sitting position. Always ask the patient to cover his/her mouth while coughing. Be sure that expectorations can be collected in a small container or in a tissue, to avoid the airborne transmission of certain pathogens.

Drug: codeine 15-60 mg PO 4-6 x daily.

Besides its anti-cough effect, codeine also works as an anti-diarrhoeal and analgesic agent. If given for cough, be sure to avoid constipation.

In case the patient has difficulty to clear the airway secretions you can use aromatherapy (eucalyptus or pine oil in hot water or on the chest). Provide massage, respiratory physiotherapy and postural drainage.

Airway secretions may be reduced by adding atropine: 0.4-0.6 mg SC, IM, IV 6-8 x daily. This causes dry mucous membranes, so for comfort, somebody needs then to moisten the lips of the patient. This should be avoided in the last hours of life because of CNS and cardio-respiratory stimulation.

5.4 Dyspnoea, respiratory distress

- Always exclude reversible causes of dyspnoea: pneumothorax, pleural effusion, pulmonary oedema, asthma)
- In case of stridor secondary to obstruction by lymph nodes give steroids: prednisone 10-60 mg daily PO or dexamethasone 1-8 mg 4 x daily (PO, IV or SC).
- Reduce environmental irritants and smoking.
- Minimise number of people in the room.
- Teach and support family.
- Oxygen is only indicated when the O₂ saturation falls below 90% (pO₂<70 mmHg). Monitor the oxygen saturation percentage to establish ongoing need for oxygen therapy.
- Manage anxiety by giving morphine (2.5 -15 mg Po or SC every hour if necessary and diazepam 5-10 mg 4 x daily PO).
- In the last hours of life, respiratory failure will result in carbonarcosis which is comfortable for the patient. Cheyne-stokes breathing means that death is imminent. This is not distressing for the patient. Reassure and support the family members who are at the bedside.

5.5 Diarrhoea

We must take time to instruct the patient's family in how to handle soiled bed linen and the disposal of faeces. Ask them if they have gloves or plastic bags to protect their hands.

The patients need to be rehydrated, the bed should be kept clean and dry. Assure ready access to a bathroom or toilet and provide privacy while toileting.

Diarrhoea can be diminished by some absorbants like Aluminium antacids 15-30 ml PO 6 x daily PRN, CaCO₃, 500 mg 3 x daily.
In case of watery diarrhoea, reduce peristalsis with loperamide (Imodium®) 4 mg PO first dose followed by 2 mg - 4 mg after each unformed stool (max 16 mg daily), or codeine 30-60 mg x 3-6/day. Opioids will also reduce the peristalsis.

5.6 Oral problems

Provide stepwise analgesia (paracetamol/NSAID-codeine-morphine). See Table 16: Stepwise approach to analgesia, page 86
NSAID may be particular helpful. Steroids may help in severe aphthous stomatitis (prednisone 40 mg daily for 1 week).
In order to be able to continue to eat it is sometimes necessary to use lidocaine mouth gel.

5.7 Difficulty when swallowing, hiccups

Test the patient’s ability to swallow with a small quantity of water before each feeding to avoid aspiration of food. Minimise oral medication. Establish whether fluids or soft foods are easiest to swallow. Cool, soft foods may be easiest to swallow. Let the family prepare small, but frequent meals. Feed slowly in the upright position. Nasogastric feeding tubes may be needed if long-term support is required, e.g. a patient who has a neurological deficit after a treated cryptococcal meningitis or toxoplasma encephalitis, but who is otherwise in good physical condition.
Give cold drinks for hiccups, or if this doesn’t work chlorpromazine. Suspect oesophagitis and treat for candida.
6 Clinical manifestations and management of HIV/AIDS related conditions in infants and children

6.1 Introduction

HIV/AIDS is a major contributor to paediatric mortality and morbidity in Sub-Saharan Africa. UNAIDS figures: in 2003 half a million children died of AIDS and 700 000 new children have been infected. By the end of 2003, the total number of children infected (end of 2003) was 2.5 million. But this is likely to be an under-estimation because of the difficulties of diagnosing HIV/AIDS in children. Counseling in children and adolescents is very important and requires special skills.

6.2 How does HIV infection in children differ from that of adults?

6.2.1 Route and timing of transmission (“perinatal transmission”)

The majority (over 95%) of HIV infected children in Africa get their infection from their mothers either in utero, during delivery, or after delivery during breast feeding. Not all children born to HIV infected mothers become infected. The rate of mother to child transmission ranges from 25-45%. Other sources of HIV infection in children include blood transfusion and sexual abuse for the older child.

