**Mycobacterium tuberculosis**

TB is a bacterial disease caused by *Mycobacterium tuberculosis* (and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum*). These organisms are also known as tubercle bacilli (because they cause lesions called tubercles) or as acid-fast bacilli (AFB). When examining sputum containing tubercle bacilli stained with certain dyes under the microscope, the bacilli look red. This is because they are acid-fast (they have kept the dye even after washing with acid and alcohol). Tubercle bacilli can remain dormant in tissues and persist for many years.

**Transmission of infection**

Transmission occurs by airborne spread of infectious droplets. The source of infection is a person with TB of the lung who is coughing. TB of the lung is pulmonary TB (PTB). This person is usually sputum smear-positive (see Chapter 3). Coughing produces tiny infectious droplets (droplet nuclei). One cough can produce 3,000 droplet nuclei. Transmission generally occurs indoors, where droplet nuclei can stay in the air for a long time. Ventilation removes droplet nuclei. Direct sunlight quickly kills tubercle bacilli, but they can survive in the dark for several hours. Two factors determine an individual's risk of exposure: the concentration of droplet nuclei in contaminated air and the length of time he breathes that air.

**Risk of infection**

An individual's risk of infection depends on the extent of exposure to droplet nuclei and his susceptibility to infection. The risk of infection of a susceptible individual is therefore high with close, prolonged, indoor exposure to a person with sputum smear-positive PTB. The risk of transmission of infection from a person with sputum smear-negative PTB is low, and with extra-pulmonary TB is even lower.

**Risk of progression of infection to disease.**

Once infected with *M. tuberculosis*, a person stays infected for many years, probably for life. The vast majority (90%) of people without HIV
infection who are infected with *M. tuberculosis* do not develop tuberculosis disease. In these healthy, asymptomatic, but infected individuals, the only evidence of infection may be a positive tuberculin skin test.

Infected persons can develop tuberculosis disease at any time. The chance of developing disease is greatest shortly after infection and then steadily lessens as time goes by. Various physical or emotional stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance, especially by HIV infection. Disease can affect most tissues and organs, but especially the lungs.

**Natural history of untreated TB**
Without treatment, after 5 years, 50% of pulmonary TB patients will be dead, 25% will be healthy (self-cured by strong immune defence) and 25% will remain ill with chronic, infectious TB.

**Epidemiology**
*M. tuberculosis* infects a third of the world's population. Worldwide in 1995 there were about 9 million new cases of TB with 3 million deaths. These deaths comprise 25% of all avoidable deaths in developing countries. 95% of TB cases and 98% of TB deaths are in developing countries. 75% of TB cases in developing countries are in the economically productive age group (15-50 years).

**Pathogenesis of TB**

**Primary infection**
Primary infection occurs on first exposure to tubercle bacilli. Inhaled droplet nuclei are so small that they avoid the mucus-ciliary defences of the bronchi and lodge in the terminal alveoli of the lungs. Infection begins with multiplication of tubercle bacilli in the lungs. This is the Ghon focus. Lymphatics drain the bacilli to the hilar lymph nodes. The Ghon focus and related hilar lymphadenopathy form the primary complex. Bacilli may spread in the blood from the primary complex throughout the body. The immune response (delayed hypersensitivity and cellular immunity) develops about 4-6 weeks after the primary infection. The size of the infecting dose of bacilli and the strength of the immune response determine what happens next. In most cases, the immune response stops the multiplication of bacilli. However, a few dormant bacilli may persist. A positive tuberculin skin test would be the only evidence of infection. The immune
response in a few cases is not strong enough to prevent multiplication of bacilli, and disease occurs within a few months.

**Outcome of primary infection**

<table>
<thead>
<tr>
<th>Primary complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>No clinical disease</td>
</tr>
<tr>
<td>Positive tuberculin skin test</td>
</tr>
<tr>
<td>(usual outcome: 90% of cases)</td>
</tr>
</tbody>
</table>

- **Hypersensitivity reactions**
  - e.g. erythema nodosum
  - phlyctenular conjunctivitis
  - dactylitis

- **Pulmonary and pleural complications**
  - e.g. tuberculous pneumonia
  - lobar collapse (bronchial compression)
  - pleural effusion

- **Disseminated disease**
  - e.g. lymphadenopathy (usually cervical)
  - meningitis
  - pericarditis
  - miliary disease

**PRACTICAL POINT**

Following primary infection, rapid progression to intra-thoracic disease is more common in children than in adults. Chest X-ray may show intrathoracic lymphadenopathy and lung infiltrates.

**Post-primary TB**

Postprimary TB occurs after a latent period of months or years after primary infection. It may occur either by reactivation or by reinfection. Reactivation means that dormant bacilli persisting in tissues for months or years after primary infection start to multiply. This may be in response to a trigger, such as weakening of the immune system by HIV infection. Reinfection means a repeat infection in a person who has already...
previously had a primary infection.

Postprimary TB usually affects the lungs but can involve any part of the body. The characteristic features of postprimary PTB are the following: extensive lung destruction with cavitation; positive sputum smear; upper lobe involvement; usually no intrathoracic lymphadenopathy.

**POST-PRIMARY TB**

**PULMONARY TB**

*examples: cavities, upper lobe infiltrates, fibrosis, progressive pneumonia, endobronchial *

**EXTRA-PULMONARY TB**

<table>
<thead>
<tr>
<th>COMMON</th>
<th>LESS COMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>Empyema</td>
</tr>
<tr>
<td>Lymphadenopathy (usually cervical)</td>
<td>Male genital tract (epididymitis, orchitis)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>(meningitis, cerebral tuberculoma)</td>
<td>Female genital tract (tubo-ovarian, endometrium)</td>
</tr>
<tr>
<td>Pericarditis (effusion/ constrictive)</td>
<td>Kidney</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td></td>
</tr>
<tr>
<td>(ileocaecal, peritoneal)</td>
<td>Adrenal gland</td>
</tr>
<tr>
<td>Spine, other bone and joint</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin (lupus vulgaris, tuberculids, miliary)</td>
</tr>
</tbody>
</table>

**PRACTICAL POINT**

Post-primary infection with pulmonary disease usually occurs in adults, with positive sputum smears.
Introduction: HIV and AIDS

Since the first description of AIDS in 1981, researchers have identified 2 serotypes of HIV, the cause of AIDS. HIV-1 is the predominant serotype worldwide. HIV-2 occurs most commonly in West Africa. They both cause AIDS and the routes of transmission are the same. However, HIV-2 transmission is slightly less easy and HIV-2 may cause slower progression to AIDS.

HIV/AIDS epidemiology

In 1995 worldwide there were about 17 million HIV-infected adults. An estimated 6 million adult and paediatric AIDS cases have occurred since the HIV pandemic began. Most of these cases of HIV and AIDS have been in sub-Saharan Africa and the Americas. There are now growing numbers in South East Asia. In some sub-Saharan African countries, HIV seroprevalence in the general population aged over 15 years is as high as 20%.

HIV transmission

The main modes of transmission of HIV are through sexual intercourse, blood and from mother to infant. Worldwide the most important route of transmission is through sexual intercourse. In most low-income countries equal numbers of men and women are HIV-infected. Other sexually transmitted diseases (especially those causing genital ulcers) increase the risk of HIV transmission. Bloodborne HIV transmission occurs through contaminated blood transfusion, injections with contaminated needles and syringes, and the use of non-sterile skin-piercing instruments. About one third of children born to HIV-infected mothers are also HIV-infected. There is a small risk of HIV transmission through breastfeeding. However, in many low-income countries breastfeeding is still a safer alternative to bottle-feeding.

There is no evidence that HIV transmission occurs through everyday contact, hugging or kissing, food or drink, or bites of mosquitoes or other insects.
**Prevention of HIV transmission in health units**

### Transmission to patients

Patients may potentially be at risk of HIV infection from HIV-positive staff and HIV-positive other patients. Known HIV-positive staff should not perform invasive procedures (surgery, invasive diagnostic or therapeutic procedures) on patients. Cross-infection between patients can occur from contaminated medical, surgical or dental equipment. It is vital to follow recommended sterilisation procedures. When and where possible, reducing injections helps to decrease the risk of cross-infection.

### Transmission to staff

Most HIV-positive health workers acquire HIV infection outside the workplace, by sexual transmission from an HIV-positive partner/spouse. The risk of transmission of HIV from patients to staff is small if staff observe standard infection control procedures. In health units, HIV transmission is less common than hepatitis B transmission. Less than 0.5% of health workers exposed by a needle-stick injury to the blood of an HIV-positive patient have acquired HIV infection. Handle all “sharps” carefully. If you have a needle-stick injury, squeeze the wound to encourage blood flow and wash well with soap and water.

In high HIV prevalence areas, assume that all blood and body fluids are potentially infectious. The table gives some guidance on prevention of transmission to health workers.

<table>
<thead>
<tr>
<th>Exposure to risk</th>
<th>Precautions for prevention of transmission of HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>venepuncture</td>
<td>wear gloves&lt;br&gt;use a closed vacuum system if available&lt;br&gt;discard needle and syringe into sharps box&lt;br&gt;discard gloves and swabs into leak-proof plastic bag for incineration&lt;br&gt;label blood bottle and request form “inoculation risk”</td>
</tr>
<tr>
<td>invasive procedure, surgery, delivery of a baby</td>
<td>wear gloves and apron&lt;br&gt;protect your eyes (glasses or protective goggles)&lt;br&gt;discard sharps into sharps box</td>
</tr>
<tr>
<td>spilled blood or other body fluids</td>
<td>clear up as soon as possible using available disinfectant (e.g. glutaraldehyde, phenol, sodium hypochlorite)</td>
</tr>
<tr>
<td>resuscitation</td>
<td>avoid mouth-to-mouth resuscitation (use bag and mask)</td>
</tr>
</tbody>
</table>
Immunopathogenesis of HIV infection

The helper subset of T-lymphocytes is 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 killing of many CD4+ lymphocytes (progressive decrease in CD4+ lymphocyte count) and poor function of the survivors. Progressive HIV infection therefore causes progressive decline in immunity.

Natural history of HIV infection

Acute HIV infection

Most people infected with HIV do not know that they have become infected. HIV-infected persons develop antibodies to HIV antigens usually 6 weeks, but up to 3 months, after infection. This “seroconversion” is when a person recently infected with HIV first tests sero-positive for HIV antibodies. Some people have a “glandular fever”-like illness (fever, rash, arthralgia and lymphadenopathy) at the time of seroconversion. Occasionally acute neurological syndromes may occur which are often self-limiting. These include aseptic meningitis, peripheral neuropathy, encephalitis and myelitis. A severe seroconversion illness may predict a worse long-term outcome.

Asymptomatic HIV infection

In adults, there is a long, variable, latent period from HIV infection to the onset of HIV-related disease and AIDS. A person infected with HIV may be asymptomatic for up to 10 years or more. The vast majority of HIV-infected children are infected in the perinatal period. The period of asymptomatic infection is shorter in children than in adults. A few infants become ill in the first few weeks of life. Most children start to become ill before 2 years of age. A few children remain well for several years.

Progression from HIV infection to HIV-related disease and AIDS

Almost all (if not all) HIV-infected people will ultimately develop HIV-related
disease and AIDS. Some HIV-infected individuals progress more quickly than others to HIV-related disease and AIDS. The rate of progression depends on virus and host characteristics. Virus characteristics include serotype and strain: HIV-1 and certain HIV strains may cause faster progression. Host characteristics which may cause faster progression include age less than 5 years, age more than 40 years, concurrent infections, and possibly genetic factors.

**Persistent generalised lymphadenopathy (PGL)**
This occurs in about one third of otherwise healthy HIV-infected people. The enlarged lymph nodes are persistent, generalised, symmetrical, and non-tender.

**Early immunosuppression**
As HIV infection progresses and immunity declines, patients become more susceptible to infections. These include tuberculosis, septicaemia, pneumonia, and recurrent fungal infections of the skin and oropharynx. Patients may develop constitutional symptoms (unexplained fever and weight loss), sometimes known as “AIDS-related complex” (ARC). Some patients develop chronic diarrhoea with weight loss, often known as “slim disease”.

**Late immunosuppression**
Any infection that can occur with early immunosuppression can also occur with late immunosuppression. In addition, certain specific HIV-related diseases occur predominantly with severe immunosuppression. These include certain opportunistic infections (e.g. cryptococcal meningitis) and certain tumours (e.g. Kaposi’s sarcoma). At this late stage, the patient usually dies in less than 1-2 years. This late stage is sometimes known as “full-blown AIDS”.

**PRACTICAL POINT**
Tuberculosis can occur at any point in the course of progression of HIV infection.

**AIDS**
AIDS is a term with an official definition used for epidemiological surveillance. This means that systematic reporting of AIDS cases is useful
in helping to monitor the HIV pandemic and to plan public health responses. The term AIDS is not useful for the clinical care of individual patients. In managing patients with HIV-related disease, the aim is to identify and treat whichever HIV-related diseases are present.

**PRACTICAL POINT**

The term AIDS is used for epidemiological surveillance, not for clinical care.

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**WHO case definitions for AIDS surveillance**

**ADULTS AND ADOLESCENTS**

WHO has recommended AIDS case definitions for use in adults and adolescents in countries with limited clinical and laboratory diagnostic facilities. The recommended case definition depends on whether HIV testing is available. One case definition is for use where HIV testing is not available. The other case definition is for use where HIV testing is available.

**WHO case definition for AIDS surveillance where HIV testing is not available.**

The case definition for AIDS is fulfilled in the presence of at least 2 major signs and at least 1 minor sign.

**Major signs**

- weight loss > 10% of body weight
- chronic diarrhoea for more than 1 month
- prolonged fever for more than 1 month

**Minor signs**

- persistent cough for more than 1 month
- generalised pruritic dermatitis
- history of herpes zoster
- oropharyngeal candidiasis
- chronic progressive or disseminated herpes simplex infection
- generalised lymphadenopathy

---

**For patients with tuberculosis, persistent cough for more than 1 month should not be considered as a minor sign.**
The presence of either generalised Kaposi’s sarcoma or cryptococcal meningitis is sufficient for the case definition of AIDS.

The advantages of this case definition are that it is simple to use and inexpensive. The disadvantages are its relatively low sensitivity and specificity. For example, HIV-negative tuberculosis cases could be counted as AIDS cases because of their similarity in clinical presentation.

**WHO case definition for AIDS surveillance where HIV testing is available**

The case definition for AIDS is fulfilled in the presence of a positive HIV test and 1 or more of the following conditions:

- weight loss > 10% body weight, or cachexia, with diarrhoea or fever, or both, for at least 1 month, not known to be due to a condition unrelated to HIV infection
- cryptococcal meningitis
- tuberculosis (pulmonary or extrapulmonary)
- Kaposi’s sarcoma
- 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, pneumonia
- invasive cervical cancer

An advantage of this case definition is that it has a higher specificity. A disadvantage is that it requires the availability of HIV serological testing, which may be logistically difficult and costly.

**CHILDREN**

**WHO case definition for AIDS surveillance where HIV testing is not available**

The case definition for AIDS is fulfilled in the presence of at least 2 major signs and 2 minor signs (if no other known cause of immunosuppression).

**Major signs**

- weight loss or abnormally slow growth
- chronic diarrhoea (> 1 month)
- prolonged fever (> 1 month)
Minor signs
• generalised lymph node enlargement
• oropharyngeal candidiasis
• recurrent common infections, e.g. ear infections, pharyngitis
• persistent cough
• generalised rash
Confirmed HIV infection in the mother counts as a minor criterion. This definition is not very specific.

WHO case definition for AIDS surveillance where HIV testing is available
This case definition is complex and depends on advanced clinical and laboratory diagnostic facilities. The applicability of this case definition is therefore limited and is beyond the scope of this manual. Those interested should see the suggestions for further reading at the end of the chapter.

HIV-RELATED TB

Epidemiology of co-infection of HIV and M. tuberculosis
In 1995, about one third of the 15 million HIV-infected people worldwide were also co-infected with M. tuberculosis. 70% of co-infected people live in sub-Saharan Africa, 20% in Asia and 8% in Latin America and the Caribbean.

HIV infection and risk of TB
HIV increases a person’s susceptibility to infection with M. tuberculosis. In a person infected with M. tuberculosis, HIV is a potent cause of progression of tuberculosis infection to disease.

Consider an individual infected with M. tuberculosis. The table shows the effect of HIV infection on his lifetime risk of developing TB.

<table>
<thead>
<tr>
<th>HIV status</th>
<th>Lifetime risk of developing TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>5-10 %</td>
</tr>
<tr>
<td>positive</td>
<td>50 %</td>
</tr>
</tbody>
</table>
HIV is the most powerful factor known to increase the risk of TB.

**Consequence of HIV/M. tuberculosis co-infection**

Compared to an individual who is not infected with HIV, an individual infected with HIV has a 10 times increased risk of developing TB. TB notifications have increased in populations where both HIV infection and *M. tuberculosis* infection are common, e.g., some parts of sub-Saharan Africa have seen a tripling in the number of notifications over the past decade. HIV seroprevalence in these TB patients is up to 70%. In sub-Saharan Africa, one third or more of HIV-infected people may develop TB.

**Impact of HIV on TB control**

The principles of TB control are the same even when there are many HIV/TB patients. However, in populations where HIV/TB is common, health services struggle to cope with the large and rising numbers of TB patients.

The consequences include the following:

- over-diagnosis of sputum smear-negative PTB
- under-diagnosis of sputum smear-positive PTB
- inadequate supervision of anti-TB chemotherapy
- low cure rates
- high mortality rates during treatment
- high default rates because of adverse drug reactions
- high rates of TB recurrence
- increased emergence of drug resistance

**Patterns of HIV-related TB**

As HIV infection progresses, CD4+ lymphocytes decline in number and function. The immune system is less able to prevent the growth and local spread of *M. tuberculosis*. Disseminated and extra-pulmonary disease is more common.

**Pulmonary TB**

Even in HIV-infected patients, PTB is still the commonest form of TB.
The presentation depends on the degree of immunosuppression. The table below shows how the clinical picture, sputum smear result and chest X-ray appearance often differ in early and late HIV infection.

**How PTB differs in early and late HIV infection**

<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</td>
</tr>
<tr>
<td></td>
<td>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>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Extra-pulmonary TB**

The commonest forms are the following: lymphadenopathy, pleural effusion, pericardial disease, miliary disease, meningitis.

**HIV-related TB in children**

As in adults, the natural history of TB in a child infected with HIV depends on the stage of HIV disease. Early in HIV infection, when immunity is good, the signs of TB are similar to those in a child without HIV infection. As HIV infection progresses and immunity declines, dissemination of TB becomes more common. Tuberculous meningitis, miliary tuberculosis, and widespread tuberculous lymphadenopathy occur.

**Impact of TB on HIV**

In an individual infected with HIV, the presence of other infections, including TB, may allow HIV to multiply more quickly. This may result in more rapid progression of HIV infection and AIDS.

**Suggestions for further reading**


HIV/AIDS

AIDS case definitions for surveillance

HIV-related Tuberculosis
W HO has declared that TB is a global emergency, because TB is out of control in many parts of the world. The following are the main reasons why TB is out of control:

a) governments in many parts of the world have neglected the disease;
b) inadequate TB control programmes have led to an increased burden of disease (inadequately treated TB patients live longer with chronic disease and infect other people) and the emergence of drug-resistant TB;
c) high rates of population growth have contributed to an increased number of TB cases;
d) the HIV epidemic has led to an enormous increase in the number of TB cases, in places where HIV and TB are both common.

W HO has developed a new framework of strategy and policy for TB control in response to this global emergency. This strategy and policy is unchanged in the face of the epidemic of TB/HIV co-infection. It is vital for successful TB control for health care workers to treat TB patients within this framework in a National TB Programme (NTP).

The framework consists of the following:

1. Overall objectives of TB control.
2. Strategy for TB control.
3. Targets for TB control.
4. TB control policy package.
5. Key operations of a national TB programme.
6. Indicators to measure progress in TB control.

