The field of TB medicine and care is constantly developing and changing. Consequently, the information presented herein may need to be updated from time to time. The Aurum Institute maintains an up-to-date version of this publication for download on its web site: www.auruminstitute.org

Whilst the editors and the Aurum Institute have exercised the utmost care in producing this publication, they are not liable for any errors or omissions.

Comments and recommendations for changes, corrections or improvements may be sent to tools@auruminstitute.org
ACKNOWLEDGEMENTS

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>3TC</td>
<td>Lamivudine</td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>Abacavir</td>
<td></td>
</tr>
<tr>
<td>ADA</td>
<td>Adenosine Deaminase</td>
<td></td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Events Following Immunisation</td>
<td></td>
</tr>
<tr>
<td>AFB</td>
<td>Acid-fast Bacilli</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
<td></td>
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<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
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<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
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<tr>
<td>AZT</td>
<td>Zidovudine</td>
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<tr>
<td>BCG</td>
<td>Bacille Calmette-Guerin</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
<td></td>
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<tr>
<td>CXR</td>
<td>Chest X-ray</td>
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<tr>
<td>D4T</td>
<td>Stavudine</td>
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<tr>
<td>DDI</td>
<td>Didanosine</td>
<td></td>
</tr>
<tr>
<td>DOT</td>
<td>Directly Observed Therapy</td>
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<tr>
<td>DR-TB</td>
<td>Drug-Resistant Tuberculosis</td>
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<tr>
<td>DST</td>
<td>Drug Susceptibility Testing</td>
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<tr>
<td>E</td>
<td>Ethambutol</td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>Efavirenz</td>
<td></td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunisation</td>
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</tr>
<tr>
<td>EPTB</td>
<td>Extra-pulmonary Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
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<tr>
<td>FLQ</td>
<td>Fluoroquinolone</td>
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<tr>
<td>FTC</td>
<td>Emtricitabine</td>
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<tr>
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<td>GeneXpert</td>
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<tr>
<td>H</td>
<td>Isoniazid</td>
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<tr>
<td>HB</td>
<td>Haemoglobin</td>
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</tr>
<tr>
<td>HCT</td>
<td>HIV Counselling and Testing</td>
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</tr>
<tr>
<td>HCW</td>
<td>Healthcare Worker</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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</tr>
<tr>
<td>ICF</td>
<td>Intensified Case Finding</td>
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</tr>
<tr>
<td>IGRA</td>
<td>Interferon Gamma Release Assay</td>
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</tr>
<tr>
<td>INH</td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>IPT</td>
<td>Isoniazid Preventive Therapy</td>
<td></td>
</tr>
<tr>
<td>IRIS</td>
<td>Immune Reconstitution Inflammatory Syndrome</td>
<td></td>
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<tr>
<td>KZN</td>
<td>Kwazulu-Natal</td>
<td></td>
</tr>
<tr>
<td>LP</td>
<td>Lumbar Puncture</td>
<td></td>
</tr>
<tr>
<td>LPA</td>
<td>Line Probe Assay</td>
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</tr>
<tr>
<td>LPV/r</td>
<td>Lopinavir/Ritonavir</td>
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</tr>
<tr>
<td>MDI</td>
<td>Metered Dose Inhaler</td>
<td></td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multi-drug Resistant Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>MGIT</td>
<td>Mycobacterial Growth Indicator Tube</td>
<td></td>
</tr>
<tr>
<td>MOTT</td>
<td>Mycobacteria Other Than Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>NaOH</td>
<td>Sodium Hydroxide</td>
<td></td>
</tr>
<tr>
<td>NHLS</td>
<td>National Department of Health</td>
<td></td>
</tr>
<tr>
<td>NDoH</td>
<td>National Health Laboratory Service</td>
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</tr>
<tr>
<td>NVP</td>
<td>Nevirapine</td>
<td></td>
</tr>
<tr>
<td>OFX</td>
<td>Ofloxacin</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>Para-aminosalicylic Acid</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
<td></td>
</tr>
<tr>
<td>PHC</td>
<td>Primary Health Care</td>
<td></td>
</tr>
<tr>
<td>PMTCT</td>
<td>Prevention of Mother to Child Transmission</td>
<td></td>
</tr>
<tr>
<td>PNP</td>
<td>Peripheral Neuropathy</td>
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<tr>
<td>PPD</td>
<td>Purified Protein Derivative</td>
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<tr>
<td>PZA</td>
<td>Pyrazinamide</td>
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<tr>
<td>R</td>
<td>Rifampicin</td>
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<tr>
<td>RIF</td>
<td>Rifampicin</td>
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<tr>
<td>S</td>
<td>Streptomycin</td>
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<td>SAT</td>
<td>Turn-around-time</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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</tr>
<tr>
<td>TDF</td>
<td>Tenofovir</td>
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<tr>
<td>TST</td>
<td>Tuberculin Skin Test</td>
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<tr>
<td>VCT</td>
<td>Voluntary Counselling and Testing</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
<td></td>
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<tr>
<td>XDR-TB</td>
<td>Extensively Drug-resistant TB</td>
<td></td>
</tr>
<tr>
<td>Z</td>
<td>Pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>ZN</td>
<td>Ziehl-Neelsen</td>
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</tbody>
</table>
TREATMENT
First-Line TB Treatment in Adults __________________________________________
Monitoring Of Patients On First-Line TB Treatment ____________________________
TB Treatment in Children ________________________________________________
Side Effects of First-Line TB Treatment ______________________________________
Mono- and Poly-Resistant TB _____________________________________________
MDR-TB Diagnosis and Management _______________________________________
Monitoring of MDR-TB Patients on Treatment ________________________________
Non-Tuberculous Mycobacteria ____________________________________________
Important TB Drug Interactions ___________________________________________
Supporting Adherence in TB Patients _______________________________________
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## Prevention

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THE GLOBAL BURDEN OF TB
- Despite the fact that TB is curable, it is still a major cause of illness and death in South Africa and globally
- TB is second only to HIV/AIDS in terms of mortality due to a single infectious agent

THE SOUTH AFRICAN TB EPIDEMIC
- Numerous factors have converged to create one of the biggest TB epidemics in the world
- Drivers of the TB epidemic include:
  - Social conditions including migrant labour, poor health infrastructure
  - Economic conditions including poverty, unemployment
  - Environmental conditions including overcrowded squatter camps
  - The HIV epidemic
- New infections have increased by over 400% in the last 15 years
- Currently, South Africa has the 3rd highest number of new TB cases in the world, after India and China

ESTIMATED TB INCIDENCE RATES, 2011

WHO Global TB Report 2012
ESTIMATED HIV PREVALENCE IN NEW TB CASES, 2011

ESTIMATED TB INCIDENCE RATES, SOUTH AFRICA, 1990-2011

TB AND HIV CO-INFECTION
- TB and HIV are closely linked
- People living with HIV and infected with TB are 21-34 times more likely to develop TB disease compared to people with TB infection who are not HIV-infected
- TB is a leading killer of people living with HIV causing 25% of all HIV-related deaths
- TB has also been shown to increase the risk of HIV progression and death, particularly if HIV is untreated
- In 2011 there were an estimated 1.1 million new cases of TB in HIV-infected individuals and 430 000 deaths due to TB in HIV-infected individuals

TB IN CHILDREN
- For many years, the prevention, diagnosis and treatment of TB among children has been relatively neglected
- The accurate diagnosis of TB in children is somewhat difficult and as a result, the extent of the disease burden in children is often underestimated
- In 2011, there were an estimated 490 000 cases and 64 000 deaths due to TB in children globally
- It is estimated that children constitute 15-20% of the total TB disease burden in highly endemic areas
- In 2010, there were about 10 million children orphaned as a result of TB deaths among parents
When someone with pulmonary TB coughs, invisible droplets containing TB bacilli are dispersed into the air. They remain suspended in the air and fall at a rate of 12mm/hr. These droplets can then be inhaled by others. When inhaled, they reach the alveoli of the lungs and TB infection may occur. The immune system may gain control of the TB bacilli, potentially resulting in latent infection. In latent infection some bacilli do not die, but remain dormant. The patient is asymptomatic. The immune system has been sensitised to TB and the tuberculin skin test may be positive. Latent infection may then progress to TB disease. This occurs if there is repeated heavy exposure to TB or a weak immune system which could occur in the following instances:

i. HIV infection with falling CD4 count
ii. Alcohol abuse
iii. Malnutrition
iv. The elderly
v. Children <5 years
vi. Chronic illnesses
vii. Smoking

The immune system is no longer able to control the TB bacilli and the TB disease becomes active. Infection may go directly to disease in some patients; with no intervening latent infection. The bacilli multiply and cause damage to the lung and/or other parts of the body. The person develops symptoms such as cough, fever, night sweats, loss of weight.
WHAT IS INTENSIFIED CASE FINDING (ICF)?
ICF refers to the process of actively screening persons for signs and symptoms of TB.

WHO SHOULD BE SCREENED FOR TB?
In SA, everyone who presents to a health care facility for any reason, including reasons not related to ill health (i.e. for preventive services, well baby clinic, family planning etc.), should be screened for TB.

IS ICF ONLY FOR HIV-INFECTED PATIENTS?
• No!
• We need to use every opportunity to ask all patients for TB symptoms at every visit to the Health Care Facility.
• This is important for:
  • detecting TB early
  • separating patients with TB symptoms from other patients to improve TB infection control.

WHO IS A HIGH PRIORITY FOR ICF?
• Children under 5 years
• The elderly
• HIV-infected persons
• Persons with a TB contact*
• Persons with Diabetes
• Persons with Silicosis
• Persons on Steroids > 4 weeks
• Persons receiving chemotherapy for malignancy

WHAT SCREENING TOOL MUST WE USE?
• The tool on the next page can be used for all patients entering the clinic (HIV-infected and uninfected).

HOW DO WE IMPLEMENT ICF IN CHILDREN?
• All children with a TB contact (smear and/or culture positive) must have a thorough history and clinical examination.
• If children are symptomatic, do the following:
  • HIV testing
  • Tuberculin skin test (TST) if <5 years
  • CXR, if available
  • Respiratory specimen(s) for TB testing
  • Additional TB investigations based on clinical findings, refer if necessary
  • Consider initiation of TB therapy
• In children < 5 years or HIV-infected (regardless of age) with no symptoms, do the following:
  • HIV testing if status unknown
  • IPT (do not need CXR and Mantoux)

* Please refer to the South African Guidelines on conducting contact investigations for TB for detailed information on undertaking household contact tracing of index patients.
TUBERCULOSIS SYMPTOM SCREENING TOOL FOR ADULTS

Surname ________________________________ M/F
First Names ________________________________
Address __________________________________________
Contact Numbers __________________________ Date __________________
Patient number or Folder number __________________________
Facility contact details __________________________

Reasoning for screening (tick ✓)
TB Contact
MDR/XDR TB Contact
HCT/PMTCT/Wellness /ART

If “yes” to one or more of the questions, suspect TB

<table>
<thead>
<tr>
<th>Symptom (tick ✓)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have a cough for more than 2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If HIV positive: do you have a cough of &gt; 24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have loss of weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you sweat a lot at night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have fever</td>
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<td></td>
</tr>
</tbody>
</table>

If “yes” to one or more of the questions, evaluate TB

Refer for clinical evaluation (for lay counselors & others)
Evaluate clinically and take sputum (for health workers)
If “no” to all the questions, and the patient is HIV positive, give information on the benefit of IPT (TB preventive therapy) and assess patient eligibility or refer the patient for IPT (tick relevant ✓)
IPT started
Referred to IPT

Name of facility the patient is referred to: __________________________
Name of counselors / health care worker: __________________________
TB Symptom screening tool for children

Surname ___________________________ First Name ________________________________
Address ___________________________ Date ________________________________
Contact number ___________________________ Date ________________________________
Patient record or Folder Number: ________________________________

Has the child been in close contact with a person diagnosed with Pulmonary TB/ DR-TB in the past 12 months history of TB contact: Yes ☐ No ☐ Type of index case: TB ☐ MDR/ XDR-TB ☐

Tick “yes” or “no” on the following questions

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough of more than 14 days which is not improving on treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent fever for the past 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented weight loss/ failure to thrive (Road to Health Card)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue (less playful/ always tired)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If “yes” to one or more of the questions, suspect TB: Collect sputum specimen if cough is present, if No cough but other symptoms present refer to clinic for investigation

Action Plan

Sputum collected:       Yes ☐ No ☐ Collection date: ________________________________
Sputum test results: ________________________________
Referred to clinic for investigation/ treatment: Yes ☐ No ☐
Facility name / contact details: ____________________________________________
_________________________________________________________________________
TB DIAGNOSIS IN A NEW CASE USING SMEAR MICROSCOPY AND CULTURE

No previous TB or less than 4 weeks of TB treatment
Send 2 sputum specimens for smear microscopy:
• 1st ‘spot’ specimen taken at the health facility under supervision
• 2nd early morning specimen

HIV-uninfected or HIV status unknown

AFB+  AFB+
AFB+  AFB-
AFB-  AFB-  

Provide Antibiotics

Treat as TB
Provide full course of treatment

AFB+ and
TB on chest X-ray

Health Care Worker decision to treat on clinical grounds

AFB- and
No TB on chest X-ray

Consider other diagnosis
Review clinical picture and progress when culture result available for smear negative cases

AFB-
and
TB on chest X-ray

Consider other diagnosis
Review TB culture result

HIV-infected

AFB+  AFB+
AFB+  AFB-
AFB-  AFB-

Treat as TB
Provide full course of treatment

AFB+  AFB-

Send 3rd specimen for smear and culture
Do chest X-ray

Provide antibiotics

AFB-

Treat as TB
Aim to provide full course of treatment

AFB- and
No TB on chest X-ray

Aim to provide full course of treatment

If an antibiotic is required the following can be used: amoxycillin 500mg 8 hourly orally for 5 days. If allergic to penicillin use erythromycin 500mg 6 hourly orally for 5 days.
TB DIAGNOSIS IN HIGH RISK PATIENTS WITH TB SYMPTOMS AND RE-TREATMENT CASES USING SMEAR MICROSCOPY, CULTURE AND DST

Previous TB (4 or more weeks of TB treatment) and high risk patient with TB symptoms (MDR contact, health care personnel, prisoner)
Send 2 sputum specimens:
- 1st “spot” specimen taken at the health facility for sputum smear microscopy
- 2nd early morning specimen for sputum smear microscopy, culture and drug susceptibility testing (DST)

HIV-uninfected or HIV status unknown

<table>
<thead>
<tr>
<th>AFB+</th>
<th>AFB+</th>
<th>AFB-</th>
<th>AFB-</th>
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<tbody>
<tr>
<td>AFB+</td>
<td>AFB-</td>
<td>AFB-</td>
<td>AFB-</td>
</tr>
</tbody>
</table>

- **Treat as TB**
  - Provide full course of treatment
  - Review drug sensitivity

<table>
<thead>
<tr>
<th>AFB+</th>
<th>AFB-</th>
<th>AFB-</th>
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<td>AFB-</td>
<td>AFB-</td>
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</tbody>
</table>

- **Treat as TB**
  - Provide full course of treatment
  - Review drug sensitivity

HIV-infected

<table>
<thead>
<tr>
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<th>AFB+</th>
<th>AFB+</th>
<th>AFB+</th>
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<tbody>
<tr>
<td>AFB-</td>
<td>AFB-</td>
<td>AFB-</td>
<td>AFB-</td>
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</tbody>
</table>

- **Send 3rd specimen for smear**
- **Do chest X-ray**
- **Provide antibiotics**

<table>
<thead>
<tr>
<th>AFB+</th>
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<th>AFB-</th>
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<tr>
<td>AFB+</td>
<td>AFB-</td>
<td>AFB-</td>
<td>AFB-</td>
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</tbody>
</table>

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  - Provide full course of treatment
  - Review drug sensitivity

<table>
<thead>
<tr>
<th>AFB+</th>
<th>AFB-</th>
<th>AFB-</th>
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<tbody>
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<td>AFB-</td>
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</tbody>
</table>

- **Treat as TB**
  - Provide full course of treatment
  - Review drug sensitivity

<table>
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<th>AFB+</th>
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<th>AFB-</th>
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<td>AFB-</td>
<td>AFB-</td>
<td>AFB-</td>
</tr>
</tbody>
</table>

- **Treat as TB**
  - Provide full course of treatment
  - Review drug sensitivity

If an antibiotic is required the following can be used: amoxycillin 500mg 8 hourly orally for 5 days. If allergic to penicillin use erythromycin 500mg 6 hourly orally for 5 days.
PATIENTS WITH TB SYMPTOMS
Collect one sputum specimen

Microscopy

Smear Negative
Collect 2nd sputum specimen
Chest x-ray
Treat with Antibiotics for 5 days
Review

Culture

- Culture Negative: No treatment
- Culture Positive: Start TB treatment

Smear Positive
Collect 2nd specimen
Start TB treatment

Line Probe Assay

- Resistant: Start MDR-TB treatment
- Sensitive: Start TB treatment

Monitor with smear microscopy and culture
Monitor with smear microscopy

If an antibiotic is required the following can be used: amoxycillin 500mg 8 hourly orally for 5 days. If allergic to penicillin use erythromycin 500mg 6 hourly orally for 5 days.
PATIENTS WITH TB SYMPTOMS
TB and DR-TB contacts, non-contact symptomatic individuals, re-treatment after relapse, failure and default. Collect one sputum specimen at the health facility under supervision.

**MTB complex detected**
- Rifampicin susceptible
  - **Treat as TB**
    - Start on regimen 1
    - Collect **ONE** specimen for microscopy, culture and DST/LPA
    - Treat with antibiotics and review after 5 days
    - Do chest X-ray
    - Follow up with microscopy and culture

- Rifampicin resistant
  - **Treat as MDR-TB**
    - Start on regimen 1
    - Collect **ONE** specimen for microscopy, culture and DST/LPA
    - Treat with antibiotics and review after 5 days
    - Do chest X-ray
    - Follow up with microscopy and culture

**MTB complex not detected**

**MTB complex detected**
- Rifampicin unsuccessful
  - **Treat as TB**
    - Start on regimen 1
    - Collect **ONE** specimen for microscopy, culture and DST/LPA
    - Treat with antibiotics and review after 5 days
    - Do chest X-ray
    - Follow up with microscopy and culture

**MTB complex detected**
- Rifampicin resistant
  - **Treat as MDR-TB**
    - Start on regimen 1
    - Collect **ONE** specimen for microscopy, culture and DST/LPA
    - Treat with antibiotics and review after 5 days
    - Do chest X-ray
    - Follow up with microscopy and culture

**GXP unsuccessful**
- Collect one sputum specimen for a repeat GXP

**HIV-infected**
- Treat as MDR-TB
  - Refer to MDR-TB unit
  - Collect one specimen for culture and DST (for R and H)
  - Treat with antibiotics
  - Review culture results

**HIV-uninfected**
- Treat with antibiotics
  - **Good Response**
    - No further follow up
    - Advise to return when symptoms recur
  - **Poor Response**
    - Consider other diagnosis
    - Refer for further investigation

**Follow up with microscopy**

**Follow up with microscopy and culture**

**If an antibiotic is required the following can be used: amoxycillin 500mg 8 hourly orally for 5 days. If allergic to penicillin use erythromycin 500mg 6 hourly orally for 5 days.**
WHY IS IT DIFFICULT TO DIAGNOSE TB IN CHILDREN?

- Bacteriological confirmation of TB infection is often not possible in children due to difficulties with sputum collection and because cavitation is rare
- Despite this, bacteriological confirmation should always be sought
- Expectorated sputum samples should be taken in those old enough to produce them
- Gastric washings and induced sputum samples can be done in children unable to produce sputum samples
- Relevant investigations for extra-pulmonary TB must be done if this is suspected
- Never rely solely on sputum microscopy to diagnose pulmonary TB in children, as these tests are very rarely positive because children usually have ‘paucibacillary’ (few bacilli) disease

WHAT TOOLS CAN BE USED TO DIAGNOSE TB?

- Taking a Detailed History
- Physical Examination
- Tuberculin Skin Test (TST)
- Chest X-ray
- Bacteriological Confirmation

1. TAKING A DETAILED HISTORY

1.1. When taking a history, what should I ask?
- Explore exposure to a TB contact
  - The source case is usually an adult or adolescent in close contact with the child, either in the same household or in regular contact, who has recently been diagnosed with TB or has symptoms suggestive of TB
- Find out about the possible presence of drug-resistant TB in the contact by:
  - enquiring about whether the contact has known drug-resistant TB or is not responding to treatment.
  - This is important because the presence of drug resistance might have implications for the treatment of the child
1.2. Which Symptoms Suggest TB?
Symptoms are often nonspecific and can overlap with other conditions, especially those that occur in HIV infection.
- The most common symptoms are:
  - A persistent cough or wheeze present for more than 2 weeks, which is not responding to antibiotics
  - Documented loss of weight or failure to thrive for 3 months. This is particularly significant if the child does not respond to nutritional intervention
  - Persistent fever for more than 2 weeks
  - Fatigue or reduced playfulness

PLEASE NOTE: ALTHOUGH ‘CHRONIC COUGH’ IS AN IMPORTANT INDICATOR OF PULMONARY TB IN CHILDREN, IT IS IMPORTANT TO REMEMBER THAT UP TO 40% OF CULTURE-CONFIRMED PULMONARY TB EPISODES IN CHILDREN MAY PRESENT IN THE CONTEXT OF A COUGH OF LESS THAN 10 DAYS DURATION

2. PHYSICAL EXAMINATION

2.1. What should I check for on physical examination?
The following signs are suggestive of TB:
- Failure to thrive
- Gibbus (suggestive of vertebral TB)
- Painless, matted, enlarged cervical lymph nodes (>2x2 cm) with fistula formation
- Meningitis not responding to antibiotics
- Pleural effusion
- Pericardial effusion
- Abdominal distension with ascites
- Painless enlarged lymph nodes without fistula formation
- Painless enlarged joint
- Signs of tuberculin hypersensitivity (phlyctenular conjunctivitis, erythema nodosum)

3. TUBERCULIN SKIN TEST (TST)

3.1. What is a TST and what is its role?
- The Mantoux is the most commonly used TST and is preferred as it is the most reliable
- It is used to identify current or previous infection with Mycobacterium tuberculosis (MTB)
- A positive result means that the child has TB infection either currently or previously, and does not necessarily mean that TB disease is present

3.2. How Does The TST Work?
- It measures delayed type hypersensitivity to tuberculin purified protein derivative (PPD) from MTB
- PPD is made up of a combination of mycobacterial antigens
- When it is injected intradermally, it causes an immune response in the form of a delayed hypersensitivity reaction
- This reaction is visible on the skin as induration which can then be measured in millimetres
- Skin tests become positive 6 weeks to 3 months after exposure
4. CHEST X-RAY (CXR)

4.1. Are CXRs Useful in Children?
- This can be a useful test as children with pulmonary TB will often have suggestive CXR changes
- X-rays should be of good quality and should be read by someone with experience

4.2. What Are The Most Common Changes On CXR?
- The most common manifestation is persistent opacification in the lung with hilar and/or paratracheal lymphadenopathy
  - A lateral X-ray helps to identify these signs
- Enlarged lymph nodes can obstruct airways
  - Complete occlusion leads to lobar collapse
  - Partial occlusion can cause a ball-valve effect with segmental or lobar hyperinflation
- Parenchymal disease may be present due to:
  - Miliary disease or
  - Spread from airway involvement
- Unilateral pleural effusions can occur (usually in children over 5 years of age)
5. BACTERIOLOGICAL CONFIRMATION

5.1. How is bacteriological confirmation obtained in children?
- Specimens from suspected sites of involvement should always be obtained for microscopy and culture or for GXP (if sputum or gastric aspirates) in order to confirm the diagnosis
- Appropriate samples include sputum obtained through expectoration or sputum induction, gastric aspirates and fine needle aspiration (FNA) or biopsies, for example of lymph nodes

5.2. When is bacteriological confirmation important?
- Bacteriological confirmation is particularly important in the following cases:
  - suspected drug resistance
  - severe or complicated cases
  - if the diagnosis is uncertain

Drug susceptibility testing (DST) of isolates should be done if drug resistance is suspected (e.g. if the source case has drug-resistant TB) and if the child is not responding to treatment.