6.2.2 Natural history/disease progression

Because the infection occurs during the development of the infants’ immune system, the course of immunological, clinical manifestations and virological markers will be different from those in adults. A bimodal disease progression has been described. The majority of the children will develop AIDS after 6 years of life with a survival rate of more than 95% at 5 years (slow evolutive form). 20% to 30% of the children will develop AIDS during the first 12-24 months of life with survival rates less than 10% at 5 years (rapid progressors). This difference in evolution is partially explained by the moment of the infection (in utero vs peripartum). Children over 15 years, living with HIV acquired from their mothers at birth, have been described.

6.2.3 Difference in clinical manifestations

Clinical signs are very common, even before the development of AIDS. Most children will have symptoms (not AIDS defining) before the age of 1 year (80 %!). In contrast to adults who more frequently present with distinct HIV associated conditions, infected children in Africa, commonly present with a disease spectrum similar to uninfected children. Clinical diagnosis of HIV infection is therefore difficult.
HIV+ children will present more often minor bacterial and fungal infections. In comparison with adults, children have more neurological involvement, increased incidence of bacterial infections, decreased growth, Lymphoid Interstitial Pneumonitis (LIP), more cardiac dysfunction and multiple endocrine abnormalities.

6.2.4 Opportunistic infections

PCP is most common in infants. It mostly occurs in young infants (3-6 months old) and is characterized by a sudden onset and high mortality. Toxoplasmosis, cryptococcal meningitis and herpes simplex infections are less common in children than in adults. The diagnosis of TB in HIV+ children is extremely difficult (see page 95 Pulmonary tuberculosis).

6.2.5 Organic diseases in HIV infected children

The following are typical pediatric AIDS problems.

**Lymphoid interstitial pneumonitis (LIP):** a chronic lung disease associated with recurrent infections and difficulties to breath. Radiographic signs are typical (even before clinical signs): bilateral reticulonodular infiltrates. Steroid therapy may be efficacious.

**PEP: progressive encephalopathy:** among the many neurological problems a child with HIV can present, the most severe manifestation is PEP. It may occur in up to 10% of infected children! (See page 99 Neurological Abnormalities in paediatric AIDS Patients)

**Growth and cognitive development**

At birth there is no difference in size between HIV+ and uninfected children. But later on (after the age of 6 months) a delay in growth and mental development can be noted frequently (importance of knowing the school performance, milestones, growth charts).

**Failure to thrive:** Important sign in HIV infected children!

6.2.6 Difference in immunological markers

The total amount of CD4 cells changes with age (higher in infants and decreases slowly to adult values at the age of 6) and can not be used as an immunologic marker (see Table 17 page 91).

The % of CD4 doesn’t change and thus should be used as a marker of disease progression. The knowledge of the immune status and clinical stage is necessary to be able to care for children (when to start/stop prophylaxis, ARV, to determine what is failure, and thus when to change the ARV regimen…) and it enables us to determine the prognosis.

Viral load is much higher in children because they have less active cytotoxic T-cell responses, less CD4 proliferative response, and other perturbations involving the thymic function that still need to be studied. The VL tends to be one log higher than adults.
The thymus is very active (it disappears round 30-35 years) and therefore children have a greater potential for immune reconstitution.

Table 17: Approximate CD4 count and CD4% according to age and immune suppression category

<table>
<thead>
<tr>
<th>Immune category</th>
<th>&lt; 1 year</th>
<th>1-5 years</th>
<th>6-12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>No/µL</td>
<td>%</td>
</tr>
<tr>
<td>Category 1: No immune suppression</td>
<td>≥ 25%</td>
<td>≥ 1.500</td>
<td>≥ 25%</td>
</tr>
<tr>
<td>Category 2: Moderate suppression</td>
<td>15-24%</td>
<td>750-1,499</td>
<td>15-24%</td>
</tr>
<tr>
<td>Category 3: Severe suppression</td>
<td>&lt; 15%</td>
<td>&lt;750</td>
<td>&lt; 15%</td>
</tr>
</tbody>
</table>

6.2.7 Diagnosis of HIV

HIV serology in children aged less than 15-18 months is not useful because of the persistence of maternal antibodies up to that age. Sophisticated tests are available to confirm HIV infection in younger children, but these are only available in a few research laboratories in Africa (see page 15. Laboratory diagnosis of HIV infection in children). Because of that WHO proposed the case definition for reporting and surveillance of paediatric AIDS (see page 19 WHO Case Definitions for AIDS Surveillance in Countries with Limited Clinical and Laboratory Diagnostic Facilities)

6.2.7.1 When to suspect HIV infection in the child?

As stated above, HIV infected children present with and die from the common disease conditions as seen in non-HIV infected children. However you should suspect HIV if any of the following signs which are not common in HIV-negative children, are present:

1. Recurrent infections like pneumonia, sepsis, and meningitis.
2. Oral thrush. After the neonatal period, the presence of oral thrush -without antibiotic treatment- or persisting or recurring after treatment, is suggestive of HIV infection.
3. Chronic parotitis: the presence of unilateral or bilateral parotid swelling for more than 2 weeks. Distinguish this from enlarged cervical glands.
4. Generalized lymphadenopathy: the presence of enlarged lymph nodes in two or more extra-inguinal regions without any apparent under-lying cause.
5. Persistent or recurrent fever: without any apparent cause.
7. Herpes zoster
8. HIV dermatitis: a non-specific erythematous papular rash.
9. Suspected or confirmed maternal HIV infection.
Signs common in HIV infected children, but also common in ill, non-HIV infected children.

