Tuberculosis / HIV co-infection in Children
FIG. 3.5
Estimated HIV prevalence in new and relapse TB cases, 2016
TB has caused more deaths than HIV since 2012

![Graph showing TB and HIV deaths from 2000 to 2016.](image)

- **HIV deaths**
  - 2000: 2.0
  - 2008: 1.3
  - 2016: 1.0

- **TB deaths, HIV-negative people**
  - 2000: 1.5
  - 2008: 1.3
  - 2016: 1.0

- **TB deaths, HIV-positive people**
  - 2000: 0.4
  - 2008: 0.4
  - 2016: 0.4

---

*World Health Organization*
Epidemiology of HIV in Children in Kenya

Children Living with HIV in Kenya – 2018 HIV estimates

Children living with HIV – 105,213
New child infections – 7978
AIDS related deaths 0-14 years – 4,312

Among Children with TB, HIV prevalence
Kenya National 2007: 38%
S. Africa (CT, 2007): 32%
Ethiopia 2009: 5%
Child TB/HIV Epidemiology

HIV epidemic

Increase in TB cases in young HIV infected adults

They transmit TB and/or HIV to their children

Increased numbers of children with TB/HIV co-infection

High risk of child progressing to TB disease due to weakening immunity
Effect of HIV on Outcome of TB in a Child

HIV infected children have:

- 20 times higher risk of developing TB disease than in HIV-negative
- Those with CD4% <15% have a FOUR-FOLD higher risk of TB than those with higher CD4
- Poorer response to anti-TB treatment in absence of antiretroviral therapy
- Higher likelihood of having recurrence / relapse of TB
- Higher TB-related mortality than HIV negative
- Increased risk of other persistent lung conditions.

Madhi SA et al, Clin Infect Dis 2000
### Child Mortality from TB / HIV

#### Causes of pneumonia

<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/PJP</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>

- Autopsy Studies of Children Dying from Pneumonia from 5 TB endemic countries
- 9% of pneumonia deaths were due to TB
- HIV infected children had higher mortality (11%) than HIV negative children (8%)
Impact of HIV on TB

- Increase TB burden
- Increased morbidity
- Increased mortality
- Program credibility
- Increased stigma
Impact of TB on HIV

- The most common opportunistic infection among PLHIV
- TB is a leading cause of HIV-related morbidity
- TB is a leading cause of mortality:
  - 1/3 of all AIDS related deaths are due to TB
- TB accelerates immuno-suppression of HIV
2012: 12 points policy package: What's new?

**A. Establish the mechanisms for integrated TB & HIV services**
1. Set up or strengthen a TB/HIV coordinating body effective at all levels
2. Conduct HIV and TB surveillance among TB and HIV patients respectively
3. Carry out joint TB/HIV planning
4. Conduct monitoring and evaluation

**B. Decrease the burden of TB in PLHIV (Three Is for HIV/TB and earlier initiation of ART)**
5. Intensify TB case finding and ensure quality TB treatment
6. Introduce TB prevention with IPT and ART
7. Infection control for TB in health care and congregate settings ensured

**C. Decrease the burden of HIV in patients with presumptive and diagnosed TB**
8. Provide HIV testing & counselling to patients with presumptive and diagnosed TB
9. Introduce HIV preventive methods patients with presumptive and diagnosed TB
10. Provide CPT for TB patients living with HIV
11. Ensure HIV prevention, treatment & care for TB patients living with HIV
12. Provide Antiretroviral therapy to TB patients living with HIV
Diagnosis of TB in HIV-infected child

- Diagnosis of TB in HIV infected children is similar as for HIV uninfected children

- History of contact with TB is extremely important

- The clinical presentation of TB is similar in those in early stages of HIV disease, however for those with advanced HIV disease
  - May not have the typical TB clinical features
  - Chronic respiratory symptoms may be due to other causes
Simplified TB Diagnosis

*Presence of 2 or more of the following symptoms*
- Persistent Cough of any duration
- Weight loss or poor weight gain
- Persistent fever and/or night sweats
- Fatigue, reduced playfulness, less active

PLUS

*Presence of 2 or more of the following:*
- Positive contact history
- Abnormal Respiratory signs
- CXR suggestive of PTB (where available)
- Positive Mantoux test (where available)

Then PTB is likely, and treatment is justified
Interpreting TST (Mantoux) in an HIV infected Child

Tuberculin skin test (Mantoux)