The process of sample collection is discussed in the Procedures Section
**EXTRA-PULMONARY TB (EPTB)**

- TB occurring in any site other than the lungs
- Caused by TB spreading to other organs through haematological and lymphatic dissemination
- EPTB is more common in people living with HIV, particularly with low CD4 counts

### WHAT ARE COMMON TYPES OF EPTB?

- Skeletal TB including spinal
- CNS including Meningitis
- TB Pericarditis
- Pleural TB
- Abdominal TB
- TB Lymphadenitis

Disseminated TB May Include Multiple Sites

### DIAGNOSIS OF EPTB

- EPTB diagnosis is difficult and invasive procedures are often required; presumptive TB treatment may be commenced.
- Note that Xpert MTB/RIF has not yet been validated for use on specimens other than sputum and gastric aspirates

### HOW SHOULD EPTB TREATMENT BE APPROACHED?

- Most cases of EPTB respond to 6 months (8 months if retreatment) of standardised TB treatment but a longer course may be required in the case of severe disease
- Disseminated TB may be fatal and TB treatment should not be delayed, especially in HIV-infected patients
- Corticosteroids may be used, especially for TB pericarditis and TB meningitis

**NB: EPTB OCCURS MORE COMMONLY IN HIV-INFECTED PATIENTS. ALL HIV-INFECTED TB PATIENTS SHOULD BE INITIATED ON ART**
## 1. TB LYMPHADENITIS

### 1.1 Peripheral Lymphadenitis

**Signs and Symptoms**
- Include:
  - large (>2 cm), tender, non-symmetrical, matted, firm to fluctuant, rapidly growing lymph node, may have skin fistula
  - needs to be differentiated from generalised lymphadenopathy which occurs in HIV:
    - occurs in up to 80% of early HIV infection
    - is typically non-tender, <2 cm in size and symmetrical

**Diagnosis and Treatment**
- Includes:
  - microscopy if exuding caseous material through a fistula
  - fine needle aspirate for microscopy, TB culture, cytology
  - if the above-mentioned negative, do lymph node biopsy – send for histology and TB culture

### 1.2 Mediastinal Lymphadenitis

**Signs and Symptoms**
- Can compress the airways leading to:
  - wheeze
  - brassy cough

**Diagnosis and Treatment**
- CXR

### 1.3 Intra-abdominal Lymphadenitis

**Signs and Symptoms**
- Obstructive symptoms
- Tenderness on palpation

**Diagnosis and Treatment**
- Sonar
- CT Scan
- Treat empirically unless nodes can be readily aspirated at a tertiary health facility

## 2. TB MENINGITIS

### SIGNS AND SYMPTOMS

- Gradual onset headache
- Malaise
- Confusion
- Decreased level of consciousness
- Vomiting
- Neck stiffness
- Seizures
- Positive Kernig’s sign

### DIAGNOSIS AND TREATMENT

- Do a lumbar puncture
  - Request differential WCC, protein, glucose, ADA, MC&Ś, TB microscopy, TB culture (include tests for cryptococcal meningitis if immunocompromised)
  - CT brain may be helpful in diagnosing TB meningitis
  - ART initiation should be delayed for at least one month after starting TB treatment as IRIS may be fatal
DIFFERENTIAL DIAGNOSIS FOR TB MENINGITIS

<table>
<thead>
<tr>
<th>Disease</th>
<th>White Cell Count</th>
<th>Protein</th>
<th>Glucose</th>
<th>Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous meningitis</td>
<td>Elevated lymphocytes (L) &gt; polymorphonucleocytes (PMN)</td>
<td>Increased</td>
<td>Decreased</td>
<td>Presence of AFB (rare)</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>Elevated PMN &gt; L (L increases with partial treatment)</td>
<td>Increased</td>
<td>Decreased</td>
<td>Presence of bacteria after gram staining (rare)</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>Elevated L &gt; PMN</td>
<td>Moderately increased</td>
<td>Normal</td>
<td>Negative</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Elevated L &gt; PMN</td>
<td>Increased</td>
<td>Decreased</td>
<td>Presence of parasites shown by India ink stain (or cryptococcal antigen test)</td>
</tr>
</tbody>
</table>

3. DISSEMINATED (MILIARY) TB

**SIGNS AND SYMPTOMS**
- High fever
- General signs and symptoms of TB
- May reflect involvement of other organs e.g. pleural effusion, digestive problems, hepatosplenomegaly
- Meningeal signs

**DIAGNOSIS AND TREATMENT**
- CXR: diffuse uniformly distributed small nodules (resembling millet seeds)
- FBC may show pancytopenia or anaemia
- Liver function tests may be abnormal
- Bacteriological confirmation is sometimes possible from sputum (may be negative due to few bacilli), CSF, bone marrow, TB blood culture or urine culture (3 early morning urine TB cultures should be requested)
- Abdominal ultrasound may show hepatosplenomegaly

4. TUBERCULOUS SEROUS EFFUSIONS

**SIGNS AND SYMPTOMS**
- Dependent on the site
- Discussed below

**DIAGNOSIS AND TREATMENT**

*Generally diagnosis* includes aspiration:
- Request the following tests: differential white cell count, total protein, LDH, glucose, ADA, TB microscopy, TB culture
- TB produces an exudate: protein content > 30g/l
- Biochemical tests not required to diagnose an exudate:
  o if aspirate clots after standing, it is an exudate (failure of aspirate to clot does not exclude TB as it may indicate low protein content as in wasted clients)
- Microscopy rarely shows AFBs (Fluid forms as an inflammatory reaction to TB lesions in the serous membrane)
### 4.1. Pleural Effusions

**Signs and Symptoms**
- Acute:
  - Non-productive cough
  - Chest pain
  - Shortness of breath
  - High fever
- Chronic weakness in elderly
- Systemic TB symptoms
- Signs can include:
  - Decreased breath sounds
  - Decreased movement of chest wall
  - Dull percussion of chest
  - Friction rub
  - Effusion unilateral

**Diagnosis and Treatment**
- CXR shows unilateral uniform white opacity, often with concave upper border
- Pleural aspiration shows:
  - Straw coloured exudate
  - Protein content >30g/l
  - White cell count is high (1000-2500 per mm³) with predominantly lymphocytes
  - Adenosine deaminase (ADA): >30 IU
- If aspiration not possible, commence TB treatment unless the CXR suggests a different diagnosis

### 4.2. Pericardial Effusions

**Signs and Symptoms**
- Low cardiac output
  - Chest pain
  - Shortness of breath
  - Cough
  - Dizziness
  - Weakness
- Right-sided heart failure
  - Leg swelling
  - Right hypochondrial pain
  - Ascites
- Tachycardia
- Low blood pressure
- Raised jugular venous pressure
- Pericardial friction rub

**Diagnosis and Treatment**
- Ultrasound
- CXR
  - Large globular heart
  - Clear lung fields
  - Bilateral pleural effusions
- ECG
  - Tachycardia
  - Flattening of ST and T waves
  - Low voltage QRS complexes
- In cases of suspected cardiac tamponade refer to a specialist for aspiration
- May be safer for the patient to start presumptive TB treatment than to undergo diagnostic pericardiocentesis
- ART initiation should be delayed for at least one month after starting TB treatment as IRIS may be fatal

### 4.3. Peritoneal Tuberculosis

**Signs and Symptoms**
- Systemic TB features
- Ascites with no signs of portal hypertension
- May be palpable abdominal masses
- Bowel obstruction may develop from adhesion of nodules to bowel

**Diagnosis and Treatment**
- Always do a diagnostic ascitic tap, fluid:
  - Usually straw coloured (may be turbid or blood-stained) exudate
  - Usually >300 white cells/mm³ with predominating lymphocytes
- Abdominal ultrasound may show retroperitoneal or mesenteric lymph node enlargement
- Biopsy from exploratory surgery or laparoscopy in doubtful cases
### 4.4. Tuberculous Empyema

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Diagnosis and Treatment</th>
</tr>
</thead>
</table>
| • Similar to pleural effusion | • Pleural tap reveals thick pus  
  ○ Send pus to laboratory for examination for TB, gram stain and bacterial culture |

### 5. Tuberculosis of the Spine

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Diagnosis and Treatment</th>
</tr>
</thead>
</table>
| • TB can affect any bone but most commonly affects the vertebral column  
  ○ If severe, may have neurological sequelae  
  • Back pain/stiffness  
  • May cause referred pain radiating out from original site  
  • Localised swelling, sometimes with an obvious lump or abnormal curvature  
  • Cold abscess can develop behind sternocleidomastoid muscle  
  • May have weakness or paraplegia | • X-rays of the spine may show:  
  ○ disc space narrowing  
  ○ slow erosion of adjacent vertebral bodies  
  ○ wedge-shaped collapse  
  ○ angulation  
  • Biopsy of cold abscess for microscopy and culture, if possible |

---

**PULMONARY AND EXTRAPULMONARY TB COMMONLY OCCUR TOGETHER**  
**ALWAYS TAKE A SPUTUM SPECIMEN FOR TB TESTING**

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http://www.meddean.luc.edu/lumen/lsmed/HealthScience/PULMONAR/cxrself/list3.htm  
http://www.naika.or.jp/im2/43/04/17c.aspx  
http://radiographics.highwire.org/content/20/2/449.full  
http://www.gpnotebook.co.uk/simplepage.cfm?ID=1174798340  
http://radiopaedia.org/cases/pericardial-effusion  
http://www.isradiology.org/tropical_diseases/tmcr/chapter8/imaging.htm
WHAT DANGER SIGNS SHOULD PROMPT URGENT REFERRAL TO A HOSPITAL?

1. Severe respiratory distress
2. Severe wheezing not responding to bronchodilators
3. Headache (especially if accompanied by vomiting, possibly indicating raised intracranial pressure), irritability, drowsiness, neck stiffness and convulsions (possible TBM)
4. Hepatosplenomegaly (possible miliary TB)
5. Angulation of the spine (gibbus – possible TB spine)
6. Breathlessness and peripheral oedema (possible TB pericardial effusion)
7. Distended abdomen with/without ascites (possible abdominal TB)

<table>
<thead>
<tr>
<th>Severe Respiratory Distress</th>
<th>Opisthotonos (Severe Neck Stiffness)</th>
<th>Hepatosplenomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Severe Respiratory Distress" /></td>
<td><img src="image2" alt="Opisthotonos" /></td>
<td><img src="image3" alt="Hepatosplenomegaly" /></td>
</tr>
</tbody>
</table>

Gibbus | Facial Oedema | Ascites |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4" alt="Gibbus" /></td>
<td><img src="image5" alt="Facial Oedema" /></td>
<td><img src="image6" alt="Ascites" /></td>
</tr>
</tbody>
</table>

 WHICH INDICATIONS FOR REFERRAL CAN BE DETECTED ON CHEST X-RAY?

- Widespread fine millet-sized (1-2 mm) lesions (possible miliary TB)
- Extensive parenchymal involvement
- Massive pleural effusion
- Pericardial effusion
- Poor radiological and clinical response to treatment

![Miliary TB](image7)
WHAT ARE THE COMMON TYPES OF EXTRAPULMONARY TB?

1. Peripheral lymphadenitis
2. Bone and Joint Disease
   2.1. Spinal TB
3. Pleural Effusion
4. Pericarditis
5. Abdominal TB
6. Meningitis

### 1. PERIPHERAL LYMPHADENITIS

- Enlarged cervical nodes
- Enlarged lymph nodes ≥14 days
- No other cause for lymphadenopathy e.g. lesion on head
- No response to antibiotics
- Usually painless, firm and matted
- Lymph nodes may become fluctuant prior to spontaneous drainage
- Sinus formation (scrofula)

### DIAGNOSIS

- TB microscopy and culture of sinus fluid where possible (although often contaminated with other bacteria)
- Fine needle aspiration (FNA):
  - microscopy and TB culture and DST
  - cytology
- Lymph node biopsy

### 2. BONE AND JOINT DISEASE (OSTEO-ARTICULAR TB)

- Most cases arise in older children
- Usually a single large joint
- Painful joint(s)
- Limp that is frequently misattributed to trauma

### DIAGNOSIS

- X-ray
- Joint aspiration with fluid sent for TB microscopy and culture
- Synovial biopsy

### 2.1 SPINAL TB (50% OF ALL OSTEO-ARTICULAR TB)

- Can present acutely as spinal cord compression with lower limb weakness and bladder and bowel neurology
- Needs emergency intervention in order to save neurological function
- Can present chronically with backache for a few weeks

### DIAGNOSIS

- Accurate history
- Detailed examination
- X-ray
- CT Scan
- MRI
- Biopsy
3. PLEURAL EFFUSION

### SIGNS AND SYMPTOMS
- Fever
- Unilateral pleuritic chest pain
- Decreased breath sounds and stony dullness
- The child may not be acutely ill, and may have minimal signs

### DIAGNOSIS
- **CXR**
- **Pleural tap:**
  - Chemistry, including ADA
  - TB microscopy and culture

---

4. PERICARDITIS

### SIGNS AND SYMPTOMS
- Features of congestive cardiac failure and pericardial constriction (elevated jugular venous pressure, palpable pulsus paradoxus, pericardial friction rub)

### DIAGNOSIS
- **Ultrasound**
- **Pericardial tap invasive, not usually performed**

---

5. ABDOMINAL TB

### SIGNS AND SYMPTOMS
- Peritonitis
- Malnutrition with protein-losing enteropathy
- Abdominal distension with ascites
- Bowel, biliary or lymphatic obstruction (compression by enlarged intra-abdominal nodes)

### DIAGNOSIS
- **Abdominal ultrasound**
- **Ascitic tap:**
  - Chemistry, including ADA
  - TB microscopy and culture
### 6. Meningitis

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often have a TB contact</td>
<td>Lumbar puncture, CSF shows:</td>
</tr>
<tr>
<td>Headache</td>
<td>○ raised protein and lymphocytes</td>
</tr>
<tr>
<td>Early morning vomiting</td>
<td>○ low glucose and chloride</td>
</tr>
<tr>
<td>Irritability, drowsiness, convulsions</td>
<td>○ gram stain is negative</td>
</tr>
<tr>
<td>Weight loss</td>
<td>○ usually no AFB, therefore mycobacterial culture is crucial</td>
</tr>
<tr>
<td>Neck pain and resistance to neck flexion due to meningeal irritation</td>
<td></td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td></td>
</tr>
<tr>
<td>Altered level of consciousness</td>
<td></td>
</tr>
<tr>
<td>Sub-acute or acute onset of central nervous system symptoms</td>
<td></td>
</tr>
<tr>
<td>New onset focal neurology and seizures</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus develops as a complication and manifests as:</td>
<td></td>
</tr>
<tr>
<td>○ vomiting without diarrhoea</td>
<td></td>
</tr>
<tr>
<td>○ early morning headaches</td>
<td></td>
</tr>
<tr>
<td>○ irritability</td>
<td></td>
</tr>
<tr>
<td>○ deteriorating level of consciousness</td>
<td></td>
</tr>
<tr>
<td>Always consider TB meningitis in children diagnosed with bacterial or viral meningitis not responding to treatment</td>
<td></td>
</tr>
</tbody>
</table>

---

**NB:** TB Meningitis is a very serious form of TB and should not be treated at a primary health facility. These children should urgently be referred to a hospital for management.
Since Robert Koch discovered MTB in 1882, smear microscopy and culture has been the mainstay of TB diagnosis. Recently, improved diagnostics have become available which will expedite TB diagnosis and management in the era of HIV.

**OVERVIEW OF TB DIAGNOSTIC TESTS**

**WHAT ARE THE STRENGTHS AND WEAKNESSES OF THE FOLLOWING DIAGNOSTIC TESTS?**

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Specimen for Testing</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Effect of HIV on Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microscopy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Visualisation of stained MTB in clinical specimens using: | • Sputum  
• Gastric aspirates, or  
• Any other clinical specimen | • Very few false positive results (high specificity)  
• Cheap (+/- R30/smear)  
• Short turn-around-time (TAT) (24 hrs) | • Many false negatives (low sensitivity)  
• HIV infection decreases bacillary load in sputum leading to more false negative results (lower sensitivity) | |
| **Culture**      |                      |           |            |                       |
| Growth of MTB on: | Any clinical specimen | Culture is the *gold standard* for TB diagnosis  
• Very few false negatives (high sensitivity) | Long TAT (2-6 weeks)  
Expensive (+/-R700) | No effect |
| **Drug Susceptibility Testing (DST)** | Cultured isolate | Gold standard for drug susceptibility testing-high sensitivity  
Accurately detects susceptibility to most TB drugs | Expensive  
Requires sophisticated laboratory | No effect |
| **Line Probe Assay (LPA)** | Smear positive sputum or  
• Culfured isolate of MTB | Short TAT  
• Detects INH and RIF susceptibility  
• Second-line assay can detect fluoroquinolone and aminoglycoside susceptibility  
• Does not miss many cases of MDR-TB (high sensitivity) | Requires sophisticated laboratory environment  
Not yet approved by the WHO as an initial diagnostic test  
Awaiting validation by the NHLS for smear negative TB | |
### Xpert™ MTB/RIF

<table>
<thead>
<tr>
<th>Xpert MTB/RIF is a:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• cartridge-based automated PCR</td>
</tr>
<tr>
<td>• used on the GeneXpert platform</td>
</tr>
<tr>
<td>• detects MTB</td>
</tr>
<tr>
<td>• detects RIF susceptibility</td>
</tr>
<tr>
<td>• Sputum, gastric aspirates</td>
</tr>
<tr>
<td>• Few false negative results (high sensitivity)</td>
</tr>
<tr>
<td>• Can be located at point of care</td>
</tr>
<tr>
<td>• Rapid TAT (2 hours)</td>
</tr>
<tr>
<td>• Does not detect INH resistance</td>
</tr>
<tr>
<td>• May over-report RIF resistance when MDR is uncommon (low positive predictive value)</td>
</tr>
<tr>
<td>• A small reduction in sensitivity because of reduced numbers of AFB</td>
</tr>
</tbody>
</table>

### Tuberculin Skin Testing (TST)

<table>
<thead>
<tr>
<th>Tuberculin Skin Testing (TST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PPD is injected into the dermis (skin) and the area of induration is read</td>
</tr>
<tr>
<td>• Left inner forearm</td>
</tr>
<tr>
<td>• Used to detect the presence of latent tuberculosis infection</td>
</tr>
<tr>
<td>• Not useful for diagnosis of active disease in adults</td>
</tr>
<tr>
<td>• Requires 2 visits</td>
</tr>
<tr>
<td>• False negatives may occur e.g. due to malnutrition, overwhelming infection, HIV</td>
</tr>
<tr>
<td>• HIV can lead to anergy, and false negative TST results</td>
</tr>
</tbody>
</table>

### Interferon Gamma Release Assay (QuantiFERON® - TB Gold Test), (IGRA)

<table>
<thead>
<tr>
<th>Interferon Gamma Release Assay (QuantiFERON® - TB Gold Test), (IGRA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Incubation of patient blood with TB antigens and measurement of gamma interferon release from white cells</td>
</tr>
<tr>
<td>• Blood</td>
</tr>
<tr>
<td>• Used to detect the presence of latent tuberculosis infection</td>
</tr>
<tr>
<td>• Not useful for diagnosis of active disease in adults</td>
</tr>
<tr>
<td>• IGRA is less likely to give false negative results in HIV-infected persons compared with TST</td>
</tr>
</tbody>
</table>

### Radiographic/Ultrasound Imaging

<table>
<thead>
<tr>
<th>Radiographic/Ultrasound Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Radiographic representation of thoracic (CXR) or abdominal (ultrasound) structures</td>
</tr>
<tr>
<td>• Performed directly on the patient</td>
</tr>
<tr>
<td>• A short TAT (a few hours)</td>
</tr>
<tr>
<td>• Noninvasive, and does not require clinical specimens</td>
</tr>
<tr>
<td>• Not specific for TB</td>
</tr>
<tr>
<td>• Cavities less common</td>
</tr>
<tr>
<td>• Often has an atypical appearance with diffuse infiltrates</td>
</tr>
</tbody>
</table>
### How are Diagnostic Tests Compared?

Diagnostic tests can be compared by evaluating their ‘sensitivity’ and ‘specificity’ when compared to the ‘gold standard’, which is the best available test for the condition. For TB, the gold standard is TB culture.

<table>
<thead>
<tr>
<th></th>
<th>Disease Positive</th>
<th>Disease Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Predictive Value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test Positive</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Test Negative</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Disease Positive</th>
<th>Disease Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative Predictive Value</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Sensitivity**: \( \frac{a}{a+c} \)
  - Sensitivity is the proportion of diseased cases identified by the test. Low sensitivity means that many cases are falsely negative.

- **Specificity**: \( \frac{d}{b+d} \)
  - Specificity is the proportion of cases without disease that are identified as being disease-free by the test. Low specificity means that many cases are falsely positive.

#### FOR EXAMPLE, WHEN PERFORMING XPERT MTB/RIF AND TB CULTURE ON 1000 CONSECUTIVE TB SUSPECTS, THE FOLLOWING RESULTS COULD BE OBTAINED:

<table>
<thead>
<tr>
<th></th>
<th>Disease Positive</th>
<th>Disease Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Predictive Value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test Positive</td>
<td>170</td>
<td>8</td>
</tr>
<tr>
<td>Test Negative</td>
<td>22</td>
<td>800</td>
</tr>
</tbody>
</table>

- **Positive Predictive Value**: \( \frac{170}{178} = 95\% \)
  - PPV is lowered by the number of diseased cases in the sample that were tested (the prevalence of TB)

- **Negative Predictive Value**: \( \frac{800}{822} = 97\% \)

- **Sensitivity**: \( \frac{170}{192} = 88\% \)
  - Sensitivity is lowered by false negative tests (if fewer than 22 were falsely negative, the test would have a higher sensitivity)

- **Specificity**: \( \frac{800}{808} = 99\% \)
  - Specificity is lowered by false positive tests (if fewer than 8 were falsely positive, the test would have a higher specificity)
**HOW IS SPUTUM PROCESSED FOR MICROSCOPY AND CULTURE?**

<table>
<thead>
<tr>
<th>Received from Clinic</th>
<th>Inactivation or Decontamination</th>
<th>Centrifuged</th>
<th>Slide Prepared or Culture Inoculated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sputum for Microscopy Only</strong></td>
<td>Inactivation in a hot air oven to heat-kill organisms to render sputum safe for laboratory workers</td>
<td>To concentrate TB organisms to increase probability of seeing organisms on smear, and growing a positive culture</td>
<td></td>
</tr>
<tr>
<td><strong>Sputum for Microscopy and Culture</strong></td>
<td>Decontamination with NaOH to kill normal bacterial organisms found in sputum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Sputum sent for microscopy only: can never be cultured because organisms are heat killed to protect laboratory workers*

**WHY IS MICROSCOPY DONE?**
- One of the first line TB diagnostic test in patients with presumptive TB
- For monitoring of smear conversion in persons on TB treatment
- Can be used on specimens other than sputum to find AFB

**WHAT ARE THE WEAKNESSES OF MICROSCOPY?**
- Microscopy can only detect AFB when more than 10 000/ml are present
- False negative results are common
- Microscopy cannot differentiate between living and dead organisms

**HOW CAN MICROSCOPY BE IMPROVED?**
Microscopy can be slightly improved by:
- Using improved staining methods (e.g. Auramine instead of Ziehl-Neelson)
- Centrifuging the sputum to concentrate the AFBs
- Using good quality clinical specimens
- Use of sputum induction to collect adequate specimens when necessary
WHAT ARE THE STRENGTHS OF CULTURE?

- Culture can detect as few as 10-100 bacilli per ml
- Culture is the gold-standard for the diagnosis of TB
- Drug susceptibility testing can be done on the culture isolate

WHAT ARE THE WEAKNESSES OF CULTURE?

- Culture takes 2-6 weeks
- Cultures can become contaminated when insufficient NaOH is added, and all normal flora are not killed

HOW IS CULTURE DONE?

SPECIMENS ARE DECONTAMINATED & INOCULATED INTO MGIT SYSTEM

SPECIMEN INCUBATED FOR 6 WKS AT 37°C TO ALLOW MTB TO GROW

IF GROWTH DETECTED, ZN STAIN PERFORMED ON CULTURE TO LOOK FOR AFB

IF AFB+, DNA BASED TEST E.G. LPA OR OTHER TEST IS USED TO IDENTIFY MTB

HOW DO I INTERPRET CULTURE RESULTS?

<table>
<thead>
<tr>
<th>Culture Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for MTB</td>
<td>Patient has TB</td>
</tr>
<tr>
<td>Negative</td>
<td>No TB OR False negative may occur if TB is killed by decontamination or if a poor specimen is sent</td>
</tr>
<tr>
<td>Contaminated</td>
<td>Bacterial flora present in the sputum has overgrown in the MGIT tube. Even if MTB was present, it could not be detected</td>
</tr>
</tbody>
</table>

UNTREATED TB HAS A HIGH MORTALITY RATE. IT IS THEREFORE ESSENTIAL TO CONSIDER A DIAGNOSIS OF TB IN PERSONS WHO HAVE NEGATIVE SPUTUM SMEAR(S).

PLEASE REFER TO DIAGNOSTIC ALGORITHMS ON PAGE 8 FOR MORE DETAIL.
### HOW ARE SPITUM SMEAR AND CULTURE RESULTS REPORTED AND INTERPRETED AND WHAT ACTION SHOULD BE TAKEN?