1. Chronic otitis media: ear discharge lasting > 14 days
2. Persistent diarrhoea: diarrhoea lasting > 14 days
3. Failure to thrive: weight loss or a gradual but steady deterioration in weight gain from the expected growth, as indicated in the child’s growth card. Suspect HIV particularly in a breast fed child < 6 months who has failure to thrive.

Signs or conditions very specific to HIV infected children.

1. Pneumocystis carinii pneumonia (PCP)
2. Oesophageal candidiasis
3. Lymphoid interstitial pneumonitis (LIP)
4. Herpes zoster across several dermatomes
5. Progressive encephalopathy (PEP)
6. Kaposi's sarcoma (KS)

While these conditions are very specific to HIV, their diagnosis is difficult in a resource-limited setting without adequate facilities.

6.2.7.2 What to do if suspect HIV infection?

If possible the child should be tested for HIV. Note the persistence of maternal antibodies up to 18 months, meaning a serologic positive test cannot confirm an HIV infection in a child aged less than 18 months.

Both pre-and post-test counselling should accompany any HIV testing. Because HIV infection may be the first indicator of HIV infection in the family, psychological considerations should be made for the entire family. Counselling and testing should therefore be offered to the mother (and father if consents) as well. Counselling should stress that although there is no cure yet, there is much that can be done to improve the quality and duration of life for the child and the mother’s relationship with the child.

It should also be noted that the older child with HIV infection has similar emotional and counselling needs as adults.

Trained staff should do counselling, as it requires time and skills. All health workers at first level of referral should therefore be trained in counseling.

6.3 Care of Infants and Children

6.3.1 Perinatal Care

Whatever PMTCT method the mother used before the delivery (HAART, or nevirapine), the child should receive a dose of nevirapine 2mg/kg within 72 hours after birth and one week of AZT syrup 4 mg/kg twice daily during one week (WHO 2004).

There is no special additional procedure necessary when delivering a baby born to an HIV infected mother in a maternity ward or in home deliveries other than observing strict universal precautions during all stages of delivery. Any traumatic procedure should be avoided when possible (episiotomy, use of forceps). The midwife or traditional birth attendant should remember, when necessary, to teach the family caregivers to observe hygienic practices at all times.
The decision on infant feeding should be according to the national policy in each country. However, careful consideration should be given to the circumstances and evidence available at the time of delivery, as well as the resources at the disposal of the mother and the household. Every HIV infected mother should be given full information about the risks associated with breast-feeding and its alternatives. The current United Nations recommendations on HIV and infant feeding are that HIV-infected women should avoid all breastfeeding when replacement feeding is acceptable, feasible, affordable, sustainable and safe. Otherwise, exclusive breastfeeding is recommended during the first months of life. Therefore, if breastfeeding is practiced, it is good to advise exclusive breastfeeding during 6 months and not mixed feeding, which increases the risk of HIV transmission. Counsellors should be available to the mother before and after the delivery. Because HIV infected children are usually normal at birth, no specific procedures are expected for them, except the ARV prophylaxis with NVP + AZT. However, just like all other children, if any abnormalities are detected at birth, they should be referred for better assessment and care.

6.3.2 Immunisation

WHO and UNICEF recommend that all infants with asymptomatic HIV should be immunized according to their national schedules. Accordingly, all children whether or not they are HIV infected should be immunized as recommended by the Ministry of Health of each country. There is usually less response and/or more rapid decrease of protection after vaccination of HIV infected people (hepatitis B, BCG, measles, yellow fever…). That is why children suspected or known to be HIV-infected should be given an extra dose of measles; one at 6 months of age, followed by a second dose at 9 months. BCG is normally given at birth when HIV infected children are not yet symptomatic. However, if the child had missed BCG at birth, and is already old enough to show symptoms, which would make you, suspect HIV infection (as stated above), then withhold BCG until HIV is excluded. If the risk of TB is low, the BCG should not be administered to children with suspected HIV infection (WHO recommendation). If the child is symptomatic, the attenuated yellow fever vaccine is contraindicated.