To reduce mortality, morbidity and disease transmission (while avoiding the development of drug resistance).
Strategy for TB control

To provide short-course chemotherapy under direct observation to, at least, all identified smear-positive TB cases (the sources of infection).

Targets for TB control

a) To cure 85% of new detected cases of sputum smear-positive PTB.
A national TB programme which achieves at least an 85% cure rate in patients with sputum smear-positive PTB has the following impact on TB:
   i) TB prevalence and the rate of TB transmission both decrease immediately;
   ii) TB incidence decreases gradually;
   iii) there is less acquired drug resistance (which makes future treatment of TB easier and more affordable).

b) To detect 70% of existing cases of sputum smear-positive PTB
It is important to expand case-finding only when a national TB programme has achieved a high cure rate. A national TB programme which has a low cure rate makes the TB problem worse:
   i) there are more cases of sputum smear-positive PTB treatment failure;
   ii) transmission of acquired drug-resistance increases.
A treatable epidemic becomes an untreatable epidemic.

AN EFFECTIVE NTP HAS A HIGH CURE RATE AND A LOW LEVEL OF ACQUIRED DRUG RESISTANCE.

In the presence of a high cure rate, increased case detection of sputum smear-positive PTB cases will decrease TB transmission.

TB control policy package

The success of the WHO strategy depends on the implementation of a 5-point package:

   i) government commitment to a national TB programme;
   ii) case detection through “passive” case-finding (sputum smear microscopy for PTB suspects);
   iii) short-course chemotherapy for all smear-positive PTB cases (under direct observation for, at least, the initial phase of treatment);
   iv) regular, uninterrupted supply of all essential anti-TB drugs;
   v) monitoring system for programme supervision and evaluation.
1) NTP has a central unit.

2) NTP manual.

3) A recording and reporting system using standardised registers.

4) A training programme covering all aspects of the policy package.

5) Medical services nationwide.

6) Treatment services integrated with existing health services, with priority for supervised short-course chemotherapy.

7) Regular supply of drugs and diagnostic materials.

8) Plan of supervision.

9) A project development plan, with details of budget, sources of funding and responsibilities.

Indicators to measure NTP progress in TB control.

1) NTP manual (reflects government commitment).

2) The number of administrative areas in the country which are implementing the new TB control strategy.

3) The cure rate.

4) The case detection rate.

What is directly observed therapy?
To ensure the treatment cures the patient, we have to ensure patient adherence to the treatment. Patient adherence to short-course chemotherapy means the patient takes every dose of the recommended treatment regimen. It is difficult for a patient to adhere to anti-TB treatment for 8 months. It is difficult to predict which TB patients will adhere to self-administered treatment. Therefore one certain way to ensure patient adherence to treatment is direct observation of therapy (DOT). This means that a supervisor watches the patient swallowing his tablets. The NTP trains and monitors the supervisors.

Directly observed therapy as close to the patient's home as possible
A TB patient is unlikely to adhere to treatment if he has far to go for treatment. One of the aims of a TB programme is to organise TB services so that the patient has TB treatment as close to home as possible. A TB
programme brings TB treatment to TB patients wherever they live. Many TB patients live close to a health facility (e.g. health centre, district hospital). For these patients, the supervisor of directly observed therapy will therefore be one of the health staff in the health facility. Some TB patients live far away from a health facility. For these patients, the supervisor will be a trained local community member or health outreach worker. Some areas have HIV/AIDS community care schemes. The HIV/AIDS home care providers with suitable training and supervision can administer directly observed therapy.

Integration of TB treatment services with general health services

In the past, some TB programmes have relied only on special TB hospitals and clinics, separate from the general health services. The big problem with that system is that many TB patients live far from TB hospitals and clinics. One reason why TB is out of control in many countries is because TB patients do not have access to TB diagnosis and treatment services. A successful NTP brings TB diagnosis and treatment services to the TB patients. This is why TB treatment services are integrated with existing health services.

SUGGESTIONS FOR FURTHER READING


CHAPTER 3  THE DIAGNOSIS OF TUBERCULOSIS IN ADULTS

3 1  PULMONARY TB

3 1 1  Diagnostic approach

The highest priority for TB control is the identification and cure of the infectious cases, i.e. patients with sputum smear-positive PTB. Therefore all patients (regardless of HIV status) with clinical features suspicious of PTB must submit sputum for diagnostic sputum smear microscopy. Most TB suspects are ambulatory. The diagnosis of PTB is therefore usually on an outpatient basis. A few TB suspects are severely ill and/or bed-bound and therefore need investigation as in-patients.

Clinical screening by assessment of symptoms identifies PTB suspects among patients attending health facilities. The most cost-effective method of screening PTB suspects in high-prevalence countries is by sputum smear microscopy. When a suspect has a positive sputum smear, he has sputum smear-positive PTB. Register him with the district TB officer and start treatment. In most cases, a chest X-ray is unnecessary.

In populations with a high TB prevalence, the tuberculin skin test is of little value in the diagnosis of TB in adults. A positive tuberculin skin test does not by itself distinguish M. tuberculosis infection from tuberculosis disease. Previous exposure to environmental mycobacteria may also result in a false-positive test result. Conversely, the tuberculin skin test result may be negative, even when the patient does have TB. Conditions often associated with a false-negative tuberculin skin test include HIV infection, severe malnutrition and miliary TB.

3 1 2  Clinical features

Symptoms
The most important symptoms in the diagnosis of PTB are the following:

- cough > 3 weeks
- sputum production
- weight loss
Over 90% of patients with sputum smear-positive PTB develop a cough soon after disease onset. However, cough is not specific to PTB. Cough is common in smokers and in patients with acute upper or lower respiratory tract infection. Most acute respiratory infections resolve within 3 weeks. Therefore a patient with a cough for more than 3 weeks is a PTB suspect and must submit sputums for diagnostic microscopy.

Patients with PTB may also have other symptoms. These may be respiratory or constitutional (general or systemic).

Respiratory: haemoptysis, chest pain, breathlessness
Constitutional: fever/night sweats, tiredness, loss of appetite

Weight loss and fever are more common in HIV-positive PTB patients than in those who are HIV-negative. Conversely, cough and haemoptysis are less common in HIV-positive PTB patients than in those who are HIV-negative. This is probably because there is less cavitation, inflammation and endobronchial irritation in HIV positive patients.

**Physical signs**
The physical signs in patients with PTB are non-specific. They do not help to distinguish PTB from other chest diseases.

**PTB suspects (patients with suggestive symptoms)** must submit sputums for sputum smear microscopy.

**PRACTICAL POINT**

**Diagnostic sputum smear microscopy**

**Collection of sputum samples**
A PTB suspect should submit 3 sputum samples for microscopy. The chances of finding tubercle bacilli are greater with 3 sputum samples than with 2 samples or 1 sample. Secretions build up in the airways overnight. So an early morning sputum sample is more likely than a sample later in the day to contain tubercle bacilli. It may be difficult for an outpatient to provide 3 early morning sputum samples. Therefore in practice an outpatient usually provides sputum samples as follows:
day 1 . . . sample 1 . . Patient provides an “on the spot” sample under supervision when he presents to the health facility. Give the patient a sputum container to take home for an early morning sample the following morning.

day 2 . . . sample 2 . . Patient brings an early morning sample.

. . . . . . . sample 3 . . Patient provides another “on the spot” sample under supervision.

If a patient can’t produce a sputum sample, a nurse or physiotherapist may help him to give a good cough and bring up some sputum. An inpatient can provide 3 early morning sputum samples under supervision in hospital.

Terminology

Mycobacteria are “acid- and alcohol-fast bacilli” (AAFB), often shortened to “acid-fast bacilli” (AFB). The waxy coat of mycobacteria retains an aniline dye (e.g. carbol fuchsin) even after decolourisation with acid and alcohol.

Ziehl-Neelsen (Z-N) stain

This simple stain detects AFB. This is how to perform the Z-N stain:

• fix the smear on the slide
• cover the fixed smear with carbol fuchsin for 3 minutes
• heat, rinse with tap water, and decolourise with acid-alcohol for 3-5 seconds
• counter-stain with methylene blue for 30 seconds
• rinse again with tap water
• observe under the microscope (use the oil immersion lens (x100) and x6 or x8 eye-piece lens)

The bacilli appear as red, beaded rods, 2-4 µm long and 0.2-0.5 µm wide.

Fluorochrome stain

This is a different stain for tubercle bacilli. A special fluorescent
microscope is necessary. The fluorochrome stain is phenolic auramine or auramine-rhodamine. After acid-alcohol decolourisation and a methylene blue counterstain, the bacilli fluoresce bright yellow against a dark background. The advantage of this method is that it is possible to scan smears quickly under low magnification. It is important to re-check fluorochrome stain positive smears using the Z-N stain.

**Slide reporting**

The number of bacilli seen in a smear reflects disease severity and patient infectivity. Therefore it is important to record the number of bacilli seen on each smear. The table below shows the standard method of reporting.

<table>
<thead>
<tr>
<th>NUMBER OF BACILLI SEEN IN A SMEAR</th>
<th>RESULT REPORTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>no AFB per 100 oil immersion fields</td>
<td>0</td>
</tr>
<tr>
<td>1-9 AFB per 100 oil immersion fields</td>
<td>scanty</td>
</tr>
<tr>
<td>10-99 AFB per 100 oil immersion fields</td>
<td>+ (1+)</td>
</tr>
<tr>
<td>1-10 AFB per oil immersion field</td>
<td>++ (2+)</td>
</tr>
<tr>
<td>&gt;10 AFB per oil immersion field</td>
<td>+++ (3+)</td>
</tr>
</tbody>
</table>

The laboratory technician must examine all 3 sputum samples from each TB suspect. He must record the result of each sputum sample with the laboratory reference number in the laboratory register and on the sputum request form.

**Sensitivity of sputum smear microscopy**

Sputum smear microscopy for tubercle bacilli is positive when there are at least 10,000 organisms present per 1 ml of sputum.

**Sputum microscopy in HIV infection**

Sputum smear positivity rates in TB/HIV patients depend on the degree of immunocompromise, as shown below.

<table>
<thead>
<tr>
<th>DEGREE OF IMMUNOCOMPROMISE</th>
<th>LIKELIHOOD OF POSITIVE SPUTUM SMEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>similar to HIV-negative patient</td>
</tr>
<tr>
<td>severe</td>
<td>decreased (decreased inflammation in lungs)</td>
</tr>
</tbody>
</table>

**False positive results of sputum smear microscopy**

A false positive result means that the sputum smear result is positive even though the patient does not really have sputum smear-positive PTB. This may arise because of the following: red stain retained by scratches on the slide;
accidental transfer of AFBs from a positive slide to a negative one; contamination of the slide or smear by environmental mycobacteria; various particles that are acid-fast (e.g. food particles, precipitates, other micro-organisms).

**False negative results of sputum smear microscopy**
A false negative result means that the sputum smear result is negative even though the patient really does have sputum smear-positive PTB. This may arise because of problems in collecting, processing, or interpreting sputum smears, or because of administrative errors.

**Causes of false negative results of sputum smear microscopy**

<table>
<thead>
<tr>
<th>TYPE OF PROBLEM</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>sputum collection</td>
<td>patient provides inadequate sample</td>
</tr>
<tr>
<td></td>
<td>inappropriate sputum container used</td>
</tr>
<tr>
<td></td>
<td>sputum stored too long before smear microscopy</td>
</tr>
<tr>
<td>sputum processing</td>
<td>faulty sampling of sample for smear</td>
</tr>
<tr>
<td></td>
<td>faulty smear preparation and staining</td>
</tr>
<tr>
<td>sputum smear interpretation</td>
<td>inadequate time spent examining smear</td>
</tr>
<tr>
<td></td>
<td>inadequate attention to smear (poor motivation)</td>
</tr>
<tr>
<td>administrative errors</td>
<td>mis-identification of patient</td>
</tr>
<tr>
<td></td>
<td>incorrect labelling of sample</td>
</tr>
<tr>
<td></td>
<td>mistakes in documentation</td>
</tr>
</tbody>
</table>

**Differential diagnosis of pulmonary TB**

A PTB suspect with 3 negative sputum smears may not have PTB at all. Reassess the patient in case he has a condition mistaken for PTB.
The table shows the differential diagnosis of PTB.

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Pointers to the Correct Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>congestive cardiac failure</td>
<td>symptoms of heart failure (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, haemoptysis, oedema, epigastric discomfort from hepatic congestion) signs of heart failure</td>
</tr>
<tr>
<td>left ventricular failure</td>
<td></td>
</tr>
<tr>
<td>asthma</td>
<td>intermittent symptoms, generalised expiratory wheezes</td>
</tr>
<tr>
<td>chronic obstructive airways disease</td>
<td>risk factor (smoking), chronic symptoms, prominent dyspnoea, generalised wheezes</td>
</tr>
<tr>
<td>bronchiectasis</td>
<td>large amounts of purulent sputum</td>
</tr>
<tr>
<td>bronchial carcinoma</td>
<td>risk factor (smoking)</td>
</tr>
<tr>
<td>other infections, e.g.</td>
<td></td>
</tr>
<tr>
<td>bacterial pneumonia</td>
<td>response to antibiotic</td>
</tr>
<tr>
<td>lung abscess</td>
<td>abscess with fluid level on chest X-ray</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>dyspnoea prominent</td>
</tr>
</tbody>
</table>

**Practical Point**

If a patient is breathless, has continuing haemoptyses, and has negative sputum smears, listen carefully for a low-pitched, rumbling, mid-diastolic murmur in case he has mitral stenosis with pulmonary oedema.

**INDICATIONS FOR CHEST X-RAY**

**Positive sputum smear**

The first screening test for PTB suspects is sputum smear microscopy. In most cases of sputum smear-positive PTB a chest X-ray is unnecessary. In those few cases of sputum smear-positive PTB when a chest X-ray is necessary, the indications are as follows:
a) suspected complications in the breathless patient, needing specific treatment, e.g. pneumothorax, pericardial effusion or pleural effusion - positive sputum smear is rare;
b) frequent or severe haemoptysis (to exclude bronchiectasis or aspergilloma);
c) only 1 sputum smear positive out of 3 (in this case, an abnormal chest X-ray is a necessary additional criterion for the diagnosis of sputum smear-positive PTB).

**Negative sputum smears**
Re-assess the patient who continues to cough despite a course of broad-spectrum antibiotic, and who has had 3 negative sputum smears. It is often worthwhile repeating the sputum smears after 2 weeks. If you still suspect TB despite negative sputum smears, the patient needs a chest X-ray.

### Patterns of disease in PTB

#### PRATICAL POINT

No chest X-ray pattern is absolutely typical of PTB.

The table shows the so-called "classical" and "atypical" patterns. The classical pattern is more common in HIV-negative patients. The atypical pattern is more common in HIV positive-patients.

<table>
<thead>
<tr>
<th>CLASSICAL PATTERN</th>
<th>ATYPICAL PATTERN</th>
</tr>
</thead>
<tbody>
<tr>
<td>upper lobe infiltrates</td>
<td>interstitial infiltrates</td>
</tr>
<tr>
<td>bilateral infiltrates</td>
<td>(especially lower zones)</td>
</tr>
<tr>
<td>cavitation</td>
<td>no cavitation</td>
</tr>
<tr>
<td>pulmonary fibrosis and shrinkage</td>
<td>no abnormalities</td>
</tr>
</tbody>
</table>

#### PRATICAL POINT

Chest X-ray changes in TB/ HIV patients reflect the degree of immunocompromise. In mild immunocompromise, the appearance is often classical (with cavitation and upper lobe infiltrates). In severe immunocompromise, the appearance is often atypical.
The chest X-ray findings associated with PTB are non-specific. Diseases other than PTB can cause both the “classical” and the “atypical” chest X-ray findings.

The vast majority of patients (over 90%) with cavitary PTB are sputum smear-positive. Therefore, a patient with cavities on chest X-ray and repeated negative sputum smears probably has a disease other than PTB.

The table shows the differential diagnosis of chest X-ray findings often associated with PTB.

<table>
<thead>
<tr>
<th>CHEST X-RAY FINDING</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cavitation</td>
<td>infections</td>
</tr>
<tr>
<td></td>
<td>some bacterial pneumonias</td>
</tr>
<tr>
<td></td>
<td>lung abscess</td>
</tr>
<tr>
<td></td>
<td>some fungal infections</td>
</tr>
<tr>
<td></td>
<td>non-infectious disease</td>
</tr>
<tr>
<td></td>
<td>bronchial carcinoma</td>
</tr>
<tr>
<td></td>
<td>connective tissue disease</td>
</tr>
<tr>
<td></td>
<td>occupational lung disease</td>
</tr>
<tr>
<td>unilateral infiltration</td>
<td>pneumonia</td>
</tr>
<tr>
<td></td>
<td>bronchial carcinoma</td>
</tr>
<tr>
<td>bilateral infiltration</td>
<td>pneumonia</td>
</tr>
<tr>
<td></td>
<td>connective tissue disease</td>
</tr>
<tr>
<td></td>
<td>occupational lung disease</td>
</tr>
<tr>
<td></td>
<td>sarcoidosis</td>
</tr>
<tr>
<td>mediastinal lymphadenopathy</td>
<td>lymphoma</td>
</tr>
<tr>
<td></td>
<td>bronchial carcinoma</td>
</tr>
<tr>
<td></td>
<td>sarcoidosis</td>
</tr>
</tbody>
</table>
This is a common, and often difficult, diagnostic problem. Several diseases in HIV-positive individuals may present in a similar way with cough, fever, sometimes chest signs, and chest X-ray shadowing. In each case it is important to make a careful clinical assessment and send sputum samples for AFBs if the patient has had cough for 3 weeks or more.

**Acute bacterial pneumonia**
This is common in HIV-positive patients. The shorter history usually differentiates pneumonia from PTB. The most common pathogen is *Streptococcus pneumoniae*. Regardless of HIV status, acute bacterial pneumonia usually responds well to standard treatment with penicillin, co-trimoxazole or ampicillin.

If pneumonia fails to respond to standard antibiotics, consider other pathogens, e.g. *M. tuberculosis*.

**Kaposi’s sarcoma (KS)**
The clinical recognition of KS is straightforward when there are typical lesions on the skin and mucous membranes. The diagnosis of pulmonary or pleural KS is more difficult. The patient usually presents with cough, fever and dyspnoea, and usually has KS elsewhere. Chest X-ray shows a diffuse nodular infiltrate or pleural effusion. The pleural fluid is usually blood-stained. Cytology may provide the diagnosis. It can be difficult to rule out concurrent PTB.

**Pneumocystis carinii pneumonia (PCP)**
PCP is less common in sub-Saharan Africa than in HIV positive populations elsewhere. The patient usually presents with dry cough and progressive dyspnoea. The table below shows the clinical and chest X-ray features which help to distinguish PCP from PTB.
Clinical and chest X-ray features of PCP in contrast with TB

<table>
<thead>
<tr>
<th></th>
<th>TYPICAL OF PCP</th>
<th>TYPICAL OF TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPTOMS</td>
<td>dry cough</td>
<td>productive cough</td>
</tr>
<tr>
<td></td>
<td>sputum mucoid if any</td>
<td>purulent sputum</td>
</tr>
<tr>
<td></td>
<td>dyspnoea</td>
<td>pleuritic chest pain, haemoptysis</td>
</tr>
<tr>
<td>SIGNS</td>
<td>normal</td>
<td>signs of consolidation</td>
</tr>
<tr>
<td></td>
<td>fine inspiratory crackles</td>
<td>signs of pleural effusion</td>
</tr>
<tr>
<td>CHEST X-RAY</td>
<td>bilateral diffuse</td>
<td>lobar consolidation</td>
</tr>
<tr>
<td></td>
<td>interstitial shadowing</td>
<td>cavitation</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td>pleural effusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intrathoracic lymphadenopathy</td>
</tr>
</tbody>
</table>

The definitive diagnosis of PCP rests on finding the cysts in induced sputum, broncho-alveolar lavage or biopsy specimens. These investigations are often unavailable in district hospitals. The diagnosis therefore depends on the clinical and chest X-ray features, exclusion of TB and response to a trial of high-dose cotrimoxazole.