<table>
<thead>
<tr>
<th>What The Lab Report Says:</th>
<th>What Could This Lab Report Mean?</th>
<th>What Should The Clinician Do?</th>
</tr>
</thead>
</table>
| **Microscopy:** positive for AFB  
**Culture:** not done | • Patient almost certainly has PTB | • Commence TB treatment  
• If patient already on TB treatment for >2/3 months, send a specimen for culture and DST |
| **Microscopy:** negative for AFB  
**Culture:** not done | • This result does not rule out TB | • Offer HIV test  
• If patient is HIV-infected, send another specimen for smear and culture or GXP, do CXR, give antibiotics and review 7 days later |
| **Microscopy:** positive for AFB  
**Culture:** positive  
**Organism:** MTB | • Patient has PTB | • Commence TB treatment  
• If patient already on TB treatment for >2/3 months, ask laboratory to perform DST on this isolate |
| **Microscopy:** negative for AFBs  
**Culture:** positive  
**Organism:** MTB | • Patient has PTB | • Commence TB treatment  
• If patient already on TB treatment for >2/3 months, ask laboratory to perform DST on this isolate |
| **Microscopy:** negative for AFBs  
**Culture:** positive  
**Organism:** contaminated | • This result does not rule out TB  
• Specimen under-decontaminated (NaOH insufficient to kill normal flora)  
• MTB could be present, but normal flora prevent it from growing  
• May be NTM | • Assess patient’s clinical and HIV status  
• Send another sample for smear and culture if appropriate |
| **Microscopy:** positive for AFBs  
**Culture:** positive  
**Organism:** contaminated | • Patient almost certainly has PTB  
• Specimen under-decontaminated (NaOH insufficient to kill normal flora)  
• MTB could be present, but normal flora prevent it from growing  
• May be NTM | • Commence TB treatment  
• Send another sample for culture if appropriate  
• Ask laboratory to do molecular test on the sputum or culture |
### TB Diagnosis Using Conventional Microscopy and Culture...continued

<table>
<thead>
<tr>
<th>What The Lab Report Says:</th>
<th>What Could This Lab Report Mean?</th>
<th>What Should The Clinician Do?</th>
</tr>
</thead>
</table>
| **Microscopy:** positive for AFB  
**Culture:** negative | • Specimen over-decontaminated  
• Patient on treatment and AFB are dead, causing culture to be negative  
• May be error in microscopy | • Send a second specimen for microscopy and culture  
• If TB likely, treat |
| **Microscopy:** negative or positive for AFBs  
**Culture:** positive  
**Organism:** Non-tuberculous Mycobacteria (NTM) | • NTMs in sputum may be colonisers (i.e. not doing any harm), or may be pathogens (i.e. causing disease)  
• If NTMs are present in more than 1 specimen, then this probably represents a clinically significant result | • Usually a contaminant and not clinically significant  
• Assess patient’s clinical and HIV status  
• Send another sample for culture if appropriate  
• Refer for specialist care if possible |
# HOW IS SPUTUM PROCESSED FOR XPERT MTB/RIF?

<table>
<thead>
<tr>
<th>RECEIVED FROM PATIENT</th>
<th>INACTIVATION</th>
<th>INOCULATION INTO XPERT MTB/RIF CARTRIDGE</th>
<th>INSERTED INTO GENEXPERT MACHINE*</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Received from patient" /></td>
<td><img src="image" alt="Inactivation" /></td>
<td><img src="image" alt="Inoculation" /></td>
<td><img src="image" alt="Inserted into machine" /></td>
</tr>
</tbody>
</table>

Inactivating agent added to sputum to make up a volume of 2ml, left for 15 mins
- kills MTB if present
- releases TB DNA

2 ml added to the cartridge
Cartridge inserted into the GeneXpert machine

*Sputum cannot be cultured/used for other tests as organisms are killed and specimen is inaccessible in cartridge

---

**WHAT ARE THE STRENGTHS OF XPERT MTB/RIF?**

- Can detect as few as 50-150 MTB organisms/ml
- False negative and false positive results uncommon
- TAT of 2 hours
- Detects susceptibility to rifampicin

**WHAT ARE THE WEAKNESSES OF XPERT MTB/RIF?**

- Not validated on extra-pulmonary specimens yet
- Cannot detect INH resistance – therefore it is a screening (not diagnostic) test for MDR-TB

---

### Why Is Smear Microscopy Done When Xpert MTB/RIF Is Positive?

- To categorise patient as ‘smear positive’ or ‘smear negative’ so that smear conversion can be demonstrated
- For monitoring and evaluation

### When Is Sputum Culture Done If Xpert MTB/RIF Is Used As The First-Line TB Test?

- When rifampicin resistance is reported
- When rifampicin susceptibility is indeterminate
- When negative and person remains symptomatic for TB
HOW ARE XPERT MTB/RIF RESULTS INTERPRETED?

**MTB Complex not Detected**
- Xpert negative for TB
- Negative results could be:
  - correctly negative (client does not have PTB) or
  - false negative - this is uncommon, only about 10% of negative Xpert MTB/RIF results will have a positive culture

**MTB Complex Detected/RIF Susceptible**
- MTB is present, and susceptible to rifampicin
- Xpert MTB/RIF is sensitive and specific for detection of TB and rifampicin resistance
- This result can be trusted

**MTB Complex Detected/RIF Resistant**
- MTB present and may be resistant to rifampicin
- Rifampicin resistance may be falsely positive (10%)
- Second sputum specimen must be sent for microscopy, culture and confirmatory DST

**MTB Complex Detected/RIF Indeterminate**
- MTB present and rifampicin resistance could not be assessed
- A second sputum must be sent for TB microscopy, culture and DST/LPA to confirm susceptibility
- Treat the patient as if they have drug sensitive TB

**Error**
- The test failed
  - Caused by problem with the cartridge, e.g. food particles
  - Submit a second specimen for Xpert MTB/RIF

Results of Xpert are graded as: Very Low, Low, Medium, High
- Xpert MTB/RIF grading does not correspond with grading for smear microscopy
- All grades indicate significant TB infection and should therefore be treated
<table>
<thead>
<tr>
<th>What The Lab Report Says:</th>
<th>What Could This Lab Report Mean?</th>
<th>What Should The Clinician Do?</th>
</tr>
</thead>
</table>
| **Xpert MTB/RIF**: MTB complex detected, rifampicin susceptible | Patient has PTB | TB treatment with first-line TB drugs  
| **Microscopy**: not done | | Send a second sputum for smear for monitoring purposes |
| **Xpert MTB/RIF**: MTB complex not detected | Does not rule out TB in a person who is HIV-infected and/or symptomatic | Offer HIV test  
| **Microscopy**: not done | | If patient is HIV-infected: send another specimen for smear and culture, do CXR, give antibiotics and review after 5 days. If poor response, clinically or on X-ray, commence TB treatment  
| | | If patient HIV-uninfected: treat with antibiotics, if poor response, consider another diagnosis and refer |
| **Xpert MTB/RIF**: MTB complex detected, rifampicin resistant | Patient has PTB | Commence TB treatment  
| **Microscopy**: not done | May be rifampicin mono-resistant or MDR-TB | Commence MDR-TB treatment (see section on MDR-TB Diagnosis And Management)  
| | | Send a second sputum for smear microscopy, culture and DST  
| | | For monitoring purposes  
| | | To confirm rifampicin resistance |
| **Xpert MTB/RIF**: MTB complex detected, rifampicin susceptible | Patient has PTB | Commence TB treatment  
| **Microscopy**: positive for AFB | | Positive smear microscopy means that the patient has ‘smear positive TB’  
| | | Send sputum after 2 months to document smear conversion |
| **Xpert MTB/RIF**: MTB complex detected, rifampicin susceptible | Patient has PTB | Commence TB treatment  
| **Microscopy**: negative for AFB | | Negative smear microscopy means that the patient has ‘smear negative TB’ |
| **Xpert MTB/RIF**: MTB complex detected, rifampicin resistant | Patient has MDR-TB | MDR-TB treatment  
| **Microscopy**: positive/negative for AFB  
| **LPA**: RIF resistant, INH resistant | | Send a sputum for culture and DST to establish susceptibility to second-line TB drugs  
| | | Record patients details in MDR-TB register |
| **Xpert MTB/RIF**: MTB complex detected, rifampicin resistant | Patient has rifampicin mono-resistant TB | MDR-TB treatment  
| **Microscopy**: positive/negative for AFB  
| **LPA**: RIF resistant, INH sensitive | | Send a sputum for culture and DST to establish susceptibility to second-line TB drugs |
| **Xpert MTB/RIF**: MTB complex detected, rifampicin resistant | Patient has fully sensitive TB | Stop MDR-TB treatment if started based on initial Xpert MTB/RIF results  
| **Microscopy**: positive/negative for AFB  
| **LPA**: RIF sensitive, INH sensitive | | Start first-line TB treatment  
| | | Send a sputum for culture and DST |
WHAT IS DRUG-RESISTANT TB (DR-TB)?

- DR-TB is any strain of MTB that is resistant to one or more anti-tuberculosis drugs
- DR-TB is always a laboratory diagnosis
  - Clinical failure to respond to TB treatment does not mean that the strain is DR-TB
  - INH and RIF susceptibility is initially performed
    - If resistance to INH or RIF detected, further DST is performed

WHEN SHOULD DRUG SUSCEPTIBILITY TESTING BE DONE?

- If Xpert MTB/RIF results show the following: MTB detected and rifampicin resistant or rifampicin indeterminate
- Repeat episode of TB
- Known DR-TB contact
- TB acquired in institutions
- Smear positive TB after intensive phase of TB treatment

WHICH DIAGNOSTIC TESTS CAN DETECT DRUG RESISTANCE AND WHAT IS THE MECHANISM OF THESE TESTS?

<table>
<thead>
<tr>
<th>Diagnostic Modality</th>
<th>Explanation</th>
<th>Additional Tests Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xpert™ MTB/RIF</td>
<td>Detects resistance to RIF on sputum (smear positive or smear negative) by detecting mutations in the rpoB gene</td>
<td>RIF-resistant TB may be mono-resistant or MDR-TB. Request culture and DST. (See algorithm on adjacent page)</td>
</tr>
<tr>
<td>MTBDRplus Line Probe Assay (LPA)</td>
<td>Detects resistance to RIF (rpoB mutations) and INH (katG and inhA mutations) on smear positive sputum, or MTB cultures</td>
<td>If RIF and/or INH resistant, request DST to RIF, INH and remaining first and second-line drugs</td>
</tr>
<tr>
<td>MTBDRs Line Probe Assay (LPA)</td>
<td>Detects resistance to fluoroquinolones and aminoglycosides on smear positive sputum, or MTB cultures, to exclude XDR or pre XDR-TB</td>
<td>Refer to specialist centre for further management if resistance is detected</td>
</tr>
</tbody>
</table>
| Culture and phenotypic DST   | • Gold standard for the detection of drug resistance
  • Requires solid media or automated liquid media technology | • Contamination may occur
  • Use this result to guide patient management |
HOW SHOULD A PATIENT WITH THE FOLLOWING XPERT MTB/RIF RESULTS BE MANAGED?

Result: MTB complex detected / rifampicin resistant

If patient does not return within 48 hrs call and/or send TB tracer

- Counsel patient that he/she might have DR-TB but that a confirmatory test must be done
- Request a second sputum specimen for microscopy, culture and phenotypic DST
  - To confirm RIF resistance
  - To determine susceptibility to other drugs
- Start MDR-TB treatment
- Register and notify the patient
- Screen contacts for TB symptoms and investigate if symptomatic

Obtain result of phenotypic DST

If result shows resistance to RIF and susceptibility to isoniazid:
- Diagnosis is rifampicin mono-resistant TB
- Continue MDR-TB treatment and add isoniazid (see page 52)

If RIF and INH resistance detected:
- Diagnosis confirmed as MDR-TB
- Continue MDR-TB treatment (see page 53-56)

If result indicates RIF and INH susceptibility:
- Diagnosis is fully sensitive TB
- Stop MDR-TB treatment
- Start patient on regimen 1

If INH resistant and RIF susceptible
- Diagnosis is isoniazid mono-resistance
- Treat with regimen 1 (see page 52)
TREATMENT
WHAT IS FIRST-LINE TB TREATMENT?
First-line TB treatment refers to the drugs and management algorithms applied to persons presenting with presumed or proven drug-sensitive TB.

WHAT IS THE DEFINITION OF ‘NEW’ VS. ‘RETREATMENT’ TB PATIENTS?

<table>
<thead>
<tr>
<th>New:</th>
<th>Retreatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A patient who has never had treatment for TB or&lt;br&gt;• who has taken anti-tuberculosis drugs for less than 4 weeks</td>
<td>• A patient who has taken TB treatment for 4 weeks or more in the past and either relapsed, defaulted or had treatment failure</td>
</tr>
</tbody>
</table>

Either group may have positive or negative smear microscopy and culture or extra-pulmonary TB disease

WHAT DRUGS ARE USED?

**Adult TB Drug Dosages**

<table>
<thead>
<tr>
<th>Essential TB Drug (abbreviation)</th>
<th>Dose mg/kg</th>
<th>Dose Range mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin (R)</td>
<td>10</td>
<td>8 - 12</td>
</tr>
<tr>
<td>Isoniazid (H)</td>
<td>5</td>
<td>4 – 6</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>25</td>
<td>20 – 30</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>15</td>
<td>15 – 20</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>15</td>
<td>12 – 18</td>
</tr>
</tbody>
</table>

WHICH FIXED-DOSE COMBINATION TABLETS ARE AVAILABLE FOR ADULTS?

<table>
<thead>
<tr>
<th>RHZE (150,75,400,275mg)</th>
<th>Intensive Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>RH(150,75mg)</td>
<td>Continuation Phase</td>
</tr>
<tr>
<td>RH(300,150mg)</td>
<td>Continuation Phase</td>
</tr>
</tbody>
</table>
**WHAT ARE THE FIRST-LINE REGIMENS IN ADULTS?**

<table>
<thead>
<tr>
<th>Regimen 1 (New Cases) for Adults</th>
<th>Pre-treatment Body Weight</th>
<th>Intensive Phase 7 days a week for 2 months</th>
<th>Continuation Phase 7 days a week for 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RHZE (150, 75, 400, 275)</td>
<td>RH (150, 75)</td>
</tr>
<tr>
<td>30-37 kg</td>
<td>2 tabs</td>
<td>2 tabs</td>
<td></td>
</tr>
<tr>
<td>38-54 kg</td>
<td>3 tabs</td>
<td>3 tabs</td>
<td></td>
</tr>
<tr>
<td>55-70 kg</td>
<td>4 tabs</td>
<td></td>
<td>2 tabs</td>
</tr>
<tr>
<td>&gt;70 kg</td>
<td>5 tabs</td>
<td></td>
<td>2 tabs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen 2 (Previously treated) for Adults</th>
<th>Pre-treatment Body Weight</th>
<th>Intensive Phase 7 days a week for 2 months</th>
<th>Intensive Phase 7 days a week for 1 month</th>
<th>Continuation Phase 7 days a week for 5 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RHZE (150, 75, 400, 275)</td>
<td>RHZE (150, 75, 400, 275)</td>
<td>RH (150, 75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin (g)*</td>
<td>RH (150, 75)</td>
<td>E (400)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RH (300, 150)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E (400)</td>
</tr>
<tr>
<td>30-37 kg</td>
<td>2 tabs</td>
<td>0.5</td>
<td>2 tabs</td>
<td>2 tabs</td>
</tr>
<tr>
<td>38-54 kg</td>
<td>3 tabs</td>
<td>0.75</td>
<td>3 tabs</td>
<td>2 tabs</td>
</tr>
<tr>
<td>55-70 kg</td>
<td>4 tabs</td>
<td>1.0</td>
<td>4 tabs</td>
<td>2 tabs</td>
</tr>
<tr>
<td>&gt;70 kg</td>
<td>5 tabs</td>
<td>1.0</td>
<td>5 tabs</td>
<td>2 tabs</td>
</tr>
</tbody>
</table>

* Streptomycin should NOT be given during pregnancy and to those over 65 years

**NB: WHERE RAPID TESTS ARE AVAILABLE (LPA OR XPERT MTB/RIF)**

- Due to the introduction of rapid tests (LPA or Xpert MTB/RIF) Regimen 2 is being phased out
- All previously treated patients diagnosed with sensitive TB must be started on Regimen 1, instead of Regimen 2
- Those confirmed as rifampicin resistant must be started on MDR-TB treatment
HOW ARE PATIENTS ON FIRST-LINE TB TREATMENT MONITORED?

**New Smear Positive PTB**

- **At 7 weeks: Take 2 sputum smears**
  - **Both Negative**
  - Commence continuation phase of treatment with daily RH at the end of the 8th week of intensive phase
  - **One/Both Positive**
  - If no clinical improvement, collect sputum specimen for microscopy, culture and DST. Continue daily RHZE for 3rd month
    - Repeat smear at 3 months and commence continuation phase of daily RH
    - **Negative**
    - **Resistant**
    - Refer MDR
    - **Sensitive**
    - Check culture and DST results
  - **Positive**

- **At 5 months: Take 2 sputum smears**
  - **Negative:** Discharge as cure when 6 months treatment completed
  - **Positive:** Register as treatment failure and investigate further for resistance and treat based on results

Contact an expert if unsure of management of a patient not responding to TB treatment
New Smear Negative, Culture Positive PTB

At 7 weeks: Take 2 sputum smears

- Two Negative Smears
  - Commence continuation phase of treatment with daily RH after 2 month intensive phase complete

- One Positive Smear
  - Repeat 3rd Smear
    - Negative: Continue treatment
    - Positive: Collect Sputum specimen for culture and DST
      - Register as a treatment failure
      - Register as treatment failure and investigate further for resistance and treat based on results

- Two Positive Smears
  - Collect Sputum specimen for culture and DST
    - Register as a treatment failure

At 5 months take 2 sputa: 1 for smear and 1 for smear and culture

- Negative:
  - Discharge as cure when 6 months treatment completed

- Positive smear/culture:
  - Register as treatment failure and investigate further for resistance and treat based on results

Please note: Xpert MTB/RIF or LPA may be used to monitor patients who are found to be smear positive at 7 weeks

Contact an expert if unsure of management of a patient not responding to TB treatment
Retreatment Smear Positive PTB

At 11 weeks: Take 2 sputum smears

Negative

Commence continuation phase of treatment with daily RHE

Positive

Continue daily RHZE for a 4th month:
Review culture and DST results

Repeat smear at 4 months and commence continuation phase with RHE

Negative

Resistant

Refer MDR

Positive

Check culture and DST results

Sensitive

At 7 months: Take 2 sputum smears

Negative: Discharge as cure when 8 months treatment completed

Positive: Register as treatment failure and investigate further for resistance and treat based on results

Contact an expert if unsure of management of a patient not responding to TB treatment
Retreatment Smear Negative, Culture Positive PTB

At 11 weeks: Take 2 sputum smears

- Two Negative Smears
  - Commence continuation phase of treatment with RHE
- One Positive Smear
- Two Positive Smears
  - Repeat 3rd Smear
    - Negative
    - Positive
      - Review culture and DST results
        - Register as a treatment failure
        - Refer accordingly

At 7 months take 2 sputa: 1 for smear and 1 for smear and culture

- Negative: Discharge as cure when 8 months treatment completed
- Positive smear/culture: Register as treatment failure and investigate further for resistance and treat based on results

Contact an expert if unsure of management of a patient not responding to TB treatment
TB TREATMENT IN CHILDREN

HOW IS PAUCIBACILLARY TB IN CHILDREN TREATED?

- Younger children often have paucibacillary TB (smear microscopy sputum negative)
- Risk of resistance is lower due to the low numbers of bacilli, fewer drugs are thus required to treat paucibacillary TB
- Younger children (<8yrs) are treated with Regimen 3:
  - 3 drugs during the intensive phase: INH, RIF, PZA (2 months)
  - 2 drugs during the continuation phase: INH and RIF (4 months)

DO CHILDREN DEVELOP POSITIVE SPUTUM SMEAR MICROSCOPY OR CAVITIES IN THE LUNGS?

Yes, they can

HOW ARE THESE CHILDREN TREATED?

- They should be treated in the same way as newly diagnosed smear positive adult clients as they have a higher bacillary load
- Regimen 3B, which is similar to Regimen 1 for adults
  - 4 drugs during the intensive phase: INH, RIF, PZA and Ethambutol (2 months)
  - 2 drugs during the continuation phase: INH and RIF (4 months)

HOW ARE SEVERE FORMS OF TB MANAGED IN CHILDREN?
(This includes meningitis, spine, peritonitis, miliary, skeletal and those suspected of having MDR-TB)

- These cases should be referred for management
- Treatment may be given for a longer time
- On discharge from the hospital, the treatment should continue at the primary health facility at the drug dosages recommended by the referral centre

WHAT ARE THE DRUG DOSAGES USED IN CHILDREN?

- This is dependent on the body weight of the child
- Should be adjusted as weight changes during the course of treatment (i.e. at each health visit)
- Treatment must be given 7 days a week

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Doses (mg/kg)</th>
<th>Maximum Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>10</td>
<td>10-15</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>15</td>
<td>10-20</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>35</td>
<td>30-40</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>20</td>
<td>15-25</td>
</tr>
</tbody>
</table>

Recommended Doses for First-Line TB Drugs in Children

Maximum Dosages
REGIMEN 3A: FOR UNCOMPLICATED TB WITH LOW BACILLARY LOAD

CHILDREN UP TO 8 YEARS

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Intensive phase (2 months)</th>
<th>Continuation phase (4 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RH 60/60</td>
<td>PZA 500mg*</td>
</tr>
<tr>
<td>2-2.9</td>
<td>½ tablet</td>
<td>Obtain expert advice on dose</td>
</tr>
<tr>
<td>3-3.9</td>
<td>¼ tablet</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>4-5.9</td>
<td>1 tablet</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>6-7.9</td>
<td>1½ tablets</td>
<td>½ tablet</td>
</tr>
<tr>
<td>8-11.9</td>
<td>2 tablets</td>
<td>½ tablet</td>
</tr>
<tr>
<td>12-14.9</td>
<td>3 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>15-19.9</td>
<td>3½ tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>20-24.9</td>
<td>4½ tablets</td>
<td>1½ tablets</td>
</tr>
<tr>
<td>25-29.9</td>
<td>5 tablets</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>

Add Pyridoxine 12.5 mg daily X 6 months if HIV-infected or malnourished

CHILDREN > 8 YEARS AND ADOLESCENTS

<table>
<thead>
<tr>
<th>Pre-treatment Body Weight (kg)</th>
<th>Intensive Phase (2 months)</th>
<th>Continuation Phase (4 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZE 150/75/400/275</td>
<td>RH 150/75</td>
</tr>
<tr>
<td>30-37</td>
<td>2 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>38-54</td>
<td>3 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>55-70</td>
<td>4 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>&gt;71</td>
<td>5 tablets</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>

Add Pyridoxine 12.5 mg for 6 months if HIV-infected or malnourished

*PZA 150mg will soon be available and can be used as an alternative
### REGIMEN 3B: FOR COMPLICATED TB, HIGH BACILLARY LOAD, RETREATMENT CASES
(All other forms of severe TB: extensive pulmonary TB, spinal or osteo-articular TB or abdominal TB)

**CHILDREN UP TO 8 YEARS**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Intensive phase (2 months)</th>
<th></th>
<th>Continuation phase (4 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RH 60/60</td>
<td>Pyrazinamide 500 mg**</td>
<td>Ethambutol 400mg tablet OR 400mg/8ml * solution</td>
</tr>
<tr>
<td>2-2.9</td>
<td>½ tablet</td>
<td>Expert advice on dose</td>
<td>1ml</td>
</tr>
<tr>
<td>3-3.9</td>
<td>¼ tablet</td>
<td>¼ tablet</td>
<td>1.5ml</td>
</tr>
<tr>
<td>4-5.9</td>
<td>1 tablet</td>
<td>¼ tablet</td>
<td>2ml</td>
</tr>
<tr>
<td>6-7.9</td>
<td>1½ tablets</td>
<td>½ tablet</td>
<td>3ml</td>
</tr>
<tr>
<td>8-11.9</td>
<td>2 tablets</td>
<td>½ tablet</td>
<td>½ tablet</td>
</tr>
<tr>
<td>12-14.9</td>
<td>3 tablets</td>
<td>1 tablet</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>15-19.9</td>
<td>3½ tablets</td>
<td>1 tablet</td>
<td>1 tablet</td>
</tr>
<tr>
<td>20-24.9</td>
<td>4½ tablets</td>
<td>1½ tablet</td>
<td>1 tablet</td>
</tr>
<tr>
<td>25-29.9</td>
<td>5 tablets</td>
<td>2 tablets</td>
<td>1½ tablets</td>
</tr>
</tbody>
</table>

Add Pyridoxine 12.5mg daily x 6 months if HIV-infected or malnourished

*For each dose, crush 400mg (1tablet) to a fine powder and dissolve in 8 ml of water to prepare a concentration of 400mg/8ml. Discard unused solution.

** PZA 150mg will soon be available and can be used as an alternative
CHILDREN > 8 YEARS AND ADOLESCENTS

<table>
<thead>
<tr>
<th>Pre-treatment Body Weight (kg)</th>
<th>Initial Phase (3 months)</th>
<th>Continuation phase (5 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZE 150/75/400/275</td>
<td>RH 150/75</td>
</tr>
<tr>
<td>30-37</td>
<td>2 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>38-54</td>
<td>3 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>55-70</td>
<td>4 tablets</td>
<td></td>
</tr>
<tr>
<td>&gt;71</td>
<td>5 tablets</td>
<td></td>
</tr>
</tbody>
</table>

Add Pyridoxine 12.5mg for 6 months if HIV-infected or malnourished

DISSEMINATED TB
Miliary TB

CHILDREN UNDER 8 YEARS: a six month regimen of the following drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>20mg/kg, oral, as a single daily dose</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>20mg/kg, oral, as a single daily dose</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>40mg/kg, oral, as a single daily dose</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>20mg/kg, oral, as a single daily dose</td>
</tr>
<tr>
<td></td>
<td>Maximum daily dose: 1000mg</td>
</tr>
</tbody>
</table>

HOW SHOULD I MANAGE A CHILD WHO DETERIORATES ON TB TREATMENT?

