Module 5

CHILD TB/HIV
The challenge of HIV and TB/HIV

- Increased caseload of child TB
- Greater difficulty with diagnosis
- Poorer response to TB treatment
- Drug interactions
- Implementation of the “three I’s” and the fourth “I”
Estimated HIV prevalence among new TB cases, 2013
National TB/HIV data

- This slide could include recent national or district data of TB/HIV indicators
Child TB/HIV epidemiology

HIV epidemic

Large increase in TB cases in young adults

Increased number of child TB cases

HIV-infected children at risk of PTB because:

1. immune suppressed
2. more likely to be a contact of an adult with TB
Risk factors for TB infection and disease in children

For TB infection
• Contact with source case
  – Closeness of contact
  – Duration of contact
• Source case
  – Smear positivity
  – Cavities on CXR
• Increased exposure
  – Living in high TB endemic communities
  – Children of families living with HIV

For TB disease
• Young age
  – Especially 0-2 years
• HIV infection
  – Risk of infection and disease
• Other immunosuppression
  – Malnutrition
  – Post-measles
• Not BCG vaccinated
  – Risk of disseminated disease
The TB notification rate and notification rate of smear-positive disease rose in Malawi in the wake of the worsening HIV epidemic.

Childhood tuberculosis notifications in Blantyre district, Malawi, increased 8-fold from 1986 to 1995 as the TB epidemic worsened.


**Figure 1** Tuberculosis notification rates in Malawi, 1985–2000. smear+ = smear positive.
Increased risk of TB exposure among young children in HIV-endemic countries
### Pathogens found in lungs from autopsy studies of African children

<table>
<thead>
<tr>
<th>Causes of pneumonia</th>
<th>HIV-infected N=473</th>
<th>HIV-uninfected N=338</th>
<th>Total N=811</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>238 (50%)</td>
<td>132 (39%)</td>
<td>370 (46%)</td>
</tr>
<tr>
<td>PcP</td>
<td>145 (31%)</td>
<td>11 (3%)</td>
<td>156 (19%)</td>
</tr>
<tr>
<td>CMV</td>
<td>121 (26%)</td>
<td>7 (2%)</td>
<td>128 (16%)</td>
</tr>
<tr>
<td>M.tuberculosis</td>
<td>50 (11%)</td>
<td>27 (8%)</td>
<td>77 (9%)</td>
</tr>
<tr>
<td>Co-infection</td>
<td>98 (21%)</td>
<td>5 (1.5%)</td>
<td>103 (13%)</td>
</tr>
</tbody>
</table>

Combined data from 7 autopsy studies from five TB endemic countries shows that tuberculosis is a common diagnosis in HIV-infected and uninfected children dying with lung disease.
Child TB and TB/HIV

In HIV-endemic Africa, 40-60% of child TB cases are HIV-infected

20 times higher risk of culture-confirming TB in HIV-infected than in HIV-uninfected children

TB risk 4-fold higher in HIV-infected children with low CD4% < 15% compared to HIV-infected children with higher CD4%
Elenga N et al, Pediatr Infect Dis J 2005

TB-related mortality significantly higher in HIV-infected children
Madhi SA et al, Clin Infect Dis 2000
Diagnosis of TB in HIV-infected child

HIV test should be routine in the assessment of a child with suspected TB
Diagnosis of TB in HIV-infected child

- HIV test should be routine in the assessment of a child with suspected TB.

- Note that excluding HIV infection decreases the number of alternative diagnoses because chronic or persistent lung disease is common in HIV-infected children.

- The approach to diagnosis of TB (PTB and EPTB) is similar in the HIV-infected child as for the HIV-uninfected child.

- Diagnostic challenges are greater because co-infection with HIV reduces the specificity of the typical and clinical and radiological features of TB.

- Samples should be taken for microscopy and culture (and sensitivity) whenever possible.

