Tuberculosis
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Objectives
1. Describe the epidemiology, clinical manifestations, diagnosis, and treatment of tuberculosis (TB).
2. Describe the interaction between anti-TB and antiretroviral drugs.
3. Describe preventive therapy for TB.

Key Points
1. Tuberculosis is the leading cause of death among human immunodeficiency virus (HIV)-infected individuals worldwide.
2. In settings of high HIV prevalence, all patients with TB should be offered HIV testing and counseling, and those who are found to be HIV infected should be offered the full range of available HIV services.
3. A negative Mantoux test does not exclude TB.
4. All children younger than 5 years and those aged 5 or more years who are symptomatic, who have been in close contact with a smear-positive TB case, must be screened for TB.
5. When any child (<15 years) is diagnosed with TB, an effort should be made to detect the source case (usually a smear-positive adult) and any other undiagnosed cases in the household.
6. Bacteriologic confirmation of Pulmonary TB (AFB smear and culture) using 3 specimens of expectorated sputum, induced sputum or early-morning gastric aspirates should be done whenever possible.
7. Principles of treating TB in HIV-infected and noninfected patients are the same, and cure is largely unaffected by HIV status.

Epidemiology of Tuberculosis
An estimated one-third of the world population is infected with Mycobacterium tuberculosis (the bacterium that causes tuberculosis [TB]), and each year an estimated 9 million people develop TB, of whom about 2 million die.

Of the 9 million annual TB cases, 1 million (11%) occur in children younger than 15 years. Of these childhood cases, 75% occur annually in 22 high-burden countries, most of which are in sub-Saharan Africa. Primary pulmonary infection with M. tuberculosis often is silent, with no obvious signs, symptoms, or radiographic abnormalities.

The likelihood of symptom development is age dependent, being greatest in infants and the elderly mainly because of their underdeveloped and waning immune systems, respectively. The risk of active TB in individuals with latent infection is increased 100-fold by HIV coinfection. TB is the most common cause of death among HIV-infected people worldwide.

HIV produces progressive loss of CD4+ lymphocytes (T cells), cells critical to the body’s defense against M. tuberculosis. HIV promotes the occurrence of TB at any stage of HIV disease, but clinical features of TB do vary by CD4+ lymphocyte count. Adults with HIV and CD4+ lymphocyte counts of more than 350 cells/µL typically manifest pulmonary disease alone, with predominantly upper-lobe infiltrates and/or cavitations. Extrapulmonary TB (including pleuritis, pericarditis, meningitis, and disseminated disease) often is observed among HIV-infected adults with CD4+ lymphocyte counts of less than 50 cells/µL. Chest radiographs often show lower- and/or middle-lobe infiltrates, sometimes miliary and typically without cavitation. The occurrence of TB is also associated with higher HIV viral load and more rapid progression of HIV disease.

A review of the natural history of pulmonary tuberculosis in childhood indicates that 50%-75% of children develop radiographically visible hilar adenopathy after primary infection with M. tuberculosis, but more than 90% of these do not progress to TB disease. Children with the highest risk of disease progression are those younger than 2 years mainly because of their underdeveloped immune systems. Younger children tend to develop noncavitary, segmental
lung lesions, whereas older children can have reactivation pulmonary TB that resembles adult disease.

Key risk factors for TB in children include the following:
1. Household contact with a newly diagnosed smear-positive TB case
2. Age younger than 5 years
3. HIV infection
4. Severe malnutrition

Diagnosis
The recommended approach to diagnosis of TB in children includes the following:
1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Bacteriological confirmation whenever possible
5. Investigations relevant for suspected pulmonary TB (mainly chest radiograph) and suspected extrapulmonary TB
6. HIV testing (in high-HIV prevalence areas)

Careful History, Including History of TB Contact and Symptoms Consistent with TB
A close contact is defined as one living in the same household as or in frequent contact with a source case with sputum smear-positive pulmonary TB. Source cases that are sputum smear negative but culture positive are also infectious, albeit to a lesser degree.

All children younger than 5 years and those aged 5 or more years who are symptomatic, who have been in close contact with a smear-positive TB case, must be screened for TB. When any child (<15 years) is diagnosed with TB, an effort should be made to detect the source case (usually a smear-positive adult) and any other undiagnosed cases in the household. If a child presents with smear-positive or cavitary pulmonary TB, child contacts must be looked for and screened. The commonest symptoms that should be looked for include
- chronic cough not improving and that has been present for more than 21 days;
- fever of more than 38°C for 14 days, after common causes such as malaria or pneumonia have been excluded; and
- weight loss or failure to thrive, for which it is necessary to look at the child’s growth chart.