Ask the following questions:

1. Is the drug dosage correct
2. Is the child taking the drugs as prescribed
3. Is the child HIV-infected
4. Is the child severely malnourished
5. Is there a reason to suspect drug-resistant TB
6. Has the child developed IRIS
7. Is there another possible diagnosis
### Side Effects of First-Line TB Treatment

#### What Are the Most Common Side Effects of First-Line TB Treatment?

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Most Likely Drugs</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>Pyrazinamide, rifampicin and isoniazid</td>
<td>Please see below and opposite page</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide most common</td>
<td></td>
</tr>
<tr>
<td>Skin Rash</td>
<td>Streptomycin, pyrazinamide, rifampicin, ethambutol and isoniazid</td>
<td>Please see below and opposite page</td>
</tr>
<tr>
<td>Joint Pains</td>
<td>PZA</td>
<td>Continue TB drugs. Treat symptomatically (aspirin). If severe, allopurinol may be required for the treatment of gout</td>
</tr>
<tr>
<td>Vertigo (dizziness) and hearing loss</td>
<td>Streptomycin</td>
<td>Stop streptomycin</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>INH (also HIV and D4T)</td>
<td>Continue TB drugs. Pyridoxine 25 mg daily, can increase to 100 mg daily</td>
</tr>
<tr>
<td>Optic Neuritis</td>
<td>Ethambutol (dose-related)</td>
<td>Patients complain of altered colour vision especially with yellow and green. Stop ethambutol immediately and never reintroduce</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Rifampicin (rare)</td>
<td>Stop rifampicin</td>
</tr>
</tbody>
</table>

#### How Is Hepatotoxicity Managed?

- A transient transaminitis (raised ALT/AST) may occur in many TB patients
  - Stop TB treatment if
    - ALT/AST five times higher than the upper limit of normal
  - OR
    - ALT/AST three times higher than upper limit of normal and symptoms of hepatitis present
- Do ALT/AST testing before starting TB treatment, especially in those with suspected disseminated TB
  - ALT/AST may be raised at baseline due to liver granulomas
    - Sonar may be helpful to determine cause of transaminitis
- If treatment is stopped and INH and RIF have been successfully reintroduced it is not necessary to reintroduce PZA

#### How Is Skin Rash Managed?

- Skin rash due to TB drugs usually begins 3-4 weeks after start of TB treatment
  - Take a careful history regarding onset of the rash
- Skin reactions are not always related to TB drugs. Consider:
  - Other drugs (co-trimoxazole, EFV, NVP)
  - Underlying causes (HIV)
  - Infectious conditions (varicella zoster virus, coxsackie virus, scabies)

#### Grading and Management of Skin Rash

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Erythema, pruritis</td>
<td>Reassure. Give oral antihistamines, topical steroids</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse maculopapular rash, dry desquamation</td>
<td>Stop TB treatment if rash is extensive. If localised, try oral antihistamines and topical steroids first</td>
</tr>
<tr>
<td>3</td>
<td>Vesiculation, ulcers</td>
<td>Stop TB treatment. Reintroduce according to algorithm on adjacent page unless skin rash was life-threatening</td>
</tr>
<tr>
<td>4</td>
<td>Exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, moist desquamation</td>
<td></td>
</tr>
</tbody>
</table>
### Side Effects of First-Line TB Treatment

#### Algorithm for Reintroducing First-Line TB Drugs Following Drug-Induced Hepatitis, or Moderate to Severe Skin Reactions

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
<th>Explanatory Notes</th>
</tr>
</thead>
</table>
| 1.   | Stop all first-line TB drugs, except if:  
- skin reaction is grade 1  
- ALT/AST are less than 5x upper limit of normal  
- ALT/AST are less than 3x upper limit of normal in patients with symptoms of hepatitis |  |
| 2.   | Start streptomycin/amikacin and  
- ethambutol and  
- ofloxacin |  
- Have low hepatotoxic and dermatotoxic potential  
- Ofloxacin is regarded as unnecessary by some experts, but must ultimately be introduced if RIF (or INH) cannot be used |
| 3.   | Monitor for improvement of the adverse effect  
- Move to step 4 once required improvement has taken place:  
  - Hepatotoxicity: reduction in ALT/AST to < 5x upper limit of normal  
  - Skin rash: re-epithelialisation of skin lesions, or resolution of pruritis |  
- Some experts recommend starting with low dose INH, increasing every 3 days  
- Skin reactions take up to 2 weeks to develop. Patients will complain of a ‘burning’ sensation in the skin when the offending drug is reintroduced |
| 4.   | Add isoniazid (in addition to streptomycin, ethambutol and ofloxacin)  
- Observe response  
- If no adverse effects take place, move to step 5  
- Hepatotoxicity usually occurs within 5-7 days  
- Skin rash usually occurs within 1-2 weeks |  
- Some experts recommend starting with low dose RIF, increasing it every 3 days |
| 5.   | Add rifampicin  
- Observe response |  
- About 50% of TB cases can have Regimen 1 successfully reintroduced with no recurrence of adverse effect |
| 6.   | Consider adding PZA  
- Hepatitis – Do not add PZA if no reaction to INH and RIF as PZA is most likely the offending drug  
- Skin rash – PZA may be added. PZA is a useful sterilizing agent when TB patients have cavities |  |
| 7.   | If reintroduction fails at any step, omit that drug, wait until the adverse effects subside, and continue with the next step |  |
| 8.   | If INH cannot be reintroduced the final regimen will be:  
- **Intensive phase:** SM/RIF/EMB/OFX +/− PZA for 2-3 months  
- **Continuation phase:** RIF/EMB/OFX for 6 months |  
- If RIF cannot be reintroduced, the final regimen will be:  
  - **Intensive phase:** SM/INH/EMB/OFX +/− PZA and ethionamide, terizidone  
  - **Continuation phase:** INH/EMB/OFX (see MDR guidelines)  
- Start date of TB treatment should be the start date of the final regimen tolerated by the patient  
- If INH cannot be reintroduced, regimen should be same as for INH mono-resistant TB  
- If rifampicin cannot be reintroduced, regimen should be same as for rifampicin mono-resistant TB  
- DST is useful to guide optimal drug selection |
HOW IS RESISTANCE TO TB DRUGS CLASSIFIED?

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-resistant TB</td>
<td>Resistance to a single anti-TB drug</td>
</tr>
<tr>
<td>Poly-resistant TB</td>
<td>Resistance to two or more first-line drugs but not including both INH and RIF</td>
</tr>
<tr>
<td>Multi-drug resistant TB</td>
<td>Resistance to both INH and RIF</td>
</tr>
<tr>
<td>Rifampicin-resistant TB</td>
<td>Resistance to Rifampicin and any other drugs except INH</td>
</tr>
</tbody>
</table>

WHAT TYPES OF RESISTENCE ARE THERE?

<table>
<thead>
<tr>
<th>Resistant Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Patients (previously called ‘primary resistance’)</td>
<td>Resistance in patients with no history of previous TB treatment or patients who have received TB treatment for less than one month previously</td>
</tr>
<tr>
<td>Previously Treated Patients (previously called ‘acquired resistance’)</td>
<td>Resistance in these patients refers to resistance in cultures from patients with one or more previous TB treatment episodes, of more than one month each</td>
</tr>
</tbody>
</table>

WHY IS IT IMPORTANT FOR US TO KNOW ABOUT MONO- AND POLY-RESISTANT TB?

• Mono- and poly-resistant TB may be a step on the way to development of MDR-TB
  ○ It is very important to manage these patients correctly
• MDR-TB may develop when persons with mono-resistant TB are not receiving a sufficient number and dosage of drugs to which the strain is susceptible

HOW IS MONO- AND POLY-RESISTANT TB TREATED?

• Treatment is complex and expert opinion should be always be sought
• Treatment is individualised according to:
  ○ drug susceptibility patterns of resistance (whether INH or RIF resistance is present)
  ○ TB treatment history
  ○ potential for development of resistance to other drugs

HOW IS MONO- AND POLY-RESISTANT TB MONITORED?

• TB microscopy and TB culture monthly during intensive phase AND continuation phase
• Repeat DST if unsatisfactory clinical progress after 3-4 months of treatment

HOW ARE MONO- AND POLY-RESISTANT PATIENTS RECORDED?

• All mono- and poly-drug resistant patients should be recorded in the DR-TB register (NOT the drug-sensitive register)
• Patients that are mono-drug resistant to rifampicin must be recorded as MDR-TB “not confirmed”
**Algorithm for the Outpatient Management of Mono- and Poly-Resistant TB**

**RIF or INH resistance confirmed by line probe assay**
1. Counsel patient regarding the implications of drug-resistant TB
2. Start patient on TB treatment regimen according to the table on the following page
3. Notify the patient to authorities
4. Request laboratory to do phenotypic (culture) drug susceptibility testing to first and second-line TB drugs
5. Send a further sputum specimen for microscopy, culture and DST
6. Offer an HIV test and initiate ART and cotrimoxazole if infected

**Review the patient culture, and DST results 4 weeks after TB treatment initiation**
1. Review laboratory DST results and confirm susceptibility results
2. Adapt TB treatment according to table on the following page
3. Send a sputum specimen for microscopy, culture and DST
4. If no clinical improvement, refer for specialist opinion
5. Manage HIV infection if present

**Review the patient and all culture, and DST results every 4 weeks until treatment completion**
1. Manage drug adverse effects
2. Manage HIV infection if present
3. Repeat sputum culture and DST at every visit to ensure the date of sputum conversion is known

* Patients must be referred to a higher level of care or expert opinion sought at any point if deemed necessary
### Suggested Regimens and Duration of Treatment for Mono- and Poly-resistant TB

<table>
<thead>
<tr>
<th>Drug Resistance Pattern</th>
<th>Suggested Regimen</th>
<th>Minimum Duration of Treatment (months)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **H**                    | RHZE for the full duration of treatment  
|                          | • In practice it is easier to use fixed drug combinations  
|                          | 6 - 9 months based on symptomatic response to treatment, weight gain and sputum culture combinations  
|                          | A minimum of 6 months treatment after culture conversion is adequate  
|                          | • Monitor the patient monthly with the following:  
|                          |  o sputum smear microscopy and culture monthly throughout treatment  
|                          |  o monthly clinical assessment required  
|                          | • Refer to MDR-TB expert if patient is not responding well to treatment |
| **R (± any other 1st line drug other than INH)** | Standardized MDR-TB regimen plus INH | 18 months treatment after culture conversion required | • These patients will need confirmation of diagnosis if diagnosed through GXP; however, LPA is a confirmatory diagnosis |
| **Poly-resistant TB cases** |                          | | • Refer to MDR-TB expert for regimen design based on resistance pattern and history of anti-TB drug use |
MDR-TB DIAGNOSIS AND MANAGEMENT

### MDR-TB vs XDR-TB

<table>
<thead>
<tr>
<th>Stands For</th>
<th>Definition</th>
<th>Stands For</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multi-Drug Resistant</strong></td>
<td>Resistance to at least INH and rifampicin <strong>WITH OR WITHOUT</strong> resistance to other drugs</td>
<td><strong>Extensively Drug Resistant</strong></td>
<td>Resistance to INH and rifampicin <strong>AND</strong> resistance to any of the fluoroquinolones <strong>AND</strong> any second-line injectable e.g. kanamycin, amikacin or capreomycin</td>
</tr>
</tbody>
</table>

### HOW DOES ONE ACQUIRE MDR-TB?

- Acquired infection with resistant bacteria
- Development in patient whose TB is not adequately treated

### HOW IS MDR-TB DIAGNOSED?

MDR-TB is a laboratory diagnosis. It may be diagnosed by:

- LPA which shows resistance to INH and RIF
- Xpert MTB/RIF only detects RIF resistance, diagnosis of MDR-TB must be confirmed by culture and DST. MDR-TB treatment must be started in the interim

### IT IS VERY IMPORTANT TO ENSURE THAT THE ORGANISM IDENTIFICATION IS MTB AND NOT ANOTHER SPECIES (NTM)

### WHAT IS THE DIFFERENCE BETWEEN RESISTANCE IN A NEW AND A PREVIOUSLY TREATED/RETREATMENT PATIENT?

**Resistances can be divided into 2 main types:**

<table>
<thead>
<tr>
<th>New Patients (previously called ‘primary resistance’)</th>
<th>Previously treated/Retreatment Patients (previously called ‘acquired resistance’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is resistance in patients with no history of previous TB treatment or patients who have received TB treatment for less than one month previously</td>
<td>Resistance in these patients refers to resistance in cultures from patients with one or more previous TB treatment episodes, of more than one month each</td>
</tr>
</tbody>
</table>

### HOW DO WE TREAT CLOSE CONTACTS OF MDR-TB PATIENTS?

- Screen and test for MDR-TB if symptomatic
- If patients are found not to have TB, they should receive screening every six months
- Asymptomatic contacts may be managed in the same way as contacts of drug-sensitive TB patients

○ Please refer for specialist opinion if in doubt, especially in the case of children

**NB: M/XDR-TB IS DIFFICULT TO TREAT, ALWAYS REFER IF ANY UNCERTAINTY**

---

### Intensive Phase: Treatment of MDR-TB: Adults and Children >8 years

A standardised MDR-TB treatment regimen should be given 7 days a week. In patients who were previously exposed to second-line anti-TB drugs for a month or more, the standardised regimen will be modified based on the history of drug usage and DST results.

**The duration of the Intensive Phase will be determined by adding 4 months to the date of TB culture conversion.**
*(Date of collection of the first sputum that turned TB culture negative)*
*It has to be six months or more.*

<table>
<thead>
<tr>
<th>Patients Weight</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33 kg</td>
<td>Kanamycin</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg (children: 7.5 to 10 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td>33-50 kg</td>
<td>Kanamycin</td>
<td>500-750 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1000-1750 mg</td>
</tr>
<tr>
<td>51-70 kg</td>
<td>Kanamycin</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1750-2000 mg</td>
</tr>
<tr>
<td>&gt;70 kg</td>
<td>Kanamycin</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>2000-2500 mg</td>
</tr>
</tbody>
</table>
PLEASE NOTE:
- Pyridoxine (Vit B6) 150 mg (maximum 200 mg) to be given daily to patients on terizidone
- Adults who may not tolerate moxifloxacin will be given levofloxacin at the following dosage:
  - 750 mg for patients weighing below 51 kg, and 1000 mg for patients with a weight equal or above 51 kg

THE DURATION OF THE CONTINUATION PHASE WILL BE DETERMINED BY ADDING 18 MONTHS TO THE DATE OF TB CULTURE CONVERSION.

<table>
<thead>
<tr>
<th>Patients Weight</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33 kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td>33-50 kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1000-1750 mg</td>
</tr>
<tr>
<td>51-70 kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1750-2000 mg</td>
</tr>
<tr>
<td>&gt;70 kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>2000-2500 mg</td>
</tr>
</tbody>
</table>
Standardised MDR-TB Treatment Regimen for Children Younger than 8 Years

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>15 - 22.5 mg/kg</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>10-15mg/kg daily for children &lt; 8 years</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>15 - 20 mg/kg</td>
</tr>
<tr>
<td>Terizidone</td>
<td>15 - 20 mg/kg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30 - 40 mg/kg</td>
</tr>
</tbody>
</table>

- NB: Ethambutol may be given at the dosage of 20 - 25 mg/kg
- High-dose INH 15-20mg/kg may be given if no katG mutation

**HOW IS XDR-TB TREATED?**

XDR-TB requires an individualised approach based on the previous history of drug use in a patient and the results of DST. Therefore, treatment of XDR-TB should always be initiated under guidance of the clinical management team and the review committees.
**MONITORING OF MDR-TB PATIENTS ON TREATMENT**

**HOW OFTEN MUST MDR-TB PATIENTS BE REVIEWED?**
- Intensive (injectable) phase: Weekly once clinically stable
- Continuation phase: Monthly

**HOW OFTEN MUST SPUTUM BE SENT?**
- One sputum specimen should be sent monthly for smear microscopy and culture (not DST)
- Only culture can determine if organisms are still viable (alive); culture is therefore required for monitoring progress

**WHAT IS SMEAR CONVERSION?**
- MDR-TB treatment started
- 1\textsuperscript{st} negative smear: At least 30 Days
- 2\textsuperscript{nd} negative smear

\[\text{Time to conversion} = \text{time from start of treatment to date first negative smear collected}\]

\[\text{SMEAR CONVERSION is 2 consecutive negative smears at least 30 days apart}\]

**WHAT IS CULTURE CONVERSION?**
- MDR-TB treatment started
- 1\textsuperscript{st} negative culture: At least 30 Days
- 2\textsuperscript{nd} negative culture

\[\text{Time to conversion} = \text{time from start of treatment to date first negative culture collected}\]

\[\text{CULTURE CONVERSION is 2 consecutive negative cultures at least 30 days apart}\]

**WHAT HAPPENS IF A PATIENT DOES NOT IMPROVE ON TREATMENT?**
- Culture conversion may take a long time but if there is no clinical improvement after 4 months, the patient must be reassessed

**ARE MDR-TB DRUGS SIDE EFFECTS DIFFICULT TO MANAGE?**
- MDR-TB treatment may have many side effects and it may be difficult to know which drug is causing these. Side effects may occur at any time. Some side effects may be severe and patients should be referred if there is any doubt about treatment. Management of drug reactions is well described in the NDoH MDR-TB guidelines
### WHAT ARE THE MOST COMMON SIDE EFFECTS OF MDR-TB TREATMENT?

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Offending Drug</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Reactions</td>
<td>• Could be several agents</td>
<td>• Desensitisation, may reintroduce drugs within one or two weeks</td>
</tr>
<tr>
<td>GIT (Nausea, Vomiting &amp; Diarrhoea)</td>
<td>• Pyrazinamide</td>
<td>• Take the medication with a non-fatty meal or before going to bed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor, if no response, investigate for liver toxicity</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>• Injectable agents</td>
<td>• Audiometry prior to initiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Repeat monthly or when indicated</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>• Cycloserine</td>
<td>• Pyridoxine or amitriptyline</td>
</tr>
<tr>
<td></td>
<td>• Terizidone</td>
<td></td>
</tr>
<tr>
<td>Electrolyte Wasting</td>
<td>• Capreomycin</td>
<td>• Is reversible once the injectable is suspended</td>
</tr>
<tr>
<td></td>
<td>• Amikacin</td>
<td>• Supplement electrolytes as needed</td>
</tr>
<tr>
<td></td>
<td>• Kanamycin</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Symptoms</td>
<td>• Cycloserine</td>
<td>• Pyridoxine</td>
</tr>
<tr>
<td></td>
<td>• Terizidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ethionamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Quinolones especially in the elderly</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>• Aminoglycosides</td>
<td>• This adverse effect is occult (not obviously noted by taking the history</td>
</tr>
<tr>
<td></td>
<td>• Capreomycin</td>
<td>of the patient or by physical examination) in onset and can be fatal</td>
</tr>
<tr>
<td>Impaired Vision</td>
<td>• Ethambutol</td>
<td>• Avoid in patients with impaired vision</td>
</tr>
<tr>
<td>Osteo-articular Pain</td>
<td>• Pyrazinamide</td>
<td>• Acetyl salicylic acid (Asprin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intermittent administration of Pyrazinamide</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>• PAS</td>
<td>• Monitor closely</td>
</tr>
<tr>
<td></td>
<td>• Ethionamide</td>
<td></td>
</tr>
</tbody>
</table>

Please consult the latest DR-TB guidelines for more in-depth guidance on managing adverse events.

### MUST THE PATIENT RECEIVE FOLLOW-UP AFTER BEING CURED?
- Yes
- Patients with MDR-TB must be followed up 6 monthly for at least 2 years after cure

### WHAT PROCEDURES MUST BE DONE AT A FOLLOW-UP VISIT?
- Clinical examination
- Sputum collection for smear and culture
## HOW IS MDR-TB MONITORED AND EVALUATED?

<table>
<thead>
<tr>
<th>Monitoring and Evaluation</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluation by Doctor</strong></td>
<td>• At baseline&lt;br&gt;• Twice to three times per week for stable patients and daily for very sick patients until conversion&lt;br&gt;• Every month or bi-monthly for outpatients in continuation phase</td>
</tr>
<tr>
<td><strong>Evaluation by Nurse</strong></td>
<td>• Daily</td>
</tr>
<tr>
<td><strong>Sputum Smear and Cultures</strong></td>
<td>• At baseline&lt;br&gt;• Monthly</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>• At baseline and weekly during intensive phase&lt;br&gt;• Monthly during continuation phase</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td>• At baseline in adults and children</td>
</tr>
<tr>
<td><strong>Body Mass</strong></td>
<td>• At baseline and then monthly</td>
</tr>
<tr>
<td><strong>DST</strong></td>
<td>• At baseline&lt;br&gt;• For patients who remain culture positive at six months</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>• At baseline&lt;br&gt;• Every six months (for children every 2 to 3 months in intensive phase)&lt;br&gt;• At treatment completion&lt;br&gt;• When requested by clinician</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
<td>• At baseline, then monthly during injectable phase</td>
</tr>
<tr>
<td><strong>Serum Potassium</strong></td>
<td>• Monthly during injectable phase</td>
</tr>
<tr>
<td><strong>Thyroid Stimulating Hormone</strong></td>
<td>• Every six months if receiving ethionamide and /or PAS&lt;br&gt;• Monitor monthly for signs of hypothyroidism&lt;br&gt;• In children every 2 months</td>
</tr>
<tr>
<td><strong>Liver Serum Enzymes</strong></td>
<td>• Periodic monitoring (every 1-3 months)&lt;br&gt;• In patients receiving pyrazinamide for an extended period&lt;br&gt;• For patients at risk of/with symptoms of hepatitis&lt;br&gt;• In Children: if symptoms or every six months if on ART</td>
</tr>
<tr>
<td><strong>HIV Screening</strong></td>
<td>• At baseline, and repeat if clinically indicated</td>
</tr>
<tr>
<td><strong>Pregnancy Test</strong></td>
<td>• At baseline for women of child bearing age and repeat if indicated</td>
</tr>
<tr>
<td><strong>Audiometry</strong></td>
<td>• At baseline, monthly during injectable phase and 3 months after completion of the injectable therapy</td>
</tr>
<tr>
<td><strong>Eye Test</strong></td>
<td>• At baseline and when indicated</td>
</tr>
<tr>
<td><strong>Lung CT-scan</strong></td>
<td>• When indicated</td>
</tr>
</tbody>
</table>
HOW IS HEARING LOSS MANAGED?

1. Previous Exposure to Aminoglycoside (e.g. Streptomycin)
   - Yes
   - No

   **Baseline Audiometry**
   - Yes
     - Assess
     - Discuss implications with patient
   - No

   **Hearing Loss confirmed**
   - Yes
     - Treatment
     - Consider administration 3x week
     - Consider using a lower dose
     - Continue/Discontinue drug after informed decision by patient
   - No

SAFETY OF SECOND-LINE DRUGS DURING PREGNANCY

<table>
<thead>
<tr>
<th>Medication</th>
<th>Safety Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>B</td>
<td>• Experience is gravid patients suggests safety</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>C</td>
<td>• Use with caution. Most references suggest it is safe to use</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>C</td>
<td>• Documented toxicity to developing foetal ear</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>D</td>
<td>• Risks and benefits must be carefully considered</td>
</tr>
<tr>
<td>Amikacin</td>
<td>D</td>
<td>• Avoid use where possible</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>D</td>
<td>• Documented toxicity to developing foetal ear</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>C</td>
<td>• Use with caution.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No teratogenic effects seen in humans when used for short periods of time (2-4 weeks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Associated with permanent damage to cartilage in weight-bearing joints of immature animals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Experience with long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>C</td>
<td>• Avoid use</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>C</td>
<td>• Teratogenic effects observed in animal studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Significantly worsens nausea associated with pregnancy</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>C</td>
<td>• No significant experience in gravid patients: animal studies have not documented toxicity</td>
</tr>
<tr>
<td>Terizidone</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

A = Safety established using human studies
B = Presumed safety based on animal studies
C = Uncertain safety, no human/animal studies show adverse effects
D = Unsafe, risk may only be justified under clinical circumstances

WHAT DOES NTM STAND FOR?
Non-Tuberculous Mycobacteria - Also called Mycobacteria Other Than Tuberculosis (MOTTs)

WHAT ARE NON-TUBERCULOUS Mycobacteria?
Mycobacteria are a diverse group of bacteria that include more than 100 different species. Mycobacterium tuberculosis is a species within this group. The non-tuberculous mycobacteria also form part of this group.

HOW DOES NTM INFECTION OCCUR?
- NTM live in the soil and water and are found throughout the world.
- NTM are acquired through environmental exposure to water, aerosols, soil, and dust – through inhalation, ingestion, and through breaks in the skin due to injuries, surgical procedures, or IV catheters.
- Unlike M. tuberculosis, they are not passed from person-to-person.