- Symptomatic screening for TB should be routine for all HIV-infected children including upon HIV diagnosis and commencement of ART.
Impact of HIV on clinical diagnosis of PTB

Features for TB diagnosis
• chronic symptoms
• positive TB contact (if parent)
• malnutrition
• tuberculin test
• CXR findings
• satisfactory response to TB treatment

Impact of HIV for TB diagnosis
• less specific
• less specific
• less specific
• less sensitive
• less specific
• less sensitive
## Impact of HIV on TST positivity in children with confirmed TB

<table>
<thead>
<tr>
<th>Country</th>
<th>HIV infected (%) TST positive</th>
<th>HIV uninfected (%) TST positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>50/83 (60%)</td>
<td>190/232 (82%)</td>
</tr>
<tr>
<td>Schaaf et al, BMC Infect Dis 2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>12/58 (21%)</td>
<td>354/438 (80%)</td>
</tr>
<tr>
<td>Palme et al, PIDJ 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>10/57 (18%)</td>
<td>21/44 (48%)</td>
</tr>
<tr>
<td>Jeena et al, Int J Tuberc Lung Dis 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cote d’Ivoire</td>
<td>9/24 (38%)</td>
<td>74/106 (88%)</td>
</tr>
<tr>
<td>Mukadi et al, AIDS 1995</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TST and HIV

Tuberculin skin test (TST):
is often unavailable
requires cold storage and repeated visits to the health facility
has low sensitivity in HIV-infected children, especially if not receiving ART

A positive history of TB contact is very important and provides similar epidemiological information to that provided by TST i.e. likely infection with *Mycobacterium tuberculosis*

*Next slide provides a diagnostic approach at the primary and secondary level of care that does not rely upon availability or use of TST*
Clinical approach to TB diagnosis in HIV-infected child

TB suspected on basis of typical and persistent symptoms

- Sputum smear-negative or not done
  - Consider contact history
    - Contact smear-negative or not known
      - Physical signs and CXR suggest other diagnosis#
    - Contact smear-positive
      - Physical signs or CXR suggestive of PTB#
  - Sputum smear-positive
    - TREAT FOR TB

# It can be difficult to clearly define what is “suggestive of PTB” on clinical or radiological findings in HIV-infected children because of clinical overlap between PTB and other forms of HIV-related lung disease: note further slides with Table and CXRs.

# CXR abnormalities of PTB in HIV-infected children are mainly similar to those in HIV-uninfected children.
HIV infection was associated with a very poor outcome from TB in children in the pre-HAART era.

<table>
<thead>
<tr>
<th>Location</th>
<th>Complete recovery HIV+</th>
<th>Complete recovery HIV-</th>
<th>Mortality HIV+</th>
<th>Mortality HIV-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>65%</td>
<td>95%</td>
<td>15%</td>
<td>0%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Jeena et al 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cote d’Ivoire</td>
<td>63%</td>
<td>97%</td>
<td>16%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mukadi et al 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>55%</td>
<td>73%</td>
<td>38%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Espinal et al 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>55%</td>
<td>73%</td>
<td>38%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Palme et al 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mortality in HIV-positive and negative children with TB

Timing of deaths in HIV-infected Ethiopian children receiving anti-TB treatment

Surviving fraction

Time (months)

HIV negative
HIV positive
Censored

Possible reasons why outcome is poorer on TB treatment in HIV-infected children

• Immunosuppression
  – emphasises the importance of early ART in reducing mortality

• High risk of co-morbidities
  – invasive bacterial disease: emphasises the importance of concurrent cotrimoxazole preventive therapy
  – severe malnutrition: emphasises the importance of nutritional support

• Poorer adherence due to pill burden and risk of illness/death of primary caregiver

• Risk of DR TB in HIV-infected populations

• Diagnosis is incorrect and child has other HIV-related lung disease, e.g. lymphocytic interstitial pneumonitis (LIP)
The diagnosis of PTB can be particularly challenging in HIV-infected child because clinical overlap with other HIV-related lung disease is common

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pneumonia</td>
<td>Recurrent episodes of cough, fever and fast breathing that usually respond to antibiotics</td>
</tr>
<tr>
<td>LIP</td>
<td>Unusual before 1 year of age</td>
</tr>
<tr>
<td></td>
<td>Associated with generalised symmetrical lymphadenopathy, clubbing, parotid enlargement.</td>
</tr>
<tr>
<td></td>
<td>Nutritional status variable.</td>
</tr>
<tr>
<td></td>
<td>CXR: diffuse reticulonodular pattern and bilateral perihilar adenopathy. No compression of airways</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Persistent respiratory symptoms not responding to antibiotics. Often poor nutritional status; positive TB contact especially in younger children</td>
</tr>
<tr>
<td></td>
<td>CXR: focal abnormalities and perihilar adenopathy</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Cough productive or purulent sputum; clubbing</td>
</tr>
<tr>
<td></td>
<td>CXR: honeycombing usually of lower lobes</td>
</tr>
<tr>
<td></td>
<td>Complicates recurrent bacterial pneumonia, LIP or TB</td>
</tr>
<tr>
<td>PcP</td>
<td>Common cause of severe, fatal pneumonia especially in infants.</td>
</tr>
<tr>
<td></td>
<td>Persistent hypoxia is common</td>
</tr>
<tr>
<td></td>
<td>Unusual after 1 year of age</td>
</tr>
<tr>
<td></td>
<td>CXR: diffuse interstitial infiltration or hyperinflation</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>Common problem: LIP, bacterial pneumonia, TB</td>
</tr>
<tr>
<td></td>
<td>Consider when poor response to first-line empiric management</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Characteristic lesions on skin or palate</td>
</tr>
</tbody>
</table>
Clinical and radiological features that differentiate causes of chronic lung disease in HIV-infected children

<table>
<thead>
<tr>
<th>Feature</th>
<th>PTB</th>
<th>Bronchiectasis</th>
<th>LIP</th>
<th>Miliary TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Persistent fever</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Wasting</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Generalised lymphadenopathy</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Parotid enlargement</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Clubbing</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal parenchymal</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diffuse micronodular</td>
<td>Negative</td>
<td>Negative</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Diffuse reticular</td>
<td>Negative</td>
<td>Negative</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Common</td>
<td>Variable</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Note that co-morbidities are common in HIV-infected children
Miliary TB
Child TB management and HIV

Principles of treatment of TB in HIV-infected children is similar to HIV-uninfected children

ART improves outcome for HIV-infected children treated for TB

It is recommended that HIV-infected children receive
1. Four first-line drugs (RHZE) in intensive phase for suspected or confirmed drug-sensitive TB irrespective of severity of disease
2. Similar duration of regimens as for HIV-uninfected
3. ART as recommended within 2-8 weeks of starting TB treatment or continue ART
4. Cotrimoxazole preventive therapy
5. Pyridoxine supplement
6. Nutritional support

HIV-infected children are at increased risk of relapse and drug resistant TB
## Child TB management and ART

<table>
<thead>
<tr>
<th>Age / weight</th>
<th>Antiretroviral therapy (ART) *</th>
</tr>
</thead>
</table>
| <3yrs or <10kg | **Retain or start on the following regimens**  
Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone – use 2 NRTIs  
Third drug  
If on nevirapine  
• switch to lopinavir/ritonavir (Kaletra®)  
  with additional ritonavir to achieve mg for mg parity with lopinavir  
• continue for 1-2 weeks after TB treatment has been stopped  
• If not possible, – continue NVP dose at the upper end of the dosage scale  
If on lopinavir/ritonavir (Kaletra®)  
• use additional ritonavir as above  
• triple NRTI therapy is an option, if baseline viral load <100 000 copies/ml |
| ≥3yrs and ≥10kg | **Retain or start on the following regimens**  
2 NRTIs as backbone  
Third drug  
If on nevirapine  
• switch to efavirenz  
• if not available continue on nevirapine dose at the upper end of the dosage scale  
If on lopinavir/ritonavir (Kaletra®)  
• consider switch to efavirenz, only if undetectable viral load*  
• alternatively use additional ritonavir as above  
• triple NRTI therapy is an option, if baseline viral load <100 000 copies/ml |

TB treatment is not adjusted - should be initiated as soon as the diagnosis is made  
No ART adjustment is necessary with INH preventive therapy

### Monitoring
- If previously on ART - monitor clinically for signs of drug toxicity.  
- If ART newly initiated - monitor ALT after 2 & 4 weeks, then clinically for signs of drug toxicity.

All newly diagnosed TB cases with HIV infection should be started on TB treatment as soon as possible after completing the first 2 weeks of anti-TB treatment

---

*Marais BJ et al. Paediatr Resp Rev 2011*
Child TB/HIV and IRIS

HIV-infected children should be regularly screened for symptoms of possible TB including on commencement of ART

TB Immune Reconstitution Inflammatory Syndrome (IRIS) can occur as:

“unmasking” IRIS – subclinical TB disease becomes evident with immune reconstitution

TB treatment should be commenced

“paradoxical” IRIS – symptomatic deterioration despite adequate TB treatment

continue TB treatment – consider steroids

TB IRIS usually occurs within 1-2 months after starting treatment and does NOT indicate failure of TB treatment

BCG (M.bovis) IRIS is common in young infants initiated on ART

TB IRIS or BCG IRIS can be associated with significant morbidity but not with a high mortality
Three “I”s for TB control

1) Intensified Case Finding
2) INH Prevention Treatment (IPT)
3) Infection Control

....and a fourth?

Integration

of TB/HIV including maternal TB/HIV

of other health services such as maternal child health/IMCI
HIV and TB contact

• HIV infected children at increased risk of exposure to TB and therefore infection

• HIV-infected children at high risk of TB disease if infected with *Mycobacterium tuberculosis*

• All HIV-infected children that are exposed to contact with a TB case should be screened using symptom-based screening approach

• All child contacts of case with TB/HIV should be tested for HIV
Management of HIV-infected contacts

• HIV-infected contacts
  – with symptoms suggestive of TB disease require assessment/referral for possible TB
  – with no symptoms suggesting TB require IPT for at least 6 months and careful follow-up

• IPT reduces risk of TB disease in HIV-infected contacts
• ART reduces risk of TB disease in HIV-infected contacts
• ART + IPT provides better protection than ART alone
Approach to management of child TB contact

IPT: isoniazid 5-15 mg/kg daily for at least 6 months

<table>
<thead>
<tr>
<th>Weight band</th>
<th>INH 300 mg tab</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-9 kg</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>10-19 kg</td>
<td>½ tablet</td>
</tr>
<tr>
<td>20-30 kg</td>
<td>1 tablet</td>
</tr>
</tbody>
</table>
Maternal/infant TB/HIV

TB in pregnancy or post-partum is common especially in HIV-infected women.

Associated with maternal mortality, low birth weight and infant mortality.

The risk of TB infection and disease to the infant of a mother with TB is extremely high.

Maternal TB increases the risk of HIV transmission to the infant.
HIV and infection control

• HIV infected children at increased risk of exposure to TB including drug resistant TB

• This risk includes health-care facilities especially also attended by adults such as HIV clinic, maternal clinic

• NTP has infection control guidelines emphasising importance of simple and feasible measures to optimize patient flow and air flow to reduce the risk of transmission
HIV and BCG

- HIV infected infants are at increased risk of disseminated BCG disease which is often fatal

- The benefits of BCG for HIV-infected infants are uncertain but may include protection against disseminated TB disease as for HIV-uninfected

- Early ART markedly reduces the risk of BCG disease

- BCG IRIS is common in infants (3-6 months) when early ART is commenced but is usually not fatal
HIV and TB in children

- HIV infected children at increased risk of exposure to TB and therefore TB infection

- HIV-infected children at high risk of TB disease in TB endemic setting

- Clinical approach to TB diagnosis in HIV-infected children is similar as for HIV-uninfected children

- Management of TB more complicated in HIV-infected children with significantly poorer outcomes

- Clinical diagnosis is more difficult especially for PTB as other HIV-related lung disease is common

- CPT and ART have a role in reducing TB-related death which is especially common within the first months following TB treatment