Clinical Examination
Physical signs suggestive of extrapulmonary TB include the following:
- Meningitis not responding to antibiotic treatment, with a subacute onset or raised intracranial pressure.
- Pleural effusion.
- Pericardial effusion.
- Ascites.
- Nonpainful enlarged lymph nodes without fistula formation.
- Documented weight loss or failure to gain weight—especially after treatment in a nutritional rehabilitation program—is a good indicator of chronic disease, of which TB may be the cause.
Mantoux Tuberculin Skin Testing
Tuberculin skin testing using purified protein derivative is performed in many settings to screen for infection with *M. tuberculosis*. However, HIV-infected individuals often are anergic (nonreactive) to purified protein derivative as a consequence of HIV-related impairment of cell-mediated (T cell) immunity. Also, interpretation of the Mantoux test in patients who have received bacillus Calmette-Guérin bacillus (BCG) vaccine can be complicated. In general, the Mantoux test should be interpreted irrespective of whether the patient has received the BCG vaccine. In HIV-infected patients and children with severe malnutrition, a Mantoux test reaction (induration) measuring 5 mm or greater in diameter is considered positive. This is in contrast with HIV-uninfected individuals, in whom a Mantoux test reaction of 10 mm or greater is considered positive. A negative Mantoux test does not exclude TB.

Bacteriological Confirmation
Bacterial confirmation for pulmonary TB consists of three morning expectorated sputum samples for acid-fast bacillus (AFB) smear and culture. If there is no sputum production, induced sputum (using hypertonic saline) or early-morning gastric aspiration can be used. The sensitivity of expectorated sputum samples for diagnosis of TB in adults with or without HIV is about 50%. This figure is comparable to that of induced sputum or bronchoscopy. Several DNA probe and nucleic acid amplification methods have been evaluated in the diagnosis of TB. The best of these may have sensitivity greater than that of AFB smear and culture. Such tests also are highly specific for *M. tuberculosis*, and their use hastens bacterial identification, but cost is prohibitive in many settings (US$50-$100 per test). Where available, these newer tests can be helpful in confirming the diagnosis of TB in moderate- or high-risk patients where other clinical and laboratory findings present a confusing picture.

Diagnosis of TB in young children (<5 years) is made more difficult by their inability to expectorate sputum suitable for AFB smear and culture. In addition, most children (especially those <5 years) have paucibacillary tuberculosis (TB with few tubercle bacilli) and therefore tend to be sputum smear negative. In children who are unable to expectorate sputum, an attempt should be made to obtain 3 specimens of induced sputum, or early morning gastric aspirates. Several recent studies have found that sputum induction using hypertonic saline and a bronchodilator such as salbutamol is safe, effective and well-tolerated in children of all ages and the bacterial yields are as good or better than for gastric aspirates. Induced sputum specimens should be sent for AFB smear and culture. Where sputum induction is not available, 3 early-morning gastric aspirate specimens should be collected on separate days, using a nasogastric tube, on awakening the child before they ambulate or eat. Gastric aspirate specimens should be cultured for *M. tuberculosis*, AFB smears are generally not useful.

Because *M. tuberculosis* is slow growing, culture confirmation prior to initiation of therapy is not always practical. A presumed diagnosis of TB can be made based on a history of contact with an individual with TB, appropriate clinical signs and symptoms, a positive Mantoux tuberculin skin test, and typical chest radiographic features. Classic signs and symptoms include chronic cough, hemoptysis (blood-stained or bloody sputum), night sweats, fever, and weight loss. Common chest radiographic findings include hilar adenopathy, pleural effusion, focal infiltrates in the upper and hilar regions, and cavitations.

Key features suggestive of TB in children include
1. chronic symptoms suggestive of TB,
2. physical signs highly suggestive of TB,
3. a positive tuberculin (Mantoux) skin test, and
4. chest x-ray features suggestive of TB.