- Induration of ≥5mm is defined as positive in HIV infected child
- HIV infected children can have poor immune response, may fail to react to TST even though they have TB
- Studies show that only ~40% will be positive (60% have TB but have negative TST)
  - Compared to HIV negative children with TB in whom >80% will be TST positive (induration ≥ 10mm)
  - Therefore a negative TST does not rule out TB in an HIV infected child
- Positive Mantoux test is not indicative of TB disease but should be used with other symptoms of TB
Interpreting CXR in HIV infected Child

- In advanced HIV disease, may not show the typical CXR changes - may have a normal CXR
- May have an abnormal CXR due to other persistent lung diseases
  - Lymphoid interstitial pneumonia (LIP) resembles miliary TB, and also causes hilar LN
  - Bronchiectasis (destruction of bronchioles and lung tissue due to recurrent severe episodes of pneumonia) causes persistent opacifications
Miliary TB or LIP

Diffuse micronodules – millet like appearance
TB Lobar pneumonia or Bronchiectasis
Clinical and radiological features that differentiate causes of chronic lung disease in HIV-infected children

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>PTB</th>
<th>Bronchiectasis</th>
<th>LIP</th>
<th>Miliary TB</th>
</tr>
</thead>
<tbody>
<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>Common</td>
<td>Common</td>
<td>Variable</td>
<td>Common</td>
</tr>
<tr>
<td>Generalised lymphadenopathy</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Parotid enlargement</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Clubbing of finger/toes</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Clinical and radiological features that differentiate causes of chronic lung disease in HIV-infected children

<table>
<thead>
<tr>
<th>Chest X-ray</th>
<th>PTB</th>
<th>Bronchiectasis</th>
<th>LIP</th>
<th>Miliary TB</th>
</tr>
</thead>
<tbody>
<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>Common</td>
<td>Negative</td>
<td>Common</td>
<td>Negative</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Negative</td>
<td>Variable</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Making the HIV Diagnosis

- An HIV test must be done to establish if the child is HIV infected
- HIV testing should be voluntary and conducted ethically
- Where Consent, Confidentiality, Counselling, Correct results and Connection (linkage) can be assured
Making the HIV Diagnosis continued..

- Age > 18 months: Positive HIV antibody rapid tests

- Age < 18 months:
  - For all children <12 months who are HIV exposed do DNA PCR
  - If the mother of the infant is unavailable, first do a HIV antibody rapid test and if positive do DNA PCR
HIV diagnosis in children >18 months

- Screening Test - Determine
- Confirmatory Test - First Response
- Tie breaker is no longer recommended
Dried Blood Spot (DBS) for Infant HIV DNA PCR testing
Treatment of TB in an HIV infected Child

- TB treatment in HIV infected children follows the same principles as in HIV negative children.
- Due to immune-suppression their response to TB treatment may be slow.
Antiretroviral therapy and anti-TB

Timing of ART for TB/HIV Co-infection

Patients who are not yet on ART
- Start TB treatment immediately
- Initiate ART as soon as anti-TB medications are tolerated, preferably within 2 weeks

Patients who are already on ART
- Start TB treatment immediately
- Continue ART, making any required adjustments to the ART regimen based on predicted drug interactions
Antiretroviral therapy and anti-TB

Principles of ART: Always give three drugs

- Usually 2 drugs from one class (Nucleoside reverse transcriptase inhibitors or NRTIs)
  - Abacavir (ABC)+lamivudine (3TC) – the preferred first line regimen

- Third drug from a different class
  - Non-nucleoside reverse transcriptase inhibitors or NNRTIs. Preferred NNRTI for those >3 years age is EFV

  - Protease inhibitors Pis e.g. LPVr for those aged <3 years

  - Intergrase inhibitors – for those >35kg is DTG, RAL

Start ART within 2 weeks of starting anti-TB therapy.

Note: Rifampicin induces metabolism of nevirapine and most protease inhibitors and reduces their levels. Need to modify ART with TB treatment.
Newly diagnosed with TB and HIV (ART naïve) child

<table>
<thead>
<tr>
<th>Age</th>
<th>1st Line if TB/HIV Co-infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 weeks</td>
<td>Start anti-TB treatment immediately; start ART after 4 weeks of age, once tolerating anti-TB drugs (follow the regimen recommendations for children 4 weeks to &lt; 3 years of age)</td>
</tr>
</tbody>
</table>
| 4 weeks - < 3 years | ABC + 3TC + LPV/r + RTV1,2  
  • If not able to tolerate super-boosted LPV/r+RTV then use ABC + 3TC+ RAL which continues for life |
Newly diagnosed with TB and HIV (ART naïve) child