WHO IS AT RISK FOR NTM INFECTION?
Anyone can become infected, but the following groups are more at risk for disease:
- people with suppressed immune systems (such as those with HIV/AIDS and transplant recipients)
- people with pre-existing lung damage

IS NTM THE SAME AS TB OR MULTI-DRUG RESISTANT TB (MDR-TB)?
- No, it is very important to note that NTM is different to TB and MDR-TB
- We can tell the difference by looking at the identification of the organism
WHAT IS THE DIFFERENCE BETWEEN DRUG-SENSITIVE TB, MDR-TB AND NTM?

<table>
<thead>
<tr>
<th></th>
<th>Drug-sensitive TB</th>
<th>MDR-TB</th>
<th>NTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear AFB</td>
<td>Smear AFB positive</td>
<td>Smear AFB positive</td>
<td>Smear AFB positive</td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
<td>MTB detected/RIF resistance not detected</td>
<td>MTB detected / RIF resistance detected</td>
<td>Negative (Xpert detects <em>mycobacterium tuberculosis</em> only)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Yes</td>
<td>Yes</td>
<td>Maybe</td>
</tr>
<tr>
<td>Extra-pulmonary Disease</td>
<td>Yes</td>
<td>Yes</td>
<td>Maybe</td>
</tr>
<tr>
<td>DST</td>
<td>Sensitive to INH and RIF</td>
<td>Resistant to INH and RIF</td>
<td>May be resistant to INH and/or RIF</td>
</tr>
<tr>
<td>Treatment</td>
<td>Must be treated</td>
<td>Must be treated</td>
<td>Does not always require treatment if asymptomatic</td>
</tr>
</tbody>
</table>

HOW DOES NTM PRESENT?

- **Pulmonary disease** – may mimic TB clinically and/or radiologically
- **Lymphadenitis**
  - more common in children aged 1-5 years
  - typically in the head and neck
  - nodes painless and non-tender
  - little systemic symptoms
- **Infections of the skin, soft tissue and bones** may occur after penetrating trauma, surgery or the insertion of catheters and prostheses
- **Disseminated disease** can present in one of two ways:
  - Clients who are immunosuppressed due to causes other than HIV may present with fever of unknown origin (commonly due to *M. avium*) or with subcutaneous nodules and abscesses that drain spontaneously (due to *M. kansasii*).
  - Severely immunosuppressed HIV-infected patients (CD4 count < 50 cells/mm³) present with a high temperature, night sweats, weight loss, abdominal pain, and diarrhoea. This is most commonly due to *M. avium* but can also be due to *M. kansasii*. 
HOW IS NTM DIAGNOSED?

- MTB and NTM cannot be differentiated by microscopy (AFBs)
- To diagnose NTM a culture and identification of the species is required
  - NTM is cultured in the same way as MTB and then differentiated using molecular or other tests.
  - Preliminary reports prior to completion of identification tests may indicate “Mycobacterial species” which could mean MTB or NTM
  - When the species is identified on the culture, it will be identified as NTM
  - Sputum, blood and biopsy specimens can be sent for culture and identification

IT IS IMPORTANT TO REMEMBER THAT MOST SMEAR POSITIVE PATIENTS HAVE TB (AND NOT NTM), IF ONLY A SMEAR RESULT IS AVAILABLE, PATIENTS MUST BE TREATED FOR TB

DOES NTM ALWAYS NEED TO BE TREATED?

- No, NTM may be a “coloniser” i.e. we find it in the sputum culture but it does not cause disease
- Clinical and radiological details, specimen type, number of isolates, and specific NTM identified are considered
- In HIV-infected patients, NTM infection may present as an unmasking Immune Reconstitution Inflammatory Syndrome (IRIS) with anaemia, fever and hepatosplenomegaly
- However, if M.Avium is isolated from blood, bone marrow or lymph node in an HIV-infected patient, the patient must be treated
- Generally the decision about whether to treat NTM should be made by an expert at a specialised centre
HOW ARE POSITIVE NTM CULTURES MANAGED?

1. POSITIVE NTM SPUTUM CULTURES ARE MANAGED AS FOLLOWS:

   Single sputum culture positive for NTM

   - If ill (low CD4 count, fever, night sweats, respiratory symptoms, weight loss, diarrhoea and abdominal pain)
     - Refer
   - If clinically well – consider contamination, repeat sputum culture
     - Second culture positive
     - Refer
     - Second culture negative
     - Continue TB treatment if already initiated; no other management required

2. ALL BLOOD CULTURES WHICH ARE POSITIVE FOR NTM MUST BE TREATED

WHEN IS NTM PROPHYLAXIS GIVEN?

- There is little agreement regarding when prophylaxis should be given
- Patients with proven M. Avium infection, must receive treatment until their CD4 count is above 200 cells/mm³

WHAT DRUGS ARE USED TO TREAT NTM?

- At least 2 (in more severe cases, 3 drugs) should be used for at least one year
- These may include clarithromycin, ethambutol, ciprofloxacin, levofloxacin, moxifloxacin (or rifabutin if it is available)
- An injectable (e.g. streptomycin, amikacin) may be used for ill patients
- HIV-infected clients should receive ART. Azithromycin should replace clarithromycin for patients receiving efavirenz
# IMPORTANT TB DRUG INTERACTIONS

## 1. ISONIAZID DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Effect of Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>• Absorption of INH is reduced by concurrent use of aluminium</td>
<td>• These agents should be administered at least 2 hours apart</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>• Serum levels of carbamazepine increase rapidly</td>
<td>• Carbamazepine toxicity can occur</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Carbamazepine dosage must be reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Must be closely monitored and dose adjusted</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>• Potential paracetamol toxicity</td>
<td>• Normal daily analgesic dosages of 4g may not be safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Warn patients to limit their use of paracetamol</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>• Phenytoin levels increased if administered with INH alone</td>
<td>• Phenytoin toxicity may occur if the dosage of phenytoin is not reduced</td>
</tr>
<tr>
<td></td>
<td>• If both rifampicin and INH are given, serum phenytoin levels may decrease in fast acetylators of INH, but may rise in slow acetylators</td>
<td>appropriately.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>• Plasma level of theophylline may be increased</td>
<td>• Monitor levels</td>
</tr>
<tr>
<td>Warfarin</td>
<td>• Warfarin levels increased</td>
<td>• Dose adjustment may be required</td>
</tr>
</tbody>
</table>

## 2. RIFAMPICIN DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Effect of Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>• Ritonavir levels reduced</td>
<td>• Adjust LPV/r dose</td>
</tr>
<tr>
<td></td>
<td>• Increased ALT/AST</td>
<td>• Monitor liver functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider change to rifabutin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>• Phenytoin serum levels reduced</td>
<td>• Monitor phenytoin levels and increase dose appropriately if used with rifampicin</td>
</tr>
<tr>
<td></td>
<td>• When INH and Rif used with phenytoin, the reduction in levels may be less</td>
<td>• Monitor closely to adequately adjust dose</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>• Clearance of zidovudine increased</td>
<td>• Monitor for reduced response to AZT</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>• Nevirapine levels reduced</td>
<td>• Consider alternative</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>• Valproate levels may be reduced</td>
<td>• Monitor valproate levels and adjust dose accordingly</td>
</tr>
<tr>
<td>Calcium channel blockers: Nifedipine, Amlodipine, Verapamil</td>
<td>• Calcium channel blocker levels reduced</td>
<td>• Monitor closely and increase calcium channel blocker dose if necessary</td>
</tr>
</tbody>
</table>
## 3. PYRAZINAMIDE DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Anti-gout agents:</th>
<th>Effect of interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol, Probenecid</td>
<td>Pyrazinamide inhibits urate clearance</td>
<td>Dose of allopurinol or probenecid may require adjustment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diuretics, Ethambutol</th>
<th>Effect of interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additive increase in serum urate</td>
<td>Monitor closely</td>
</tr>
</tbody>
</table>

## 4. ETHAMBUTOL DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Pyrazinamide, Diuretics</th>
<th>Effect of interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additive potential for increase in serum urate</td>
<td>Monitor closely</td>
</tr>
</tbody>
</table>
SUPPORTING ADHERENCE IN TB PATIENTS

WHY IS ADHERENCE SUPPORT IMPORTANT?

- TB is a complex disease that has biological, social, economic and cultural effects on the patient
- These factors affect adherence, which in turn affects treatment outcome
- Health care providers should thus take a comprehensive approach and consider the impact of TB on the patient’s life as a whole

WHAT ARE THE FACTORS THAT INFLUENCE TREATMENT OUTCOME?

<table>
<thead>
<tr>
<th>Social And Economic Factors</th>
<th>Health System Factors</th>
<th>Patient Related Factors</th>
<th>Therapy Related Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme poverty</td>
<td>Poor health infrastructure</td>
<td>Stigma</td>
<td>Complex treatment regimens</td>
</tr>
<tr>
<td>Poor support networks</td>
<td>Poorly trained or supervised health care personnel</td>
<td>Depression</td>
<td>Large pill burden</td>
</tr>
<tr>
<td>Unstable living circumstances</td>
<td>Poor relationships with patients</td>
<td>Disempowerment</td>
<td>Adverse effects of medication</td>
</tr>
<tr>
<td>Beliefs about TB and its treatment</td>
<td>Inadequate development of community based support for patients</td>
<td>Poor knowledge about TB and the efficacy of treatment</td>
<td>Long treatment duration</td>
</tr>
</tbody>
</table>

WHO SHOULD DO ADHERENCE COUNSELLING?

- Appropriately trained nurses, lay counsellors or community health workers can do adherence counselling
- When possible a clinic staff member or a health care worker should accompany the patient home to:
  - screen household contacts
  - identify social problems

WHAT SHOULD BE INCLUDED IN ADHERENCE COUNSELLING?

- Information about TB:
  - what it is; how it is transmitted and how to protect those around you from infection
- Discuss medication used to treat TB:
  - when and how to take it; possible side effects and what to do about them
- The importance of:
  - adherence to treatment
  - completing treatment
  - HIV and the need for HIV testing
  - healthy lifestyle
- Identify barriers to treatment and address these
- Develop a clear treatment plan:
  - highlight duration of treatment, dates when sputa are due, when medication will be changed

NO PATIENT SHOULD BE DENIED TREATMENT DUE TO NOT HAVING A TREATMENT SUPPORTER!
SUPPORTING ADHERENCE IN TB PATIENTS...CONTINUED

HOW CAN ADHERENCE BE SUPPORTED?

- The role of the treatment supporter is to support adherence and motivate the patient to complete treatment
- The treatment supporter must be acceptable to the patient
- Treatment supporters may be health care workers or trained workplace or community members
- It is recommended for all patients for the entire treatment duration
- Directly observed treatment (DOT) means a treatment supporter watches the patient swallowing his/her medication
- DOT allows non-adherence and adverse effects to be picked up at an early stage

Always ensure that you have the patients latest contact details, including address, so that he/she can be readily contacted if necessary.
Ensure that treatment taken daily is recorded in order to detect defaulters timeously.

HOW CAN WE APPLY DOT TO FIT PATIENTS’ NEEDS?

- Patients should receive treatment as close to home or work as possible
- DOT may occur at the clinic, workplace or in the community, depending on the patients’ needs
- Community DOT is often more accessible and convenient for patients

HOW SHOULD THE FAMILY BE INVOLVED IN TREATMENT?

- A family member or friend should be counselled with the patient and provided with the necessary information to support the patient and assist with treatment
- This is particularly important in the treatment of children and the elderly
- They should be told to contact the clinic if any problems are observed
- Community health workers can assist by visiting the family
- Ensure that the family member selected to assist is acceptable to the patient

HIV counselling and testing should be provided to all TB patients in order to comprehensively care for the patient.

Patients should be provided with both TB and HIV care at clinical visits.

Ensure that patients discharged from the TB programmes access on-going HIV care.
WHAT ARE THE RISKS ASSOCIATED WITH TB IN PREGNANCY?

MOTHER • TB is a major cause of maternal mortality, especially in HIV-infected women

BABY • Prematurity • Low birth weight • Perinatal death • TB infection and disease, either before or after birth • Increased risk of HIV transmission to the baby in HIV-infected pregnant women with TB, compared to HIV-infected pregnant women without TB

HOW IS TB DIAGNOSED IN PREGNANCY?

• Use the four TB screening questions in all pregnant women at every visit; which are:
  1. Are you coughing?
  2. Are you losing weight (or not gaining weight adequately)?
  3. Are you sweating at night?
  4. Do you have a fever?
• If any one of these symptoms is present, investigate for TB as per national diagnostic algorithms (see pages 8-11)

WHAT TB TREATMENT CAN BE USED FOR THE MOTHER?

<table>
<thead>
<tr>
<th>Pregnancy:</th>
<th>Breastfeeding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line TB drugs</td>
<td>All first-line TB drugs are safe</td>
</tr>
<tr>
<td><strong>DO NOT USE</strong> streptomycin (ototoxic to foetus)</td>
<td></td>
</tr>
</tbody>
</table>

*Please see MDR section for treatment of M/XDR-TB in pregnancy*

HOW SHOULD TB TREATMENT IN AN HIV-INFECTED PREGNANT WOMAN BE APPROACHED?

<table>
<thead>
<tr>
<th>If already on ART</th>
<th>If not on ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Start TB treatment</td>
<td></td>
</tr>
<tr>
<td>• Continue ART</td>
<td></td>
</tr>
<tr>
<td>• If on Lopinavir/ritonavir, the dose should be doubled slowly over 2 weeks</td>
<td></td>
</tr>
<tr>
<td>• Monitor for hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>• Decrease the dose of LPV/r to the standard dose 2 weeks after completing TB treatment</td>
<td></td>
</tr>
<tr>
<td>• Start TB treatment</td>
<td></td>
</tr>
<tr>
<td>• Start AZT monotherapy</td>
<td></td>
</tr>
<tr>
<td>• Change from AZT monotherapy to the FDC (TDF+FTC+EFV) after about 2 weeks of TB treatment (once stable on treatment)</td>
<td></td>
</tr>
<tr>
<td>• Counsel and monitor for IRIS</td>
<td></td>
</tr>
</tbody>
</table>
ARE HIV-INFECTED PREGNANT WOMEN ELIGIBLE FOR IPT?

• Yes, pregnancy is not a contra-indication to IPT
• All HIV-infected pregnant women with a negative TB symptom screen must be considered for IPT
• However ART is the priority and IPT should be started once the patient is stable on ART
• TST should be done to determine duration of IPT:
  o If TST positive and on lifelong ART – IPT for 36 months
  o If TST positive and on PMTCT prophylaxis – IPT for 12 months
• If TST not done - IPT for 6 months

HOW SHOULD MDR-TB IN PREGNANCY BE TREATED?

• Refer to a specialist site

HIV & AIDS Information: HATIP #203, February 14th 2013 - HIV and TB in Practice for Nurses: Pregnancy and HIV
TREATING AN INFANT BORN TO A MOTHER WHO HAS TB

WHICH PREGNANCIES SHOULD I BE CONCERNED ABOUT?

• A mother diagnosed with TB in the last two months of pregnancy
• A mother who has not shown good clinical response to therapy and/or whose smear microscopy has not converted

HOW DO I EXCLUDE TB IN THIS INFANT?

• Do a clinical examination, including an abdominal examination
• Look for the following signs and symptoms:
  ○ respiratory rate ≥60/min OR difficulty breathing
  ○ feeding problems OR poor weight gain
  ○ abdominal distension, enlarged liver OR spleen
  ○ jaundice

CAN A MOTHER WITH TB STILL BREASTFEED HER INFANT?

• YES
• Maternal TB infection is not an indication to separate mother and child, and is not a contraindication to breastfeeding

ALL MOTHERS, INCLUDING THOSE ON TB TREATMENT AND/OR HIV-INFECTED, SHOULD BE ENCOURAGED TO BREASTFEED

WHAT ARE SOUTH AFRICA’S CURRENT GUIDELINES REGARDING INFANT FEEDING?

South Africa adopts the 2010 WHO Guidelines as follows:
• All mothers can safely breastfeed
• SA supports and promotes exclusive breastfeeding for 6 months irrespective of HIV status, followed by appropriate complementary feeding
• If mother is HIV-uninfected continue breastfeeding for 2 years and beyond
• SA Guidelines recommend that HIV-infected women breastfeed for maximum 12 months

WHAT ARE THE INFANT FEEDING RECOMMENDATIONS FOR HIV-INFECTED MOTHERS?

• Exclusive breastfeeding for 6 months
• Introduction of complementary feeding after 6 months with continued BF for 12 months, AND
  ○ the mother should be on lifelong ART or
  ○ the infant should be on daily nevirapine prophylaxis for the duration of breastfeeding, to a maximum of 12 months

HOW DO I MANAGE AN INFANT BORN TO A MOTHER WITH TB?

• Vitamin K should be administered as part of routine care at birth, especially if the mother is taking rifampicin (to avoid postnatal haemorrhage)
TREATING AN INFANT BORN TO A MOTHER WHO HAS TB

A Baby Born to a Mother with TB

- Send a portion of the placenta in sterile saline for TB culture and another portion in formalin for histology
- Assess baby for TB symptoms and do not give BCG to the baby at birth
- Make a record in the Road-to-Health Booklet that the child was exposed to TB in utero
- All mothers should be encouraged to breastfeed, regardless of TB and/or HIV status

TB signs/symptoms in infant

Refer baby to hospital for assessment to exclude TB. At the referral centre, the TB work-up in the baby should include:
- submission of gastric aspirates and blood for TB culture, DST
- CXR
- abdominal sonar (as the liver is often the primary site in congenital TB)

TB Diagnosed

Start Regimen 3 at the referral centre to ensure correct dosage. Fast-track for ART if baby is HIV-infected

No TB Diagnosed

Isoniazid preventive therapy
10 mg/kg/day for 6 months

- Stop INH and give BCG if HIV-uninfected
- If HIV-infected give BCG if asymptomatic

No TB signs/symptoms in infant

BCG can be given if HIV-uninfected or asymptomatic infection

TB treatment should be initiated at a referral centre as dosing may be difficult in small infants

**WHAT DO WE MEAN BY TB/HIV INTEGRATION?**
Both TB and HIV services are provided by the same provider at the same visit, a “one-stop-shop”.

**WHY SHOULD WE WORK TOWARDS INTEGRATED TB AND HIV SERVICES?**
- It is a patient-centered approach
- Decreases illness and death from both TB and HIV
  - HIV-infected patients have higher risk of dying from TB (16-35% compared to 5-8% in HIV-uninfected)
- Improved efficiency and reduced workload
- To adopt a family-oriented approach for children with HIV and TB
- It is a more efficient use of resources

**WHAT IS THE DIFFERENCE BETWEEN INTEGRATION AND COLLABORATION?**
- Collaboration: cross referral of patients between TB and HIV services
- Integration: one provider

**WHAT DOES TASK SHIFTING MEAN?**
- Distribution of tasks among levels of healthcare staff

**EXAMPLES OF TB/HIV SERVICE RELATED TASK SHIFTING**

<table>
<thead>
<tr>
<th>Health Care Professional</th>
<th>Traditional Role</th>
<th>Expanded (Task-Shifting) Role to Achieve Integrated TB/HIV Services at PHC Facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>Initiating patient on ART</td>
<td>Managing complicated HIV &amp; TB referred by PHC facility nurse</td>
</tr>
<tr>
<td>Professional Nurse</td>
<td>Managing clinically stable patients already initiated on ART</td>
<td>• Prescribing and dispensing ART (Schedule 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Managing patients on ART</td>
</tr>
<tr>
<td>Counsellor</td>
<td>• Adherence Counselling • HIV Testing</td>
<td>Finger-prick of consenting adults to obtain blood for rapid HIV testing</td>
</tr>
<tr>
<td>Administrative staff including security personnel</td>
<td>Data Collection</td>
<td>• Screening for TB symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Help to enforce TB Infection Control measures through education of waiting patients in cough etiquette/hygiene</td>
</tr>
</tbody>
</table>

1 National Department of health. A ‘hands-on’ guide to integration of TB/HIV services including antiretroviral therapy at primary health care facilities in South Africa. 2010
WHAT ARE THE KEY TB/HIV INTEGRATION ACTIVITIES?

For People Living With HIV to Reduce the Burden of TB (4Is)
- Intensified Case Finding for TB
- IPT
- Infection control for TB
- Initiate ART early

For Patients With Presumptive TB And Diagnosed TB to Reduce the Burden of HIV
- Provider Initiated Counselling and Testing
- HIV prevention interventions for HIV negative and HIV positive patients
- For HIV positive TB patients
  - Cotrimoxazole prophylaxis
  - ART
WHY IS THE MANAGEMENT OF TB/HIV CO-INFECTED PATIENTS DIFFICULT?

- Drug interactions - rifampicin interacts with NNRTIs and PIs
- Increased risk of drug toxicity
- Increased pill burden with possible impact on adherence
- Tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS)

WHICH ADULTS ARE ELIGIBLE FOR LIFELONG ART?

- CD4<350 cells/mm$^2$
- Stage 3 or 4 irrespective of CD4 count
  - This includes all patients with TB – pulmonary, extra-pulmonary, drug sensitive and drug-resistant

WHAT ARE THE RECOMMENDED ART REGIMENS ADULTS?

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommended regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All new patients eligible for treatment, including pregnant women</td>
<td>TDF + (FTC or 3TC) + EFV OR FDC formulation which is preferred</td>
</tr>
<tr>
<td>Contraindications to EFV</td>
<td>TDF + (FTC or 3TC) + NVP</td>
</tr>
<tr>
<td>Contraindication to TDF</td>
<td>AZT+ 3TC + EFV (or NVP)</td>
</tr>
<tr>
<td>Contraindication to TDF and AZT</td>
<td>d4T + 3TC + EFV (or NVP)</td>
</tr>
<tr>
<td>Contraindication to TDF, AZT and d4T</td>
<td>ABC + 3TC + EFV (or NVP)</td>
</tr>
<tr>
<td>Currently on d4T based regimen</td>
<td>TDF + (FTC or 3TC) + EFV</td>
</tr>
</tbody>
</table>

2nd line:
- Failing on a TDF-based 1st line regimen AZT+3TC+ LPV/r
- Failing on a d4T-based 1st line regimen TDF+3TC (or FTC) and LPV/r
- Dyslipidaemia or diarrhoea associated with LPV/r Switch LPV/r to ATV/r

WHICH SIDE EFFECTS ARE SHARED BY TB DRUGS AND ART?

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Antiretroviral Treatment</th>
<th>Tuberculosis Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and Vomiting</td>
<td>Didanosine, zidovudine, protease inhibitors</td>
<td>Pyrazinamide, ethionamide, PAS</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>• Nevirapine, efavirenz • Protease inhibitors (especially when dose is increased to overcome rifampicin induction)</td>
<td>Rifampicin, isoniazid, pyrazinamide</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Stavudine, didanosine</td>
<td>Isoniazid, ethionamide, terizidone/cycloserine</td>
</tr>
</tbody>
</table>
WHICH TB DRUG AND ART COMBINATIONS ARE PROBLEMATIC?

- Rifampicin reduces the levels of PIs and also NNRTIs, but does not require dose adjustment
- Of the NNRTIs, efavirenz (EFV) is preferred to nevirapine; used at standard doses with standard TB treatment

### ART AND TB TREATMENT....Continued

**Neuropsychiatric Side Effects**
- Efavirenz
  - Isoniazid, terizidine/cycloserine, quinolones, ethionamide

**Renal Toxicity**
- Tenofovir
  - Aminoglycosides, capreomycin, rifampicin

**Rash**
- Nevirapine, efavirenz
  - Rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin

**Note that cotrimoxazole can also cause rash, hepatitis, neutropaenia and other haematological effects**

### WHICH TB DRUG AND ART COMBINATIONS ARE PROBLEMATIC?

- Rifampicin reduces the levels of PIs and also NNRTIs, but does not require dose adjustment
- Of the NNRTIs, efavirenz (EFV) is preferred to nevirapine; used at standard doses with standard TB treatment

**NVP & RIF**
- Start NVP at 200mg bd in adults i.e. omit lead-in dose

**LPV/r & RIF**
- Increase LPV/r dose as in table below

**TDF & amikacin or kanamycin or capreomycin**
- Avoid combination (nephrotoxicity)
  - AZT can be used in place of TDF
  - If HB <8 g/dl, use D4T
  - Can be switched back to TDF on completion of aminoglycoside if creatinine clearance >50ml/min

### ANTIRETROVIRAL TREATMENT FOR ADULTS ON CONCOMITANT TB TREATMENT

<table>
<thead>
<tr>
<th>If TB develops while on ART</th>
<th>If TB diagnosed before starting ART</th>
</tr>
</thead>
</table>
| • Continue ART throughout TB treatment  
  • If on first-line ART regimen  
    - Patient can remain on this regimen  
    - Some clinicians advocate switching NVP to EFV, but this is not necessary if the patient is stable on NVP | • Start TB treatment first  
  • All TB patients qualify for ART  
    - Timing of ART initiation depends on CD4 count and clinical status – see table on following page  
    - Avoid NVP if possible  
    - If EFV contraindicated, use NVP, starting with 200 mg bd (i.e. omit lead-in dose) |
WHEN SHOULD ART BE STARTED IN HIV-INFECTED PATIENTS DIAGNOSED WITH TB?

- All HIV-infected TB patients qualify for life-long ART, regardless of CD4 count.
- If an HIV-infected patient is not on ART and is diagnosed with TB, TB treatment must be started first. ART must be started thereafter, as per the following table:

<table>
<thead>
<tr>
<th>CD4 count &lt; 50 cells/mm³</th>
<th>CD4 count &gt;50 cells/mm³ with severe clinical disease*</th>
<th>Other patients with CD4 count &gt;50 cells/mm³</th>
<th>Drug resistant TB</th>
<th>HIV-infected pregnant woman with active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start within 2 weeks of starting TB therapy</td>
<td>Start within 2-4 weeks of starting TB therapy</td>
<td>Can delay ART initiation until 2-8 wks after starting TB therapy</td>
<td>Start ART within 2-4 wks after confirmation of resistance, initiation of second-line TB therapy</td>
<td>Start ART as early as feasible</td>
</tr>
</tbody>
</table>

*Low Karnofsky score, low body mass index, low haemoglobin, low albumin, organ system dysfunction, extent of disease

WHAT ARE THE CRITERIA FOR STARTING ART IN CHILDREN?

<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical Stage</th>
<th>CD4 Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>All stages</td>
<td>All CD4 counts</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>WHO Stage 3 or 4</td>
<td>Absolute CD4 count &lt;350 cells/mm³</td>
</tr>
</tbody>
</table>
WHAT ARE THE RECOMMENDED ART REGIMENS FOR CHILDREN?

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants and children under 3 years (or &lt; 10kg)</td>
<td>ABC + 3TC + LPV/r</td>
</tr>
<tr>
<td>Children ≥ 3 years (and ≥ 10kg)</td>
<td>ABC + 3TC + EFV</td>
</tr>
<tr>
<td>Currently on d4T-based regimen</td>
<td>• Change d4T to ABC if Viral Load is undetectable</td>
</tr>
<tr>
<td></td>
<td>• If Viral load &gt;1000 copies/ml manage as treatment failure</td>
</tr>
<tr>
<td></td>
<td>• If Viral load between 50 – 1000 copies/ml</td>
</tr>
<tr>
<td></td>
<td>– consult with expert for advice</td>
</tr>
</tbody>
</table>

WHEN SHOULD ART BE INITIATED IN CHILDREN WITH TB?

• Since TB is a stage 3 disease, children with TB will need to be started on ART
• It should be initiated 2-4 weeks after starting TB treatment
• If the child is already on ART when TB is diagnosed:
  ◦ continue with ART and start TB treatment, see below for instances in which treatment should be adjusted

HOW SHOULD THE REGIMENS BE CHANGED IN CHILDREN ON TB TREATMENT AND ART?

• Rifampicin reduces the levels of lopinavir/ritonavir. If on rifampicin and LPV/r:
  ◦ LPV/r dose must be increased by giving additional ritonavir
  ◦ See Antiretroviral Drug Dosing Chart for Children2013 (page 81):
    – Column titled ‘ritonavir boosting’ indicates the dose of ritonavir that must be given in addition to the standard dose of LPV/r, depending on the weight
    ◦ Alternatively, if ritonavir syrup is not available, the dose of LPV/r can be doubled but this is less effective
• All other antiretrovirals should be continued at standard doses
• TB treatment should be given at standard doses in children on ART

∞ Children ≥ 3 years and exposed to NVP for 6 weeks or longer (PMTCT) should be initiated on ABC + 3TC + LPV/r
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>*1ml bd</td>
<td>1ml bd</td>
<td>6ml bd</td>
<td>Avoid</td>
<td>6ml bd</td>
<td>9ml bd</td>
<td>1ml bd</td>
<td>6ml bd</td>
</tr>
<tr>
<td>3-3.9</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>1.5ml bd</td>
<td>1.5ml bd</td>
<td>2.5ml bd</td>
<td>1.5ml bd</td>
<td>1.5ml bd</td>
<td>1.5ml bd</td>
<td>1.5ml bd</td>
<td>1.5ml bd</td>
</tr>
<tr>
<td>4-4.9</td>
<td>6ml bd</td>
<td>6ml bd</td>
<td>2ml bd</td>
<td>1.5ml bd</td>
<td>2.5ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
</tr>
<tr>
<td>5-5.9</td>
<td>12ml od</td>
<td>12ml od</td>
<td>3ml bd</td>
<td>2ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
<td>3ml bd</td>
</tr>
<tr>
<td>6-6.9</td>
<td>30mg nocte</td>
<td>200mg nocte</td>
<td>2.5ml bd</td>
<td>1.5ml bd</td>
<td>2.5ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
</tr>
<tr>
<td>7.7-8.9</td>
<td>60mg nocte</td>
<td>200mg nocte</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
</tr>
<tr>
<td>9-9.9</td>
<td>120mg nocte</td>
<td>300mg nocte</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
<td>2ml bd</td>
</tr>
<tr>
<td>10-10.9</td>
<td>600mg nocte</td>
<td>600mg nocte</td>
<td>5ml bd</td>
<td>5ml bd</td>
<td>5ml bd</td>
<td>5ml bd</td>
<td>5ml bd</td>
<td>5ml bd</td>
<td>5ml bd</td>
<td>5ml bd</td>
</tr>
<tr>
<td>11-13.9</td>
<td>1200mg nocte</td>
<td>1200mg nocte</td>
<td>10ml bd</td>
<td>10ml bd</td>
<td>10ml bd</td>
<td>10ml bd</td>
<td>10ml bd</td>
<td>10ml bd</td>
<td>10ml bd</td>
<td>10ml bd</td>
</tr>
<tr>
<td>14-16.9</td>
<td>3000mg nocte</td>
<td>3000mg nocte</td>
<td>20ml bd</td>
<td>20ml bd</td>
<td>20ml bd</td>
<td>20ml bd</td>
<td>20ml bd</td>
<td>20ml bd</td>
<td>20ml bd</td>
<td>20ml bd</td>
</tr>
<tr>
<td>17-19.9</td>
<td>6000mg nocte</td>
<td>6000mg nocte</td>
<td>30ml bd</td>
<td>30ml bd</td>
<td>30ml bd</td>
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<td>30ml bd</td>
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<tr>
<td>20-22.9</td>
<td>9000mg nocte</td>
<td>9000mg nocte</td>
<td>40ml bd</td>
<td>40ml bd</td>
<td>40ml bd</td>
<td>40ml bd</td>
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<td>40ml bd</td>
<td>40ml bd</td>
<td>40ml bd</td>
</tr>
<tr>
<td>23-24.9</td>
<td>14000mg nocte</td>
<td>14000mg nocte</td>
<td>50ml bd</td>
<td>50ml bd</td>
<td>50ml bd</td>
<td>50ml bd</td>
<td>50ml bd</td>
<td>50ml bd</td>
<td>50ml bd</td>
<td>50ml bd</td>
</tr>
<tr>
<td>25-29.9</td>
<td>20000mg nocte</td>
<td>20000mg nocte</td>
<td>60ml bd</td>
<td>60ml bd</td>
<td>60ml bd</td>
<td>60ml bd</td>
<td>60ml bd</td>
<td>60ml bd</td>
<td>60ml bd</td>
<td>60ml bd</td>
</tr>
<tr>
<td>30-34.9</td>
<td>30000mg nocte</td>
<td>30000mg nocte</td>
<td>70ml bd</td>
<td>70ml bd</td>
<td>70ml bd</td>
<td>70ml bd</td>
<td>70ml bd</td>
<td>70ml bd</td>
<td>70ml bd</td>
<td>70ml bd</td>
</tr>
<tr>
<td>35-39.9</td>
<td>40000mg nocte</td>
<td>40000mg nocte</td>
<td>80ml bd</td>
<td>80ml bd</td>
<td>80ml bd</td>
<td>80ml bd</td>
<td>80ml bd</td>
<td>80ml bd</td>
<td>80ml bd</td>
<td>80ml bd</td>
</tr>
<tr>
<td>≥40</td>
<td>≥40</td>
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<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
</tr>
</tbody>
</table>

* Avoid LPV/rtv solution in any full term infant <14 days of age and any premature infant <14 days after their date of delivery (40 weeks post conception) or obtain expert advice.

** Children 25-34kg may be also dosed with LPV/rtv 200/50mg adult tabs: 2 tab/s am, 1 tab pm

<table>
<thead>
<tr>
<th>Wt. (kg)</th>
<th>Weight (kg)</th>
<th>Cotrimoxazole Dose</th>
<th>Multivitamin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>2.5ml od</td>
<td>5ml od</td>
<td>5ml od</td>
</tr>
<tr>
<td>3-9.9</td>
<td>5ml od</td>
<td>5ml od</td>
<td>5ml od</td>
</tr>
<tr>
<td>10-13.9</td>
<td>10ml od</td>
<td>10ml od</td>
<td>10ml od</td>
</tr>
<tr>
<td>14-29.9</td>
<td>2 tabs od</td>
<td>2 tabs od</td>
<td>2 tabs od</td>
</tr>
<tr>
<td>≥30</td>
<td>10ml od</td>
<td>10ml od</td>
<td>10ml od</td>
</tr>
</tbody>
</table>

Note: Wt. (kg) refers to weight in kilograms.
WHAT IS IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)?

- It refers to a worsening in the clinical status of patients after ART initiation
  - After ART initiation, the immune system begins to recover
  - As a result, inflammatory symptoms worsen in the presence of an opportunistic infection (OI)
- IRIS may occur with a number of opportunistic infections including TB, cryptococcal meningitis, hepatitis B etc.
- It may manifest 1 week to several months after ART initiation
- May occur in:
  - patients already on treatment for the OI at ART initiation – paradoxical IRIS
  - patients in whom the OI is unrecognised at the time of ART initiation – unmasking IRIS

HOW DOES TB IRIS PRESENT?

- These patients develop a recurrence/progression of TB symptoms or develop new features of TB in the first few weeks after starting ART
- Common clinical features include:
  - enlarging lymph nodes
  - fevers
  - worsening CXR infiltrates
  - enlarging pleural effusions
- Meningitis or enlarging tuberculomas may be life-threatening

HOW IS TB IRIS DIAGNOSED?

- Diagnosis of exclusion-exclude other possible causes of clinical deterioration including:
  - MDR-TB
  - Alternative diagnoses e.g. bacterial pneumonia, Pneumocystis pneumonia, Kaposi’s sarcoma etc
  - Poor adherence
  - Malabsorption
  - Drug toxicity

HOW IS IRIS MANAGED?

- If life-threatening IRIS develops, the patient requires specialist referral
- IRIS does not indicate drug failure or a drug side effect
  - It is almost never a reason to stop antiretroviral therapy
- There is evidence that corticosteroids improve symptoms, but they should only be used when the diagnosis is certain and the symptoms severe

TB-IRIS is infrequently fatal. ART should not be delayed in patients with low CD4 counts to prevent TB-IRIS as the mortality is high when ART is delayed.
MONITORING AND EVALUATION OF PATIENTS WITH PRESUMPTIVE TB

WHY IS MONITORING AND EVALUATION (M&E) IMPORTANT?

• To ensure that each patient with TB symptoms and each TB case receives appropriate management
• For facilities, districts and sub-districts to monitor their performance and allocate resources appropriately
• For NDoH to allocate resources appropriately

WHICH TOOLS ARE USED FOR MONITORING TB PATIENTS?

• TB Case Identification and Follow-Up Register
• TB Case Register (‘TB register’) for drug-sensitive TB
• TB Drug-resistant register for mono and poly-resistant TB, M/XDR-TB
• TB Notification forms

WHAT ARE KEY ISSUES IN COMPLETING THE TB CASE IDENTIFICATION AND FOLLOW-UP REGISTER?

• Use NHLS barcode sticker to document specimen number
• If testing was done by Xpert MTB/RIF indicate this in the ‘Comments’ section
  ❏ NB: Patients diagnosed with Xpert MTB/RIF also need to have a smear taken to monitor treatment response
• Offer all patients with presumptive TB HIV testing. An extra column can be added to record HIV result
• Remember to complete the monthly summary sheet at the back of the Case Identification and Follow-up Register

WHAT ARE KEY ISSUES IN COMPLETING THE TB CASE REGISTER/TB DRUG-RESISTANT REGISTER?

• Complete and update HIV and ART data

WHAT ARE KEY ISSUES IN COMPLETING THE TB NOTIFICATION FORMS?

• TB is an infectious disease with major public health significance; therefore a notifiable medical condition
• TB notifications are reported to the South African Disease Notification System which is a passive surveillance system
• Complete and submit a notification form for each newly diagnosed TB case

WHAT HAPPENS TO TB DATA?

• TB data collected at the facility is reported to various levels: sub-district, district, provincial and national
• TB register data is collated electronically at the sub-district level into the electronic TB register (ETR.net) which forms the basis of the M&E system for the TB programme

OBTAIN ACCURATE CONTACT AND ALTERNATE CONTACT DETAILS TO ENSURE FOLLOW-UP IN THE EVENT OF DEFAULT. CONFIRM CONTACT DETAILS AT EACH VISIT
HOW SHOULD PATIENTS BE CATEGORISED IN ORDER TO BE ENTERED IN THE REGISTER?

1. **Smear Microscopy Positive PTB Case:**
   - At least 1+ acid-fast bacilli in at least 1 sputum smear examination
   - A single positive result confirms the diagnosis of TB

2. **Smear Microscopy Negative PTB Case:**
   - Patient with presumptive TB with at least one sputum smear negative for AFBs and
     - Sputum culture is positive for MTB or
     - Xpert MTB/RIF is positive for MTB or
     - CXR abnormal, no response to broad-spectrum antibiotics and HCW decided to treat

3. **Definition Of ‘Smear Not Done’:**
   - Patient with presumptive TB diagnosed with pulmonary TB without smear microscopy results and
     - CXR abnormal, no response to broad-spectrum antibiotics and HCW decided to treat
     - Xpert MTB/RIF is positive for MTB

CATEGORIES OF NEW/ RETREATMENT TB

1. **New:** A client who has never had treatment for TB or who has taken anti-TB drugs for less than 4 weeks

2. **Retreatment:** A client who has taken TB treatment for 4 weeks or more in the past and either relapsed, defaulted or had treatment failure

**Categories of Retreatment Patients:**

<table>
<thead>
<tr>
<th>Retreatment Patient Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>A client who received treatment and was declared cured or treatment completed at the end of the treatment period and has now developed sputum smear or culture positive pulmonary TB again</td>
</tr>
<tr>
<td>Retreatment After Failure</td>
<td>A pulmonary TB client who is still sputum smear or culture positive at the end of the treatment period.</td>
</tr>
<tr>
<td>Retreatment After Default</td>
<td>A client who completed at least one month of treatment and returns after interrupting treatment for two months or more, and is still sputum smear or culture positive</td>
</tr>
</tbody>
</table>

3. **Other:**
   All cases that do not fit the above definitions such as:
   - those without a clear history of previous TB treatment
   - those with unknown outcomes of previous TB treatment
   - those who have been previously treated but have smear/culture negative PTB and/or EPTB
CASE IDENTIFICATION AND FOLLOW-UP REGISTER

1. The following presumptive TB patients should be entered in this register:
   a. All clients with presumptive TB (5 years and older)
   b. Patients for whom two sputum specimens for smear microscopy have been collected

2. The “TB Suspect Number” needs to be chronologically numbered – as patients present themselves, e.g. 1/2007; 2/2007 (in hospitals the OPD number can used as it may be easier to follow up the patient).

3. The “Specimen Code” = barcode on the laboratory request form. The barcode must be affixed into the register.
   a. It is important to make sure that each specimen has the correct code-label attached to it

4. The treatment start date and TB Registration number needs to be recorded.
   a. If the patient died before treatment started – patient still needs to be registered, but as a “Died before Rx started”.
   b. If a patient is lost to follow-up, they are then registered as a “did not start treatment” = Primary Defaulter

5. Summary for TB Case Identification and Follow-up Register: At the end of each register is a copy of the summary that needs to be filled in:
   a. at the end of each month and
   b. summarised at the end of each quarter
   c. these totals need to be sent to province as part of the quarterly report

TUBERCULOSIS REGISTER

1. The revised TB Recording and Reporting System depends on the flow of information from several sources:

   Patient/Clinic Hospital Card ➔ Facility Register ➔ Sub-district TB Register

2. Each register page is followed by three carbonized pages. The set of four must be separated by the thick divider (on the right side of the register) to prevent bleed-through.

3. Use only a BALL-POINT pen to fill in the register. PRESS FIRMLY.

4. The facility name is entered at the top right of each set of pages. This must be included in order for the pages to be re-assembled at sub-district-level.

5. As patients are diagnosed, they are entered into the register.

6. A new page is started at the beginning of each new quarter even if the previous page has space for more patient entries.

7. Flow of information from the facility to sub-district-level:
IPT REGISTER
1. ALL patients initiated on IPT must be entered into this register
2. Each month should start on a new page
3. Each page should have the year and month clearly written at the top of the page.
4. The patient number should consist of a number/mm/yy. Eg. 001/11/2012.
5. The registration date is the date the patient was initiated.

WHAT ARE THE KEY IPT INDICATORS?
• Number started on IPT
• Number who develop TB while on IPT

<table>
<thead>
<tr>
<th>Page</th>
<th>Use</th>
<th>Action</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pink</td>
<td>Initial</td>
<td>Define case finding cohort</td>
<td>Send to sub-district</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Submit to the sub-district for capturing as soon as the page is full and accurately filled. (E.g. Information of ten patients up to the pre-sputum)</td>
</tr>
<tr>
<td>Yellow</td>
<td>Follow-up 1</td>
<td>Update patient information (smear conversion)</td>
<td>Send to sub-district</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Submit to the sub-district for capturing as soon as the page is full and accurately filled. (E.g. Information of ten patients up to the smear conversion at 2/3 months)</td>
</tr>
<tr>
<td>Green</td>
<td>Follow-up 2</td>
<td>Update patient information (outcome)</td>
<td>Send to sub-district</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Submit to the sub-district for capturing as soon as the page is full and accurately filled. (E.g. Information of ten patients)</td>
</tr>
<tr>
<td>White</td>
<td>Facility record</td>
<td>Retain in facility</td>
<td>Retain in facility</td>
</tr>
</tbody>
</table>

8. At sub-district level, the tuberculosis co-ordinator (or other designated person responsible for TB) is responsible for re-assembling the submitted registers into facility-specific order and entering the new or updated information into the TB Registration software.
9. The ‘new’ TB Treatment Register will replace the DOT Register, the Annex Register for data on TB & HIV and the Notification forms as the route of the TB notification will be through the ETR.Net
10. No overwriting is allowed as this might not transfer properly to the carbonated papers below.
11. Care should be taken to strike the number where a mistake has been made and the proper number written within the row provided.
**TB PREVENTION BY BCG VACCINE**

**WHAT DOES BCG STAND FOR?**

**BACILLUS CALMETTE-GUÉRIN**

**WHAT IS THE BCG VACCINE AND WHAT DOES IT DO?**

- Live attenuated form of *Mycobacterium bovis* (part of *Mycobacterium tuberculosis* complex)
- Routinely given intradermally in the right deltoid region soon after birth
- Part of the South African Expanded Programme on Immunisation (EPI) schedule
- It provides 60-80% protection against disseminated forms of TB, including TB meningitis and miliary TB
- It provides limited and inconsistent immunity against pulmonary TB for not longer than 10 years

**THE VACCINATION SCHEDULE IS UNCHANGED IN HIV-EXPOSED CHILDREN. IF CHILD ASYMPTOMATIC AT BIRTH, ADMINISTER BCG REGARDLESS OF HIV STATUS**

**WHO IS AT RISK OF ADVERSE EVENTS?**

- Immunocompromised infants, including HIV-infected

**WHAT IS A NORMAL BCG REACTION?**

- A red, indurated area 5-15 mm in diameter appears 3-4 weeks after vaccination
- There may be central crusting which later falls off, leaving an ulcer
- Upon healing of the ulcer a 3-7 mm scar is left
- Ulceration and scarring at the site is common and may indicate a better immunological response to the vaccine

**WHAT ADVERSE EVENTS CAN OCCUR WITH BCG?**

Adverse events related to BCG vaccination are classified according to the site of disease:

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| Local BCG disease  | A local process at the site of vaccination. This includes any of the following:  
• BCG infection site abscess conforming to EPI definitions: ≥ 10 mm X 10 mm  
• Severe BCG inoculation site ulceration |
| Regional disease   | Involvement of any regional lymph nodes or other regional lesions beyond the vaccination site: ipsilateral axillary, supraclavicular, cervical and upper arm glands. Lymph node involvement must conform to EPI definition and may include enlargement, suppuration and fistula formation. |
| Distant disease    | Involvement of any site beyond a local or regional ipsilateral process. This includes: BCG confirmed from at least 1 distant site beyond the vaccination site, e.g. pulmonary secretions (gastric aspirate, tracheal aspirate, sputum), cerebrospinal fluid, urine, osteitis (usually right humerus), distant skin lesions |
| Disseminated disease | BCG confirmed from >1 remote site, as described under distant disease, and/or from at least 1 blood or bone marrow culture. |

**ASK PARENT TO RETURN WITH CHILD IF SIDE EFFECTS OCCUR, E.G. INOCULATION SITE ABSCESS OR ENLARGED RIGHT AXILLARY OR SUPRACLAVICULAR NODES**
WHAT IS BCG IRIS?

- Occurs in HIV-infected children within 3 months of initiation of antiretrovirals
- Categorisation is the same as for BCG disease, being divided into local, regional, distant or disseminated disease
- It is one of the most common forms of IRIS in infants in South Africa
- Expected to improve slowly with time, but while mortality is low, morbidity is high

THE CHER STUDY SHOWED THAT EARLY INITIATION OF ART BEFORE 12 WEEKS OF AGE AND BEFORE CLINICAL AND IMMUNOLOGICAL DETERIORATION OCCURRED WAS ASSOCIATED WITH A SIGNIFICANTLY REDUCED INCIDENCE OF BCG IRIS

HOW DO I DIAGNOSE BCG DISEASE?

- *M. bovis* BCG is a member of the MTB complex of organisms
- When it is isolated at a laboratory it will be reported as “MTB complex” and not as “*M. bovis* BCG”
- If clinical suspicion/confirmation of BCG is required, this must be indicated on the laboratory request form so that additional confirmatory testing can be done in the form of a BCG PCR
- It is important to confirm the diagnosis, especially in supraclavicular and cervical lymphadenitis and in disseminated BCG disease, as TB can present in a very similar manner

HOW SHOULD BCG ADVERSE EVENTS BE REPORTED?

- Any suspected BCG related adverse event must be reported as an Adverse Event Following Immunisation (AEFI) to the EPI – See Annexures for AEFI Reporting Template

HOW SHOULD I MANAGE BCG ADVERSE EVENTS?

- Children with local or regional BCG disease can often be safely monitored without using antimycobacterial treatment
- However, HIV-infected children must be monitored closely for the development of disseminated BCG disease
- If suppurative, take a swab and send specimen for TB investigations
- Needle aspiration of purulent material can be considered as a means to relieve symptoms
- May need incision and drainage
- Treat conservatively; if TB confirmed (i.e. BCG disease excluded on the basis of a negative BCG PCR result), treat using 2-4 drugs for 6 months
- Start ART in HIV-infected children, if not already initiated
- Monitor closely for drug-drug interactions and side effects

ISONIAZID PREVENTIVE THERAPY (IPT)

HOW DOES IPT WORK?

WHY SHOULD WE OFFER IPT?

- Multiple studies have shown that IPT reduces tuberculosis incidence in HIV-infected patients:
  - by 62% in those with a positive TST
  - 11% in those with a negative TST
- Although ART reduces the likelihood of developing TB disease, TB incidence amongst HIV-infected patients receiving ART is still 10 times greater than the general South African population

HOW DO WE EXCLUDE ACTIVE TB?

Answering ‘no’ to the following four questions has been shown to be 98% effective in ruling out active TB disease in high prevalence settings:

- Cough for more than 24 hours?
- Any fever?
- Any weight loss?
- Drenching night sweats?

WHICH ADULTS ARE ELIGIBLE FOR IPT?

HIV-infected adults who:

- are not on TB treatment
- are asymptomatic for TB (as above)
- have no active liver disease
- do not consume large amounts of alcohol
  - Large amounts = men >28 units per week / women >21 units per week
- have no history of psychosis, convulsions, neuropathy

NB:

- POSITIVE TST IS NOT A REQUIREMENT TO INITIATE IPT
- PATIENTS ON ART AND HIV-INFECTED PREGNANT WOMEN ARE ELIGIBLE FOR IPT
- PATIENTS WITH PREVIOUS TB MAY RECEIVE IPT
- IPT MAY BE COMMENCED AND MONITORED BY A NURSE
- TST SHOULD BE DONE AS SOON AS POSSIBLE AFTER INITIATING IPT AND TREATMENT CONTINUED AS BELOW

ISONIAZID PREVENTIVE THERAPY....CONTINUED

IPT DURATION BASED ON TST RESULT

<table>
<thead>
<tr>
<th>Pre-ART (CD4 &gt; 350)</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST not done</td>
<td>6 months</td>
</tr>
<tr>
<td>TST negative</td>
<td>6 months</td>
</tr>
<tr>
<td>TST positive</td>
<td>36 months</td>
</tr>
</tbody>
</table>

NB: The above-mentioned guidelines also apply for pregnant women except for those on FDC (CD4>350) - IPT for 12 months

WHICH CHILDREN ARE ELIGIBLE FOR IPT?

All children under 5 years of age in close contact with an infectious case of TB and who are asymptomatic for TB, should receive IPT to prevent development of TB disease
- If asymptomatic – start IPT
- If symptomatic – investigate thoroughly for TB

All HIV-infected children are eligible for IPT once active TB is excluded
- Exclusion of active TB may be difficult
- All HIV-infected children should receive a TB symptom screen at every visit

IS TB THAT OCCURS AFTER IPT MORE LIKELY TO BE INH RESISTANT?

- No
- TB that occurs after starting IPT is not more likely to be INH resistant
- If the patient does have INH mono-resistance, first-line TB treatment is generally effective

WHAT DOSE OF IPT SHOULD BE GIVEN?

- Adults: INH 300 mg dly for 6 months + pyridoxine (Vit B6) 25 mg daily
- Children: INH 10-15 mg/kg/day (maximum dose 300 mg /day) for 6 months+ pyridoxine 25 mg daily
  - If INH is unavailable as liquid, tablets may be used
  - Break 100 mg tablets and dissolve in water/multi-vitamin syrup

---

Dosage recommendations for INH preventive therapy in children

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Daily Isoniazid (INH) 100 mg Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 3.4 kg</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>3.5 - 6.9 kg</td>
<td>½ tablet</td>
</tr>
<tr>
<td>7 - 9.9 kg</td>
<td>1 tablet</td>
</tr>
<tr>
<td>10 - 14.9 kg</td>
<td>1 ¼ tablets</td>
</tr>
<tr>
<td>15 - 19.9 kg</td>
<td>1 ½ tablets</td>
</tr>
<tr>
<td>20 - 24.9 kg</td>
<td>2 tablets</td>
</tr>
<tr>
<td>25 - 29.9 kg</td>
<td>2 ½ tablets</td>
</tr>
<tr>
<td>≥ 30 kg</td>
<td>3 tablets</td>
</tr>
</tbody>
</table>

NOTE: THE MAXIMUM DAILY DOSE OF INH MUST NOT EXCEED 300mg

MANAGEMENT OF ADULTS AND CHILDREN ON IPT

Monthly follow up:
- ‘Fast-track’ patients through the clinic
- Accurate serial weights
- Monitor for side effects of IPT – be especially vigilant with elderly or alcohol history
  1. Right upper quadrant pain
  2. Nausea and vomiting
  3. Dark urine and pale stools
  4. Jaundice
  5. Rash (hypersensitivity)
  6. Peripheral neuropathy (tingling hands and feet)
  7. Psychosis (hearing voices or seeing things that are not actually there)
- TB symptom screen
- Patient education (please see adjacent page)

NOTE: MONITORING OF LIVER ENZYMES IS NOT REQUIRED UNLESS INDICATED BY HISTORY OR CLINICAL SIGNS

WHEN SHOULD CONSIDERATION BE GIVEN TO STOPPING IPT?

1. When active TB is suspected
   - Investigate for TB, STOP IPT until TB excluded. If no TB, recommence IPT

2. Hepatotoxicity possibly due to IPT
   - Discontinue IPT immediately and refer to hospital

3. Hypersensitivity rash
   - If mild, stop INH until rash resolves and then restart INH
   - If severe, stop INH and refer urgently

The South African Antiretroviral Treatment Guidelines 2013, 14Mar2013
4. Peripheral neuropathy (PNP) possibly due to IPT
   - Assess severity and rate of progression
   - If patient has difficulty in walking or complains of excessive pain, stop IPT
   - If PNP symptoms are mild, continue IPT. Counsel and treat:
     - Counsel that PNP may be due to HIV infection and/or IPT
     - Counsel patient that PNP resolves after IPT course is completed
     - Increase pyridoxine from 25 mg to 100mg dly
     - For adults, medicate with amitryptiline 25mg nocte if PNP is uncomfortable
     - If on D4T switch to AZT or TDF

5. Fits or psychosis
   - Stop INH and refer

6. Poor adherence
   - If patient interrupts IPT once:
     - Counsel and restart if no active TB and adherence obstacles have been addressed (should complete the initial 6 months of IPT within 9 months)
   - If patient interrupts a second time:
     - Consider stopping IPT

PATIENT EDUCATION SHOULD INCLUDE:

- Adherence to daily INH and monthly visits
- Minimal alcohol
- Patient should return to clinic immediately if they have:
  - Pain in the right abdomen
  - Nausea and vomiting
  - Dark urine and pale stools
  - Yellow eyes
  - Severe rash
  - Tingling hands and feet
  - Hearing voices or seeing things that are not actually there
- Symptoms of active TB:
  - Cough
  - Fever
  - Loss of weight
  - Night sweats
- Patients do not need to take IPT with meals
- If patients see another health care worker it is important that they understand that they are not receiving TB treatment but only taking one drug for TB prevention
- HIV counselling, including:
  - Prevention – use of condoms
  - Need to stay in care – regular monitoring
  - Need for ART as soon as eligible
SCREENING ALGORITHM FOR IPT

HIV-INFECTED PATIENTS

Assess for contraindications and do TB symptom screen

If contraindications present – No IPT

NO TB signs or symptoms and no contraindications

Counsel patient about IPT

Start IPT if patient consents

Do TST to determine IPT duration

If good response consider IPT after 3 months

TB signs or symptoms

Investigate for TB

Patient diagnosed with TB – Start TB treatment

TB not diagnosed

Treat with antibiotics

If poor response, refer for further investigation for TB or other conditions
WHY DO WE NEED INFECTION CONTROL?

TB patients may produce infectious droplets when they cough, these are suspended in the air for prolonged periods and may be inhaled leading to possible TB infection and disease.

TB Infection Control

Committee

One person ultimately responsible for TB infection control

TB Infection control policy and plan (see annexures)

Quarterly TB infection control assessment (see next page)

Training of staff

Education of patients and the community

HIERARCHY OF TB INFECTION CONTROL

PERSONAL RISK REDUCTION

Clients & staff to know their HIV status

IPT where indicated

Training to recognise TB symptoms

N95 for high risk areas e.g. bronchoscopy

ENVIRONMENTAL CONTROLS

Well ventilated waiting areas, preferably outside & sheltered from the rain and sun

Open windows

Ceiling fans where there is poor natural ventilation

Airflow away from staff, towards patients

ADMINISTRATIVE CONTROLS

Screen all for cough as they enter facility

Educate on cough hygiene, “cover your cough”

Provide masks/tissues to coughing clients

Separate coughing clients, reduce their waiting time, investigate and refer early

Safe environment for sputum collection, preferably outside, private and sheltered

Reduce waiting times for ALL patients, careful management of patient bookings

*UVGI is an additional environmental control but are expensive to install and maintain annually. UVGI is only effective if there is good air flow past the lights. UVGI and may give a false sense of security which results in other controls e.g. open windows, cough hygiene not being practised. Skin and eye damage can result from over-exposure.
TB INFECTION CONTROL ASSESSMENT TOOL

1. MANAGERIAL CONTROLS

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there one person at site designated for TB infection control?</td>
<td></td>
</tr>
<tr>
<td>Is there a TB infection control committee?</td>
<td></td>
</tr>
<tr>
<td>Has the committee met in the last 4 weeks?</td>
<td></td>
</tr>
<tr>
<td>Is there a site-specific TB infection control plan?</td>
<td></td>
</tr>
<tr>
<td>Was an assessment done in the last quarter?</td>
<td></td>
</tr>
<tr>
<td>Are the DOH TB infection control guidelines accessible?</td>
<td></td>
</tr>
<tr>
<td>Is staff training on infection control recorded in the last quarter?</td>
<td></td>
</tr>
</tbody>
</table>

*Use increase in score to monitor improvement in TB infection control between assessments. Facilities should adapt the Infection Control Plan (see annexure) to address specific gaps identified in the infection control assessment.

Total score* (maximum=14)

2. ADMINISTRATIVE CONTROLS

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are patients screened for TB at every visit?</td>
<td></td>
</tr>
<tr>
<td>Are all patients educated on TB &amp; cough hygiene as they enter the facility?</td>
<td></td>
</tr>
<tr>
<td>Are coughing patients provided with masks or tissues?</td>
<td></td>
</tr>
<tr>
<td>Are coughing patients and known TB patients separated from others?</td>
<td></td>
</tr>
<tr>
<td>Are coughing patients and TB patients “fast-tracked”? (limit time in facility)</td>
<td></td>
</tr>
<tr>
<td>Are coughing patients referred immediately for diagnostic assessment?</td>
<td></td>
</tr>
<tr>
<td>Are there separate and well-ventilated designated areas for sputum collection?</td>
<td></td>
</tr>
</tbody>
</table>

Total score* (maximum=14)

3. ENVIRONMENTAL CONTROLS

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are windows open?</td>
<td></td>
</tr>
<tr>
<td>Is there good cross ventilation in all waiting and consulting rooms?</td>
<td></td>
</tr>
<tr>
<td>Do staff sit with their back towards direction of airflow when consulting?</td>
<td></td>
</tr>
<tr>
<td>If UV lights are used, is the maintenance schedule documented and up to date?</td>
<td></td>
</tr>
</tbody>
</table>

Total score* (maximum=8)

4. PERSONAL RISK REDUCTION

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were staff trained on TB symptoms and diagnosis in the last quarter?</td>
<td></td>
</tr>
<tr>
<td>Were staff encouraged to know their HIV status this quarter?</td>
<td></td>
</tr>
<tr>
<td>Are respirators (N95 masks) available?</td>
<td></td>
</tr>
</tbody>
</table>

Total score* (maximum=6)

IS TB A PROBLEM AMONGST HEALTH CARE WORKERS (HCWs)?

- Yes
- Health care workers are at high risk of occupationally-acquired tuberculosis, especially if they are HIV-infected

HOW CAN HCWs PROTECT THEMSELVES?

- They must be aware of the signs and symptoms of TB and present early for testing if they develop any symptoms
- All HCW must know their HIV status and take care of themselves accordingly
- They should be trained on TB upon induction and annually

WHAT ARE EXAMPLES OF SOUTH AFRICAN POLICIES AND ACTS REGARDING TB IN HCWs?

- The Constitution of South Africa in Act 108 of 1996 and its Bill of Rights:
  - “Everyone has the right to an environment that is not harmful to their health and wellbeing”
- Public Service Regulations, Part 6, 2001
  - “Government will work towards the improvement of a working environment…to include employees health”
- Occupational Health and Safety Act
  - Outlines the general duties of employees and employers
- Compensation for Occupational Injuries and Diseases Act (COIDA)
  - Allows for compensation under very specific circumstances

WHAT ARE KEY ASPECTS OF TB PREVENTION AND MANAGEMENT AMONGST HCWs?

1. Ensure adherence to TB infection control principles
   - TB Education and training focussing on:
     - TB symptoms
     - Infection control measures
   - Promote HIV testing
   - Allow priority and private access to HCWs for TB and HIV management:
     - Prevention
     - IPT
     - Diagnosis
     - Management, including ART

2. Administrative Management Of TB Disease Amongst HCWs
   - Ensure that the HCWs take sick leave until smear microscopy is negative
   - Complete administrative procedures for diseased/injured HCWs:
     - Employer’s Report of an Occupational Disease
     - First Medical Report in respect of an Occupational Disease
     - Notice of an Occupational Disease and Claim for Compensation
     - The laboratory results demonstrating Mycobacterium tuberculosis or NTM
     - Exposure history or an appropriate history
     - Progress Medical Report in respect of an Occupational Disease
     - Medical report detailing the employee’s symptoms and clinical features
     - Final Medical Report and lung function tests must be submitted 12 months after completion of treatment of tuberculosis or when treating medical practitioner considers that no further improvement is anticipated
     - CXR and/or radiology reports where applicable

## WHAT PROCESSES SHOULD BE IN PLACE IN ORDER TO PROTECT HCWs IN THE WORKPLACE?

<table>
<thead>
<tr>
<th>Area:</th>
<th>Implementation:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB SCREENING</strong></td>
<td>• All staff should receive TB symptom screening at baseline, biannually and on exit</td>
</tr>
<tr>
<td><strong>OCCUPATIONAL HIV</strong></td>
<td>• Written and disseminated Post Exposure Prophylaxis policy/guideline&lt;br&gt;• Named person/committee responsible for infection prevention&lt;br&gt;• Refresher training on safe injection techniques&lt;br&gt;• Gloves, soap, running water, sharps bins available&lt;br&gt;• Safe sharps disposal&lt;br&gt;• Safe injection technique</td>
</tr>
<tr>
<td><strong>HIV (SEXUALLY TRANSMITTED) PREVENTION</strong></td>
<td>• Written facility policy/guideline&lt;br&gt;• Ongoing education on safe sex&lt;br&gt;• Condoms available in both female and male toilets</td>
</tr>
<tr>
<td><strong>PROMOTION OF HIV TESTING FOR STAFF</strong></td>
<td>• Written facility policy/guideline concerning HIV testing of staff and what is provided for staff who test HIV-infected&lt;br&gt;• Ongoing education or promotion of benefits of knowing status&lt;br&gt;• Facilitated access for staff wanting HIV testing</td>
</tr>
<tr>
<td><strong>ACCESS TO ART FOR STAFF</strong></td>
<td>• Written facility policy/guideline/directive concerning access to ART for staff&lt;br&gt;• Ongoing education or promotion of benefits of knowing status and getting tested&lt;br&gt;• Facilitated access to free ART for staff</td>
</tr>
<tr>
<td><strong>ACCESS TO ART FOR FAMILY OF STAFF</strong></td>
<td>• Written facility policy/guideline/directive concerning access to ART for family of members of staff&lt;br&gt;• Access to HIV diagnosis for family members&lt;br&gt;• Facilitated access to free ART for family of staff</td>
</tr>
<tr>
<td><strong>TB INFECTION CONTROL</strong></td>
<td>• Written policy/guideline including TB infection control&lt;br&gt;• Named person/committee responsible for infection control&lt;br&gt;• Refresher training/monitoring of control practices&lt;br&gt;• Education on cough hygiene&lt;br&gt;• TB suspected in anyone with prolonged cough&lt;br&gt;• TB patients or those with presumptive TB should be separated from other patients&lt;br&gt;• TB diagnosed &amp; treated promptly</td>
</tr>
<tr>
<td><strong>PREVENTION OF TB IN STAFF</strong></td>
<td>• Written policy/guideline/training material/directive concerning TB as an occupational health risk&lt;br&gt;• Refresher education/training of staff on HIV/TB&lt;br&gt;• Promotion of HIV testing among staff with high exposure to TB patients</td>
</tr>
</tbody>
</table>

**NB:** **ALL ABOVE MEASURES REQUIRE A SUPPORTIVE ENVIRONMENT AND SENIOR STAFF AND MANAGEMENT NEED TO MAKE AN EFFORT TO ENSURE EFFECTIVE TRANSLATION OF POLICY INTO PRACTICE**
WHAT EQUIPMENT IS REQUIRED?

- 2 units (0.1 ml) of tuberculin purified protein derivative PPD-RT23 2 TU
- A tuberculin syringe with a short 27-gauge needle with a short bevel
- Check the expiration date on the vial

WHAT SHOULD I TELL THE PATIENT?

- Explain the procedure to the caregiver or to the patient if age-appropriate
- Explain the need to return in 48-72 hours for TST reading

WHAT DOES THE PROCEDURE ENTAIL?

a) Choose an Injection Site
   - Place the left forearm on a well-lit surface with the palm facing upwards
   - Locate an area midway between the elbow and wrist which is free of any scars or sores

b) Prepare the Tuberculin
   - Draw up 0.1 ml of tuberculin

c) Inject Tuberculin
   - Insert the needle slowly with the bevel facing upwards at an angle of 5-15 degrees and inject the tuberculin
   - The needle bevel should be visible just below the surface of the skin
   - The PPD is injected between layers of skin (intradermally)

d) Check Injection Site
   - After the injection is given, a flat wheal of 8-10 mm in diameter should be visible
   - If it is not visible the PPD has been injected too deeply and the injection should be repeated at a site at least 5 cm away from the first injection or on the right forearm
   - A pen can be used to draw a wide circle around the injection site to indicate the area

e) Record Information
   - Record the relevant information including the date, time and location of the test

Figure: TST: Administration of PPD.
HOW DO I READ A TST?

WHAT EQUIPMENT IS REQUIRED?

- Pen
- Clear flexible ruler

WHAT DOES THE PROCEDURE ENTAIL?

a) Read the results 48-72 hours after administration of TST

b) Palpate and identify the induration
   - Inspect the site under good lighting and identify the induration (not the erythema)
   - Palpate the induration by using your fingertips to identify the edges of the induration
   - The edges of the induration should be marked with a pen to help measure accurately
     - Draw horizontal lines from the periphery towards the area of induration
     - The raised edges of the area of induration will prevent the pen from drawing onto the indurated area

c) Measure the diameter of the induration
   - Use the ruler to measure the widest transverse diameter in millimetres

d) Record the diameter of the induration
   - Do not record as positive or negative
   - Record the measurement in millimetres

WHAT ARE THE CRITERIA FOR A POSITIVE TST RESULT?

<table>
<thead>
<tr>
<th>IMMUNE STATUS</th>
<th>HIV-INFECTED / SEVERE MALNUTRITION</th>
<th>HIV-UNINFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAMETER OF INDURATION</td>
<td>5 mm or more</td>
<td>10 mm or more</td>
</tr>
</tbody>
</table>
WHAT EQUIPMENT IS REQUIRED?

- Sterile specimen jar (label with patient details)
- NHLS specimen request form and plastic specimen packet
- Private well-ventilated area
  - Preferably outside in a private area, sheltered from rain
  - Can be done in a dedicated room with good ventilation
    - HCW should leave the room while sputum being produced
  - Must not be done in bathrooms

ALWAYS LABEL SPECIMEN JARS WITH:

- Patient name
- Clinic or hospital name
- Clinic or hospital number
- Date of specimen collection
- Whether it is a
  - pre-treatment specimen
  - follow-up (2 - 3 months) specimen
  - end-of-treatment (5 - 7 months) specimen
- Attach NHLS barcode

WHAT SHOULD I TELL THE PATIENT?

- Explain that sputum is required to diagnose TB
- Ask the patient to do the following:
  - Rinse his/her mouth with water
  - Take a deep breath
  - After exhalation, inhale sharply and cough strongly
  - Expectorate sputum into the jar
  - Close the jar tightly
  - Clean the outside of the jar
  - Place the jar in the plastic specimen packet

WHAT SHOULD I DO ON RECEIPT OF THE SPECIMEN FROM THE PATIENT?

- Label the specimen request form clearly
- Indicate exactly what tests are required:
  - Microscopy only, or
  - Microscopy, culture and sensitivity, or
  - Xpert MTB/RIF
- Send the specimen to the lab as soon as possible or store in a fridge if awaiting transport

WHAT SAFETY PRECAUTIONS SHOULD I ADHERE TO?

- The HCW should not be near the patient when he/she coughs

HOW SHOULD I RECORD THE TEST?

- Record the patient’s details in the TB Case Detection and Follow-up Register, include the NHLS barcode
- Record the NHLS barcode and details of the test in the patients’ record
**How to Collect a Sputum Sample**

Your nurse will give you a special plastic cup for collecting your sputum. Follow these steps very carefully.

1. The cup is very clean. Don’t open it until you are ready to use it.

2. As soon as you wake up in the morning (before you eat or drink anything), brush your teeth and rinse your mouth with water. Do not use mouthwash.

3. If possible, go outside, or open a window before collecting the sputum sample. This helps protect other people from TB germs when you cough. Take a very deep breath and hold the air for 5 seconds. Slowly breath out. Take another deep breath and cough hard until some sputum comes up into your mouth.

4. Spit the sputum into the plastic cup. Keep doing this until you have about 1 teaspoon of sputum.

5. Screw the lid on the cup tightly so it doesn’t leak. Wash and dry the outside of the cup. Put the cup into the bag the nurse gave you. Return the cup to the clinic on the same day that you coughed into it.

**Contact details of PHC:**

- Clinic name:
- Facility manager:
- Clinic telephone number:

**Tips:** If you cannot cough up sputum, try breathing steam from a hot shower or pan of boiling water first, and then cough.
**WHAT EQUIPMENT IS REQUIRED?**

- Sterile specimen jars identified with patient’s details
- NHLS specimen request form and plastic specimen packet
- Gloves
- Nebulising mask and nebuliser
- Bronchodilator e.g. salbutamol
- Oxygen supply
- N95 mask for HCW
- Hypertonic saline solution 5%
- 19 gauge needle
- 20 ml syringe
- Cup of water

**WHAT SHOULD I TELL THE PATIENT?**

- The procedure should be fully explained to adults and older children, including the risks and benefits

**WHAT DOES THE PROCEDURE ENTAIL?**

- The patient should rinse his/her mouth with water prior to starting
- Pre-medicate with salbutamol in patients with asthma or severely impaired lung function
- Load 5-10 ml of 5% hypertonic saline solution into the nebuliser cup
- Instruct the patient to take deep breaths while being nebulised
- Nebulise the patient for approximately 5 minutes
- If the patient does not cough spontaneously, ask him/her to attempt a forced cough
- If necessary, use gentle chest physiotherapy
- Deep cough sputum specimens should be expectorated into the specimen jar
- Saliva should be discarded into a separate container
- Stop the procedure when:
  - The patient has produced 5-10 ml of sputum
  - The patient has been nebulised for 15 minutes
  - The patient feels dyspnoeic, light-headed, nauseous or develops respiratory distress
- Observe the patient at all times during the procedure

**INDUCED SPUTUM COLLECTION IN ADULTS AND OLDER CHILDREN**

- This procedure is used in the diagnosis of TB when patients are unable to expectorate spontaneously
- Hypertonic saline is nebulised in order to irritate the airway, increase and liquefy secretions and induce coughing and expectoration
WHAT SAFETY PRECAUTIONS MUST BE ADHERED TO?

FOR THE PATIENT:
• Safe even in young infants, but staff must be adequately trained
• Low-risk procedure, but may be poorly tolerated in children with high supplementary oxygen requirements
• Contra-indications are severe respiratory distress, reduced level of consciousness, severe bronchospasm, bleeding tendency (as the procedure may precipitate severe nosebleeds)
• Adverse events include coughing, mild wheezing and nosebleeds
• Children requiring supplemental oxygen should have continuous saturation monitoring during the procedure
• If saturation drops below 88% for longer than one minute, the procedure should be abandoned and the child stabilised before the procedure reattempted

FOR HEALTH CARE WORKER:
• This procedure is high-risk when done on a patient with suspected TB - health care workers present should wear an N95 mask
• This is an aerosol-generating procedure and should thus be done in an isolation room with adequate infection control

WHAT SHOULD I DO ON RECEIPT OF THE SPECIMEN?
• Ensure the patient’s details are recorded on the specimen jar
• Place the NHLS barcode on the specimen
• Label the specimen request form clearly
• Indicate what tests are required (microscopy only, or microscopy, culture and sensitivity, or Xpert MTB/RIF)
• Send the specimen to the lab as soon as possible or store in a fridge if awaiting transport

HOW IS THE TEST RECORDED?
• Record the patient’s details in the TB Case Detection and Follow-up Register
• Record the NHLS barcode and details of the test on the patient’s record
WHAT EQUIPMENT IS REQUIRED?

- Sterile specimen jar (label with patient details)
- NHLS specimen request form and plastic specimen packet
- Gloves
- Nebulising mask and nebuliser
- Bronchodilator (e.g. salbutamol)
- Oxygen supply
- Metered dose inhaler (MDI)
- Spacer device and BabyMask (with which to administer the bronchodilator)
- N95 mask for person(s) conducting the procedure
- 5 ml hypertonic (5%) saline
- Mucus extractor with feeding tube catheter (usually 5 to 8 French)
- Wall or portable suction
- Normal saline flush with syringe (5 ml)
- Alcohol or chlorhexidine

WHAT SHOULD I TELL THE PATIENT?

- The procedure must be explained to the parent and the child, if age-appropriate
- The child must be nil per os for at least 3 hours

WHAT DOES THE PROCEDURE ENTAIL?

- It should ideally be performed by two health care professionals: one to collect the specimen, and another to restrain the child
- If the child is medically stable, the caregiver can restrain the child (the caregiver need not wear an N95 mask if he/she resides with the child)
- Because hypertonic saline nebulisation may precipitate wheezing in children, two puffs of a bronchodilator are administered using an MDI, via a spacer device and BabyMask, 5 minutes before giving the nebulisation
- Administer 5 ml hypertonic saline via a nebulising mask, for 10-15 minutes.
- If necessary, gentle chest physiotherapy, using cupped hands, can be performed to loosen secretions
- Older children who are able to expectorate can do so
- If the child is unable to expectorate, collect nasopharyngeal secretions:
  - gently insert a 5 to 8 French feeding tube into the nasopharynx
  - apply suction when the tip of the catheter is in the nasopharynx (this prevents the collection of nasal secretions which may reduce the quality of the specimen)
  - Once an adequate volume (1-2 ml) of sputum has been collected into the mucus extractor chamber, discontinue suctioning and withdraw the feeding tube from the nasopharynx
  - Use 5 ml normal saline to flush residual secretions adhering to the walls of the feeding tube into the mucus extractor chamber. This also helps to optimise the volume of the induced sputum specimen
- Observe the patient at all times during the procedure
- Disinfect and sterilise any equipment (i.e. spacer device, BabyMask) that will be reused
- Discard nebulising mask and used feeding tubes
INDUCED SPUTUM COLLECTION IN CHILDREN...Continued

WHAT SAFETY PRECAUTIONS MUST BE ADHERED TO?