Other conditions

Two other rare conditions are cryptococcosis and nocardiosis. They may present in a similar way to TB. The diagnosis of pulmonary cryptococcosis rests on finding the fungal spores in sputum smears. Nocardiosis may be particularly difficult to differentiate from TB. The chest X-ray often shows upper lobe, cavitary infiltrates. The organism may also stain weakly acid-fast. Associated soft-tissue and brain abscesses raise clinical suspicion. The diagnosis rests on finding beaded and branching Gram positive rods on sputum smear.

EXTRAPULMONARY TB

The common forms of extrapulmonary TB associated with HIV are the following: lymphadenopathy, pleural effusion, pericardial disease, miliary, meningitis.

Patients usually present with constitutional features (fever, night sweats, weight loss) and local features related to the site of disease. The local features related to the site of disease are similar in adults and children.
THE DIAGNOSIS OF TUBERCULOSIS IN ADULTS

Diagnostic approach

Extrapulmonary TB is common in HIV-positive patients. Many patients with extrapulmonary TB also have co-existent pulmonary TB.

PRACTICAL POINT

If a patient has extrapulmonary TB, look for pulmonary TB. Send sputum samples for AFBs and, if sputum AFBs are negative, do a chest X-ray.

Definitive diagnosis of extrapulmonary TB is often difficult. Diagnosis may be presumptive, provided you can exclude other conditions. The degree of certainty of diagnosis depends on the availability of diagnostic tools, e.g. specialised X-rays, biopsy procedures.

Tuberculous lymphadenopathy

Regardless of HIV status, the lymph nodes most commonly involved are the cervical nodes. The usual course of lymph node disease is as follows:

- firm, discrete nodes
- fluctuant nodes matted together
- skin breakdown, abscesses, chronic sinuses
- healing with scarring

PRACTICAL POINT

In severe immunocompromise, tuberculous lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis.

The differential diagnosis of tuberculous lymphadenopathy includes the following: persistent generalised lymphadenopathy (PGL), lymphoma, Kaposi’s sarcoma, carcinomatous metastases, sarcoid, drug reactions (e.g. phenytoin).

Persistent generalised lymphadenopathy (PGL)

PGL is a feature of HIV infection which develops in up to 50% of HIV-infected individuals. There is no specific treatment. The diagnostic criteria for PGL are as follows:
lymph nodes larger than 1 cm in diameter
in 2 or more extra-inguinal sites
for 3 or more months duration

The nodes are non-tender, symmetrical, and often involve the posterior cervical and epitrochlear nodes. PG L may slowly regress during the course of HIV infection and may disappear before the onset of AIDS. In populations with a high HIV prevalence, PG L is the commonest cause of lymphadenopathy. In HIV-positive individuals PG L is a clinical diagnosis. Only investigate further if there are features of another disease. The table below shows the features of lymph nodes which indicate further investigation, including biopsy.

**Features of lymph nodes which indicate further investigation**
- large (> 4 cm diameter) or rapidly growing lymph nodes,
- asymmetrical lymphadenopathy,
- tender/painful lymph nodes not associated with local infection,
- matted/fluctuant lymph nodes,
- obvious constitutional features (e.g. fever, night sweats, weight loss),
- hilar or mediastinal lymphadenopathy on chest X-ray.

**Practical approach to investigation of lymphadenopathy**
(if clinical features suggest a cause of lymphadenopathy other than PG L).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Test</th>
<th>Result</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle aspirate of lymph node</td>
<td>look at material aspirated</td>
<td>caseation</td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td>smear for AFBs</td>
<td>AFBs present</td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td>smear for cytology</td>
<td>malignant cells seen</td>
<td>malignancy</td>
</tr>
<tr>
<td></td>
<td>e.g. KS, lymphoma, carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>if no diagnosis after aspirate</td>
<td>look at cut surface</td>
<td>caseation</td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td>smear from cut surface</td>
<td>AFBs seen</td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td>fresh node sent for TB culture</td>
<td>positive TB culture</td>
<td>TB</td>
</tr>
<tr>
<td>lymph node biopsy</td>
<td>node in formalin for histology</td>
<td>granuloma and AFBs</td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>malignant cells</td>
<td>malignancy</td>
</tr>
</tbody>
</table>
Diagnosis of tuberculous lymphadenopathy is possible even without laboratory facilities for histology or TB culture. Diagnostic sensitivity of tuberculous lymphadenopathy by aspirate and smear for AFBs is 70%. Diagnostic sensitivity increases to 80% if you excise a lymph node, look at the cut surface, and do a smear for AFBs.

The histological appearance of tuberculous lymph nodes from HIV positive patients depends on the degree of immunocompromise, as shown below.

<table>
<thead>
<tr>
<th>DEGREE OF IMMUNOCOMPROMISE</th>
<th>HISTOLOGICAL APPEARANCE OF LYMPH NODES</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>caseating lesions with few or no AFBs</td>
</tr>
<tr>
<td>severe</td>
<td>little cellular reaction with many AFBs</td>
</tr>
</tbody>
</table>

**Miliary TB**

Miliary TB results from widespread blood-borne dissemination of TB bacilli. This is either the consequence of a recent primary infection or the erosion of a tuberculous lesion into a blood vessel.

**Clinical features**

The patient presents with constitutional features. He may have hepatosplenomegaly and choroidal tubercles (fundoscopy). Miliary TB is an underdiagnosed cause of end-stage wasting in HIV-positive individuals.

**Diagnosis**

Chest X-ray shows diffuse, uniformly distributed, small miliary shadows. "Miliary" means "like small millet seeds". Full blood count may show pancytopenia. Liver function tests may be abnormal. Bacteriological confirmation is sometimes possible from sputum, C.S.F., or bone marrow.

**Differential diagnosis**

The differential diagnosis includes the following: slim disease, bacteraemia (including typhoid fever), disseminated carcinoma, disseminated infection with "atypical" mycobacteria, trypanosomiasis (in endemic regions).

**Tuberculous serous effusions**

Inflammatory tuberculous effusions may occur in any of the serous cavities of the body, i.e. pleural, pericardial or peritoneal cavities. They are a more common form of TB in HIV-positive than in HIV-negative individuals.
**Approach to diagnosis**
The presentation is usually with constitutional and local features. Microscopy of the aspirate from tuberculous serous effusions rarely shows AFBs because the fluid forms as an inflammatory reaction to TB lesions in the serous membrane. TB culture, even if available, is of no immediate help. A culture result usually takes 4-6 weeks. The white cell content is variable, usually with predominant lymphocytes and monocytes. The aspirate is an exudate (i.e. protein content is more than 30 g/l).

**PRACTICAL POINT**
A biochemistry laboratory is not essential to diagnose an exudate. Simply leave the aspirate standing: if it clots, it is an exudate.

In high HIV prevalence populations in sub-Saharan Africa, TB is the commonest cause of an exudative serous effusion. The diagnosis is usually presumptive (i.e. without microbiological or histological confirmation). It is important to exclude other causes of an exudate.

**PRACTICAL POINT**
Interpret with caution the laboratory result of protein concentration in any aspirated fluid. If there has been a delay in laboratory analysis, a protein clot may have formed in the sample. The laboratory result may be falsely low.

**TUBERCULOUS PLEURAL EFFUSION**
The clinical and chest X-ray diagnosis of a pleural effusion is straightforward. The typical clinical features are constitutional and local (chest pain, breathlessness; tracheal and mediastinal shift away from the side of the effusion; decreased chest movement, percussion note and breath sounds on the side of the effusion). Chest X-ray shows unilateral, uniform white opacity, often with a concave upper border. If available, ultrasound confirms the presence of fluid in the pleural space in case of doubt.

Always perform diagnostic pleural aspiration if a patient has a pleural effusion. The fluid is usually straw-coloured. The white cell count is usually
high (about 1,000 - 2,500 per mm³) with predominant lymphocytes. Occasionally the fluid is blood-stained. The presence of pus on aspiration indicates an empyema (purulent effusion).

**PRACTICAL POINT**

In a hospital with limited facilities serving a high TB prevalence population you should treat a patient with a unilateral exudative pleural effusion with anti-TB drugs.

If facilities are available, closed pleural biopsy using an Abrams needle is useful for histological diagnosis. Since the distribution of TB lesions in the pleura is patchy, the diagnostic yield of closed pleural biopsy is about 75%. Multiple biopsies increase the diagnostic yield. A small open pleural biopsy increases the yield even further but is not usually necessary.

**Differential diagnosis**

The differential diagnosis of an exudative pleural effusion includes malignancy, postpneumonic effusion, pulmonary embolism and amoebic liver abscess (extending on the right).

**TUBERCULOUS EMPYEMA**

This usually arises when a tuberculous cavity in the lung ruptures into the pleural space. The physical signs are those of a pleural effusion, but aspiration reveals thick white/yellow pus. If the pus is too thick to remove using a needle and syringe, use an intercostal drain. Send the pus to the laboratory for examination for TB and also for Gram stain and bacterial culture. If facilities are available, closed pleural biopsy is useful for histological diagnosis.

The main differential diagnosis is bacterial empyema, when the patient is usually more acutely ill and toxic. It may be possible to confirm bacterial empyema by Gram stain and/or culture of the aspirated pus.

A succussion splash is a splashing sound heard with the stethoscope while shaking the patient's chest. A succussion splash indicates a pyopneumothorax (pus and air in the pleural space). After chest X-ray confirmation, insert a chest drain with underwater seal.
Always test a patient with signs of a pleural effusion for a succussion splash.

**TUBERCULOUS PERICARDIAL EFFUSION**

**Diagnosis**
The diagnosis usually rests on suggestive constitutional and cardiovascular features and investigation findings (ECG, chest X-ray and echocardiography). It is important to exclude uraemia and Kaposi’s sarcoma.

**Cardiovascular symptoms**
- chest pain
- shortness of breath
- cough
- dizziness and weakness (low cardiac output)
- leg swelling
- right hypochondrial pain (liver congestion)
- abdominal swelling (ascites)

**Cardiovascular signs**
- tachycardia
- low blood pressure
- pulsus paradoxus
- raised jugular venous pressure (JVP) with small amplitude “a” and “v” waves
- impalpable apex beat
- quiet heart sounds
- pericardial friction rub
- signs of rightsided heart failure (e.g. hepatomegaly, ascites, oedema)

The signs may be subtle. Assess carefully any patient with oedema and/ or ascites with the possibility of pericardial effusion in mind.
**Chest X-ray**
- large globular heart
- clear lung fields
- pleural fluid

**ECG**
- tachycardia
- ST and T wave changes
- low voltage QRS complexes

**Echocardiography**
- pericardial fluid
- strands crossing between visceral and parietal pericardium

**Pitfalls in diagnosis of pericardial effusion**
Clinicians have misdiagnosed pericardial effusion as the following:
- congestive cardiac failure;
- hepatoma or amoebic liver abscess (enlarged liver);
- bilateral pleural effusions.

**Pericardiocentesis**
This is only safe under the following conditions:
- echocardiography has confirmed a moderate to large pericardial effusion;
- the operator is experienced.

Therapeutic pericardiocentesis is necessary if there is cardiac tamponade (acute life-threatening cardiac impairment).

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**PRACTICAL POINT**

In high TB/ HIV prevalence populations, TB is the most likely treatable cause of pericardial effusion. It may be safer for the patient to start presumptive anti-TB treatment rather than undergo diagnostic pericardiocentesis.

Treatment with steroids and anti-TB drugs, without pericardiocentesis, usually results in satisfactory resolution of tuberculous pericardial effusion.
**Outcome**

A possible complication despite TB cure is the development of pericardial constriction. Medical management of heart failure due to pericardial constriction helps in some cases. A surgeon may weigh up the possible benefit to the patient of pericardiectomy, set against the operative risks.

**Differential diagnosis**

Apart from TB, the differential diagnosis of pericardial effusion includes the following:

- **Transudates**: uraemia, heart failure, liver failure
- **Exudates**: malignancy, bacterial pericardial empyema, inflammatory diseases, hypothyroidism

**Tuberculous ascites**

Ascites results from peritoneal TB. Routes of spread of TB to the peritoneum include the following:

- a) from tuberculous mesenteric lymph nodes;
- b) from intestinal TB (pulmonary TB patients may develop intestinal ulcers and fistulae as a result of swallowing infected sputum);
- c) blood-borne.

**Clinical features**

Patients present with constitutional features and ascites. There may be palpable abdominal masses (mesenteric lymph nodes). Adhesion of nodes to bowel may cause bowel obstruction. Fistulae may develop between bowel, bladder and abdominal wall.

**Investigations**

Do a chest X-ray to look for associated PTB. Always do a diagnostic ascitic tap. The aspirated fluid is usually straw-coloured, but occasionally turbid or blood-stained. The fluid is an exudate, usually with more than 300 white cells per mm² and predominantly lymphocytes. Ultrasound, if available, may show features consistent with TB, including enlarged mesenteric or retroperitoneal lymph nodes.
An ill, wasted patient with TB ascites may have a low serum albumin concentration. In this case, the usual threshold of 30 g/l albumin concentration for diagnosing an exudate is too high. Instead, calculate the difference between the albumin concentrations in serum and ascites. A serum-ascites albumin difference of less than 11 g/l means that the ascites is an exudate.

**Diagnosis**
The diagnosis is usually presumptive. Definitive diagnosis rests on a peritoneal biopsy, available in some hospitals. Blind percutaneous needle biopsy of the peritoneum has a low pick-up rate and a high complication rate. In experienced hands, laparoscopy under local anaesthetic has a high pick-up rate. Laparoscopy enables direct visualisation and biopsy of peritoneal TB lesions. Laparotomy will confirm the diagnosis in nearly every case but is too invasive for routine use.

**Differential diagnosis**
Apart from tuberculosis, the differential diagnosis of ascites includes the following:

**TRANSUDATES**
- heart failure
- renal failure
- nephrotic syndrome
- liver failure
- hypoproteinaemia

**EXUDATES**
- malignancy
- other infections causing peritonitis.

### Tuberculous meningitis

Routes of spread of TB to the meninges include the following:

a) from rupture of a cerebral tuberculoma into the subarachnoid space;
b) blood-borne.

**Clinical features**
The patient may present with constitutional features and a chronic meningitis. There is gradual onset and progression of headache and decreased consciousness. Examination often reveals neck stiffness and a
positive Kernig’s sign. Cranial nerve palsies result from exudate around the base of the brain. Tuberculomas and vascular occlusion may cause focal neurological deficits and seizures. Obstructive hydrocephalus may develop. Spinal meningeal involvement causes paraplegia (spastic or flaccid).

**Diagnosis**

The diagnosis usually rests on clinical grounds and cerebrospinal fluid (C.S.F.) examination. In most cases of clinically suspected TB meningitis, lumbar puncture is safe.

**PRACTICAL POINT**

Lumbar puncture is hazardous if the patient has a focal neurological deficit (cerebral space-occupying lesion) or if fundoscopy shows papilloedema (raised intra-cranial pressure). In these circumstances, a C.A.T. brain scan is helpful, if available. Otherwise, it may be safer to start presumptive treatment with anti-TB drugs rather than risk lumbar puncture.

The C.S.F. opening pressure is high. The C.S.F. may look clear or cloudy. The white cell count is usually about 500 per mm$^3$ with predominantly lymphocytes (or early in the course of infection, predominantly polymorphs). Usually the protein level is high and the glucose low. C.S.F microscopy shows AFBs in a minority of cases. It is possible to increase the diagnostic pick-up rate by the following:

a) examine the deposit on centrifugation of a 10 ml C.S.F. sample;

b) examine the deposit for at least half an hour before reporting it as negative;

c) examine several C.S.F samples obtained over a few days.

**PRACTICAL POINT**

Always exclude cryptococcal meningitis by C.S.F. microscopy (India ink stain) and, if available, fungal culture.
**Difficulties in interpreting C.S.F. findings**

Some of the C.S.F. findings may be normal, especially in HIV positive patients. The percentages of HIV-positive TB meningitis patients with normal C.S.F. findings are as follows: glucose 15%, protein 40%, white cell count 10%.

**Differential diagnosis**

The table below shows the differential diagnosis of TB meningitis, with typical C.S.F. abnormal findings.

### Differential diagnosis of tuberculous meningitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>CSF White Cells</th>
<th>Protein</th>
<th>Glucose</th>
<th>Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>tuberculous meningitis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Decreased</td>
<td>AFB (in some cases)</td>
</tr>
<tr>
<td>cryptococcal meningitis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Decreased</td>
<td>Positive India ink staining</td>
</tr>
<tr>
<td>partially treated bacterial meningitis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Decreased</td>
<td>Bacteria on Gram stain (rarely)</td>
</tr>
<tr>
<td>viral meningitis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal (low in mumps or H. simplex)</td>
</tr>
<tr>
<td>acute syphilis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Normal</td>
<td>Motile trypanosomes</td>
</tr>
<tr>
<td>late stage trypanosomiasis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Decreased</td>
<td>Cytology shows malignant cells</td>
</tr>
<tr>
<td>tumour (carcinoma/lymphoma)</td>
<td>Elevated</td>
<td>Increased</td>
<td>Decreased</td>
<td>Leptospires</td>
</tr>
<tr>
<td>leptospirosis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Decreased</td>
<td>Amoebae</td>
</tr>
<tr>
<td>amoebic meningitis</td>
<td>Elevated</td>
<td>Increased</td>
<td>Decreased</td>
<td></td>
</tr>
</tbody>
</table>

PMN = polymorphonuclear leucocytes; L = lymphocytes

* common differential diagnoses
Other forms of extrapulmonary TB

Other forms of extrapulmonary tuberculosis are less common. There is no information as to whether they occur any more frequently in HIV-positive than in HIV-negative individuals. The table below shows the usual clinical features and diagnostic tests.

<table>
<thead>
<tr>
<th>SITE OF DISEASE</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>Back pain, Gibbus</td>
<td>Plain X-ray, Tissue biopsy</td>
</tr>
<tr>
<td></td>
<td>Psosas abscess, Radicular pain, Spinal cord compression</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Chronic osteomyelitis</td>
<td>Tissue biopsy</td>
</tr>
<tr>
<td>Peripheral joints</td>
<td>Usually monoarthritis</td>
<td>Plain X-ray, Synovial biopsy</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal mass, Diarrhoea</td>
<td>Barium X-rays</td>
</tr>
<tr>
<td>Liver</td>
<td>Right upper quadrant, pain and mass</td>
<td>Ultrasound and biopsy</td>
</tr>
<tr>
<td>Renal and urinary tract</td>
<td>Urinary frequency, Dysuria, Haematuria, pain / swelling</td>
<td>Sterile pyuria, Urine culture, Intravenous pyelogram</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>Features of hypoadrenalism, (hypotension, low serum sodium, normal/ high potassium, raised urea, low glucose)</td>
<td>Plain X-ray (calcification), Ultrasound</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>Hoarseness, Pain in ear, Pain on swallowing</td>
<td>Usually complication of pulmonary disease</td>
</tr>
<tr>
<td>Female genital tract</td>
<td>Infertility, Pelvic inflammatory disease, Ectopic pregnancy</td>
<td>Pelvic examination, X-ray genital tract, Tissue biopsy</td>
</tr>
<tr>
<td>Male genital tract</td>
<td>Epididymitis</td>
<td>Often evidence of renal/ urinary tract TB</td>
</tr>
</tbody>
</table>
Spinal TB.
Tuberculosis of the spine is important. The disastrous consequence for the patient of a missed diagnosis of thoracic or cervical spinal TB is paralysis. TB starts in an intervertebral disc, spreads along the anterior and longitudinal ligaments, then involves the adjacent vertebral bodies. In areas of high TB prevalence, plain X-ray of the spine is usually diagnostic. The typical appearance is erosion of the anterior edges of the superior and inferior borders of adjacent vertebral bodies. The disc space is narrowed. The sites most commonly involved are the lower thoracic, lumbar and lumbosacral.