HIV Testing
In settings of high HIV prevalence, all patients with TB should be offered HIV testing and counseling, and those who are found to be HIV infected should be offered the full range of available HIV services.
HIV-infected individuals are more prone than HIV-uninfected individuals to develop extrapulmonary TB. One form appears as diffuse lymphadenopathy. Biopsy or fine-needle aspirate will reveal necrotizing and nonnecrotizing granulomas. Young children with TB are at increased risk of extrapulmonary TB and disseminated disease with meningitis, pleural or pericardial effusion, or involvement of the spine. **Table 1** summarizes forms of extrapulmonary TB in children and the practical approach to diagnosis.

**Table 1. Forms of extrapulmonary TB in children and relevant investigations**

<table>
<thead>
<tr>
<th>Site</th>
<th>Practical Approach to Diagnosis</th>
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<tbody>
<tr>
<td>Peripheral lymph nodes (especially cervical)</td>
<td>Lymph node biopsy or fine needle aspiration</td>
</tr>
<tr>
<td>Military TB (e.g., disseminated)</td>
<td>Chest x-ray and lumbar puncture (to test for meningitis)</td>
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<tr>
<td>TB meningitis</td>
<td>Lumbar puncture (and computerized tomography where available)</td>
</tr>
<tr>
<td>Pleural effusion (older children and adolescents)</td>
<td>Chest x-ray, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture</td>
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<tr>
<td>Abdominal TB (e.g., peritoneal)</td>
<td>Abdominal ultrasound and ascitic tap</td>
</tr>
<tr>
<td>Osteoarticular</td>
<td>X-ray, joint tap or synovial biopsy</td>
</tr>
<tr>
<td>Pericardial TB</td>
<td>Ultrasound and pericardial tap</td>
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</table>
Management and Treatment

The main objectives of anti-TB treatment are to
1. cure the patient of TB (by rapidly eliminating most of the tubercle bacilli),
2. prevent death from active TB or its late effects,
3. prevent relapse of TB (by eliminating the dormant tubercle bacilli),
4. prevent development of drug resistance (by using a combination of effective drugs), and
5. decrease TB transmission.

Children usually have paucibacillary pulmonary tuberculosis (i.e., TB with low numbers of organism); cavitating TB is relatively rare (≤6%) in those younger than 13 years. Extrapulmonary disease and severe or disseminated TB occur especially more commonly in the youngest children (<2 years). Both the organism load and the type of disease may influence the effectiveness of treatment regimens. Treatment outcomes in children are, however, generally good even in young and immunocompromised children, provided that treatment is commenced promptly.

Ideally, patients newly diagnosed with TB should be managed in coordination with public health professionals (e.g., the National TB Control Program) who are well versed in contact investigation, local factors influencing treatment choices (e.g., local prevalence of drug resistance), and available local resources. Treatment choices generally are dictated by relevant national protocols.

Principles of treating TB in the HIV-infected and non-infected patients are the same:
- Goals and case definitions are the same.
- Dosing and duration of anti-TB therapy regimens are the same.
- Laboratory and clinical monitoring are the same.
- Cure is largely unaffected by HIV status.

In both adults and children, a commonly prescribed regimen for drug-susceptible TB is isoniazid, rifampicin, and pyrazinamide (with ethambutol often added for adults and older children and for children with severe forms of tuberculosis or TB with severe HIV/AIDS) for 1 or 2 months, followed by isoniazid and rifampicin alone. Rifabutin can be substituted for rifampicin. In settings where directly observed therapy for TB is available, twice-weekly treatment with isoniazid and rifampicin often is given after an initial 1- or 2-month period of daily three- or four-drug treatment. Response to TB treatment is largely unaffected by HIV status. Thus, most current international guidelines recommend that TB in HIV-infected adults and children should be treated with a 6-month regimen, as in HIV-uninfected patients. However, some national guidelines recommend that patients with pulmonary TB be treated for 9 months and those with extrapulmonary TB be treated for 12 months.

The recommended daily dose of ethambutol is higher in children (20 mg/kg of body weight) than in adults (15 mg/kg) because the pharmacokinetics is different—peak serum concentrations are lower in children than in adults receiving the same milligram-per-kilogram dose. Although ethambutol was frequently omitted from treatment guidelines partly because of concerns about difficulty of monitoring for toxicity (particularly for optic neuritis) in young children, recent data indicate that it is safe in children at a dose of 20 mg/kg (range, 15-25 mg/kg) daily. Streptomycin should be avoided when possible in children because the injections are painful and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dose</th>
<th>Daily</th>
<th>Three times weekly</th>
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<tbody>
<tr>
<td></td>
<td>Dose and range (mg/kg of body weight)</td>
<td>Maximum (mg)</td>
<td>Dose and range (mg/kg of body weight)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 (4-6)</td>
<td>300</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 (8-12)</td>
<td>600</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 (20-30)</td>
<td>—</td>
<td>35 (30-40)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Children 20 (15-25)</td>
<td>—</td>
<td>30 (25-35)</td>
</tr>
<tr>
<td></td>
<td>Adults 15 (15-20)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 (12-18)</td>
<td>—</td>
<td>15 (12-18)</td>
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irreversible auditory nerve damage may occur. The use of streptomycin in children is reserved mainly for the first 2 months of treatment of TB meningitis.

Corticosteroids may be used for the management of some complicated forms of TB, such as TB meningitis, complications of airway obstruction by tuberculous lymphadenopathy, and TB pericarditis. Steroids are recommended for all cases of TB meningitis, where they improve both survival and morbidity. The most commonly used drug is prednisone 2 mg/kg daily, increased up to 4 mg/kg daily in the most severe cases, with a maximum dose of 60 mg/day for 4 weeks. The dose should then be tapered over 1-2 weeks before stopping.

**Multidrug-Resistant TB**

Multidrug-resistant (MDR) TB is resistant to both isoniazid and rifampicin, with or without resistance to other ant-TB drugs. In children MDR-TB is usually a result of transmission of a resistant strain of TB from an adult source. As a result MDR is usually diagnosed late in children unless there is a clear history of contact with an adult case of MDR-TB. Treatment of MDR-TB is difficult and referral to a specialist is highly recommended. Some basic principles of management of MDR-TB are as follows:

- Do not add one drug to a failing regimen.
- It is best to treat MDR-TB according to drug-susceptibility patterns (use the adult source case susceptibility pattern if the child’s is not available).
- Use at least four drugs.
- Daily directly observed therapy is essential.
- Provide consistent ongoing counseling and support to the caregiver and educate about the importance of completion of the treatment course.
- Clinical, radiological, and bacteriological follow-up are essential.
- Treatment duration depends on the extent of disease but is generally 12 months or longer (or ≥12 months after the last positive culture).
- With correct dosing, few long-term adverse events are seen with any of the more toxic second-line TB drugs, including ethionamide and the fluoroquinolones.

**Table 4** summarizes the second-line (reserve) drugs used to treat MDTR-TB in children.
Extensively Drug-Resistant TB

Extensively drug-resistant (XDR) TB is resistant to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, capreomycin, kanamycin) in addition to isoniazid and rifampicin. This form of TB should be managed by experts in tertiary centers. Detailed discussion of XDR TB is beyond the scope of this publication.

Follow-Up and Monitoring

Patients on anti-TB therapy should ideally be monitored at least at the following intervals: 2 weeks after initiation of treatment, at the end of the intensive phase (usually 2 months), and every 2 months until completion of the treatment. Assessment should include (but not be limited to) assessment of symptoms and signs, medication adherence, drug toxicity and other adverse events, and weight gain. Doses should be adjusted according to weight gain. Liver enzymes must be monitored in patients concomitantly receiving antiretroviral and TB medications. Pyridoxine (10 mg by mouth daily) is recommended for all HIV-infected adults and children receiving isoniazid to help prevent drug-associated peripheral neuropathy. Signs and symptoms of peripheral neuropathy include numbness, tingling or prickling sensations in the hands and feet, absent deep-tendon reflexes, and foot drop. A follow-up sputum sample at 2 months post anti-TB therapy initiation should be obtained for all patients who were sputum positive at baseline. Follow-up chest radiographs are not routinely required, especially in children, who tend to have slow radiological response to treatment.

Interactions Between Anti-TB and Antiretroviral Drugs

Many medications used to treat TB interact with medications used to treat HIV. Of particular note is the interaction between rifampicin and either nonnucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs). Also, anti-TB and antiretroviral drugs have overlapping toxicities; the many drugs involved in treating the two diseases concomitantly poses significant adherence challenges, and paradoxical reactions due to immune reactivation or reconstitution after initiation of antiretroviral therapy may occur in 7%-36% of patients. In addition, very few studies have examined the optimal timing of antiretroviral therapy in TB/HIV co-infected individuals.