FOR THE PATIENT:
- Safe even in young infants, but staff must be adequately trained
- Low-risk procedure, but may be poorly tolerated in children with high supplementary oxygen requirements
- Contra-indications are severe respiratory distress, reduced level of consciousness, severe bronchospasm, bleeding tendency (as the procedure may precipitate severe nosebleeds)
- Adverse events include coughing, mild wheezing and nosebleeds
- Children requiring supplemental oxygen should have continuous saturation monitoring during the procedure
- If saturation drops below 88% for longer than one minute, the procedure should be abandoned and the child stabilised before the procedure reattempted

FOR HEALTH CARE WORKER:
- This is an aerosol-generating procedure and should therefore be done in an isolation room with adequate infection control
- Staff members performing the procedure should wear N95 masks

WHAT SHOULD I DO ON RECEIPT OF THE SPECIMEN?
- Record the patient’s details on the specimen jar
- Place the barcoded NHLS sticker on the specimen
- Send the specimen to the lab as soon as possible or store in a fridge if awaiting transport

WHICH TESTS SHOULD I REQUEST IN CHILDREN?
- Indicate clearly which tests are required:
  - microscopy, culture and DST or
  - Xpert MTB/RIF
- TB microscopy is usually negative in small children, and should not be relied upon in making a diagnosis of childhood TB

HOW IS THE TEST RECORDED?
- Record the patient’s details in the TB Case Detection and Follow-up Register
- Record the NHLS barcode and details of the test on the patient’s record
**WHAT EQUIPMENT IS REQUIRED?**

- Sterile specimen jar (label with patient details)
- Nasogastric tube (usually 10 French or larger)
- Syringe (5, 10, 20, or 30 ml)
- Litmus paper
- Tape measure
- Normal saline
- Sodium bicarbonate solution (8%)
- Alcohol or chlorhexidine
- NHLS specimen request form and plastic specimen packet

**WHAT SHOULD I TELL THE PATIENT?**

- Explain the procedure to the child’s parents
- Children should be nil per os for 4 hours and infants for 3 hours prior to the procedure.

**WHAT DOES THE PROCEDURE ENTAIL?**

- **One specimen should be taken on each of 3 three consecutive mornings as soon as the child wakes up**
- Position the child on his/her back or side and have an assistant hold the child
- Measure the distance between the nose and stomach to gauge the distance required to insert the tube into the stomach
- Attach a syringe to the nasogastric tube
- Gently insert the tube through the nose and advance it into the stomach
- Aspirate 2-5 ml of gastric content
- Check the position of the tube:
  - This can be done by testing the aspirated contents with litmus paper
    - Due to their acidity, gastric contents turn blue litmus paper red
  - The tube position can also be checked by pushing 3-5 ml of air into the stomach using the syringe and listening over the stomach with a stethoscope.
- If no fluid is withdrawn during the aspiration, insert 5-10 ml of normal saline and aspirate again
- This can be repeated up to 3 times
- Then withdraw 5-10 ml of gastric contents if possible and transfer the fluid into the specimen jar
- Add an equal volume of sodium bicarbonate solution to the fluid to neutralise the gastric contents and prevent destruction of the mycobacteria if present
- Make sure that the cap of the specimen jar is securely fastened, to prevent leakage of the specimen
- Wipe the specimen jar with alcohol and label it
  - The patient’s details, the collection date and time should be written on the container
  - Place the NHLS barcoded sticker on the specimen
- Fill out the lab requisition forms clearly
- The specimens should be transported to the lab as soon as possible
- If the wait for transport is more than 4 hours, keep specimens in a fridge at 4-8°C until transported
- Feed the child normally after the procedure
WHAT SAFETY PRECAUTIONS MUST BE ADHERED TO?

FOR THE PATIENT:
• This is a low-risk procedure, so intensive monitoring of the child is not required
• Children with a low platelet count or bleeding tendency should not undergo this procedure as insertion of a feeding tube may precipitate severe nose bleeds

FOR THE HEALTHCARE WORKER:
• Gastric aspiration is not an aerosol-generating procedure and young children are not highly infectious
• It is therefore considered a low-risk procedure for TB transmission and can be done at the child’s bedside or in a routine procedure room

HOW IS THE TEST RECORDED?
• Record the NHLS barcode number on the patient’s record
• The patients details and the specimen type must be recorded in the TB Case Identification and Follow-up Register
FINE NEEDLE ASPIRATION

- Fine needle aspiration is a simple procedure and can be performed safely by trained nurses in out-patient and in resource-limited settings
- It provides material for smear microscopy, culture and DST

WHAT EQUIPMENT IS REQUIRED?
- Liquid culture medium (TB Bactec bottle)
- 22 or 23G cutting needles
- 10 ml disposable plastic syringes
- Alcohol swabs
- NHLS specimen request form and plastic specimen packet
- Gloves
- Glass cytology slides
- Spray fixative or 95% alcohol

WHAT SHOULD I TELL THE PATIENT?
- Explain the procedure
- Warn the patient that pain might be experienced

WHAT DOES THE PROCEDURE ENTAIL?
- Identify the best site for aspiration
- Prepare the TB Bactec bottle by removing the lid and cleaning the rubber stopper with alcohol
- Clean the skin and wait for the area to dry
- Immobilise the mass
- Position the needle so as to be able to access the entire mass without passing through muscles e.g. sternocleidomastoid
- Insert the needle firmly and apply constant suction throughout of no more than 1 ml
- Aspirate, moving the needle in a fan-like motion throughout the mass
- When there is material in the hub of the needle, release suction and withdraw the needle
- Ask the assistant to apply pressure to the wound
- Prepare the smear:
  - remove the needle from the syringe
  - pull 10 ml of air into the syringe and reattach the needle
  - use the air to expel the material in the needle onto the slide
  - place the second slide face down on the first; allow the material to spread
  - gently separate the slides
  - fix one slide with alcohol or spray fixative and allow the other to air dry

Figure 1: Process of Aspiration
FINE NEEDLE ASPIRATION....CONTINUED

WHAT SAFETY PRECAUTIONS ARE REQUIRED?

- Observe universal precautions
- Do not recap the needle and dispose of all sharps into a biohazard container

WHAT COMPLICATIONS OCCUR?

- Complications such as haematoma are rare

HOW DO I RECORD THE TEST?

- Record the NHLS barcode number on the patient’s record
- The patients details and the specimen type must be recorded in the TB Case Identification and Follow-up Register

- For the culture:
  - withdraw liquid media from the liquid culture bottle into the syringe
  - expel the liquid back into the bottle, thereby using the culture medium to rinse the syringe in a sterile manner

Figure 2: Aspirate being placed on glass slide

Figure 3: A 2nd slide is used to smear the aspirate evenly over the surface of the slide
# Adverse Drug Reaction and Product Quality Problem Report Form

**ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM**

**NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE**

Medicines Control Council, The Registrar of Medicines, Department of Health

In collaboration with the WHO International Drug Monitoring Programme

---

### Patient Information

<table>
<thead>
<tr>
<th>Name (or initials):</th>
<th>Age:</th>
<th>Weight (kg):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex:</th>
<th>DOB:</th>
<th>Height (cm):</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Adverse Reaction/Product Quality Problem

**Adverse reaction** and/or **Product Quality problem**

<table>
<thead>
<tr>
<th>Date of onset of reaction:</th>
<th>Time of onset of reaction:</th>
</tr>
</thead>
<tbody>
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</table>

**Description of reaction or problem (Include relevant tests/lab data, including dates):**

---

### 1. Medicines/Vaccines/Devices (include all concomitant medicines)

<table>
<thead>
<tr>
<th>Trade Name &amp; Batch No. (Asterisk Suspected Product)</th>
<th>Daily Dosage</th>
<th>Route</th>
<th>Date Started</th>
<th>Date Stopped</th>
<th>Reasons for use</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

### Adverse Reaction Outcome (Check all that apply)

- Death
- Life-threatening
- Disability
- Hospitalisation
- Congenital anomaly
- Other
- Event reappeared on rechallenge: **Y**  **N**
- Rechallenge not done: **Y**  **N**
- Treatment (of reaction): .................................................................

<table>
<thead>
<tr>
<th>Sequelea:</th>
<th>Recovered:</th>
<th>Describe Sequelea:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Y</strong></td>
<td><strong>N</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Sequelea:**

---

### Comments:

(e.g. Relevant history, Allergies, Previous exposure, Baseline test results/lab data)

---

### 2. Product Quality Problem:

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Batch No</th>
<th>Registration No</th>
<th>Dosage form &amp; strength</th>
<th>Expiry Date</th>
<th>Size/Type of container</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

**Product available for evaluation?:**  **Y**  **N**

---

### Reporting Doctor/Pharmacist Etc:

**NAME:** .........................................................  **QUALIFICATIONS:** .........................................................

**ADDRESS:** ...............................................................  ...

**TEL:** (___) ...............................................................

**Signature**  **Date**

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Version: MCC2003/1
ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM...CONTINUED

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:
- medications (drugs, vaccines and biologicals)
- medical devices (including in-vitro diagnostics)
- traditional and herbal remedies
- For Adverse Events Following Immunisation (AEFI), please follow the reporting procedure recommended by the Expanded Programme in Immunisation (EPI)

Please report:
- adverse drug reactions to recently marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert.

Report even if:
- you’re not certain the product caused the event
- you don’t have all the details

Report Product Quality Problems such as:
- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Important numbers:
Investigational Products and Product Quality Problems:
- (012) 326-4344 to fax a report
- (012) 312-0000 to report by phone
Registered Medicines and Traditional and Herbal remedies:
- (021) 448-6181 to fax a report
- (021) 447-1618 to report by phone
Adverse Events Following Immunisation:
- (012) 312 0110 to phone for information
- (012) 321 9882 to fax a report

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council’s adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of drug safety and therapy in South Africa.

PLEASE USE ADDRESS PROVIDED BELOW- JUST FOLD IN THIRDS, TAPE and MAIL

BUSINESS REPLY SERVICE
BESIGHEIDSANTWOORDDIENS
Free Mail Number: BNT 178

DEPARTMENT OF HEALTH
DEPARTEMENT VAN GESONDHEID
REGISTRAR OF MEDICINES
REGISTRATEUR VAN MEDISYNE
PRIVATE BAG/PRIVAATSAK X828
PRETORIA
0001

Version: MCC2003/1
EPI DISEASE SURVEILLANCE GUIDE
**Case Investigation Form: ADVERSE EVENTS FOLLOWING IMMUNISATION (AEFI)**

**Official use only: EPIDNUMBER:**

<table>
<thead>
<tr>
<th>RESPONSE TO THIS EVENT</th>
<th>Admission date: <em><strong>/</strong></em>/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated at OPD</td>
<td>Yes</td>
</tr>
<tr>
<td>Admitted to hospital for treatment</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of hospital:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Event explained to parent/guardian?</th>
<th>Interview date: <em><strong>/</strong></em>/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccinator guidance / retraining given?</th>
<th>Interview date: <em><strong>/</strong></em>/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**HISTORY OF PREVIOUS REACTIONS TO IMMUNISATION AND/OR TREATMENT**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unk</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

- Has this child had any previous reaction after immunisation?
- Was a history of any allergies in this child obtained?
- Was any information given prior to immunisation?
- Was the health status of the child assessed before immunisation?
- Were any other AEFIs reported from this clinic in the last 30 days?

**FINAL CLASSIFICATION**

(By provincial EPI coordinator in cooperation with national office)

<table>
<thead>
<tr>
<th>Programme Error</th>
<th>Coincidental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faulty vaccine</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Give a brief reason for the classification: __________________________
__________________________________________

Date of final classification: ___/___/19

**INVESTIGATOR:** Name __________________________ Tel: __________________________

Position and facility/district __________________________ Fax: __________________________

*An AEFI should be reported within 24 hours of the event and the case investigation done within 36 hours. Please keep the district and provincial EPI coordinators informed about your progress and any problems. Send a copy of this form to the Provincial EPI Coordinator.*

*In addition, please complete an EVENT DESCRIPTION REPORT (EDR) on a separate page where you describe step by step the development of the adverse event and its consequences and the actions taken in the treatment and investigation.*

*THANK YOU FOR YOUR RAPID RESPONSE!*
A. The plan will include, but not be limited to, the following policy areas:

1. Screening patients to identify persons with symptoms of TB disease or who report being under investigation or treatment for TB disease.
2. Providing face masks or tissues to persons with symptoms of TB disease or who report being under investigation or treatment for TB disease, and providing waste containers for disposal of tissues and masks.
3. Placing patients with presumptive TB and cases in a separate waiting area.
4. Triaging patients with presumptive TB and cases to the front of the line to expedite their receipt of services in the facility.
5. Referring patients with presumptive TB to TB diagnostic services and confirming that TB cases are adhering to treatment.
6. Using and maintaining environmental control measures.
7. Educating staff periodically on signs and symptoms of TB disease, specific risks for TB for HIV-infected persons, and the need for diagnostic investigation for those with signs or symptoms of TB.
8. Training and educating staff on TB, TB control, and the TB infection prevention and control plan.
9. Monitoring the TB infection and control plan’s implementation.

B. The facility will implement each policy by following the procedure(s) that accompany it.

**POLICY AND PROCEDURES**

**Purpose:** Early identification, separation, receipt of services, and referral of patients with TB disease is essential in preventing spread of TB.

**Lead:** _____________________ has the responsibility for overseeing the implementation of these policies and its procedures, and reports to (District health executive committee, etc).

**POLICY 1: SCREENING PATIENTS TO IDENTIFY PERSONS WITH SYMPTOMS OR RECENT HISTORY OF TB DISEASE**

**Procedures:**

(i) Before patients enter an enclosed part of the facility, a designated staff person should ask each adult and any child capable of coughing forcefully (usually age 14 or older) about symptoms or recent history of TB. The questioning should occur before patients wait in line for long periods to register or obtain services.

(ii) Many combinations of symptoms have been recommended as sensitive and specific for TB. A simple screen is:

"Do you have a cough?" If patient answers "yes," ask 
"For how long have you been coughing?"

An adult who has coughed for two weeks or more may be considered a patient with presumptive TB.

To determine whether a patient may be under investigation or a diagnosed case of TB, who may still be infectious, ask -

"Are you being investigated or treated for TB?"

If the answer to either is "yes," the screen classifies the patient as a patient with presumptive TB or a TB case, and he should be managed as described in the procedures under policies 2 – 5 below.

(iii) As patients who are not identified as a patient with presumptive TB or a TB case on the initial symptoms screen enter an examination room with the clinical officer, nurse, or counsellor, they should again be asked the simple screening questions. Those patients who report a cough of two or more weeks or who are being investigated or treated for TB should be managed as follows in the procedures under policies 2 – 5 below. Staff seeing patients in examination rooms should report patients they find to be patients with presumptive TB or a TB case to the infection control officer in a timely manner so that factors contributing to the potential exposure (e.g. an emergency or short staffing interfering with the designated person screening all patients) can be documented and corrected.

**POLICY 2: INSTRUCTIONS ON COUGH HYGIENE**

**Procedures:**

(i) Patients who are found to have presumptive TB or TB cases should immediately be informed about the importance of cough hygiene and be handed tissues (or pieces of cloth) and instructed to cover their mouths and noses when they cough. Alternatively, patients should be given a facemask and asked to wear it while in the facility. Patients should also be instructed to dispose of used tissues or masks in identified no-touch receptacles and not on the ground or on the benches.
When tissues, cloths or facemasks are not available, clients should be instructed to lift their arm up and cover their nose and mouth with the inner surface of the arm or forearm when they cough or sneeze. *M. tuberculosis* cannot be spread from the hands, but other serious lung infections can.

(ii) No-touch receptacles for disposal of used tissues and masks should be available in the waiting areas.

**POLICY 3: PLACING TB SUSPECTS AND CASES IN A SEPARATE WAITING AREA**

Procedures

(i) A staff person should direct or escort the patient to a separate waiting area. This special waiting area should have the highest natural ventilation possible. Patients should be assured of their place in the line for registration and/or services.

**POLICY 4: TRIAGING TB SUSPECTS AND CASES TO THE HEAD OF THE LINE TO RECEIVE SERVICES IN THE FACILITY**

Procedures

(i) Patients with presumptive TB and cases should be moved to the head of the line for whatever services they want or need. e.g. VCT, medication refills, or medical investigation. This reduces the duration of potential exposure while they wait in the facility and may be an incentive to disclose information during screening.

**POLICY 5: REFERRING TB SUSPECTS TO TB DIAGNOSTIC SERVICES**

Procedures

(i) ____________________ is the designated staff person to counsel patients about obtaining TB diagnostic services.

(ii) Patients will be referred to ____________________________ (a TB diagnostic centre with which the health care facility has a previously negotiated agreement).

(iii) Patients should be given a card with the name, location, and operating hours of the TB diagnostic centre. The card should also have the name of the referring facility on it, with date of referral marked. These cards can be collected at the TB centre and used as an anonymous check on number of referrals that successfully obtain TB services.

**POLICY 6: USING AND MAINTAINING ENVIRONMENTAL CONTROL MEASURES**

Procedures

(i) ____________________ is the designated staff person to check on environmental control measures and maintain a log of monitoring and maintenance.

(ii) Windows and doors should be checked on a daily basis to assure they are in proper position (open or closed as called for in the plan). Generally, all windows and doors should be open when natural ventilation is the primary environmental control to allow for the free, unencumbered movement of air (e.g. across room, from window to door or vice versa). Generally, all windows and doors should be closed when using mechanical ventilation to ensure air movement in a controlled manner (air from supply vent and from slots either under or in door toward the exhaust vent).

(iii) Fans should be checked on a monthly basis to assure they are clean, are pulling (or pushing) the correct amount of air, and are pulling (or pushing) air in the correct direction.

**POLICY 7: PROVIDING CONFIDENTIAL TB AND HIV SERVICES TO HEALTH CARE WORKERS AND STAFF**

Procedures

(i) Health care workers and all other staff working at the facility should be educated about the signs and symptoms of TB and encouraged to seek investigations promptly if they develop symptoms and signs suggestive of TB.

(ii) Health care workers and other staff should be informed about the special specific risks for TB for HIV-infected persons (see section on training of staff).

(iii) Health care workers and staff should be encouraged to undergo HIV testing, and given information on relevant HIV care resources.

(iv) Staff training should include reduction of stigma of TB and HIV.
(v) _____________________ is responsible for determining when staff who develop TB disease may return to work.

(vi) Staff who develop TB disease may return to work when determined to be no longer infectious after:
   a. Having completed at least two weeks of standard anti-TB therapy;
   b. Exhibiting clinical improvement;
   c. Having continued medical supervision and monitoring of treatment until cured; and
   d. Where possible, having had three consecutive negative sputum smears obtained on three different days with at least one
      morning specimen. (Note: Frequent evaluation of sputum smear status may not be done routinely in resource-limited
      settings.)

**POLICY 8: TRAINING OF STAFF ON ALL ASPECTS OF TB AND THE TB INFECTION PREVENTION AND CONTROL PLAN**

Procedures
(i) _____________________ is the designated staff person to provide training to new staff as they are employed and to maintain a
    log indicating who has had initial training.
(ii) _____________________ is the designated staff person to provide annual training to all staff and to maintain a log indicating
    who has attended training. This may be incorporated into a broader training topic or it could be stand-alone TB infection control
    training.

**POLICY 9: MONITORING THE TB INFECTION PREVENTION AND CONTROL PLAN’S IMPLEMENTATION**

Procedures
(i) Determine the frequency of the infection prevention and control plan evaluation.
   a. During initiation of procedures, monitoring and evaluation should be done frequently, perhaps monthly or bi-monthly.
   b. When procedures are running well, less frequent evaluation will be necessary – at a minimum, annually.
(ii) Evaluate the screening process.
   a. Were patients with significant cough missed when entering the facility and only detected at a later time or in the examination
      room?
   b. What correctable factors were associated with these potential exposures?
(iii) Evaluate the success of referrals to the TB diagnostic centre.
   a. Did referred patients access care?
   b. Did referred patients have TB disease?
   c. What changes in screening or referral process should be made, if any?
(iv) Evaluate the training process.
   a. Did all new staff receive training on TB infection prevention and control during their induction?
   b. Did all staff receive annual re-training on TB infection control?
(v) Revise the infection prevention and control plan to reflect changes in staff responsibilities, policies, and procedures.
(vi) Develop a plan for correcting inappropriate practices or failure to adhere to institutional policies.
   a. Identify incentives to participate fully and adhere to policies.
   b. Identify corrective actions if policies are not followed.
SUMMARY OF TUBERCULOSIS ICD CODES

(A15-A19)

Includes:
- Infections due to Mycobacterium tuberculosis and Mycobacterium bovis

Excludes:
- Congenital tuberculosis (P37.0)
- Human immunodeficiency [HIV] disease resulting in tuberculosis (B20.0)
- Pneumoconiosis associated with tuberculosis (J65)
- Sequelae of tuberculosis (B90)
- Silicotuberculosis (J65)

A15 Respiratory tuberculosis, bacteriologically and histologically confirmed
A15.0 Tuberculosis of lung, confirmed by sputum microscopy with or without culture
A15.1 Tuberculosis of lung, confirmed by culture only
A15.2 Tuberculosis of lung, confirmed histologically
A15.3 Tuberculosis of lung, confirmed by unspecified means
A15.4 Tuberculosis of intrathoracic lymph nodes, confirmed bacteriologically and histologically
A15.5 Tuberculosis of larynx, trachea and bronchus, confirmed bacteriologically and histologically
A15.6 Tuberculous pleurisy, confirmed bacteriologically and histologically
A15.7 Primary respiratory tuberculosis, confirmed bacteriologically and histologically
A15.8 Other respiratory tuberculosis, confirmed bacteriologically and histologically
A15.9 Respiratory tuberculosis unspecified, confirmed bacteriologically and histologically

A16 Respiratory tuberculosis, not confirmed bacteriologically or histologically
A16.0 Tuberculosis of lung, bacteriologically and histologically negative
A16.1 Tuberculosis of lung, bacteriological and histological examination not done
A16.2 Tuberculosis of lung, without mention of bacteriological or histological confirmation
A16.3 Tuberculosis of intrathoracic lymph nodes, without mention of bacteriological or histological confirmation
A16.4 Tuberculosis of larynx, trachea and bronchus, without mention of bacteriological or histological confirmation
A16.5 Tuberculous pleurisy, without mention of bacteriological or histological confirmation
A16.7 Primary respiratory tuberculosis without mention of bacteriological or histological confirmation
A16.8 Other respiratory tuberculosis, without mention of bacteriological or histological confirmation
A16.9 Respiratory tuberculosis unspecified, without mention of bacteriological or histological confirmation

A17+ Tuberculosis of nervous system
A17.0+ Tuberculous meningitis (G01)
A17.1+ Meningeal tuberculoma (G07)
A17.8 +Other tuberculosis of nervous system
A17.9 +Tuberculosis of nervous system, unspecified (G99.8)
A18 Tuberculosis of other organs
A18.0 Tuberculosis of bones and joints
A18.1 Tuberculosis of genitourinary system
A18.2 Tuberculous peripheral lymphadenopathy
A18.3 Tuberculosis of intestines, peritoneum and mesenteric glands
A18.4 Tuberculosis of skin and subcutaneous tissue
A18.5 Tuberculosis of eye
A18.6 Tuberculosis of ear
A18.7 Tuberculosis of adrenal glands
A18.8 Tuberculosis of other specified organs

A19 Miliary tuberculosis
A19.0 Acute miliary tuberculosis of a single specified site
A19.1 Acute miliary tuberculosis of multiple sites
A19.2 Acute miliary tuberculosis, unspecified
A19.8 Other miliary tuberculosis
A19.9 Miliary tuberculosis, unspecified
### WHO CLINICAL STAGING IN ADULTS

#### CLINICAL STAGE 1
- Asymptomatic
- Persistent generalised lymphadenopathy

#### CLINICAL STAGE 2
- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

#### CLINICAL STAGE 3
- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant for longer than one month)
- Persistent oral candidiasis (after first 6–8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anaemia (< 8 g/dL), neutropaenia (< 0.5 × 10^9 per litre)
- And/or chronic thrombocytopenia (< 50 × 10^9 per litre)

#### CLINICAL STAGE 4
- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month’s duration or visceral at any site)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
- Extra-pulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extra-pulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy
- HIV-associated rectovaginal fistula
WHO CLINICAL STAGING IN CHILDREN

CLINICAL STAGE 1

- Asymptomatic
- Persistent generalised lymphadenopathy

CLINICAL STAGE 2 - MILD SYMPTOMS

- Unexplained persistent hepatosplenomegaly
- Popular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations

CLINICAL STAGE 3 - MODERATE SEVERITY

- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant for longer than one month)
- Persistent oral candidiasis (after 6-8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis

CLINICAL STAGE 4 - SEVERE

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month’s duration or visceral at any site)
- Extra pulmonary tuberculosis
- Kaposi sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy

- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month.
- Extra pulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non tuberculous mycobacterial infection
- Cerebral or B- cell non Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy
- HIV-associated rectovaginal fistula