The main differential diagnoses are malignancy and pyogenic spinal infections. Malignant deposits in the spine tend to erode the pedicles and spinal bodies, leaving the disc intact. Pyogenic infection tends to be more acute than TB with more severe pain.

Gastrointestinal TB.
Ileo-caecal TB may present with constitutional features, chronic diarrhoea, subacute obstruction, or a right iliac fossa mass. Diagnosis rests on barium examination of the small and large bowel, or on colonoscopy, if available. The differential diagnosis includes ileo-caecal Crohn’s disease, carcinoma of the caecum, appendix abscess, lymphoma, amoeboma and tubo-ovarian abscess.

Hepatic TB
Miliary TB may involve the liver. Hepatic TB can cause diagnostic confusion. Solitary or multiple TB abscess formation can mimic amoebic liver abscess. Nodular hepatic TB can mimic hepatoma. In these situations, ultrasound examination is useful. Liver biopsy, available in some hospitals, is diagnostic.

SUGGESTIONS FOR FURTHER READING
HOW DOES TB IN CHILDREN DIFFER FROM TB IN ADULTS?

Transmission of TB to children
The source of transmission of TB to a child is usually an adult (usually a family member) with sputum smear-positive PTB.

Public health importance
Cases of TB in children usually represent between 5-15% of all TB cases. The frequency of childhood TB in a given population depends on the following: the number of infectious cases, the intensity of transmission, and the age structure of the population. Children rarely have sputum smear-positive TB. So they are rarely infectious. TB in children is therefore due to failure of TB control in adults. Failure of TB control in adults means failure to cure the infectious cases (patients with sputum smear-positive PTB).

A good TB control programme is the best way to prevent TB in children.

The highest priority in TB control is to cure the infectious cases. Children are rarely infectious. However, it is still important to cure them! Good treatment of TB in childhood will result in the following: a) decreased morbidity and mortality; b) improved NTP credibility and reputation.

Risk of infection
Risk of infection depends on 2 factors: a) extent of exposure to infectious droplet nuclei, and b) susceptibility to infection. Consider an infant whose mother has sputum smear-positive PTB. The infant has a high risk of acquiring infection: he is in very close contact with his mother; his immune defences are poor. An infant with HIV infection has an even greater susceptibility to infection with tubercle bacilli.

Risk of progression of infection to disease.
The vast majority of HIV-negative children infected with M. tuberculosis do not develop TB disease. In these healthy, asymptomatic, but TB-infected children, the only evidence of infection may be a positive tuberculin skin
test. However, an infected child can develop TB disease at any time. The chance of developing disease is greatest shortly after infection and then steadily decreases as time goes by. Various physical or emotional stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance, especially by HIV infection. Other important triggers include the following: other infections (especially measles and whooping cough) and malnutrition.

**Pathogenesis**

The usual route of infection and early sequence of events in primary pulmonary infection are similar in adults and children. TB disease in children is usually primary TB. A child may have asymptomatic *M. tuberculosis* infection: the tubercle bacilli can lie dormant for many years. If the tubercle bacilli reactivate some years later, causing postprimary TB, the child has usually grown into an adult by then. The age when a child is infected determines the pattern of primary disease. Up to puberty, blood-borne spread is common. This results in disseminated (miliary and extrapulmonary) disease. After puberty, pulmonary spread is more common.

**PRACTICAL POINT**

Malnourished children may develop severe PTB at any age.

**APPRAOCH TO DIAGNOSIS**

If you find the diagnosis of TB in children easy, you are probably over-diagnosing TB. If you find the diagnosis of TB in children difficult, you are not alone. It is easy to overdiagnose TB in children. It is also easy to miss TB in children. Carefully assess all the evidence before making the diagnosis.

Adults with PTB usually present with cough and sputum. Although sputum culture is the definitive test, in practice the readily available usual "gold standard" test for adults with PTB is sputum smear microscopy. However, there is no such "gold standard" test in children. TB in children is a general disease which may appear in any part of the body. Also, under the age of 10 years, children with PTB rarely cough up sputum. They usually swallow their sputum. Gastric suction and laryngeal swabs are generally not useful unless facilities are available for *M. tuberculosis*.
The diagnosis of TB in children is therefore nearly always presumptive. This means that bacteriological confirmation is usually not possible. This situation in children is similar to that in adults with sputum smear-negative PTB or extrapulmonary TB.

The clinical features are constitutional and local (depending on the part of the body affected). The local clinical features related to the site of disease are similar in children and adults (see Chapter 3 for details). The diagnosis rests on consistent clinical features and investigation findings. If available, a tuberculin skin test may be helpful. In most cases of suspected PTB, the child has usually received treatment with a broad-spectrum antibiotic, with no clinical response. In some hospitals, helpful special diagnostic investigations may be available. These may include specialised X-rays, biopsy and histology, and TB culture.

Always look for the following 2 important clues to TB in children: 1) it is usually possible to identify the adult source of infection; 2) failure to thrive or weight loss (growth faltering). In the absence of these 2 clues, TB is less likely.

Ask the mother of a child with suspected TB for the child’s “road to health” card (growth card). Look at the card for growth faltering or weight loss.
### Score chart for the diagnosis of TB in children

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</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>local</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 symptoms of meningitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other deformity of spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE**
This is a controversial topic. In the past, some doctors have advocated a treatment trial with anti-TB drugs as a diagnostic manoeuvre. The idea is that if the child responds to treatment with anti-TB drugs, then the diagnosis is TB. There are some problems with this approach:

a) some anti-TB drugs also kill other bacteria, so response to anti-TB drugs may be because the child has another (bacterial) infection;
b) compliance with a “treatment trial” is often poor, because of the lack of certainty surrounding the decision to treat;
c) there may be a tendency to jump too quickly to a “treatment trial” without the necessary careful and thoughtful approach to diagnosis.

On account of these problems, it is better to try to come to a decision: yes, the child has TB; or, no, the child does not have TB. The process of coming to a decision is an active process. The process involves weighing up the clinical evidence and investigation findings, careful thought, and often a period of observation.

Tuberculin is a purified protein derived from tubercle bacilli. Thus, another name for tuberculin is PPD (Purified Protein Derivative). Following infection with M. tuberculosis, a person develops hypersensitivity to tuberculin. Tuberculin injected into the skin of an infected person produces a delayed local reaction after 24-48 hours. We quantify this reaction by measuring the diameter of skin induration (thickening) at the site of the reaction. Various conditions may suppress this reaction. The reaction indicates hypersensitivity. In other words, the reaction only shows that the person has at some time had infection with M. tuberculosis.

A tuberculin test does not measure immunity. By itself, it does not indicate the presence or extent of tuberculosis disease; it only indicates infection.

The technical details about tuberculins and how to administer and read a tuberculin test are beyond the scope of this book. “Clinical Tuberculosis” (Crofton, Horne and Miller) gives a good account.
**Value of a negative tuberculin test**
A tuberculin test is negative when the diameter of skin induration is less than 10 mm. This is regardless of whether or not the person has had BCG. A negative tuberculin skin test does not exclude TB. In other words, a negative test is of no help in deciding that someone does not have TB. The table shows the conditions which may suppress a tuberculin skin test in a person with active TB.

**Conditions which may suppress the tuberculin skin test**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Severe bacterial infections, including TB itself</td>
</tr>
<tr>
<td>Viral infections, e.g. measles, chickenpox, glandular fever</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Immunosuppressive drugs, e.g. steroids</td>
</tr>
</tbody>
</table>

**Value of a positive tuberculin skin test**
The criterion for a positive tuberculin test depends on whether a child has previously had BCG vaccination or not. This is because a reaction to tuberculin is usual after a previous BCG, at least for several years. This reaction is usually a weaker reaction (diameter often less than 10 mm) than the reaction to natural infection with M. tuberculosis. Therefore, in a child who has not had BCG, a tuberculin test is positive when the diameter of skin induration is 10 mm or more. In a child who has had BCG, a test is positive when the diameter of induration is 15 mm or more. A positive tuberculin test is only one piece of evidence in favour of the diagnosis of TB. The younger the child and the greater the diameter of induration (above 10-15 mm), the stronger is that one piece of evidence.

**The impact of HIV on the diagnosis of TB in children**
HIV makes the diagnosis of TB in children even more difficult than usual, for the following reasons:

a) Several HIV-related diseases, including TB, may present in a similar way (see section 4.7 for differential diagnosis).

b) The interpretation of tuberculin skin testing is even more unreliable than usual. An immunocompromised child may have a negative tuberculin skin test despite having TB.

c) A child with HIV infection usually comes from a household where the
parents have HIV infection. One or both parents may have died from AIDS. It may be difficult for the child to attend a health facility.

**DIFFERENTIAL DIAGNOSIS OF PTB IN HIV-INFECTED CHILDREN**

- bacterial pneumonia
- viral pneumonia, e.g. cytomegalovirus
- fungal pneumonia, e.g. candida, cryptococcus
- *Pneumocystis carinii* pneumonia
- lymphocytic interstitial pneumonitis
- pulmonary lymphoma

**MANAGEMENT OF CHILD CONTACTS OF INFECTIOUS ADULTS**

Children with TB may present to health units when they are ill. However, most National TB Control Programmes also recommend active contact tracing of children who are household contacts of infectious adults. In order to be effective, this screening must be systematic. If you don’t have a systematic, organised process for child contact screening where you work, could you start one?

The scheme below shows how to manage child contacts of infectious adults (with sputum smear-positive PTB). Suspicion that a child contact is HIV-infected may arise because of the following: the child has clinical evidence of HIV infection; the parent (the infectious TB patient) is known, or suspected to be, HIV-positive. If you suspect a child contact is HIV-infected, it is important to counsel the parents before HIV-testing the child.
Consider a child under 5 years of age living with a sputum smear-positive PTB patient. This child household contact is at high risk of TB infection and developing TB disease, especially if HIV-positive. Tuberculin skin testing is often not available. Also, tuberculin skin testing is not a reliable way of distinguishing TB-infected from non-TB-infected children. The IUATLD therefore recommends isoniazid preventive treatment for all child household contacts (under 5 years of age) of sputum smear-positive PTB patients.
CLINICAL RECOGNITION OF HIV INFECTION IN TB PATIENTS

In many TB/HIV patients in sub-Saharan Africa, the only HIV-related illness present is TB. However, certain clinical features are more common in HIV-positive TB patients than in HIV-negative TB patients. The table below shows these clinical features suspicious of HIV infection.

<table>
<thead>
<tr>
<th>Clinical features suspicious of HIV co-infection in TB patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Past history</strong></td>
</tr>
<tr>
<td>sexually transmitted disease (STD)</td>
</tr>
<tr>
<td>herpes zoster (shingles)</td>
</tr>
<tr>
<td>recurrent pneumonia</td>
</tr>
<tr>
<td>bacteraemia (especially <em>Salmonella typhimurium</em>)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>weight loss (&gt; 10 kg or &gt; 20% of original weight)</td>
</tr>
<tr>
<td>diarrhoea (&gt; 1 month)</td>
</tr>
<tr>
<td>pain on swallowing (suggests oesophageal candida)</td>
</tr>
<tr>
<td>burning sensation of feet (peripheral sensory neuropathy)</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
</tr>
<tr>
<td>scar of herpes zoster</td>
</tr>
<tr>
<td>pruritic papular rash</td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
</tr>
<tr>
<td>symmetrical generalised lymphadenopathy</td>
</tr>
<tr>
<td>oral candidiasis</td>
</tr>
<tr>
<td>oral hairy leukoplakia</td>
</tr>
<tr>
<td>persistent painful genital ulceration</td>
</tr>
</tbody>
</table>

PRACTICAL POINT

Full blood count (FBC) findings suspicious of HIV infection are unexplained anaemia, leucopenia or thrombocytopenia.

The definitive diagnosis of HIV infection rests on a positive HIV test.
There are different ways of testing for HIV. The most widely available way of identifying HIV-infected individuals is the detection of HIV antibodies in serum or plasma samples. The table below shows the 3 main methods of HIV-testing. The technical details of these tests are beyond the scope of this manual, but there is a good account in “AIDS in Africa: a manual for physicians”.

### HIV TESTING METHODS WITH ADVANTAGES AND DISADVANTAGES

<table>
<thead>
<tr>
<th>HIV TESTING METHOD</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUSA</td>
<td>less expensive than immunoblot</td>
<td>some specialised laboratory equipment necessary</td>
</tr>
<tr>
<td></td>
<td>large numbers of sera can be tested daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sensitive and specific</td>
<td></td>
</tr>
<tr>
<td>simple/ rapid (e.g. rapid immunobinding assay)</td>
<td>simple, rapid</td>
<td>older tests less sensitive and less specific but newer tests improved</td>
</tr>
<tr>
<td></td>
<td>less expensive than immunoblot</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no specialised equipment necessary</td>
<td></td>
</tr>
<tr>
<td>immunoblot</td>
<td>most sensitive and specific</td>
<td>expensive specialised laboratory equipment necessary</td>
</tr>
</tbody>
</table>

The usual type of test for HIV antibodies is the EUSA (Enzyme-Linked ImmunoSorbent Assay). The cost per individual EUSA test is about US $0.75-1.75. There are EUSA tests available which test for both HIV-1 and HIV-2.
Objectives of HIV antibody testing in TB patients

There are 3 main possible objectives in performing HIV antibody tests in TB patients:

a) diagnosis of HIV infection in individual TB patients;

b) surveillance (anonymous testing to monitor epidemiological trends);

c) research (voluntary testing for epidemiological, clinical, or virological studies).

Strategy for HIV antibody testing in TB patients

(WHICH TESTS TO USE AND WHEN TO USE THEM)

HIV testing methods vary in accuracy and cost. In general, WHO recommends different HIV-testing strategies, depending on the objective of testing. The aim is to maximise accuracy and minimise cost. The table below shows the strategy appropriate for the objective of testing.

<table>
<thead>
<tr>
<th>OBJECTIVE</th>
<th>TESTING STRATEGY</th>
<th>INTERPRETATION OF RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of HIV infection in individual TB patients (a group with a high HIV seroprevalence)</td>
<td>Test sample with EUSA or simple/rapid assay</td>
<td>1st assay negative = patient HIV negative</td>
</tr>
<tr>
<td></td>
<td>If 1st assay positive, re-test using EUSA or simple/rapid assay based on a different antigen preparation or test</td>
<td>1st assay positive + 2nd assay positive = patient HIV positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st assay positive + 2nd assay negative -&gt; repeat both assays</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results remain discordant -&gt; repeat sample and testing</td>
</tr>
<tr>
<td>Surveillance (in population with HIV prevalence &gt; 10%)</td>
<td>Test sample with EUSA or simple/rapid assay</td>
<td>Assay negative = patient HIV negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assay positive = patient HIV positive</td>
</tr>
</tbody>
</table>
Many low-income countries cannot afford the cost of the strategy of 2 positive tests in order to diagnose HIV infection in an individual patient. In practice, a patient has 1 test only: test negative = patient HIV negative; test positive = patient HIV positive.

Diagnosis of HIV infection in individual TB patients

The link between HIV and TB is well known to many members of the public. A patient with TB may therefore be well aware of the possibility he also has HIV infection. It is important to offer counselling and voluntary HIV testing, if available, to TB patients on account of the following possible benefits:

a) the patient may want the chance to know his HIV status;
b) better diagnosis and management of other HIV-related illnesses;
c) avoidance of drugs associated with a high risk of side-effects;
d) increased condom use and decreased HIV transmission.

Anti-TB drug treatment is the same for HIV-positive and HIV-negative TB patients, with one exception: do not give thiacetazone to HIV-positive TB patients (increased risk of severe and sometimes fatal skin reactions).

A policy of compulsory HIV testing (even if this were legal) of TB patients would be counter-productive. This type of policy would have the following results:

a) patients deterred from seeking care;
b) decreased case-finding in at-risk groups;
c) reduced credibility of health services.

HIV counselling

Confidential counselling is essential before and after HIV antibody testing. The patient gives explicit informed consent to have the test, i.e. he understands what the test involves and the implications of testing. The counsellor provides support. Counselling is a dialogue between patient and counsellor.
Counsellors

With suitable training, anyone who works with patients and families can be a counsellor. Counsellors may be members of the community or health workers. Many health workers have had counselling training. In the course of their duties they have the opportunity to counsel patients for HIV testing. Doctors and other clinicians are often in a good position to counsel patients for HIV testing. This is because clinicians have already established a relationship with the patient, who usually trusts the clinician.

Pre-test counselling

The aim is to enable the patient to make an informed decision to have the test or not. The patient needs to know what the test involves and what are the implications of the result. The main issues for discussion are assessments of the following: a) the patient's likelihood of having acquired HIV infection, b) his knowledge about HIV, and c) his ability to cope with a positive result.

**PRACTICAL POINT**

In sub-Saharan Africa, anyone with TB is in a high risk group for HIV.

| a) Assessment of risk of having acquired HIV infection | • multiple sex partners  
| • sex with commercial sex workers  
| • for men, sex with other men  
| • non-sterile skin piercing, e.g. scarification, tattooing  
| • previous blood transfusion  
| • intravenous drug use  
| • sexual partner/spouse of person at risk |
| b) Assessment of knowledge about HIV | • what does the test involve and mean?  
| • how does HIV transmission occur?  
| • what is high risk behaviour? |
| c) Assessment of ability to cope with result | • patient's expected reaction to result  
| • who will provide emotional support?  
| • impact of a positive result on  - relationships  
| - social issues, e.g. employment  
| - future health |
The HIV test does not become positive until usually 6 weeks, and up to about 3 months, after infection (the "window period").

**Post-test counselling**

The content of post-test counselling depends on the HIV test result. The aims are to discuss the result, share information, provide support, and encourage future safe sexual behaviour. Always ensure confidentiality. Break the news openly and sympathetically. When someone has a positive HIV test result, common reactions at different times may include shock, anger, guilt, grief and depression. Patients will need continuing support.

**Issues for discussion when the HIV test result is negative.**

- A negative result does not mean that the patient definitely does not have HIV infection (the test could be in the seroconversion “window period”).
- Avoidance of unsafe sexual behaviour.
- Promotion of healthy behaviour.

**Issues for discussion when the HIV test result is positive.**

- General health (good diet, balance of rest and exercise, avoiding infections, when to seek advice about symptoms of other HIV-related illnesses).
- Awareness of possible anti-TB drug side-effects.
- Safe sexual behaviour.
- Avoidance of blood or organ donation.
- The patient’s reaction to the test result.
- Emotional and psychological support for the patient.
- How to tell friends, family and lovers.
- Counselling partner(s) if possible.
- Referral to local community services and support groups, if available.
- Social implications, e.g. employment, life insurance.

**Suggestions for further reading**

HIV infection in children may show in many ways. The clinical signs are often not specific for HIV infection. For example, weight loss, fever and cough are common in TB, with or without HIV infection. The clinical definition of HIV infection is therefore difficult.

Parents provide important clues to possible HIV infection in their children. Ask the parents about their health. Sometimes parents may reveal their own HIV status.

The table below shows clinical signs suspicious of HIV infection in children.

<table>
<thead>
<tr>
<th>Clinical signs suspicious of HIV infection in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>weight loss or abnormally slow growth</td>
</tr>
<tr>
<td>chronic diarrhoea (&gt; 1 month)</td>
</tr>
<tr>
<td>prolonged fever (&gt;1 month)</td>
</tr>
<tr>
<td>generalised lymph node enlargement</td>
</tr>
<tr>
<td>oropharyngeal candidiasis</td>
</tr>
<tr>
<td>recurrent common infections, e.g. ear infections, pharyngitis</td>
</tr>
<tr>
<td>persistent cough</td>
</tr>
<tr>
<td>generalised rash</td>
</tr>
<tr>
<td>neurological problems</td>
</tr>
<tr>
<td>delay in development</td>
</tr>
<tr>
<td>bilateral parotid gland enlargement</td>
</tr>
<tr>
<td>enlarged spleen</td>
</tr>
<tr>
<td>enlarged liver has</td>
</tr>
<tr>
<td>recurrent abscesses</td>
</tr>
<tr>
<td>meningitis</td>
</tr>
<tr>
<td>recurrent herpes simplex</td>
</tr>
</tbody>
</table>
HIV TESTING

Positive and negative HIV tests are not always reliable. Rarely, a baby with HIV infection has a negative HIV antibody test. The reason for this is not known.