6.3.3 Management of HIV related conditions in children

6.3.3.1 General principles

The aim of management of symptomatic HIV infection includes:

2. Growth monitoring and proper nutrition.
3. Psychosocial support to cope with feeling of rejection, guilt and denial.
4. Proper nursing care of the patient
5. Make patient free from pain
6. Adequate rest & sleep
7. Maintaining normal body temperature and minimize contact with other patients with infectious disorders.
9. Antiretroviral treatment (see national antiretroviral therapy guidelines)
6.3.4 Management of specific disease conditions

As stated above, HIV infected children get similar disease conditions like non-HIV infected children. Therefore for acute diarrhoea, fever, anaemia, cough, ear infection, meningitis, failure to thrive, the children should be managed according to the national IMCI guidelines. However recovery in HIV infected children is often slower and treatment failures are common. In cases of failed treatment, consider using a second line drug.

See special notes on children in the chapters on the management of opportunistic infections in adults.

Some HIV-related conditions require specific mention in their management as described below.

6.3.4.1 Oropharyngeal Candidiasis (Thrush)

See page 41: Oropharyngeal Candidiasis (thrush) and Oesophageal Candidiasis (OC).

6.3.4.2 Persistent and chronic diarrhoea

Assessment of dehydration in accordance to the IMCI Guidelines
Outpatient management is indicated if the child is older than 6 months of age, not severely dehydrated and not severely malnourished.

Management

1. Maintain hydration with ORS: deficit & ongoing loss replacement
2. Support nutritionally
   o Continue breast-feeding in breast-fed infants
   o Introduce in non-exclusively breast-fed infants, a frequent cereal-based feeding with added oil is suitable.
   o Animal milks ½ diluted or yoghurt
   o A total daily intake of 150 kcal/kg should be maintained
3. For treatment of specific causes of diarrhoea see page 39 (Chronic diarrhoea).
4. If there is fever 38.5 °C or more, give antipyretics, then look for other causes of infection. Pneumonia, otitis media, malaria and skin infections are common causes of fever in HIV-infected children.

Note: Persistent diarrhoea is a common presentation in HIV-infected children. If the child is not severely ill (no blood in the stool, no fever and not dehydrated) observe for 7 days while hydrating and maintaining nutrition.

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*IMCI guidelines are very useful for the management of childhood diseases at health center level. The IMCI guidelines have been adapted to include more HIV related conditions.*
Indications for referral to hospitals with superior diagnostic and treatment facility whenever possible include:
1. Age less than 6 months;
2. Dehydration difficult to manage as an outpatient;
3. Severe malnutrition;
4. Persistence of blood in the stool, 48 hours after initiation of treatment with 1st line antibiotic for presumed shigellosis;
5. Febrile and toxic patients;
6. Failure to gain weight and more than 5 liquid stool /24 hours after 7 days of observation despite maintenance of fluid and nutrition
7. Associated severe diseases such as advanced cases of pneumonia and malaria.

**Note:** The management of advanced case of pneumonia and malaria are defined in the IMCI guidelines.

**Management of persistent diarrhoea**
Hospital procedures should include the basic management of fluid, electrolyte balance and nutrition.
The following are routine management procedures for the HIV-infected child:

1. **Breast-feeding** should continue
2. **Hydration** with ORS or parenteral fluids which is dictated by the status of dehydration;
3. Treating specific infections accordingly;
4. **Maintaining nutrition** with frequent feeds of cereal-based feedings, with added oil; animal and poultry proteins;
5. Diluted animal milk, fermented milk or lactose free milk
6. Vitamin A can be given for prophylactic purposes. For children < 6 months of age = 50,000 IU P/0. For children > 6 months of age = 100,000 IU P/0
7. Other minerals and vitamins supplements according to specific deficiencies.

**Criteria for Discharge**
- Weight gain
- Cessation or decreased frequency of diarrhoea stools to less than three per day

**Prevention**
- Proper food handling
- Breast-feeding
- Using clean safe water
- Universal precaution of body secretions
- Immunization (measles).

**6.3.4.3 Pulmonary tuberculosis**
HIV infection causes an increase in the child’s susceptibility to TB and the risk of tuberculosis disease. The case-fatality rate associated with TB is higher in HIV infected than non-infected.
The diagnosis of TB in children is always difficult, but it is even more difficult in HIV infected children. Pulmonary tuberculosis is still the commonest form of tuberculosis, even in HIV infected children. As HIV infection progresses and immunity declines, dissemination of TB becomes more common. TB meningitis, miliary tuberculosis, and widespread tuberculous lymphadenopathy occur. In contrast to adults, children will
have more generalized **symptoms** (weight loss, fever and inactivity) and less cough. On the **chest X-ray** children will seldom present with apical lobe infiltrates or cavities. The chest X-ray in children can show mediastinal and hilar lymph adenopathy, interstitial infiltrates (difficult to distinguish from bacterial infection) or pleural effusion. It is common to have a normal chest X-ray. **TST**, if positive, may be suggestive, but a negative result doesn't rule out TB because AIDS patients may be relatively anergic. **Sputum** for acid-fast bacilli (AFB) is rarely positive, or difficult to obtain. The technique to induce sputum or early morning gastric aspirate staining can be tried. A blood culture is often not available. Biopsy from peripheral lymph nodes may reveal the diagnosis, but requires the skills of an experienced pathologist.