<table>
<thead>
<tr>
<th>Age</th>
<th>1st Line if TB/HIV Co-infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-14 years And &lt; 35 kg body weight</td>
<td>ABC + 3TC + EFV</td>
</tr>
<tr>
<td>≥ 35 kg body weight And &lt;15 Years</td>
<td>ABC + 3TC + DTG (give DTG 50 mg BD for duration of rifampicin-containing TB treatment, then reduce to DTG 50 mg once daily after TB treatment is completed)</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>TDF + 3TC + DTG</td>
</tr>
</tbody>
</table>
Preferred ART Regimens for TB/HIV Co-infection for Patients Currently on 1st Line

<table>
<thead>
<tr>
<th>Current Regimen</th>
<th>Age</th>
<th>Recommended Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI/r-based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 years old</td>
<td></td>
<td>Super-boost LPV/r with additional RTV If not able to tolerate super-boosted LPV/r + RTV then use RAL at double the standard weight-based dose for the duration of TB treatment. After completion of TB treatment continue RAL, but at standard weight-based dosing</td>
</tr>
<tr>
<td>3 years – 15 years (weight &lt; 35kg)</td>
<td></td>
<td>Super-boost LPV/r with additional RTV</td>
</tr>
<tr>
<td>Child ≤ 15 years and ≥ 35 kg</td>
<td></td>
<td>Continue PI/r; use rifabutin for anti-TB Treatment</td>
</tr>
<tr>
<td>&gt; 15 years (any weight)</td>
<td></td>
<td>Continue PI/r; use rifabutin for anti-TB treatment</td>
</tr>
</tbody>
</table>
Preferred ART Regimens for TB/HIV Co-infection for Patients Currently on 1st Line

<table>
<thead>
<tr>
<th>Current Regimen</th>
<th>Age</th>
<th>Recommended Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV-based</td>
<td>Any age</td>
<td>Continue same regimen</td>
</tr>
<tr>
<td>RAL-based</td>
<td>All ages</td>
<td>Give double the standard dose of RAL</td>
</tr>
<tr>
<td>DTG-based</td>
<td>All ages</td>
<td>Give standard dose of DTG twice daily (i.e. double the daily dose)</td>
</tr>
</tbody>
</table>
Use of EFV in children < 3 years

- EFV is NOT recommended for children < 3 years old because of highly variable EFV metabolism at that age
<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Common offending drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Most anti TB drugs</td>
</tr>
<tr>
<td></td>
<td>ARVs-AZT, LPV, Ritonavir</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Anti-TB INH, RIF, PZA</td>
</tr>
<tr>
<td></td>
<td>ARVs- NVP</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Anti TB-INH, RIF,</td>
</tr>
<tr>
<td></td>
<td>ARVs- NVP, ABC</td>
</tr>
<tr>
<td></td>
<td>Others- Cotrimoxazole (CTX)</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Anti TB-INH</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Anti TB-PZA</td>
</tr>
<tr>
<td>CNS-nightmares, Hallucinations</td>
<td>ARVs- EFV</td>
</tr>
</tbody>
</table>
Interactions between ARVs and TB drugs

Rifampicin
- Reduces NVP, IDV, NFV levels.
  If a patient is already on NVP and develops TB, change NVP to EFV

INH and Nevirapine
- Additive /overlapping toxicity- hepatotoxic
- Monitor patient when on both medicines
Immune Reconstitution Inflammatory Syndrome (IRIS)

- As the child’s immune system recovers after ART initiation, their ability to mount an inflammatory response returns.
- If they have a pre-existing infection like TB, they may then appear to initially get worse despite being on anti-TB therapy.
- This reaction is usually mild and self-limited, especially if the preexisting infection is effectively treated.
- **Action:** Continue anti-TB, continue ART.
- **If the reaction is severe** – e.g. worsening TB pleural effusion causing respiratory distress – give prednisone 2mg/kg daily for 4 weeks, then taper down slowly.
Prevention of TB in an HIV infected Child

Pillars of prevention of TB in HIV infected children include:

- Isoniazid prophylactic therapy
  - Any HIV infected child above 1 yr should receive 6 months of IPT provided that they have no signs or symptoms of TB disease
  - Infants under 1 yr – only those exposed to an adult with TB should receive IPT as long as they do not have TB disease
  - This has reduced TB incidence by 75%

- Antiretroviral therapy – greatly reduces TB incidence

- Contact tracing & Environmental considerations (refer to module on prevention)
HIV and BCG

BCG should be given to all newborns soon after birth

Any infant who failed to get BCG at birth, before giving it at a later age:

- Determine their HIV status

  - If they are HIV free – give the BCG
  - If they have symptomatic HIV disease – DO NOT GIVE BCG