The definitive diagnosis of HIV infection rests on a positive HIV test. However, a positive HIV antibody test is not a reliable indicator of HIV infection in early childhood (up to 18 months of age). During the pregnancy of a mother with HIV infection, the mother’s antibodies to HIV cross the placenta. Therefore almost all children born to HIV-positive mothers have HIV antibodies in their blood at birth. However, only about one third of children born to HIV-infected mothers are infected. Initially, HIV antibody testing cannot therefore distinguish uninfected from infected children. In uninfected children, these maternal antibodies usually become undetectable by 9 months of age. Occasionally maternal antibodies remain detectable until 18 months. Most infected children make their own antibodies, so the HIV antibody test will still be positive after 18 months.

PRACTICAL POINT

In children under 18 months, the diagnosis of HIV infection rests on clinical features in the baby and a positive HIV test in the mother.

COUNSELLING

A child with suspected HIV generally means a family with suspected HIV. Counselling therefore has to take into consideration the mother and, if possible, the father. See Chapter 5 for the issues for discussion with adults with suspected HIV.

Pre-test counselling

It is important to counsel the mother and obtain her consent before testing her blood (if the child is under 18 months) or the child’s blood (if the child is over 18 months) for HIV. If her child tests HIV positive, then it is extremely likely that she is the source of infection and is HIV positive.
Consider the bad news for the mother when she hears that her child may have HIV infection:
- her child may have an incurable and fatal disease;
- she herself may have HIV;
- her husband may have HIV;
- any future children may have HIV.

Her decision to have a test or not is difficult. She will need time and support while she considers the advantages and disadvantages of a test. If she knows she is HIV-positive, the main advantage is that she can plan for the future. The main disadvantage is the fear that her husband may beat her or leave her if she tells him that she is HIV-positive.

The mother may like to bring her husband for joint pre-test counselling. It is usually easier for a woman to tell her husband she may be HIV-positive than to tell him afterwards that she is HIV-positive.

Post-test counselling
Consider a mother whose child has TB and suspected or known HIV infection. See Chapter 5 for the issues for discussion relevant to anyone who tests HIV-positive. There are other issues specific to a mother who tests HIV-positive. These include the poor outlook for the child and the risk for future babies of HIV infection. About one third of children born to HIV-positive women are also HIV-infected.

When counselling women who are breastfeeding or who have delivered recently it is important to discuss breastfeeding. There may be a small risk of HIV transmission by breastfeeding. However, in many low-income countries, breastfeeding is still a safer alternative to bottle-feeding. For example, consider a child whose mother is HIV-positive and who lives in an environment where there is no clean water. The child is probably at higher risk of dying from diarrhoea if bottle-fed than from AIDS if breastfed.
SUGGESTIONS FOR FURTHER READING


STANDARDISED CASE DEFINITIONS

Introduction

The diagnosis of TB means that a patient has TB. But what type of TB? It is important to answer this question before starting treatment. A case definition tells us the type of TB. We define TB cases in a standardised way. This means that when we talk about a certain type of TB, we are all talking about the same thing.

On making the diagnosis of TB, you must also decide on the TB case definition.

Questions and answers about case definitions

Why make case definitions? There are 2 purposes:

a) to determine treatment;
b) for recording and reporting (see Chapter 2).

Why do case definitions determine treatment? There are 3 reasons:

a) to identify priority cases;
b) to make the most cost-effective use of resources (by targeting resources on priority cases);
c) to minimise side-effects for patients (by using the most intensive regimens only for certain cases).

What determines a case definition? There are 4 determinants:

a) site of TB
b) result of sputum smear
c) previous TB treatment
d) severity of TB

Always ask a “new” TB patient if he has ever had TB treatment before.
The table below shows the determinants of case definition and their importance.

<table>
<thead>
<tr>
<th>DETERMINANT OF CASE DEFINITION</th>
<th>IMPORTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>site of TB</td>
<td>some authorities recommend a more intensive regimen for certain sites (e.g. pulmonary compared to extrapulmonary)</td>
</tr>
<tr>
<td></td>
<td>recording and reporting (in a good NTP, at least 50% of total cases will be pulmonary)</td>
</tr>
<tr>
<td>result of sputum smear for AFBs</td>
<td>priority is to identify sputum smear-positive cases (since these are the infectious cases)</td>
</tr>
<tr>
<td></td>
<td>recording and reporting (monitoring of bacteriological cure is readily available only in this group)</td>
</tr>
<tr>
<td>previous TB treatment</td>
<td>the previously treated patient who is still sputum smear-positive has a high risk of drug-resistant TB and so needs a different and more powerful regimen</td>
</tr>
<tr>
<td>severity of TB</td>
<td>most authorities recommend a more intensive regimen for smear-negative PTB patients with extensive disease rather than limited disease</td>
</tr>
</tbody>
</table>

### Case definitions by site and result of sputum smear

**PTB**

Smear positive case: at least 2 sputum smears positive for AFBs OR 1 sputum smear positive for AFBs and chest X-ray abnormalities consistent with active TB.

Smear negative case: at least 2 (and preferably 3) sputum smears negative for AFBs AND chest X-ray abnormalities consistent with active TB. In most cases, the patient will have had treatment with a broad-spectrum antibiotic, with no response.
Extrapulmonary TB
Clinical and/or histological evidence consistent with active TB.

The following are forms of extrapulmonary TB: pleural effusion (pleura are outside the lungs); hilar lymphadenopathy (hilar lymph nodes are outside the lungs); miliary (TB is widespread throughout the body and not limited to the lungs).

Case definitions by previous treatment

New
A patient who for sure has never taken anti-TB drugs for more than one month.

Relapse
A TB patient who
a) previously received treatment and was declared cured AND
b) has once again developed sputum smear-positive TB.

Treatment failure
A new TB patient who is still sputum smear-positive 5 months or more after starting treatment.

Return after interruption of treatment (default)
A new TB patient who
a) completed at least one month of treatment AND
b) returned after at least 2 months’ interruption of treatment.

Transfer in
A TB patient already registered for treatment in one district who transfers to another district where he continues treatment.

Other
A TB patient who does not easily fit into one of the above case definitions. One example is a chronic case (a TB patient who remains sputum smear-positive after completing a supervised re-treatment regimen).
Based on case definition, a TB patient falls into 1 of 4 categories for treatment. The categories are in order of priority. The highest priority is to treat Category 1 patients. The lowest priority is to treat Category 4 patients. The table below shows the patients belonging to each category.

<table>
<thead>
<tr>
<th>TB TREATMENT CATEGORY</th>
<th>PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>new sputum smear-positive PTB newly diagnosed seriously ill patients with severe forms of TB</td>
</tr>
<tr>
<td>Category 2</td>
<td>relapse treatment failure return after default</td>
</tr>
<tr>
<td>Category 3</td>
<td>sputum smear-negative PTB with limited parenchymal involvement extrapulmonary TB (less severe forms)</td>
</tr>
<tr>
<td>Category 4</td>
<td>chronic cases</td>
</tr>
</tbody>
</table>

The table below shows the severe and less severe forms of extrapulmonary TB.

<table>
<thead>
<tr>
<th>SEVERE EXTRAPULMONARY TB</th>
<th>LESS SEVERE EXTRAPULMONARY TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• meningitis</td>
<td>• lymph node</td>
</tr>
<tr>
<td>• miliary</td>
<td>• pleural effusion (unilateral)</td>
</tr>
<tr>
<td>• pericarditis</td>
<td>• bone (excluding spine)</td>
</tr>
<tr>
<td>• peritonitis</td>
<td>• peripheral joint</td>
</tr>
<tr>
<td>• bilateral or extensive pleural effusion</td>
<td>• adrenal gland</td>
</tr>
<tr>
<td>• spinal</td>
<td></td>
</tr>
<tr>
<td>• intestinal</td>
<td></td>
</tr>
<tr>
<td>• genito-urinary</td>
<td></td>
</tr>
</tbody>
</table>

Children

Children and adolescents often fall into Category 3. PTB in children is almost always “smear-negative” (actually smear not done, since children rarely cough up sputum). Young people infected during adolescence may develop primary TB. This usually presents as pleural effusion or small parenchymal lesions in the lungs. In one series of adolescents with pleural effusion, without treatment about 25% went on to develop PTB.

SUGGESTED FURTHER READING

8 1 INTRODUCTION

**Aims of anti-TB drug treatment**
- To cure the patient of TB.
- To prevent death from active TB or its late effects.
- To prevent TB relapse.
- To decrease TB transmission to others.

**PRACTICAL POINT**
Properly applied anti-TB drug treatment will achieve these aims and prevent the emergence of drug resistant *M. tuberculosis*.

**Effective anti-TB drug treatment = properly applied Short-Course Chemotherapy**
We have known for over 100 years that *M. tuberculosis* causes TB. We have had effective anti-TB drugs for nearly 50 years. Yet the world’s TB problem is now bigger than ever. Why? The problem is not the lack of an effective treatment. Properly applied short-course chemotherapy (SCC) fulfills the above aims of anti-TB drug treatment. The problem is an organisational problem: how to apply SCC properly? The answer is a properly managed TB control programme. Chapter 2 describes the organisational framework of an effective TB control programme.

**Standardised TB treatment regimens**
There are many different possible anti-TB treatment regimens. The World Health Organisation (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend standardised TB treatment regimens. The national TB control programme (NTP) in your country will recommend which regimens to use. When properly applied, these standardised regimens fulfill the above aims of anti-TB drug treatment. The regimens are affordable. The World Bank recognises short-course chemotherapy (SCC) as one of the most cost-effective of all health interventions.
The essential anti-TB drugs

The table shows the essential anti-TB drugs and their mode of action, potency, and recommended dose.

<table>
<thead>
<tr>
<th>ESSENTIAL ANTI-TB DRUG (ABBREVIATION)</th>
<th>MODE OF ACTION</th>
<th>POTENCY</th>
<th>RECOMMENDED DOSE (MG/KG)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DAILY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3X/WK</td>
</tr>
<tr>
<td>isoniazid (H)</td>
<td>bactericidal</td>
<td>high</td>
<td>5</td>
</tr>
<tr>
<td>rifampicin (R)</td>
<td>bactericidal</td>
<td>high</td>
<td>10</td>
</tr>
<tr>
<td>pyrazinamide (Z)</td>
<td>bactericidal</td>
<td>low</td>
<td>25</td>
</tr>
<tr>
<td>streptomycin (S)</td>
<td>bactericidal</td>
<td>low</td>
<td>15</td>
</tr>
<tr>
<td>ethambutol (E)</td>
<td>bacteriostatic</td>
<td>low</td>
<td>15 (30)</td>
</tr>
<tr>
<td>thiacetazone (T)</td>
<td>bacteriostatic</td>
<td>low</td>
<td>3</td>
</tr>
</tbody>
</table>

The available formulations and combinations of these drugs vary from country to country. Follow the recommendations in your NTP manual.

Intermittent use

Thiacetazone is the only anti-TB drug not effective when given intermittently (2 or 3 times a week). The efficacy of intermittent ethambutol is not proven.

Modes of action of anti-TB drugs

Consider a population of TB bacilli in a TB patient. This population of bacilli consists of the following groups:

a) metabolically active, continuously growing bacilli inside cavities;

b) bacilli inside cells, e.g. macrophages;

c) semi-dormant bacilli (persisters) which undergo occasional spurts of metabolism;

d) dormant bacilli which fade away and die on their own.

Different anti-TB drugs act against different groups of bacilli.

Anti-TB drug treatment is so long because it is difficult to kill the semi-dormant TB bacilli.
**Bactericidal drugs**

*Isoniazid* kills 90% of the total population of bacilli during the first few days of treatment. It is most effective against the metabolically active, continuously growing bacilli.

*Rifampicin* can kill the semi-dormant bacilli which *isoniazid* cannot.

*Pyrazinamide* kills bacilli in an acid environment inside cells, e.g. macrophages.

**Sterilising action**

This means killing all the bacilli. The persisters are hardest to kill. The aim of killing all the bacilli is to prevent relapse. *Rifampicin* is the most effective sterilising drug. Its effectiveness makes short-course chemotherapy possible. *Pyrazinamide* is also a good sterilising drug, since it kills the bacilli protected inside cells.

**Preventing drug resistance**

Consider a population of *TB* bacilli never previously exposed to anti-TB drugs. There will be a few naturally-occurring drug-resistant mutant bacilli. Faced with anti-TB drugs, these drug-resistant mutant bacilli will grow and replace the drug-sensitive bacilli under the following circumstances:

a) inadequate anti-TB drug combinations;

b) anti-TB drug treatment not properly applied.

Isoniazid and rifampicin are most effective in preventing resistance to other drugs. *Streptomycin* and ethambutol are slightly less effective.
dose. This protects rifampicin against the development of drug resistance. The risk of drug resistance is higher during the early stages of anti-TB drug treatment when there are more TB bacilli.

**Continuation phase (4-6 months)**

Fewer drugs are necessary, but for a longer time, in the continuation phase. The drugs eliminate the remaining TB bacilli. Killing the persisters prevents relapse after completion of treatment. Directly observed therapy is the ideal when the patient receives rifampicin in the continuation phase. If local conditions do not allow directly observed therapy, the next best is close supervision as possible, for example weekly supervision. The risk of drug resistance is less during the continuation phase when there are fewer TB bacilli.

The patient usually receives monthly drug supplies for self-administered treatment during a continuation phase which does not include rifampicin.

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### Retreatment cases

The initial phase lasts 3 months, with directly observed therapy. The continuation phase lasts 5 months, with close supervision.

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### Standard code for TB treatment regimens

There is a standard code for TB treatment regimens. Each anti-TB drug has an abbreviation (shown in the table on page 84). A regimen consists of 2 phases. The number before a phase is the duration of that phase in months. A number in subscript (e.g. 1) after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in brackets.

Example

2 SHRZ / 6 HE. This is a common regimen.

The initial phase is 2 SHRZ. The duration of the phase is 2 months. Drug treatment is daily (no subscript number, e.g. 1 after the letters), with streptomycin (S), isoniazid (H), rifampicin (R) and pyrazinamide (Z).

The continuation phase is 6 HE. The duration of the phase is 6 months. Drug treatment is daily, with isoniazid (H) and ethambutol (E).

2 SHRZ / 4 H.R. In some countries, resources are available to provide
rifampicin in the continuation phase as well as in the initial phase. The intensive phase (2 SHRZ) is the same as before. The continuation phase is 4 H3R3. The duration is 4 months, with isoniazid and rifampicin three times per week (subscript number 3 after the letters).

### Recommended treatment regimens

There are several different possible regimens. The regimen recommended depends on the patient treatment category (see Chapter 7). The table shows possible alternative regimens for each treatment category. Follow the regimens recommended by your NTP in your country. Look in your NTP manual.

**ALTERNATIVE TREATMENT REGIMENS FOR EACH PATIENT TREATMENT CATEGORY**

<table>
<thead>
<tr>
<th>TB TREATMENT CATEGORY</th>
<th>TB PATIENTS</th>
<th>ALTERNATIVE TB TREATMENT REGIMENS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>INITIAL PHASE</strong></td>
</tr>
<tr>
<td>New smear-positive PTB</td>
<td></td>
<td>2 SHRZ (EH RZ)</td>
</tr>
<tr>
<td>Seriously ill:</td>
<td></td>
<td>2 SHRZ (EH RZ)</td>
</tr>
<tr>
<td>Extrapulmonary or</td>
<td></td>
<td>2 SHRZ (EH RZ)</td>
</tr>
<tr>
<td>Smear-negative PTB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miliary TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal TB with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear-positive:</td>
<td></td>
<td>2 SHRZE/ 1 HRZE</td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td>2 SHRZE/ 1 HRZE</td>
</tr>
<tr>
<td>Treatment failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Return after default</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic case (still</td>
<td></td>
<td>2 HRZ or 2 H3R3Z3</td>
</tr>
<tr>
<td>Sputum positive after</td>
<td></td>
<td>2 HRZ or 2 H3R3Z3</td>
</tr>
<tr>
<td>Supervised re-treatment</td>
<td></td>
<td>2 H3R3 / 4 H</td>
</tr>
</tbody>
</table>

Some authorities recommend a 7 month continuation phase with daily isoniazid and rifampicin (7 HR) for Category 1 patients with the following forms of TB: TB meningitis, miliary TB, spinal TB with neurological signs.
Use of streptomycin and thiacetazone in areas of high HIV prevalence

**Streptomycin**
- In high TB/HIV prevalence populations, overcrowding is common in TB wards. The high staff workload may result in inadequate sterilisation of needles and syringes used for streptomycin injections. There is a risk of transmission of HIV and other blood-born pathogens between patients.
- Streptomycin injections are very painful in wasted HIV-infected TB patients.
- Many NTPs now recommend the use of ethambutol in place of streptomycin.

**Thiacetazone**
- Thiacetazone is associated with a high risk of severe, and sometimes fatal, skin reaction in HIV-infected individuals.
- Use ethambutol instead of thiacetazone in patients with known or suspected HIV infection.
- At present some countries do not have the resources to substitute ethambutol for thiacetazone. The most effective treatment available in some countries may still include thiacetazone. Where it is not possible to avoid the use of thiacetazone, it is essential to warn patients about the risk of severe skin reactions. Advise the patient to stop thiacetazone at once and report to a health unit if itching or a skin reaction occurs.

TB TREATMENT REGIMENS: QUESTIONS AND ANSWERS

**Why use 4 drugs in the initial phase?**
- There is a high degree of initial resistance in some populations.
- Use of a 3-drug regimen runs the risk of selecting out drug-resistant mutants. This may happen especially in patients with high bacillary loads, e.g. cavitary pulmonary TB.
- A 4-drug regimen decreases the risks of drug resistance, treatment failure, and relapse.

**Why use pyrazinamide only in the initial phase?**
- Pyrazinamide has its maximum sterilising effect within the first 2 months. There is less benefit from longer use.

**Is a 4 month continuation phase possible?**
- A 4 month continuation phase is possible with rifampicin throughout (e.g. 2 SHRZ/4 HR). This is because isoniazid and rifampicin are
both potent bactericidal drugs. In the usual 6 month continuation phase (6 HE or 6 HT), the only potent bactericidal drug is isoniazid.

**Why not always use regimens containing rifampicin throughout?**
- Rifampicin is too expensive for many countries to afford these regimens.

**Why is it so important to prevent rifampicin resistance?**
- Rifampicin is the most effective anti-TB drug. It is unlikely that a new anti-TB drug will become widely available in the near future. If rifampicin resistance becomes widespread, TB will be effectively untreatable.

**How do we prevent rifampicin resistance?**
- Bad TB control programmes, lack of supervision of anti-TB treatment, bad prescribing by clinicians, and the use of rifampicin alone generate acquired drug resistance. The best way to prevent rifampicin resistance is to strengthen NTPs and ensure directly observed therapy when and where possible. It is important to use methods of drug administration which avoid the danger of the use of rifampicin alone. These include the use whenever possible of fixed-dose combination tablets and of anti-TB drugs supplied in blister packs.

**What is the treatment for multi-drug resistant TB?**
- Multi-drug resistant TB arises from failure to deliver anti-TB drug treatment properly. Multi-drug resistance represents NTP failure. In many high TB prevalence countries, second-line drugs are prohibitively expensive and unavailable, e.g. ethionamide, cycloserine, kanamycin, capreomycin. Multi-drug resistant TB is therefore often untreatable.

**What should we do when faced with multi-drug resistant TB?**
- The cause of the problem is NTP failure. The answer is to devote time, effort and resources to improving the NTP. In some countries, one or two specialist centres may have the specialist expertise and second-line drugs available to treat patients with multi-drug resistant TB.