Because of all these reasons, the diagnosis of TB is nearly always presumptive in children!
**Scoring System for the Diagnosis of TB in Children**

A scoring system is one way of trying to improve the diagnosis of childhood TB. A score above a certain threshold indicates a high likelihood of TB. The table shows a scoring chart (adapted from Crofton) to help to diagnose childhood TB. A score of 7 or more indicates a high likelihood of TB.

**Table 18: A scoring system for the diagnosis of TB in children**

<table>
<thead>
<tr>
<th>Feature</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (weeks)</td>
<td>&lt;2</td>
<td>2-4</td>
<td>&gt;4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition (% weight for age)</td>
<td>&gt;80</td>
<td>60-80</td>
<td>&lt;60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of TB</td>
<td>None</td>
<td>Reported by family</td>
<td>Proved sputum positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculin test</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Not improving after 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained fever and night sweats</td>
<td>No response to malaria treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint or bone swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal mass or ascites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.N.S. signs, and usually abnormal C.S.F. findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angle deformity of spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*b Adapted from MSF Malawi*
Treatment
Treatment is like for non-HIV infected children and according to National TB Control guidelines. If TB is miliary, meningeal, renal or bone, treatment should be continued for 12 months.

Thiacetazone should be avoided because of the high risk of toxic reaction in HIV infected children.

6.3.4.4 Lymphocytic interstitial pneumonitis (LIP)

The cause of LIP is unknown, but often associated with the presence of Epstein Barr virus infection.

Presentation
Onset is usually insidious with chronic non-productive cough with or without difficulty in breathing and signs of hypoxia such as finger clubbing. Other associated features are generalized symmetrical lymphadenopathy and non-tender parotid enlargement and finger clubbing. LIP is often complicated by acute bacterial pneumonia.

Diagnosis is presumptive based on clinical and chest X-ray findings, which typically show diffuse reticulonodular shadowing for which TB has to be excluded.

Treatment
Give a trial of antibiotic therapy for bacterial pneumonia first, before starting oral prednisolone 1-2mg/kg/d for 2-4 weeks, followed by a gradual decrease over 2 weeks. Steroids are immunosuppressive and may increase the risk of tuberculosis and other opportunistic infections. You should therefore weigh the benefits of steroid therapy against these potential adverse effects. Start steroids only if X-Ray findings are suggestive, there is no response to antibiotics, there is difficulty in breathing, cyanosis and finger clubbing. Oxygen may be required for hypoxemia. HAART will improve symptoms. In case of obstructive pattern, give beta-mimetic bronchodilators via nebulizer. Always give cotrimoxazole prophylaxis.

6.3.4.5 Pneumocystis Carinii Pneumonia (PCP)

In some areas P. Carinii pneumonia is very common in children. PCP may take a rapidly progressive course and distinction between PCP and bacterial infection can be difficult. Acute onset of disease with high fever elevated WBC with a shift to the left and abnormal chest X-ray may suggest a more bacterial pneumonia than PCP. Consider the possibility of PCP, in a child known or suspected to have HIV, whose ordinary pneumonia does not respond to treatment. PCP occurs most frequently in infants (especially < 6 months of age) and is often associated with hypoxia. Fast breathing is the most common presenting sign. Rales on auscultation are rare or absent.

Treatment (see also page 47)
High doses of cotrimoxazole (Trimethroprim 5 mg/kg, Sulfamethoxazole 25 mg/kg every 6 hour IV (if available) for 21 days. Otherwise give oral treatment same dose. If treatment cannot be continued because of severe drug reaction, pentamidine (4 mg/kg daily IV can substitute).
For children who are hypoxic add steroids from the start of the treatment with cotrimoxazole (see Table 9: Cotrimoxazole dosing for PCP page 48). Lifelong secondary prophylaxis with cotrimoxazole is necessary, until immune reconstitution following HAART (CD4>200 for 6 months).