Because of these considerations, most physicians have been reluctant to simultaneously start anti-TB and antiretroviral medications. However, there is some recent evidence which suggests that starting HAART as soon as possible after starting anti-TB medications may improve survival in TB/HIV co-infected individuals. A recent Randomized Controlled Trial (SAPIT trial) done in South Africa found that starting Anti-retroviral therapy in TB/
HIV co-infected patients with CD4 counts less than 500 cells/mm³ who are on anti-TB medications (concurrent regimen) reduced mortality by up to 55% (HR 0.451, 95% CI: 0.26 to 0.79; p = 0.0049) when compared to delaying HAART until after completion of anti-TB therapy (sequential regimen). In this study, those on the concurrent regimen started HAART, on average, 67 days after starting anti-TB treatment compared to a 261 days delay for those on the sequential regimen. The observed mortality reduction was significant regardless of CD4 count. In addition, mathematical modeling done in Russia suggests that universal HAART coverage among TB/HIV co-infected individuals would significantly reduce TB incidence and mortality. World Health Organization (WHO) recommendations are as follows:

1. Start ART in all HIV-infected individuals with active tuberculosis (TB) irrespective of CD4 cell count.
2. Start TB treatment first, followed by ART as soon as possible after starting TB treatment.
3. Use efavirenz (EFV) as the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on TB treatment.

If a patient already is receiving antiretroviral medications when TB is diagnosed, these medications should not be discontinued. If possible, anti-TB medications that have fewer interactions with antiretroviral medications should be used (e.g., substituting rifabutin for rifampicin). Alternatively, one may consider using an antiretroviral regimen with fewer interactions with the anti-TB medications.

Interaction between rifampicin and many antiretroviral drugs occurs largely because these antiretroviral drugs are metabolized by the cytochrome P450 system of enzymes that is induced by rifampicin. The affected antiretroviral drugs are broken down at an accelerated rate, thus lowering their blood levels. Nucleoside reverse transcriptase inhibitors (NRTIs) are not metabolized by cytochrome P450 and are unaffected by rifampicin.

Pharmacological studies with few patients indicate that serum levels of the NNRTIs (nevirapine and efavirenz) and PIs are reduced in patients who are simultaneously treated with rifampicin. Blood levels of antiretroviral drugs are affected by coadministration of rifampicin as follows:

- Nevirapine, reduced by 37%
- Efavirenz, reduced by 25%
- Indinavir, reduced by 89%
- Ritonavir, reduced by 35%
- Saquinavir, reduced by 84%
- Nelfinavir, reduced by 82%
- Lopinavir/r, reduced by 75%

It is not known whether this type of interaction is serious enough to compromise the antiretroviral efficacy of NNRTIs; there are few clinical outcome data from controlled studies. Further, it is not known whether there are racial differences in these drug interactions. However, some recent data indicate that rifampicin can be used for treatment of active TB in patients whose antiretroviral regimen includes the NNRTI efavirenz and two NRTIs. The U.S. Centers for Disease Control and Prevention (CDC) guidelines suggest that rifampicin may also be used in antiretroviral regimens that include the NNRTI nevirapine.

The interaction between rifampicin and the PI class of drugs is problematic; there is strong evidence to indicate that rifampicin-induced reductions in the blood level of PIs may cause failure of antiretroviral treatment. In industrialized countries, rifabutin often is substituted for rifampicin. However, rifabutin is not part of TB treatment guidelines in most developing countries; it is expensive, and problems have been reported in obtaining sufficient supplies because of a world shortage of the drug. One way to overcome the difficulty of low PI serum levels is to give ritonavir concomitantly with the PI. Because ritonavir is the preferred substrate of the cytochrome P450 system, the system metabolizes ritonavir while allowing the concentration of the other PI to rise to levels similar to those that would be achieved without rifampicin. This is the principle that underpins PI boosting.

### Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical clinical deterioration, with new or worsening symptoms, signs, or radiological

#### Table 5. Overlapping toxicities between anti-TB and anti-retroviral medications.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Antituberculosis Drugs</th>
<th>Antiretroviral Drugs</th>
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</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>INH</td>
<td>D4T, DDI (also HIV)</td>
</tr>
<tr>
<td>Rash</td>
<td>SM, PZA, RIF, INH, EMB</td>
<td>NVP, EFV, ABC (also CTX)</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>PZA, RIF, INH</td>
<td>ZDV, PIs</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>PZA, RIF, INH</td>
<td>NVP, EFV, PIs</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>RIF</td>
<td>ZDV (also CTX)</td>
</tr>
</tbody>
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manifestations. IRIS sometimes occurs after beginning anti-TB therapy with or without antiretroviral therapy because of restoration of the capacity to mount an inflammatory immune response. This can simulate worsening disease, with fever and increased size of lymph nodes or tuberculomas. In TB patients who are coinfected with HIV, clinical deterioration due to immune reconstitution commonly occurs after initiation of antiretroviral therapy. This is especially more likely in those patients who begin anti-TB and antiretroviral therapy when they are severely immunocompromised (with very low CD4 counts) and who have a rapid improvement in their CD4 counts. In all cases of IRIS, anti-TB therapy should be continued. In some severe cases of IRIS, corticosteroids can be helpful in dampening the vigorous immune response. If there is any doubt, the patient should be referred to the next level of care, ideally to be managed by experts in a tertiary setting.

**TB Preventive Therapy (Isoniazid TB Preventive Therapy)**

Preventive therapy against TB includes giving one or more anti-TB drugs to individuals with latent *M. tuberculosis* infection to prevent progression to active disease. Before a person is considered for TB preventive therapy, active TB should be excluded. In 1998, the WHO and UNAIDS developed recommendations for preventive therapy. Preventive therapy is recommended in countries that have established HIV care and TB control programs. Also, resources must be available to

1. distinguish active from latent TB,
2. ensure appropriate monitoring and follow-up,
3. ensure consistent supply of medications, and
4. link preventive therapy against TB to voluntary counseling and testing for HIV.

Preventive TB therapy is recommended for HIV-infected individuals with a positive Mantoux skin test who do not have evidence of active TB (i.e., who have a normal chest radiograph and no suggestive clinical symptoms). In areas where Mantoux testing is not feasible, preventive therapy should be considered for the following high-risk individuals if they are infected with HIV:

- Persons living in populations with a high prevalence of TB (> 30%)
- Health care workers
- Household contacts of TB patients
- Prisoners
- Miners

Preventive therapy with isoniazid in adults is recommended at the dose of 5 mg/kg (maximum, 300 mg) by mouth daily for 6 months with clinical monitoring for adverse effects and active TB.

Until recently, isoniazid preventive therapy had not been studied in HIV-infected children. In a recent placebo-controlled randomized trial, isoniazid dosed at 10 mg/kg orally once daily or three times weekly was associated with a 53% reduction in mortality. The survival benefit occurred early (within 50 days) and was apparent in all CDC HIV categories of disease. The population studied lived in the Western Cape Province of South Africa, a region with one of the highest incidence rates of TB worldwide (4.1% annualized risk for children); therefore, the study’s findings are highly applicable to other countries with high TB prevalence. WHO recommends isoniazid prophylaxis (5 mg/kg daily) for at least 6 months for all asymptomatic children younger than 5 years and for all HIV-infected children, including those aged 5 or more years who are household contacts of adults with smear-positive tuberculosis. In all these cases it is essential that clinicians rule out active TB prior to commencing the children on isoniazid TB preventive therapy. The best way to detect TB infection is tuberculin skin testing, and chest x-ray is the best method to screen for TB disease among contacts. These tests should be used where they are readily available to screen exposed contacts. However, doing so may not be possible when tuberculin solution is unavailable, as is often the case in many developing countries. Clinical assessment alone is sufficient to decide whether the contact is well or symptomatic. Routine assessment of exposed contacts does not require chest x-ray or tuberculin skin testing.

**BCG Disease**

BCG is a live, attenuated vaccine derived from *Mycobacterium bovis*. WHO’s Expanded Program on Immunization recommends BCG vaccination for all newborns in high-burden countries.

BCG is a safe vaccine. However, 1%-2% of children will develop some complications after BCG vaccination. The most common complications include local reactions, localized abscesses, bacterial superinfection, suppurative adenitis, and local keloid formation. Most of these reactions resolve within a few weeks. However, those children who develop disseminated BCG disease should be investigated for immunosuppression (mainly HIV) and treated for TB with a standard first-line regimen (excluding pyrazinamide, to which *M. bovis* is universally resistant). Some children with persistent localized
abscesses may require surgical drainage. Management of adverse reactions in the setting of advanced HIV/AIDS or other immunodeficiencies is more complicated and may be best managed by specialists at tertiary centers.

REFERENCES