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**Pregnancy**
- Streptomycin during pregnancy can cause permanent deafness in the baby.
- Do not give streptomycin in pregnancy. Use ethambutol instead.
Renal failure
- Rifampicin, isoniazid and pyrazinamide are safe.
- The excretion of streptomycin is renal. The excretion of ethambutol and thiacetazone is partly renal.
- Avoid streptomycin and ethambutol if there are alternatives. Otherwise give in reduced doses at less frequent intervals.
- Do not give thiacetazone. The margin is too narrow between the therapeutic and toxic dose.

Liver disease
- Most anti-TB drugs can cause liver damage. Jaundiced patients who develop TB should receive treatment with the following regimen: 2 SHE / 6 HE.
- Do not give pyrazinamide to patients with liver disease.

What is adjuvant steroid treatment?
Adjuvant steroid treatment is steroid treatment given in addition to anti-TB drug treatment. Prospective controlled clinical trials have confirmed the benefit of steroids in TB meningitis and pleural and pericardial TB.

What are the indications for treatment with steroids?
- TB meningitis (decreased consciousness, neurological defects, or spinal block).
- TB pericarditis (with effusion or constriction).
- TB pleural effusion (when large with severe symptoms).
- Hypo-adrenalism (TB of adrenal glands).
- TB laryngitis (with life-threatening airway obstruction).
- Severe hypersensitivity reactions to anti-TB drugs.
- Renal tract TB (to prevent ureteric scarring).
- Massive lymph node enlargement with pressure effects.

What are the recommended treatment doses of prednisolone?
Rifampicin is a potent inducer of hepatic enzymes which metabolise steroids. The effective dose of prednisolone is therefore half the prescribed treatment dose given to the patient. The table below shows suggested treatment doses of prednisolone.
### Indications for Prednisolone Treatment

- **TB meningitis**: 60 mg daily for weeks 1-4, then decrease over several weeks.
- **TB pericarditis**: 60 mg daily for weeks 1-4, then 30 mg daily for weeks 5-8, then decrease over several weeks.
- **TB pleural effusion**: 40 mg daily for 1-2 weeks.

---

**Is steroid treatment safe in TB/HIV patients?**

Steroids are immunosuppressants. The worry is that steroids may further depress immunity and increase risk of opportunistic infections in HIV-positive patients. However, on balance, TB/HIV patients are still likely to benefit from the use of steroids for the above indications.

---

### Monitoring of TB Patients During Treatment

Bacteriological monitoring is readily available only for patients with sputum smear-positive pulmonary TB. Routine monitoring of treatment response by chest X-rays is unnecessary and wasteful of resources. For other TB patients, clinical monitoring is the usual guide to treatment response.

---

**Recording treatment results in sputum smear-positive pulmonary TB patients is vital to monitor patient cure and NTP effectiveness (see Chapter 2).**

---

### Monitoring of patients with sputum smear-positive PTB

- **When to monitor**: 8 month treatment regimen vs. 6 month treatment regimen.
- **At time of diagnosis**: SPUTUM SMEAR.
- **At end of initial phase**: SPUTUM SMEAR.
- **In continuation phase**: SPUTUM SMEAR (MONTH5) for 8 months, SPUTUM SMEAR (MONTH5) for 6 months.
- **On completion of treatment**: SPUTUM SMEAR (MONTH8) for 8 months, SPUTUM SMEAR (MONTH6) for 6 months.
Sputum smear at end of initial phase
The vast majority of patients have a negative sputum smear at the end of the initial phase. If the sputum smear is still positive at the end of the initial phase, continue initial phase treatment with the same 4 drugs for 4 more weeks. If you check the sputum smear again at this point, it is unlikely still to be positive. Go on to the continuation phase (even if the sputum smear after the extra 4 weeks of initial phase treatment is still positive).

Sputum smear in continuation phase
In 8 month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. In 6 month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. A common cause of treatment failure is the failure of the programme to ensure patient adherence to treatment. The patient changes treatment category to Category 2 and starts the re-treatment regimen.

Sputum smear on completion of treatment
In 8 month regimens, negative sputum smears at 5 and at 7 or 8 months mean bacteriological cure. In 6 month regimens, negative sputum smears at 5 and 6 months mean bacteriological cure.

872 Recording treatment outcome in sputum smear-positive patients
At the end of the treatment course in each individual patient, the District TB Officer should record the treatment outcome as follows:

<table>
<thead>
<tr>
<th>Cure</th>
<th>patient who is smear negative at (or one month prior to) the completion of treatment and on at least one previous occasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completed</td>
<td>patient who has completed treatment but in whom smear results are not available on at least two occasions prior to the completion of treatment</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>patient who remains or becomes again smear positive at 5 months or later, after starting treatment</td>
</tr>
<tr>
<td>Died</td>
<td>patient who dies for any reason during the course of chemotherapy</td>
</tr>
<tr>
<td>Defaulted (treatment interrupted)</td>
<td>patient whose treatment has been interrupted for more than 2 consecutive months before the end of course of treatment</td>
</tr>
<tr>
<td>Transferred out</td>
<td>patient who has been transferred to another treatment centre and whose treatment results are not known</td>
</tr>
</tbody>
</table>
Cohort analysis: questions and answers

**What is cohort analysis?**
A cohort of TB patients consists of all those sputum smear-positive PTB patients registered during a certain time. The time period may be a quarter of a year or one year. For example, consider all those sputum smear-positive PTB patients registered from 1 January to 31 March in any year. They form a cohort for that quarter-year. Cohort analysis refers to the statistical breakdown of that cohort according to certain indicators. These indicators are the standardised case definitions and treatment categories (see Chapter 7) and the 6 treatment outcomes shown above.

**Who performs cohort analysis and how often?**
Cohort analysis is a continuous process. The District TB Officer performs cohort analysis on TB patients registered in his district every quarter-year and at the end of every year. The Regional TB Officer performs cohort analysis on all TB patients registered in the region. The NTP directorate performs cohort analysis on all TB patients registered nationally.

**What is cohort analysis for?**
Cohort analysis is the key management tool used to evaluate the effectiveness of TB control programme delivery. It enables regional NTP staff and the NTP directorate to identify districts with problems. Examples of problems identified include the following: low cure rate, high default rate, higher than expected proportions of sputum smear-negative PTB or extrapulmonary TB, lower than expected case detection rate. Identification of problems enables the NTP to overcome them and improve programme delivery.

RESPONSE OF HIV-POSITIVE TB PATIENTS TO ANTI-TB TREATMENT

**Mortality**
The mortality of TB/ HIV patients 1 year after starting TB treatment is about 20%. This mortality is greater than the mortality in HIV-negative TB patients. The excess mortality in TB/ HIV patients during and after treatment is partly due to TB itself and partly due to other HIV-related problems. These other HIV-related problems include the following: septicaemia, diarrhoea, pneumonia, anaemia, Kaposi’s sarcoma, cryptococcal meningitis.

Mortality is less in TB/ HIV patients treated with SCC than with the old standard regimen (1 SHT or SHE / 11 HT or HE). This is partly because SCC is a more effective anti-TB treatment. Also, rifampicin has broad-
spectrum antimicrobial activity as well as anti-TB activity. This may decrease mortality due to HIV-related bacterial infections during anti-TB treatment.

**Response in survivors**

Several studies have assessed the clinical, radiological, and microbiological response to SCC in HIV-positive and HIV-negative TB patients. Excluding patients who died, response rates were similar in HIV-positive and HIV-negative TB patients. The only exception was that on average weight gain was less in HIV-positive than in HIV-negative TB patients.

**RECURRENCE OF TB AFTER COMPLETING ANTI-TB TREATMENT**

**Old standard treatment**

The recurrence rate is higher in HIV-positive than in HIV-negative TB patients. In one study of TB/HIV patients there was an association between recurrence and cutaneous reaction to thiacetazone. A severe thiacetazone reaction necessitated interruption of treatment and a change to ethambutol. There are several possible explanations for the link between increased risk of recurrence and thiacetazone reaction. These include treatment interruption, subsequent poor compliance, more advanced immunocompromise, and change to the combination of isoniazid and ethambutol in the 11 months continuation phase.

**SCC**

The recurrence rate is similar in HIV-positive and HIV-negative TB patients who complete treatment.

**Recurrence: relapse or re-infection?**

When TB recurs after previous cure, there are 2 possibilities:

a) true relapse (reactivation of persisters not killed by anti-TB drugs);

b) re-infection (due to re-exposure to another source of infection).

The proportions of recurrences due to these 2 possibilities are not known.

**SUGGESTIONS FOR FURTHER READING**


CHAPTER 9  SIDE EFFECTS OF ANTI-TB DRUGS

9 1  INTRODUCTION

Most TB patients complete their treatment without any significant drug side effects. However, a few patients do develop side effects. So clinical monitoring of all TB patients for side effects is important during TB treatment. Routine laboratory monitoring is not necessary.

How do health personnel monitor patients for drug side effects?

a) by teaching patients how to recognise symptoms of common side effects and to report if they develop such symptoms.

b) by asking specifically about these symptoms when they see all patients at least monthly during treatment.

9 2  PREVENTION OF SIDE EFFECTS

Health personnel should be aware of the special situations which influence the choice and dose of anti-TB drugs (see Chapter 8).

It is possible to prevent the peripheral neuropathy caused by isoniazid. This neuropathy usually shows as a burning sensation of the feet. It occurs more commonly in HIV-positive individuals and in drinkers (alcohol). These patients should receive preventive treatment with pyridoxine 10 mg daily. Ideally, where possible, pyridoxine 10 mg daily should routinely accompany isoniazid.

9 3  WHERE TO MANAGE DRUG REACTIONS

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Where to manage reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>minor, e.g. gastro-intestinal</td>
<td>outpatient setting</td>
</tr>
<tr>
<td>joint pains</td>
<td></td>
</tr>
<tr>
<td>major, e.g. jaundice</td>
<td>refer to district or central hospital</td>
</tr>
<tr>
<td>severe rash</td>
<td></td>
</tr>
</tbody>
</table>

9 4  WHEN TO STOP ANTI-TB DRUGS

When a patient has minor drug side-effects, explain the situation, offer symptomatic treatment, and encourage him to continue treatment.
When a patient has a major reaction, stop the suspected drug(s) responsible at once. If a patient develops one of the following reactions, he must never receive that drug again:

<table>
<thead>
<tr>
<th>REACTION</th>
<th>DRUG RESPONSIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe rash, agranulocytosis</td>
<td>thiacetazone</td>
</tr>
<tr>
<td>hearing loss or disturbed balance</td>
<td>streptomycin</td>
</tr>
<tr>
<td>visual disturbance (poor vision and colour perception)</td>
<td>ethambutol</td>
</tr>
<tr>
<td>renal failure, shock, or thrombocytopenia</td>
<td>rifampicin</td>
</tr>
</tbody>
</table>

### SIDE EFFECTS OF ANTI-TB DRUGS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COMMON SIDE EFFECTS</th>
<th>RARE SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>• peripheral neuropathy</td>
<td>convulsions, pellagra, joint pains, agranulocytosis, lupoid reactions, skin rash</td>
</tr>
<tr>
<td>rifampicin</td>
<td>• gastrointestinal: anorexia, nausea, vomiting, abdominal pain, hepatitis, reduced effectiveness of oral contraceptive pill</td>
<td>acute renal failure, shock, thrombocytopenia, skin rash, “flu syndrome” (intermittent doses), pseudomembranous colitis, pseudoadrenal crisis</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>• joint pains, hepatitis</td>
<td>gastrointestinal symptoms, skin rash, sideroblastic anaemia</td>
</tr>
<tr>
<td>streptomycin</td>
<td>• auditory and vestibular nerve damage (also to foetus), renal damage</td>
<td>skin rash</td>
</tr>
<tr>
<td>ethambutol</td>
<td>• optic neuritis</td>
<td>skin rash, joint pains, peripheral neuropathy</td>
</tr>
<tr>
<td>thiacetazone</td>
<td>• skin rash, often with mucous membrane involvement</td>
<td>hepatitis, agranulocytosis</td>
</tr>
</tbody>
</table>
Rifampicin reduces the effectiveness of the oral contraceptive pill. Advise a woman to use another form of contraception.

Side effects of anti-TB drugs in TB/HIV patients

Adverse drug reactions are more common in HIV-positive than in HIV-negative TB patients. Risk of drug reaction increases with increased immunocompromise. Most reactions occur in the first 2 months of treatment.

**Skin rash**
This is the commonest reaction. Fever often precedes and accompanies the rash. Mucous membrane involvement is common. The usual drug responsible is thiacetazone. Streptomycin and rifampicin are sometimes to blame. Severe skin reactions, which may be fatal, include exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

**Other reactions**
The commonest reactions necessitating change in treatment include gastrointestinal disturbance and hepatitis. There may be an increased risk of rifampicin-associated anaphylactic shock and thrombocytopenia.
## Symptom-Based Approach to Management of Drug Side Effects

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Drug(s) Probably Responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>continue anti-TB drugs</td>
<td></td>
</tr>
<tr>
<td>anorexia, nausea</td>
<td>rifampicin</td>
<td>give tablets last thing at night</td>
</tr>
<tr>
<td>abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>joint pains</td>
<td>pyrazinamide</td>
<td>aspirin</td>
</tr>
<tr>
<td>burning sensation in feet</td>
<td>isoniazid</td>
<td>pyridoxine 100 mg daily</td>
</tr>
<tr>
<td>orange/red urine</td>
<td>rifampicin</td>
<td>reassurance</td>
</tr>
<tr>
<td>Abdominal pain at night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint pains</td>
<td>pyrazinamide</td>
<td>aspirin</td>
</tr>
<tr>
<td>Burning sensation in feet</td>
<td>isoniazid</td>
<td>pyridoxine 100 mg daily</td>
</tr>
<tr>
<td>Orange/red urine</td>
<td>rifampicin</td>
<td>reassurance</td>
</tr>
</tbody>
</table>

### Major

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Drug(s) Probably Responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin itching/ rash</td>
<td>thiacetazone</td>
<td>stop anti-TB drugs (see below)</td>
</tr>
<tr>
<td>Deafness</td>
<td>streptomycin</td>
<td>stop streptomycin, ethambutol instead</td>
</tr>
<tr>
<td>(No wax on auroscopy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>streptomycin</td>
<td>stop streptomycin, ethambutol instead</td>
</tr>
<tr>
<td>(Vertigo and nystagmus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>most anti-TB drugs</td>
<td>stop all anti-TB drugs until jaundice resolves (see below)</td>
</tr>
<tr>
<td>(Other causes excluded)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting and confusion</td>
<td>most anti-TB drugs</td>
<td>stop anti-TB drugs, urgent liver function tests</td>
</tr>
<tr>
<td>(Suspected drug-induced pre-icteric hepatitis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual impairment</td>
<td>ethambutol</td>
<td>stop ethambutol</td>
</tr>
<tr>
<td>Generalised, including shock and purpura</td>
<td>rifampicin</td>
<td>stop rifampicin</td>
</tr>
</tbody>
</table>

### Management of Skin Itching/Rash

The approach depends on whether or not the patient is receiving thiacetazone. In populations with a high TB/HIV prevalence, thiacetazone is the drug most likely to cause skin reactions.
If a patient starts to itch, and there is no other obvious cause (e.g., scabies), stop the anti-TB drugs at once. The itching may be a warning sign of severe skin reaction. Stopping the thiacetazone at once may avert, or decrease the severity, of the skin reaction.

Give the patient intravenous fluids if the skin reaction is severe:
- exfoliative dermatitis or toxic epidermal necrolysis
- mucous membrane involvement
- hypotension

Many physicians give steroid treatment, although there is no firm evidence that this helps. A typical dose schedule consists of 60 mg daily of oral prednisolone until there is some improvement. A gradual reduction in dose over the next few days depends on the patient's response. Initially, if a patient is unable to swallow, give intravenous hydrocortisone 100-200 mg daily (instead of oral prednisolone). On recovery, restart anti-TB drugs, replacing thiacetazone with ethambutol.

Never give a patient thiacetazone again after any thiacetazone reaction.

A severe reaction may mean stopping anti-TB treatment for 3-4 weeks. A severely ill TB patient may die without anti-TB treatment. In this case, give him 2 or more previously unused drugs until the reaction has resolved. Then reintroduce the initial regimen (with ethambutol instead of thiacetazone).

If a patient starts to itch, exclude other obvious causes. Try treatment with anti-histamines, continue anti-TB treatment and observe the patient closely. In some cases, the itching resolves. In other cases, a rash develops. In this case, stop the anti-TB drugs. Wait for the rash to resolve. If the reaction is severe, the patient may need supportive treatment as above.

The problem now is re-introducing TB treatment when we don't know which anti-TB drug was the drug responsible for the reaction. The table shows the standard approach to re-introducing anti-TB drugs after a drug reaction.
**Re-introduction of anti-TB drugs following drug reaction**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Likelihood of causing a reaction</th>
<th>Challenge doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Least likely</td>
<td>50 mg 300 mg 300 mg</td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td>75 mg 300 mg Full dose</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td>250 mg 1 gram Full dose</td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
<td>100 mg 500 mg Full dose</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Most likely</td>
<td>125 mg 500 mg Full dose</td>
</tr>
</tbody>
</table>

If possible, while the patient undergoes drug challenging, give him 2 anti-TB drugs which he has not had before. The idea of drug challenging is to identify the drug responsible for the reaction. Drug challenge starts with the anti-TB drug least likely to be responsible for the reaction (i.e. isoniazid). Start with a small challenge dose. If a reaction occurs to a small challenge dose, it will not be such a bad reaction as to a full dose. Gradually increase the dose over 3 days. Repeat the procedure, adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction.

If the drug responsible for the reaction is pyrazinamide, ethambutol, or streptomycin, resume anti-TB treatment without the offending drug. If possible, replace the offending drug with another drug. It may be necessary to extend the treatment regimen. Consider the start of the resumed regimen as a new start of treatment. This prolongs the total time of TB treatment, but decreases the risk of recurrence.

**Practical Point**

Refer patients with severe drug reactions to specialist centres.
DESENSITISATION

Rarely, patients develop hypersensitivity reactions to the 2 most potent anti-TB drugs, isoniazid and rifampicin. These drugs form the cornerstone of SCC. If an HIV-negative patient has had a reaction (but not a severe reaction) to isoniazid or rifampicin, it may be possible to desensitise the patient to the drug. However, never attempt desensitisation in TB/HIV patients because of the high risk of serious toxicity.

The following method for desensitisation is for reference only, since it applies to HIV-negative TB patients, but not to TB/HIV patients. Start desensitisation with a tenth of the normal dose. Then increase the dose by a tenth each day, until the patient has the full dose on the tenth day. Once drug sensitisation is over, give the drug as part of the usual treatment regimen. If possible, while carrying out desensitisation, give the patient 2 anti-TB drugs which he has not had before. This is to avoid the risk of drug resistance developing during desensitisation.

PRACTICAL POINT

Never attempt desensitisation in TB/HIV patients.

MANAGEMENT OF HEPATITIS

Most anti-TB drugs can damage the liver. Isoniazid and pyrazinamide are most commonly responsible. Ethambutol is rarely responsible. When a patient develops hepatitis during anti-TB treatment, the cause may be the anti-TB treatment or another cause. It is often difficult to find out. Try to rule out other possible causes before deciding that the hepatitis is drug-induced. Hepatitis presents with anorexia, jaundice and often liver enlargement.

If you diagnose drug-induced hepatitis, stop the anti-TB drugs. Wait until the jaundice resolves. It is strange, but fortunate, that in most cases the patient can re-start the same anti-TB drugs without hepatitis returning. A severely ill TB patient may die without anti-TB drugs. In this case, treat the patient with 2 of the least hepatotoxic drugs, streptomycin and ethambutol. When the hepatitis resolves, re-start usual anti-TB treatment.
SUGGESTIONS FOR FURTHER READING


INTRODUCTION

TB/HIV patients may have other HIV-related diseases. This chapter is a brief guide to their management at district hospital level. Therapies in "bold" are available in most district hospitals. See the WHO guidelines "Clinical management of HIV infection" and "Management of sexually transmitted diseases" for a more complete account.