6.3.4.6 **Neurological Abnormalities in paediatric AIDS Patients**

**Definition:** Neurological abnormalities in a child with symptomatic HIV infection may include the following presentations:

**6.3.4.6.1 Progressive encephalopathy**

(PEP) progressive decline in motor, cognitive or language function evident as loss of, or delay in developmental milestone. Onset can be as early as the first year of life but can occur at any time. Characterized by:

(a) Impaired brain growth (abnormal small head size)
(b) Progressive decline in motor function
(c) Cognitive and language impairment
(d) Delay in developmental milestones

Serial measurements of head circumferences (up to the age of 2 years) will show a plateau in these children. In the beginning the child loses the ability to perform fine movements with the hand and fingers. Later on bigger muscle groups become involved, they become rigid (severe hypertonia or spastic quadriparesis) or flaccid with involuntary movements. The child loses the ability to walk or sit or will never be able to achieve age-appropriate milestones (sit, walk...)

Age appropriate milestones are not achieved or lost: sit, speak, ability to learn and understand, school failure...

**6.3.4.6.2 Static encephalopathy**

It presents also with motor dysfunction and other developmental deficits of varying severity, but is non progressive as documented on serial neurological and development examination. Static encephalopathy can be due to the effect of HIV on the developing CNS or related, to non-HIV-factors, such as asphyxia, prematurity, or the effect of in-uterus drug exposure. Static HIV encephalopathy is diagnosed in the absence of an alternative explanation.

Children with HIV infection may develop neurological complications as a result of direct effect of HIV on CNS. These direct and indirect effects of HIV on the CNS are difficult to differentiate clinically although the direct HIV encephalopathy often involves symmetrical motor impairment and more insidious decline of cognitive and behavioural function.

**6.3.4.6.3 CNS infections in children with AIDS**

Acute episodes with acute onset of seizures, focal neurological deficits as in toxoplasmosis, meningitis and fever (e.g. cryptococcal, bacterial, tuberculous meningitis or CMV encephalitis) occur as in adults, but less frequent.
Neurological conditions that often accompany HIV infection include:
- Pyogenic meningitis
- Cryptococcal meningitis
- TB meningitis, abscess or tubercles
- CNS toxoplasmosis
- CMV encephalitis
- CNS bleeding
- CNS lymphoma
- Malaria
- HIV encephalopathy.

**Diagnosis**
The diagnosis is based on history and physical examination including complete neurological and developmental assessment. The following investigations help to identify the cause wherever possible.
- CSF examination
  - Microscopy
  - Chemistry
  - Cells count and differential
  - Gram stain
  - AFB stain
  - Indian Ink
  - Culture (bacterial, fungal, mycobacterial)
- Serology of CSF or blood (VDRL, cryptococcal antigen detection, pyogenic bacteria)
- EEG and CT scan or MRI

**Table 19: The value of CSF examination in the HIV infected child with neurological abnormalities**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Microscopy</th>
<th>Culture</th>
<th>Cell count</th>
<th>Serology</th>
<th>Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyogenic bacteria</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>M. Tuberculosis</em></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Key: (+) useful, (-) not useful, (+/-) may be useful.

**Note:** In a malaria endemic area, a diagnosis of cerebral malaria should be considered as differential diagnosis and hence proper treatment according to the national guideline given before proceeding to further study HIV related neurological disorders.

The management of common CNS problems is summarized below (see also Opportunistic infections involving the brain page 54)

**6.3.4.6.3.1 HIV Encephalopathy**
Direct involvement of HIV on CNS is common from different reports.
Presentation looks like:
- Symmetrical motor deficit, muscle tone and reflex changes, ataxia, spasticity.
- Delayed or regression of developmental milestones and cognitive function - speech & language disability
- Acquired microcephalus and blindness.
- Seizure is infrequent, often secondary to intercurrent opportunistic infection.
The involvement of CNS can be static, rapid or intermittent of course. Factors that may modify progression include: age at the onset of the disease (younger > older), route of transmission (transplacental infection > infection later in life) or other non HIV-related factors which may affect neurological development. Neurological signs of the congenitally infected patients may appear during early infancy or be delayed as late as 5 years of age.

**Diagnosis**
The diagnosis of HIV encephalopathy is made on clinical grounds by serial measurements of head circumference, developmental milestone (delay, loss or decreased rate of acquisition over time) or symmetric muscle tone and reflex abnormalities. CT scan (or MRI) (if available) will demonstrate diffuse cerebral atrophy. CSF cells & biochemical studies are usually normal except for the mild non-specific pleocytosis and increased protein noted occasionally.

**Treatment**
- Supportive care
- Physiotherapy
- HAART (especially those containing drugs which cross the blood brain barrier: AZT, D4T, Abacavir, Indinavir and Nelfinavir) is reported to improve neuro-behavioural deficits and prolongs life.

### 6.3.4.6.3.2 Pyogenic Meningitis

The typical clinical picture of meningitis is sudden onset of high-grade fever, behavioural change, refusal to drink, vomiting, fontanel bulging and positive Kernig and Bruzdinsky's signs.

**Diagnosis**
- CSF: purulent and turbid;
- CSF WBC count increased, sometimes > 500, polymorphonuclear predominance, protein increased and glucose reduced (to < 40 mg/l)
- Gram stain
- Antigen detection on CSF
- Culture

**Treatment**
If the aetiology is not identified or pending microbiological result, empirical treatment should be started.
<table>
<thead>
<tr>
<th>AGE</th>
<th>Possible Agents</th>
<th>Recommended treatment</th>
<th>Alternative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 months</td>
<td>Enteric pathogens, gram negative, Streptococcus group B, Haemophilus influenza, S.pneumoniae, Listeria monocytogenes</td>
<td>Ampicillin 200 mg/kg/24 hours in 4 divided doses and Gentamycin 2.5 mg/kg every 8 hours IV for a period of 3 weeks</td>
<td>if no response and pathogen not identified Ceftriaxone IM 100 mg/kg/day for 10 days.</td>
</tr>
<tr>
<td>3 months – 5 years</td>
<td>Haemophilus influenza S.pneumoniae, Non-Typhoidal Salmonella, N.meningitidis</td>
<td>Benzyl-penicillin 450,000 IU/kg/day divided over 4 doses and chloramphenicol 25 mg/kg every 6 hours IV for 2-4 weeks</td>
<td>if no response and pathogen not identified Ceftriaxone IM 100 mg/kg/day for 10 days.</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>S.pneumoniae and N.meningitidis</td>
<td>Benzyl-penicillin 450,000 IU/kg/day divided over 4 doses and chloramphenicol 25 mg/kg every 6 hours IV for 2-4 weeks</td>
<td>if no response and pathogen not identified Ceftriaxone IM 100 mg/kg/day for 10 days.</td>
</tr>
</tbody>
</table>
Table 21: Antibiotic treatment in paediatric pyogenic meningitis according to the identified organism

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<th>Organism</th>
<th>Recommended regimen</th>
<th>Alternative regimen</th>
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<tr>
<td>H. influenza</td>
<td>Ampicillin, 200 mg/kg/day in doses divided every 4-6 hours for 2-3 weeks (max dose: 12g/day)</td>
<td>Chloramphenicol, 25 mg/kg every 6 hours IV for 2-3 weeks or Ceftriaxone IM 100 mg/kg/day for 10 days.</td>
</tr>
<tr>
<td>S. Pneumoniae</td>
<td>Benzyl-penicillin 450,000 IU/kg/day IV in divided doses every 6 hours for 2-3 weeks Max dose: 24 million IU/day</td>
<td>Ceftriaxone IM 100 mg/kg/day for 10 days.</td>
</tr>
<tr>
<td>N. Meningitidis</td>
<td>Benzyl-penicillin 450,000 IU/kg/day IV in divided doses every 6 hours for 2-3 weeks Max dose: 24 million IU/day</td>
<td>Ceftriaxone IM 100 mg/kg/day for 10 days.</td>
</tr>
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</table>

6.3.4.6.3.3 TB Meningitis, Abscess or Tuberculoma
See tuberculous meningitis in adults, page 59.

6.3.4.6.3.4 Cytomegalovirus (CMV) CNS Infections
See CMV encephalitis in adults, page 61.

6.3.4.6.3.5 Cryptococcal Meningitis
See Cryptococcal Meningitis in adults, page 54

6.3.4.6.3.6 CNS Toxoplasmosis
Toxoplasmosis encephalitis can have a subtle or acute onset with headache, fever, vomiting, seizures, focal neurological signs.

Congenital toxoplasmosis has a rapid progression in infants with hepatosplenomegaly, jaundice, thrombocytopenia, rash and microcephalus. Late presentation is characterised by learning difficulties, mental retardation, visual problems. Acquired toxoplasmosis present with fever, lymphadenopathy, hepatosplenomegaly, rash. Toxoplasmosis can also present with pneumonitis, hypoxaemia, dyspnoea, bilateral pulmonary infiltrates.

\[\text{\textsuperscript{c}}\text{ If in a country more than 10\% of the isolates of S. Pneumoniae are resistant to penicillin resistance, do not use benzyl penicillin as first line treatment for meningitis}\]
Diagnosis
CSF may be abnormal, but is usually normal; Toxoplasma serology may be helpful, in the sense that a negative serology virtually excludes a toxoplasmosis. CT scan or MRI shows calcification and multiple hypodense or isodense masses with ring enhancement.

Treatment
Cotrimoxazole (5 mg TMP + 25mg SMX)/kg/dose PO twice daily during 4 weeks, followed by secondary prophylaxis (see Prevention of bacterial infections, PCP and toxoplasmosis, using cotrimoxazole page 30)

Pyrimethamine, sulfadiazine and folinic acid are not available.
In case it becomes available Pyrimethamine, loading dose 2 mg/kg for 2 days then 1 mg/kg daily orally for 6 weeks plus sulfadiazine, 40 mg/kg orally every 12 hours for 6 weeks. Folinic acid 5 mg every 3 days orally during pyrimethamine therapy.

Suppressive therapy (in children over 6 years) must be given due to frequent relapse. Pyrimethamine, 25 mg and sulfadiazine 2 gm daily, with folinic acid 25 mg per week.

6.3.4.6.3.7 Lymphoma
See page 63: Primary Central Nervous system lymphoma

6.3.4.7 Persistent Fever or Recurrent Fever
Fever is one of the most frequent clinical presentations of HIV infection in children. Persistent fever is defined as a body temperature of >38°C for more than 5 days duration and recurrent fever is defined as a body temperature of > 38°C for more than one episode over a period of 5 days. Children may have fever as a consequence of concurrent common childhood illness, endemic diseases, serious bacterial or opportunistic infection, neoplasm and/or HIV itself. Under many of these circumstances, the fever will be associated with specific localizing signs and symptoms (e.g. CNS, respiratory tract etc.)

However, fever may not be with any specific focal localizing signs. Patient may have simple acute infections or a serious (e.g. sepsis) infection that requires specific treatment immediately. In a setting of HIV and potential immunosuppression, the following conditions should be considered:

- Occult bacterial infection (Otitis media, UTI, chronic sinusitis, salmonellois, abscess, osteomyelitis, syphilis)
- Mycobacterial infections
- Parasitic infections (e.g. malaria, toxoplasmosis)
- Chronic viral infection (e.g. CMV, Epstein Barr virus, Measles, Herpes, Varicella zoster)
- Fungal infections (e.g. candidia)
- Neoplasm, e.g. lymphoma
Diagnostic work up

- WBC, differential count
- ESR
- Urine analysis
- CSF, blood, urine and sputum culture, microscopy studies
- TST
- Serology of suspected aetiologies (Toxoplasmosis, VDRL, SCrAg)
- Chest X-ray
- CT scan, MRI, ultrasound.

Treatment

1. If a child has fever and is not seriously ill and is stable (i.e. the child is attentive, eats and drinks and smiles and cries strongly), empirical treatment intended to treat occult non-serious bacterial infection such as sinusitis or urinary tract infections should be considered, e.g. ampicilline or cotrimoxazole syrup
2. In malaria endemic areas give specific treatment immediately, according to National Guidelines.
3. The possibility of tuberculosis should always be considered in an HIV-infected child with recurrent fever.
4. If the child is severely ill (i.e. weakly crying, not smiling, not reacting to stimulation and inattentive and not eating or drinking), broad-spectrum antibiotic (e.g. chloramphenicol + ampicillin) or (chloramphenicol + gentamycin) or ciprofloxacin (15 mg/kg twice daily) or ceftriaxone 50-100 mg/kg daily for presumed sepsis or meningitis should be started.
5. Additional investigations can be undertaken if indicated and available including
   - LP, urine analysis and culture
   - Chest & sinus X-ray
   - Blood culture
   - Stool microscopy and culture
   - Ultrasound, CT, MRI
6. Close follow up is essential, as the clinical picture may become more distinct.
7. Antipyretic management and hydration are part of the treatment of a febrile patient.

6.3.4.8 Skin Manifestations
See Skin Manifestations in HIV/AIDS, page 65

6.3.5 Follow up of children with HIV/AIDS

Serious illnesses in HIV infected children should be managed as for other children. If the general condition of these children is good they do not need to remain in hospital, but can be discharged to be seen regularly as outpatients.

Discharge from hospital should take into account available community or home based care programmes for further counselling and continuing psychosocial support.

When not ill, HIV infected children should attend well-baby clinics like other children to receive regular immunizations and growth monitoring.

Make sure the child gets all the necessary immunisations and is put on cotrimoxazole prophylaxis daily or thrice weekly.
6.3.6 Palliative care and pain control

An HIV infected child in the terminal stages often has considerable discomfort and pain; so good palliative care is essential. Take all decisions together with the mother and communicate to them clearly. Give palliative care (in the sense of end of life support) only when:

The child has had a progressively worsening illness and everything possible has been done to treat the presenting illness, or to exclude treatable conditions like TB.

For pain control give analgesia by mouth where possible, in increasing doses, and regularly. For mild to moderate pain paracetamol is normally adequate. Other drugs for specific pain problems are diazepam for muscle spasm, carbamazepine for neuralgic pain. Potent analgesics such as opiates may be used for severe pain, but careful monitoring for respiratory depression is required (see page 85 Palliative care and symptom management)
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