(Note that references to trimethoprim-sulfamethoxazole (TMP-SMX) are to the standard strength tablet, which contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole).

SEXUALLY TRANSMITTED DISEASES

A person who has unsafe sex is at risk of several sexually transmitted diseases (STDs). So a patient with one STD is at increased risk of having another STD. HIV is usually sexually transmitted. STDs other than HIV are common in TB/HIV patients. This chapter gives a brief account of the drug treatment of STDs. When you treat a patient with STD, also remember patient education, counselling, condom provision and partner management.

Syndromic management

Accurate STD diagnosis is often not feasible. WHO has developed a "syndromic management". This is based on the recognition of consistent groups of symptoms and signs (syndromes). The treatment recommended for each syndrome cures the majority of infections responsible for causing each syndrome. The table shows the recommended plans of treatment for the common STD-associated syndromes where laboratory investigations are not available.
### Treatment regimens for common STDs

The table shows treatment regimens for the common STDs.

Do not use ciprofloxacin or tetracyclines in pregnancy or in childhood.

<table>
<thead>
<tr>
<th>STD</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>gonorrhoea</td>
<td>ciprofloxacin 500 mg orally as a single dose OR</td>
</tr>
<tr>
<td>(uncomplicated)</td>
<td>ceftriaxone 250 mg by i.m. injection as a single dose OR</td>
</tr>
<tr>
<td></td>
<td>cefixime 400 mg orally as a single dose OR</td>
</tr>
<tr>
<td></td>
<td>spectinomycin 2 g by i.m. injection as a single dose OR</td>
</tr>
<tr>
<td></td>
<td>trimethoprim (80 mg)/ sulfamethoxazole (400 mg) (TMP-SMX) 10 tablets orally as a single dose OR</td>
</tr>
<tr>
<td></td>
<td>gentamicin 240 mg by i.m. injection as a single dose OR</td>
</tr>
<tr>
<td>chlamydia</td>
<td>doxycycline 100 mg orally 2x daily for 7 days OR</td>
</tr>
<tr>
<td></td>
<td>tetracycline 500 mg orally 4x daily for 7 days OR</td>
</tr>
<tr>
<td></td>
<td>erythromycin 500 mg orally 4x daily for 7 days OR</td>
</tr>
<tr>
<td>primary syphilis</td>
<td>benzathine penicillin G 2.4 million IU, by i.m. injection at a single session OR</td>
</tr>
<tr>
<td>(chancre)</td>
<td>procaine penicillin G 1.2 million IU daily by i.m. injection for 10 consecutive days OR</td>
</tr>
<tr>
<td></td>
<td>tetracycline 500 mg orally 4x daily for 15 days OR</td>
</tr>
<tr>
<td></td>
<td>doxycycline 100 mg orally 2x daily for 15 days OR</td>
</tr>
<tr>
<td></td>
<td>erythromycin 500 mg 4x daily for 15 days OR</td>
</tr>
</tbody>
</table>

### Syndrome | Plan of treatment
---|-------------------
Men | urethral discharge | **treat for gonorrhoea and chlamydia**
    | cervicitis | **treat for uncomplicated gonorrhoea and chlamydia**
    | vaginitis | **treat for candidiasis and Trichomonas vaginalis/bacterial vaginosis**
    | vaginal discharge | **treat for cervicitis and vaginitis**
Women | genital ulcers | **treat for syphilis and chancre**
    | inguinal bubo | **treat for syphilis and chancre**
    | - with ulcers | **treat for syphilis and chancre**
    | - without ulcers | **treat for lymphogranuloma venereum**
Men and women | urethral discharge | **treat for gonorrhoea and chlamydia**
    | cervicitis | **treat for uncomplicated gonorrhoea and chlamydia**
    | vaginitis | **treat for candidiasis and Trichomonas vaginalis/bacterial vaginosis**
    | vaginal discharge | **treat for cervicitis and vaginitis**
    | genital ulcers | **treat for syphilis and chancre**
    | inguinal bubo | **treat for syphilis and chancre**
    | - with ulcers | **treat for syphilis and chancre**
    | - without ulcers | **treat for syphilis and chancre**
Men and women | urethral discharge | **treat for gonorrhoea and chlamydia**
    | cervicitis | **treat for uncomplicated gonorrhoea and chlamydia**
    | vaginitis | **treat for candidiasis and Trichomonas vaginalis/bacterial vaginosis**
    | vaginal discharge | **treat for cervicitis and vaginitis**
    | genital ulcers | **treat for syphilis and chancre**
    | inguinal bubo | **treat for syphilis and chancre**
    | - with ulcers | **treat for syphilis and chancre**
    | - without ulcers | **treat for syphilis and chancre**
chancroid  
erythromycin 500mg orally 3x daily for 7 days OR  
ciprofloxacin 500mg orally as a single dose OR  
ceftriaxone 250mg by i.m. injection as a single dose OR  
spectinomycin 2g by i.m. injection as a single dose OR  
TMP-SMX 2 tablets orally 2x daily for 7 days

lymphogranuloma venereum  
doxycline 100mg orally 2x daily for 14 days OR  
tetracycline 500mg orally 4x daily for 14 days OR  
erthyromycin 500mg orally daily for 14 days OR  
sulfadiazine 1g orally 4x daily for 14 days

candidiasis  
nystatin 10,000U intravaginally once daily for 14 days OR  
miconazole or clotrimazole 200mg intravaginally once daily for 3 days OR  
clotrimazole 500mg intravaginally as a single dose

Trichomonas vaginalis  
metronidazole 2g orally as a single dose OR  
metronidazole 400-500mg orally 2x daily for 7 days

diagnosis of these HIV-related skin and mouth problems usually rests on characteristic clinical features. The tables show diagnoses and treatments.

Skin and Mouth Problems

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex (oral and genital)</td>
<td>Local lesion care. Acyclovir 200 mg five times daily until healed.</td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>Local lesion care. Acyclovir 800 mg po 5x/ day for at least 7 days.</td>
</tr>
<tr>
<td>Anal/ genital warts (human papilloma virus)</td>
<td>Topical 20% podophyllin 1-2 times per week until cleared. Trichloracetic acid. Cryotherapy.</td>
</tr>
</tbody>
</table>
### Molluscum contagiosum
Leave the lesions alone OR
Prick each lesion with a needle or sharpened orange stick and touch with phenol.

### Fungal Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea</td>
<td>Whitfield's ointment or Castellani's paint Topical antifungals.</td>
</tr>
<tr>
<td>(pedis/corpus/cruris)</td>
<td>1% Clotrimazole.</td>
</tr>
<tr>
<td></td>
<td>2% Miconazole.</td>
</tr>
<tr>
<td></td>
<td>In resistant cases use griseofulvin 500 mg 2 x daily.</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Local application of 1% aqueous gentian violet or nystatin ointment 2 x daily until lesions are cleared. Topical antifungals.</td>
</tr>
<tr>
<td>Cutaneous cryptococcosis/histoplasmosis</td>
<td>Systemic antifungal therapy.</td>
</tr>
</tbody>
</table>

### Bacterial Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papular folliculitis (pruritic papular dermatosis)</td>
<td>Calamine lotion. Antihistamines. Topical antifungals combined with 1% hydrocortisone. Strong topical corticosteroids.</td>
</tr>
<tr>
<td>Impetigo, furunculosis</td>
<td>Penicillin V 500 mg orally OR Flucloxacillin or erythromycin 500 mg orally 4 x daily for 1 - 2 weeks</td>
</tr>
<tr>
<td>Pyomyositis</td>
<td>Surgical drainage plus antibiotics (as for impetigo)</td>
</tr>
</tbody>
</table>

### Other

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>Antifungal shampoos OR topical antifungals with steroids OR topical 1% hydrocortisone. Strong topical corticosteroids.</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Conventional antipsoriasis treatment, eg coal tar in salicylate ointment 2 x daily.</td>
</tr>
<tr>
<td>Scabies</td>
<td>Topical benzyl benzoate 25%</td>
</tr>
<tr>
<td>Kaposi's Sarcoma</td>
<td>Local lesion care. Radiotherapy, chemotherapy.</td>
</tr>
</tbody>
</table>
MOUTH PROBLEMS

Oral candidiasis  
Topical antifungals such as amphotericin lozenges, nystatin pastilles/pessaries:  
nystatin drops 100,000 units 3 x daily OR  
nystatin pessaries one every 4 hours OR  
nystatin tabs 500,000 units 4 x daily.  
In resistant cases oral ketoconazole 200 mg  
2 x daily.  
In all cases treat for 7 - 14 days.  
Recurrence is common without prophylaxis.

Hairy leukoplakia  
No treatment

Angular cheilitis  
Topical antifungals eg 1% clotrimazole.

Gingivitis / dental abscesses  
Oral metronidazole 400 mg 3 x daily and/or  
penicillin V 500 mg 4 x daily for 7 days.

Aphthous ulcers  
Mouth rinses with steroid and tetracycline.  
Topical corticosteroids.  
Oral prednisolone.  
Oral acyclovir.  
(Oral thalidomide in refractory cases).

GASTROINTESTINAL PROBLEMS

Dysphagia  
There are various HIV-related causes of oesophageal inflammation.  
They present in a similar way with pain on swallowing.  
O esophageal candidiasis is the commonest HIV-related cause of dysphagia.  
The diagnosis of the other causes needs endoscopy, biopsy and a good laboratory.

Where there are no facilities for investigation of a known HIV-positive patient with dysphagia, treat empirically with an oral anti-fungal agent.  
Where available, barium swallow shows characteristic appearances of fine mucosal ulceration.  
Upper gastrointestinal endoscopy shows white plaques and biopsy allows confirmation.
The table shows the treatment of the causes of dysphagia.

<table>
<thead>
<tr>
<th>CAUSE OF DYSPHAGIA</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida oesophagitis</td>
<td>Nystatin 500,000 units 4 x daily.</td>
</tr>
<tr>
<td></td>
<td>Nystatin pessaries 100,000 units every 4 hours.</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole 200 mg twice daily OR fluconazole 100 mg od.</td>
</tr>
<tr>
<td></td>
<td>(All medications taken for 1-14 days).</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis with nystatin pastilles OR fluconazole 100 mg daily for life</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Acyclovir 800 mg po five times daily for 7-10 days.</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Treatment usually not available and too expensive (intravenous gancyclovir).</td>
</tr>
<tr>
<td>Ulcers of unknown cause</td>
<td>Prednisolone 40 mg daily for 2 weeks, then slowly taper to zero.</td>
</tr>
</tbody>
</table>

**Diarrhoea**

**Introduction**

Chronic diarrhoea is very common, affecting up to 60% of HIV-positive individuals at some time in their illness. Common accompanying features include the following: nausea, vomiting, abdominal cramps, flatulence, weight loss and dehydration.

**Rehydration**

Always assess the state of hydration of any patient with diarrhoea. Most patients with mild to moderate dehydration will receive oral rehydration solution. A few patients, with severe dehydration, need intravenous fluids.

**Investigation**

Where facilities are available, send multiple stool samples for microscopy and culture. With appropriate stains it is possible on microscopy to diagnose the following pathogens: Cryptosporidium, Isospora belli, Microsporidia. Stool culture can enable the diagnosis of Salmonella, Shigella, Clostridium difficile.

**Treatment**

In most cases, the cause is not known. So treatment in these cases is empirical. Some cases (probably due to Isospora belli) respond to
treatment with trimethoprim-sulfamethoxazole (TMP-SMX). Other cases (probably due to *Microsporidia*) respond to treatment with metronidazole. Sometimes you do find a specific cause of diarrhoea. The table shows specific causes with the appropriate treatment.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BACTERIAL INFECTIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>TMP-SMX 2 tablets 2x daily for 7 days OR chloramphenicol 500 mg 4x daily for 7 days.</td>
</tr>
<tr>
<td>Shigella</td>
<td>TMP-SMX 2 tablets 2x daily for 7 days OR nalidixic acid 1g 4x daily for 5 days</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>metronidazole 400 mg 3x daily for 7 days.</td>
</tr>
<tr>
<td><strong>PROTOZOA INFECTIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>symptomatic treatment only</td>
</tr>
<tr>
<td>Isospora belli</td>
<td>TMP-SMX 2 tablets 2x daily for 7 days</td>
</tr>
<tr>
<td><em>Microsporidia</em></td>
<td>metronidazole 400 mg 3x daily for 7 days.</td>
</tr>
</tbody>
</table>

**Persistent diarrhoea**

Give symptomatic treatment if diarrhoea persists, the cause is not known, and there is no response to TMP-SMX then metronidazole. Anti-diarrhoeal agents for symptomatic treatment include codeine and loperamide.

**RESPIRATORY PROBLEMS**

Some TB/HIV patients fail to improve, or even deteriorate, during anti-TB treatment. They continue to have, or develop new, respiratory problems, e.g. cough, breathlessness, chest pain. First check that the patient has really been taking his anti-TB drugs. Then consider the following possibilities:

<table>
<thead>
<tr>
<th>Original Diagnosis</th>
<th>Possibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>sputum smear-negative PTB</td>
<td>incorrect diagnosis e.g. other pathogens, heart failure, chronic obstructive airways disease</td>
</tr>
<tr>
<td>sputum smear-positive PTB</td>
<td>patient not adherent to anti-TB treatment; drug-resistant TB; superimposed infection with other pathogens.</td>
</tr>
</tbody>
</table>
The flow chart shows the management approach in HIV-positive PTB patients who fail to respond or deteriorate while on anti-TB treatment.

The table below shows the main bacterial pathogens responsible for super-imposed pneumonia in smear-positive PTB patients and the treatment.

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td><strong>penicillin or TMP-SMX</strong></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td><strong>amoxicillin or TMP-SMX</strong></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td><strong>flucloloxacin or chloramphenicol</strong></td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td><strong>chloramphenicol (and gentamicin if necessary)</strong></td>
</tr>
</tbody>
</table>
NEUROLOGICAL PROBLEMS

A wide variety of neurological problems may occur in TB/HIV patients. The common presentations are the following:

- acute confusion
- chronic behaviour change
- persistent headache
- difficulty in walking
- poor vision
- burning sensation in the feet

Neurological problems by reputation are difficult to diagnose. In fact, they are no more difficult to diagnose than other problems, provided that you take time and care. You have to take time and care to obtain a detailed history and perform a proper neurological examination. It is usually necessary to obtain some, if not all, of the history from the patient’s relatives or friends. Some simple district level laboratory tests on blood and cerebrospinal fluid (CSF) are often helpful.

1 Acute confusion

The differential diagnosis when a TB/HIV patient becomes acutely confused includes the following:

a) acute super-imposed infection, e.g. septicaemia, meningitis, malaria;
b) hypoxaemia, e.g. pneumothorax, pneumonia, heart failure, anaemia;
c) metabolic disturbance, e.g. secondary to diarrhoea, hypo-adrenalism;
d) adverse drug reaction, e.g. acute confusion may be the first sign of drug-induced acute fulminant liver failure (a useful test, if available, is the prothrombin time).

Always check a blood film for malaria. Do a lumbar puncture if the patient has meningism and it is safe to do a lumbar puncture. Other investigations depend on the laboratory facilities available and clinical clues to the diagnosis.

2 Chronic behaviour change

Chronic behaviour change, i.e. over a period of months, is usually due to AIDS dementia or progressive multi-focal leucoencephalopathy. These are untreatable. Since the diagnoses are clinical, you must rule out other treatable possibilities. Send blood for syphilis serology and (in endemic areas) microscopy for trypanosomes. If lumbar puncture is safe, send CSF to the laboratory to exclude chronic meningitis (e.g. cryptococcal, TB).
The flow chart below shows the management approach to the TB/HIV patient with headache. The following features may accompany headache: reduced level of consciousness, confusion, convulsions.

Flow chart showing management approach for persistent headache

- Exclude a local cause, e.g., sinusitis, cerebral abscess
- Persistent headache
- Blood tests: malaria parasites, syphilis serology, film for trypanosomes (in endemic areas)
- Clinical assessment
- Evidence of space-occupying lesion (e.g., papilloedema, focal neurological defect)
- Clinical diagnosis of space-occupying lesion (infectious causes are syphilitic, toxoplasma, or Nocardia brain abscess)
- Empirical treatment: dexamethasone 4 mg 3 x daily AND chloramphenicol 1 g 4 x daily (pyogenic brain abscess) AND sulfadiazine 500 mg + pyrimethamine 25 mg (S-P) 2 tablets 2 x daily for 6 weeks (cerebral toxoplasmosis or nocardiosis), Maintenance S-P 1 tablet weekly
- Usually unrecognizable causes: fungal brain abscess, cerebral lymphoma, cerebral Kaposi's sarcoma
- N.B. definitive diagnosis of cerebral space-occupying lesions is usually not possible without CT/brain scan and sophisticated laboratory investigations
- Meningism
- Lumbar puncture (if safe)
- CSF investigations: white cell count and differential, protein and glucose concentrations, stains (Gram, ZN, India ink), culture for bacteria and fungi, cytology (if available)
- Cryptococcus (positive India ink stain or culture)
- Acute bacterial meningitis (e.g., Pneumococcus, identified on Gram stain or culture)
- Malignancy (positive cytology)
- Anti-fungal drugs if available
- Chloramphenicol 1 g 4 x daily for 7 - 10 days
It is possible, but rare, for TB meningitis to develop after a TB patient has already started anti-TB treatment. For example, a cerebral tuberculoma could rupture into the subarachnoid space releasing TB bacilli not yet killed by anti-TB drugs. A commonly recommended treatment regimen for TB meningitis is as follows: 2 SHRZ, 7 HR.

It is unlikely, but possible, that a patient already on TB treatment could develop acute bacterial meningitis. The diagnosis rests on CSF examination.

**Cryptococcal meningitis**

The outcome is fatal without treatment and often very poor with treatment. In many countries the drugs for treating cryptococcal meningitis are prohibitively expensive in most cases. The treatment for most patients is therefore symptomatic with analgesia and sedation. For those patients who can afford specific anti-fungal drug treatment, they should receive fluconazole 400 mg daily initially for 10 weeks. An alternative is intravenous amphotericin B (0.5 mg/kg/day) for 6 weeks. Life-long maintenance treatment with fluconazole 200 mg daily is then necessary to prevent relapse.

**Difficulty in walking**

Spinal TB may cause difficulty in walking. So first make sure (by clinical examination and spine X-ray) that the patient does not also have spinal TB.

The cause of difficulty walking in a TB/HIV patient may be HIV-related (spinal cord myelopathy and occasionally peripheral neuropathy) or unrelated to HIV. A patient with difficulty walking and HIV myelopathy usually has a spastic paraparesis. It is only possible to make this diagnosis by excluding the causes of spinal cord disease unrelated to HIV. The table below shows these main causes of spinal cord disease unrelated to HIV, and the diagnostic tests. In HIV-related peripheral neuropathy, sensory disturbance tends to predominate over motor weakness.

<table>
<thead>
<tr>
<th>Cause of spinal cord disease</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>cervical spondylosis</td>
<td>cervical spine X-ray, myelography</td>
</tr>
<tr>
<td>prolapsed intervertebral disc</td>
<td>myelography</td>
</tr>
<tr>
<td>epidural abscess</td>
<td>myelography</td>
</tr>
<tr>
<td>treatable tumours</td>
<td>myelography</td>
</tr>
<tr>
<td>(neurofibroma, meningioma)</td>
<td></td>
</tr>
</tbody>
</table>
Schistosomiasis... identification of eggs in stool, urine, or rectal snips

Myelography

Neurosyphilis... syphilis serology, CSF findings

Subacute combined... anaemia with raised MCV, low serum vitamin B12 level

Spinal cord schistosomiasis is difficult to diagnose, but schistosomiasis is easy to treat. Consider a patient with a spinal cord problem who lives in an area endemic for schistosomiasis. Give empirical treatment with a stat dose of praziquantel (40 mg/kg) while pursuing further management.

Poor vision

If a patient receiving ethambutol develops difficulty seeing clearly, or has problems perceiving colours, stop ethambutol.

Cytomegalovirus retinitis can cause poor vision but is rare in African AIDS patients. The diagnosis rests on the characteristic appearance on fundoscopy of a necrotising retinitis with perivascular haemorrhages and exudates. The treatment with ganciclovir or foscarnet is prohibitively expensive in many countries.

Burning sensation in the feet

HIV may cause a peripheral neuropathy, often worse when a TB patient starts isoniazid. The features which may accompany the painful burning sensation in the feet include distal weakness and atrophy with absent ankle jerks.

Prevention

If resources allow, all TB patients should receive pyridoxine 10 mg daily as prophylaxis against isoniazid neuropathy. Otherwise reserve pyridoxine prophylaxis for HIV-positive TB patients and TB patients who drink alcohol.
**Treatment**

Treat patients with established isoniazid neuropathy with pyridoxine 100 mg daily. Amitryptiline (25-75 mg at night), phenytoin (100-300 mg at night), or carbamazepine (100-200 mg 2 x daily) may relieve symptoms in HIV neuropathy.

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**FEVER**

1. **Approach to management**

   Fever usually settles within 2-3 weeks of starting anti-TB treatment. Further fever may signal a drug reaction or a disseminated infection. The table below shows the approach to management of further or persistent fever.

<table>
<thead>
<tr>
<th>FEATURES ACCOMPANYING FEVER</th>
<th>LIKELY CAUSE</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>rash</td>
<td>drug reaction</td>
<td>Stop anti-TB drugs</td>
</tr>
<tr>
<td>weight loss</td>
<td>disseminated infection</td>
<td>Examine patient</td>
</tr>
<tr>
<td>progressive anaemia</td>
<td></td>
<td>Investigations:</td>
</tr>
<tr>
<td>or pancytopenia</td>
<td></td>
<td>• blood film for malaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• blood cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• consider lumbar puncture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Start antibiotics for suspected septicaemia</td>
</tr>
</tbody>
</table>

2. **Disseminated infection**

   Disseminated infection carries a high mortality. The table below shows the wide variety of pathogens which can cause disseminated infection in TB/HIV patients.

   **Pathogens causing disseminated infection in TB/HIV patients**

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>MYCOBACTERIA</th>
<th>VIRUSES</th>
<th>OTHERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella typhimurium</td>
<td>M. avium complex (MAC)</td>
<td>CMV</td>
<td>Leishmania</td>
</tr>
<tr>
<td>Staphylococcus pneumoniae</td>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Gram-negative bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Bacterial septicaemia**

*S. typhimurium* and *Pneumococcus* are the commonest identified causes of septicaemia in HIV-positive patients in sub-Saharan Africa. Many strains of *S. typhimurium* are resistant to several antibiotics. If you suspect septicaemia, treat the patient with chloramphenicol or ampicillin and gentamicin.

**Disseminated M. avium complex (MAC)**

This occurs less frequently in AIDS patients in sub-Saharan Africa than elsewhere. Diagnostic facilities and treatment are generally not available in district hospitals and many central hospitals.

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**Tumours . . . . . KAPOSI’S SARCOMA (KS)**

KS can affect many parts of the body, but usually the skin and mouth, and sometimes the lung and pleura, gastrointestinal tract, and pericardium. The clinical appearance is usually distinctive. There is often oedema with KS on the face and legs. Diagnostic confusion can arise with keloids, leprosy, sarcoidosis, and melanoma. In case of doubt, a biopsy is diagnostic. Histology shows typical proliferation of spindle cells and small blood vessels.

Consider a TB/HIV patient with KS. Development of a pleural effusion or progressive lung infiltrations during anti-TB treatment is probably due to KS.

Many countries have limited resources for treating KS. Treatment is often unsatisfactory. Non-steroidal anti-inflammatory drugs (NSAIDs) may help relieve pain. Cytotoxic chemotherapy and radiotherapy may be available in some central hospitals.

**. . . . . . . . . . . . LYMPHOMA**

AIDS patients are at increased risk of developing atypical, aggressive lymphomas. Prognosis is poor even with cytotoxic chemotherapy.

**Anaemia**

Anaemia in TB/HIV patients may be due to any of the following: TB, HIV-induced marrow suppression, concurrent infections, drug side-effects. Treatment is supportive: iron and folic acid; blood transfusion if essential.
**Thrombocytopenia**
The main causes are HIV-induced autoimmune thrombocytopenia and drug side-effects. High-dose steroids may help if there is bleeding and the platelet count is low (less than \( 20 \times 10^9 / \ell \)).

**Renal disease**
HIV-related nephropathy causes nephrotic syndrome and progressive renal damage. There is no specific treatment. Treat urinary tract infections in the usual way.

**Congestive cardiomyopathy**
Consider HIV-related congestive cardiomyopathy in the differential diagnosis of heart failure. Treat heart failure in the usual way.

**Arthropathy**
Pyrazinamide often causes joint pains but rarely arthritis. HIV-related arthropathy usually affects small joints. NSAIDs may help relieve pain.

**Hypoadrenalism**
Cytomegalovirus can cause necrotising adrenalitis. This is difficult to distinguish from TB of the adrenal glands or pseudoadrenal crisis (rifampicin). Treatment is with steroid supplements.

**Suggestions for Further Reading**

INTRODUCTION

TB/HIV patients may receive care in different settings. These settings include the patient’s home, local health centre, district hospital, and tertiary referral hospital. Coordination of care in different settings promotes continuity of care for the patient.

In the case of TB/HIV patients, sometimes the patient knows that he is HIV-positive and later on develops TB. More often, he only finds out that he is HIV-positive after he has developed TB. In either case, the TB control programme needs to collaborate closely with other services providing support and care for HIV-positive individuals. The clinician who treats the TB/HIV patient is in a key position to refer the patient to appropriate services.

BENEFITS OF SUPPORT FROM LOCAL HIV/AIDS CARE SERVICES

The HIV/AIDS care services available vary from place to place. They include HIV/AIDS community support groups and HIV/AIDS home care schemes. The TB/HIV patient may gain the following benefits from the support of local HIV/AIDS services:

a) emotional support;

b) early identification of any new infections;

c) symptomatic treatment in end-stage disease;

d) support for his family.

INTEGRATED SYSTEM OF HIV/AIDS AND TB CARE

An integrated system of HIV/AIDS and TB care uses available health systems to provide continuity of care for TB/HIV patients. The chart below shows an integrated system of HIV/AIDS and TB care.
Referral to local HIV/AIDS care services

One of the important features of a successful NTP is integration of TB control activities with the general health services (see Chapter 2). This means that at the district and primary health care levels, the general health service staff manage TB patients according to NTP guidelines, supported by NTP staff.

General health service and NTP staff need to know what local HIV/AIDS services are available for HIV-positive patients. Providers of local HIV/AIDS services include Ministry of Health, non-governmental organisations (NGOs) and community organisations. Often it is possible to refer patients directly to HIV/AIDS services.

Some TB/HIV patients choose not to accept referral to HIV/AIDS services. It is important to respect patients’ wishes and confidentiality. In many districts there is a district coordinator for HIV/AIDS. District NTP staff liaison with the district coordinator for HIV/AIDS promotes the easy referral of TB/HIV patients to HIV/AIDS services.
In many towns and cities there are now HIV counselling and voluntary testing centres. Some of the people attending these centres may have TB. A study in Kampala, Uganda showed that 6% of people attending the HIV counselling and voluntary testing centre had undiagnosed TB. NTP collaboration with these centres is important. Staff in the centres should ask clients about chronic cough and refer TB suspects to the NTP for sputum microscopy.

General health services staff can refer patients directly to HIV/AIDS care services. Community care means providing the patient with access to care as close to home as possible. Some HIV/AIDS care services provide home care for AIDS patients. The home care provider may be a health care worker or community volunteer. See the WHO "AIDS Home Care Handbook" for more information.

Home care alone is not enough for a TB/HIV patient on a home care scheme. The TB patient needs to continue to receive his anti-TB treatment, under direct observation by a trained and supervised home care provider. The HIV/AIDS home care scheme and the NTP can collaborate to train and supervise the HIV/AIDS home care provider to provide directly observed therapy. Also, the HIV/AIDS home care provider can recognise problems with anti-TB treatment and refer as necessary to the NTP.

A good NTP is integrated with general health services (see Chapter 2). So primary health care staff are in a good position to identify and treat common HIV-related problems in patients during or after anti-TB treatment. Good communication between general health service staff and HIV/AIDS care workers is important for continuity of care of TB/HIV patients.

The private sector includes private medical practitioners and traditional healers. Many patients choose to go to either or both.

**Private medical practitioners**

Ideally there should be close collaboration between private practitioners and the NTP. This results in improved management of TB patients according to NTP.
guidelines. However, a private practitioner serves the community and guarantees his TB patients good care by following NTP guidelines. A private practitioner can register the patient with the NTP and share continued management. A private practitioner does not have to give up his patient entirely to the NTP if he does not want to. Some TB/ HIV patients prefer to go to a private practitioner for perceived reasons of confidentiality. In a country where the NTP is very good, many patients will prefer the NTP to a private practitioner.

**Traditional practitioners**

TB is a difficult disease for traditional practitioners. Many don't understand it, don't know how to cure it, and don't have the drugs. General health services can collaborate with traditional practitioners. For example, traditional practitioners can recognize who is a TB suspect and refer to the general health services. Traditional healers often have an important role in providing support to people with HIV-related diseases.

### Care at District Level

Primary health care staff can manage many HIV-related problems in the health centers and dispensaries. Sometimes TB/ HIV patients develop problems requiring investigations and treatment unavailable at primary health care level. Then they need referral to the District Hospital, either to the outpatient department or for admission. After appropriate district hospital management, often the district level staff can refer the patient back to the primary health care or community level. Good channels of communication promote continuity of care.

### Tertiary referral care

District level staff sometimes deal with difficult problems of diagnosis or treatment. The patient may benefit from transfer to a tertiary referral hospital. It is usually wise to obtain advice on the telephone before transferring the patient. This is to ensure that the specialist agrees that the patient is likely to benefit from the referral.

**SUGGESTIONS FOR FURTHER READING**


From the public health point of view, the best way to prevent TB is to provide effective treatment to the infectious TB cases. This interrupts the chain of transmission. Good treatment programmes are the best prevention programmes. HIV-infected individuals are particularly susceptible to infection with *M. tuberculosis* and the development of TB.

What are the ways of protecting HIV-infected individuals from exposure to TB in health care settings? What is the role of BCG? Can we do anything about those HIV-infected individuals who are already infected with *M. tuberculosis* and have a high risk of developing active TB? This chapter addresses these questions.

**PROTECTION OF HIV-POSITIVE PERSONS AGAINST EXPOSURE TO TB.**

HIV-positive patients and staff in health units face daily exposure to TB. The risk of exposure is greatest in adult medical wards and TB wards where there are many PTB cases. Often the wards are crowded and badly ventilated. We do not yet know the size of this risk.

Prompt diagnosis and treatment of patients with sputum smear-positive PTB helps to reduce exposure to TB. Outpatient diagnosis and treatment of PTB patients avoids hospital admission. This is an advantage in decreasing exposure to TB in hospital wards. In some NTPs there is a move away from an in-patient intensive phase towards outpatient management.

Known HIV-positive health workers should not work with PTB patients. They should therefore not work in TB wards or adult medical wards.

**Environmental control**

Good ventilation helps reduce TB transmission indoors. Sunlight is a source of ultraviolet light which can kill TB bacilli. So ideally, wards should have large windows.
In wards, out-patient clinics, sputum collection rooms, and microbiology laboratories, keep the doors closed and the windows open.

**Face-masks**

A face-mask decreases the risk that the person wearing the mask can infect other people. So a TB suspect or a TB patient, if possible, should wear a mask if moving from one part of a hospital to another.

Often a health worker wears a mask to protect himself against TB, e.g. when working on the TB ward. In fact, a mask is generally not very good at protecting the person wearing the mask from inhaling other people's infectious droplets. The exception is when the health worker is supervising a cough-inducing procedure, e.g. bronchoscopy, or sputum induction using nebulised hypertonic saline.

**Patient education**

Health workers should teach TB suspects and TB patients simple measures how to decrease the risk of transmitting TB. These include covering the mouth with the hand when coughing, and using sputum pots with lids. When examining TB patients or suspects, ask the patient to turn his head. This is to avoid him coughing directly at the health worker.

**PTB suspects**

In the majority of cases, PTB suspects attend as outpatients for the diagnosis of TB. In some cases it is necessary to admit PTB suspects to hospital. If possible admit them to a separate ward from other patients. There are often no facilities to separate PTB suspects from other patients. At least try to keep PTB suspects in a part of the ward away from other patients.

**Patients with sputum smear-positive PTB**

In many NTPs, sputum smear-positive PTB patients spend at least part, and often all, of the intensive phase of anti-TB treatment in hospital. Isolation of
these patients in TB wards helps reduce the risk of TB exposure to other patients. Do not admit a patient to the TB ward until you have made the diagnosis of TB. A TB suspect with HIV infection and high susceptibility to TB should avoid exposure to TB. He may not turn out to have TB.

THE ROLE OF BCG IN PREVENTING TB IN HIV-INFECTED INDIVIDUALS

1 Background

BCG (Bacille Calmette-Gue{\textregistered}rin) is a live attenuated vaccine derived originally from \textit{M. bovis}. The route of injection is intra-dermal. The usual dose is 0.05 ml in neonates and infants under the age of 3 months, and 0.1 ml in older children. In high TB prevalence countries, WHO recommends a policy of routine BCG immunisation for all neonates shortly after birth.

The benefit of BCG is in protecting young children against disseminated and severe TB, e.g. TB meningitis and miliary TB. BCG has little or no effect in reducing the number of adult cases of PTB.

2 BCG protection against TB in HIV-infected children

It is not known if HIV infection reduces the protection of BCG against TB in children. There is some evidence that conversion to a positive tuberculin test after BCG is less frequent in HIV-infected children. The significance of this finding for protection against TB is not clear.

3 BCG safety in HIV-infected children

There have been a few case reports of local complications and disseminated BCG infection after BCG immunisation of HIV-infected children. However, prospective studies comparing BCG immunisation in HIV-infected and uninfected infants showed no difference in risk of complications. So, in the vast majority of cases, BCG immunisation is safe.

4 WHO recommended policy on BCG and HIV

WHO recommended policy depends on the TB prevalence in a country, as shown on the next page. In a high TB prevalence country, the possible benefits of BCG immunisation outweigh the possible disadvantages.
**THE ROLE OF THE EXPANDED PROGRAMME ON IMMUNISATION (EPI)**

BCG is not the only immunisation in the EPI which may help to protect a child against TB. Measles and whooping cough lower a child’s resistance to TB. So whenever you treat a child for TB, check his immunisation record. If he has not received scheduled immunisations, encourage the mother to bring him for immunisations, once symptoms of TB have resolved. WHO has collaborated with UNICEF in establishing guidelines for immunisation. The recommendation is that individuals with known or suspected asymptomatic HIV infection should receive all EPI vaccines, according to national schedules.

**PREVENTIVE TREATMENT**

The aim of preventive treatment is to prevent progression of *M. tuberculosis* infection to disease. A 6 month course of preventive treatment with daily isoniazid (5 mg/kg) is effective. However, preventive treatment for all individuals infected with *M. tuberculosis* is not a recommended TB control strategy. It is not feasible to try to identify all individuals infected with *M. tuberculosis*. TB disease develops in only 10% of all individuals infected with *M. tuberculosis*. So it is not cost-effective to identify and treat all infected individuals in order to prevent disease in 10%.

However, it is possible to identify certain groups at high risk of progressing from *M. tuberculosis* infection to TB disease. It may be cost-effective to target preventive treatment at these high-risk groups.

**Target groups for preventive treatment**

Young children are at special risk, especially if they are HIV-infected. HIV infection, in children and in adults, is a potent cause of progression of *M. tuberculosis* infection to TB disease (see Chapter 1).

**Infants of mothers with PTB**

A breastfeeding infant has a high risk of infection from a mother with PTB,
and a high risk of developing TB. The infant should receive 6 months’ isoniazid treatment, followed by BCG immunisation. An alternative policy is to give 3 months’ isoniazid, then perform a tuberculin skin test. If the skin test is negative, stop the isoniazid and give BCG. If the skin test is positive, continue another 3 months’ isoniazid, then stop isoniazid and give BCG.

**Children under 5 years of age**

It is important to screen child household contacts of adults with sputum smear-positive PTB (see Chapter 4). Screening identifies those children under 5 years of age without symptoms. Give these children 6 months’ isoniazid preventive treatment. Children under 5 years of age with symptoms need investigation for TB. If investigations show TB, the child receives anti-TB treatment. If investigations do not show TB, the child should receive isoniazid preventive treatment.

**HIV-infected individuals**

Controlled clinical studies have shown that isoniazid preventive treatment reduces the risk of TB disease in HIV-positive individuals also infected with *M. tuberculosis*. The evidence of *M. tuberculosis* infection is a positive tuberculin skin test. In HIV-positive individuals, the extra benefit of a reduced risk of TB may also be a reduced rate of progression of HIV infection.

### Role of isoniazid preventive treatment in HIV-positive individuals

The theoretical benefits of isoniazid preventive treatment are attractive. The table shows the potential disadvantages and necessary precautions.

<table>
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<th>Necessary precaution</th>
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<td>risk of drug toxicity (especially liver damage)</td>
<td>do not give to people with chronic disease or who drink alcohol regularly</td>
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<td>emergence of drug-resistance (if the patient has undetected TB disease and not just <em>M. tuberculosis</em> infection)</td>
<td>in all cases exclude TB disease by chest X-ray, in cases with cough of 3 weeks’ duration or more by sputum microscopy</td>
</tr>
<tr>
<td>diversion of resources from NTP activities</td>
<td>funding must be from sources other than NTP (e.g. AIDS control programme, voluntary sector)</td>
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There are limitations in the feasibility of isoniazid preventive treatment on a wide scale in developing countries.

a) Voluntary HIV testing is not widely available, so the number of suitable known HIV-positive persons is a small proportion of all HIV-positive persons.

b) Resources are often inadequate to ensure satisfactory exclusion of TB disease, treatment compliance and patient monitoring for drug toxicity.

c) When HIV-positive persons develop TB, we do not know how many are due to reactivation of old infection and how many to new infection. Isoniazid preventive treatment will protect against new infection only during the 6 months of treatment. So the effectiveness of a course of isoniazid preventive treatment will be limited if TB is often due to new infections.

d) Many HIV-positive persons infected with \textit{M. tuberculosis} have a negative tuberculin skin test. So screening for \textit{M. tuberculosis} by tuberculin skin testing will not identify all persons infected with \textit{M. tuberculosis}.

e) HIV-positive persons who feel well may be reluctant to accept TB screening and consideration of isoniazid preventive treatment.

Isoniazid preventive treatment programmes need evaluation. We need to know their cost, sustainability, potential impact, and effect on drug resistance. WHO does not at present recommend widespread isoniazid preventive treatment for HIV-positive persons in high TB prevalence countries. Isoniazid preventive treatment may have a role in selected groups (e.g., workers in a factory, health workers, soldiers) and in selected individuals.

\textbf{SUGGESTIONS FOR FURTHER READING}


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The tuberculosis epidemic is growing larger and more dangerous each year. The World Health Organization's Global Tuberculosis Programme (GTB) monitors and surveys this epidemic. More importantly, GTB helps countries to control the epidemic by working with them to develop and implement the technical inputs, training, and research necessary to establish effective tuberculosis control programmes.

If you would like further information about the tuberculosis epidemic or the WHO Global Tuberculosis Programme, please call 41 22 791 2853, send an e-mail to FightTB@WHO.CH, or write to: Documentalist, Global Tuberculosis Programme, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland.