Management of HIV-TB coinfection

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• Estimated number of new cases: 9.6 million, including 1.0 million children
  – 12% of new cases (1.2M) were HIV-infected
  – African region: 28% of cases
  – India, Indonesia & China had largest number of cases, 23%, 10% & 10% of global total

• TB deaths: 1.5 million, including 140,000 children

• 480,000 cases of MDR-TB
TB: South African estimates, 2014

- 450,000 new cases (400,000 – 510,000)
  - 270,000 new cases in HIV-infected individuals
- Incidence: 834 per 100,000 population
- Number of TB deaths: 96,000, including 72,000 HIV-infected TB cases
- Lab-confirmed MDR-TB cases: 18,734
  - 11,538 commenced on treatment
- Number of children with TB: 50,474 (2010)
## TB risk in HIV-infected children

Table 2. Estimated incidence of culture-confirmed tuberculosis (TB) among HIV-infected and HIV-uninfected infants.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>No. of TB cases per 100,000 population (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All infants</td>
<td>HIV-uninfected infants</td>
</tr>
<tr>
<td>Tuberculosis incidence</td>
<td>83.1 (73–94)</td>
<td>65.9 (57–75)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis incidence</td>
<td>78.7 (69–89)</td>
<td>62.5 (53–72)</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis incidence</td>
<td>28.2 (22–34)</td>
<td>22.9 (18–29)</td>
</tr>
<tr>
<td>Disseminated tuberculosis incidence*</td>
<td>16.6 (12–21)</td>
<td>14.1 (10–18)</td>
</tr>
<tr>
<td>Miliary tuberculosis incidence</td>
<td>10.9 (7–15)</td>
<td>9.3 (6–13)</td>
</tr>
<tr>
<td>Tuberculosis meningitis incidence</td>
<td>9.2 (6–13)</td>
<td>7.9 (5–11)</td>
</tr>
</tbody>
</table>

* Disseminated tuberculosis was defined as miliary tuberculosis, tuberculosis meningitis, or disseminated disease, diagnosed on the basis of positive culture results of isolates from blood culture and/or bone marrow.
# Impact of ART on TB risk

<table>
<thead>
<tr>
<th>Ref</th>
<th>Country</th>
<th>TB incidence rate / TB risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SA n=1132</td>
<td>Pre-cART: 21.1 / 100 py vs on cART: 6.4 / 100 py a crude reduction of 70%</td>
</tr>
<tr>
<td>2</td>
<td>DRC n=6535</td>
<td>On-cART: 10.2 / 100 py vs not on-cART: 20.4 / 100 py Model-estimated TB Hazard ratio for cART: 0.51 [0.27-0.94]</td>
</tr>
<tr>
<td>3</td>
<td>Kenya n=364</td>
<td>On cART: 7.2 / 100 py vs not on-cART: 22.2 / 1– py; IRR for cART = 0.32 [0.26-0.40] Adjusted for other factors, cART was associated with marked reduction in TB risk; AHR: 0.15 [0.12-0.20]</td>
</tr>
<tr>
<td>4</td>
<td>Uganda n=311</td>
<td>Pre-ART incidence: 10.0 per 100 py, 1st 100 days of ART risk of new TB was 2.7-fold higher; after 100 days TB incidence rate decline to below pre-ART level, RR=0.41, p=0.002</td>
</tr>
<tr>
<td>5</td>
<td>Côte d’Ivoire N=2110</td>
<td>6.28/100 child-years (day 0-90 of ART), 2.52/100 cy (day 91-180 of ART), 0.56/100 cy thereafter</td>
</tr>
</tbody>
</table>

TB diagnosis

- Medical history
  - History of TB contact
  - Symptoms consistent with TB
- Clinical examination (including growth assessment)
- Tuberculin skin testing (TST)
- Other relevant investigations
  - Suspected pulmonary TB: CXR
  - Suspected extrapulmonary TB: depends on the site of disease
- Laboratory confirmation / support
  - Smear microscopy
  - Interferon-\(\gamma\) release assay
  - Nucleic acid-based tests: Xpert MTB/RIF, Line probe assays
  - Mycobacterial culture & sensitivities
  - Histological results
## Impact of HIV on TB diagnosis

<table>
<thead>
<tr>
<th>History including contact history</th>
<th>NB because of poor sensitivity of TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms consistent with TB</td>
<td>Lower specificity due to overlap between symptoms of TB &amp; HIV; considered important because of poor sensitivity of TST for identifying TB infection</td>
</tr>
<tr>
<td>Examination including growth</td>
<td>Lower specificity; malnutrition is common in TB &amp; HIV</td>
</tr>
<tr>
<td>Tuberculin skin testing</td>
<td>Lower sensitivity; TST positivity declines with increasing immunosuppression</td>
</tr>
<tr>
<td>Chest radiograph findings</td>
<td>Lower specificity: overlap with HIV-related disease</td>
</tr>
<tr>
<td>Bacteriological confirmation</td>
<td>Important but beyond capabilities of many settings</td>
</tr>
<tr>
<td>Investigations relevant for suspected PTB and EPTB</td>
<td>Wide range of diagnostic possibilities because of other HIV-related disease</td>
</tr>
</tbody>
</table>

Contact history

Close contact: living in the same household or in frequent contact with a source case (e.g. caregiver) with sputum smear-positive TB.

- Children < 5 years in close contact with a smear-positive TB should be evaluated for TB
- Children of all ages living with HIV who are in close contact with a TB case should be evaluated for TB
- After TB is diagnosed in a child or adolescent, an effort should be made to detect the adult source cases
- When a child is diagnosed with TB, efforts should be made to detect the source case & other undiagnosed household
- If a child presents with infectious TB, other child contacts must be sought and evaluated. Children should be regarded as infectious if they have smear-positive PTB or cavitary TB on CXR

Outbreak: Children’s home, Khayalitsha

- Index case: 8 year old, CP, culture-confirmed TB
- 38 screened: 32 children, 6 adults
- 46% (n=26): Mantoux ≥ 10mm, 4 commenced on anti-TB RX (3/4 culture-confirmed disease)
- Index strain and 2 contact strains related on genotyping

Spoligotyping

W-Beijing Strain

David Moore, 2010
Symptoms suggesting TB

Most children with symptomatic disease develop chronic symptoms (>2 weeks).

- Unremitting, persistent cough,
- Fever (>38°C)
- Not eating well / anorexia, weight loss (>5%) or failure to thrive (growth faltering in the last 3 months, or WAZ / WHZ ≤ -2 in the absence of information about recent growth trajectory).
- Fatigue / lethargy, reduced playfulness, decreased activity
## Physical examination

### Signs of hypersensitivity
- Phlyctenular conjunctivitis, erythema nodosum, polyarthritis (Poncet arthritis)

### PTB: no specific signs

### Signs highly suggestive of EPTB
- Non-painful enlarged cervical adenopathy – matted ± fistula formation
- Gibbus, especially recent onset

### Signs requiring investigation to exclude EPTB
- Non-painful enlarged lymph nodes without fistula formation
- Pleural effusion
- Pericardial effusion
- Unexplained hepatomegaly, splenomegaly, hepatosplenomegaly
- Distended abdomen with ascites
- Papable abdominal lymphadenopathy
- Meningitis not responding to antibiotic treatment, with sub-acute onset or raised intracranial pressure
- non-painful monoarthritis
- Cutaneous manifestations e.g. Papulonecrotic-type TB

Adapted from: WHO, Int J Tuberc Lung Dis 2006;10(10): 1091-7
Phlyctenular conjunctivitis & erythema nodosum
Tuberculin skin test (TST)

- 5 TU of PPD or 2 TU of RT23 (0.1ml)
- Intradermal administration
- Position: left forearm, palm-side up
- Read between 48-72 hours after administration
- Measure horizontal diameter of induration using a clear flexible ruler

TU=tuberculin units; PPD=purified protein derivative
# TST Interpretation

<table>
<thead>
<tr>
<th>Positive TST</th>
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<tbody>
<tr>
<td>▪ induration ≥ 5 mm in HIV and severely malnourished children; ≥ 10 mm in all other children</td>
</tr>
<tr>
<td>▪ Infection vs disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Negative TST</th>
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<tbody>
<tr>
<td>▪ Never rules out a diagnosis of TB</td>
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<table>
<thead>
<tr>
<th>False-positive TST</th>
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<tbody>
<tr>
<td>▪ Incorrect interpretation of test</td>
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<tr>
<td>▪ BCG vaccination</td>
</tr>
<tr>
<td>▪ Infection with nontuberculous mycobacteria</td>
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</table>

<table>
<thead>
<tr>
<th>False-negative TST</th>
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</thead>
<tbody>
<tr>
<td>▪ Incorrect administration or interpretation</td>
</tr>
<tr>
<td>▪ HIV infection</td>
</tr>
<tr>
<td>▪ Improper storage of tuberculin</td>
</tr>
<tr>
<td>▪ Severe TB</td>
</tr>
<tr>
<td>▪ Viral infection (e.g. measles, varicella)</td>
</tr>
<tr>
<td>▪ Vaccinated with live virus vaccines (within 6 weks)</td>
</tr>
<tr>
<td>▪ Malnutrition</td>
</tr>
<tr>
<td>▪ Immunosuppressives (e.g. glucocorticosteroids)</td>
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<tr>
<td>▪ Neonatal period</td>
</tr>
<tr>
<td>▪ Primary immunodeficiency diseases</td>
</tr>
<tr>
<td>▪ Low protein states</td>
</tr>
<tr>
<td>▪ Diseases of lymphoid tissue (e.g. Hodgkin disease, lymphoma, leukemia, sarcoidosis)</td>
</tr>
</tbody>
</table>
Chest radiographs of HIV-infected children with culture-confirmed TB
Key features suggestive of TB

Presence of three or more of the following is strongly suggestive of TB:

- Chronic symptoms suggestive of TB
- Physical signs highly suggestive of TB
- A positive TST
- Chest radiograph suggestive of TB
Microbiological Diagnosis

- Sputum:
  - Spontaneously expectorated
  - Induced after 3% NaCl nebulisation (MSF video: http://www.youtube.com/watch?v=sbGICTrNP8j8)
- Gastric aspirate / gastric lavage aspirate
- Nasopharyngeal aspirate
- Fine needle aspirate
- Lymph node biopsy
- Bronchoalveolar lavage
- Ear swab
- Other extrapulmonary specimens
## Xpert MTB / RIF: limitations

<table>
<thead>
<tr>
<th><strong>Lower sensitivity than culture</strong></th>
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<tr>
<td>- 58/452 (13%) vs 70/452 (16%)</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Serial testing required to optimise sensitivity</strong></th>
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<tbody>
<tr>
<td>- Of 385 children with 2 independent specimens, 58 had culture-confirmed TB; Xpert detected 34/58 (58.7%) on 1(^{st}) sputum &amp; 44/58 (75.9%) on 2 specimens</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Poor sensitivity in children with probable and possible TB</strong></th>
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<tbody>
<tr>
<td>- Xpert detected 21/28 (75%) confirmed TB, 4/47 (8.5%) highly probable TB, 0/67 (0%) possible TB</td>
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<table>
<thead>
<tr>
<th><strong>Xpert can’t be used as a rule out test on a single specimen</strong></th>
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<table>
<thead>
<tr>
<th><strong>Xpert MTB/RIF is not a <em>M. tuberculosis</em> specific test but identifies all mycobacteria within the <em>M. tuberculosis</em> complex</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- MTB complex: <em>M. tuberculosis</em>, <em>M. bovis</em>, <strong>M. bovis BCG</strong>, <em>M. africanum</em>, <em>M. microti</em>, <em>M. canetti</em>, <em>M. caprae</em>, <em>M. pinnipedi</em>, <em>M. suricattae</em>, <em>M. mungi</em></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>Xpert is currently unable to identify INH-monoresistent TB isolates</strong></th>
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<tbody>
<tr>
<td>- Drug-susceptible TB: 2RHZ/4RH vs 2RHZE/4RH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Xpert is a costly assay</strong></th>
</tr>
</thead>
</table>
Limitations of Xpert MTB/RIF in paediatric practice

- Lower sensitivity than culture (RXMCH: 13% vs 16%; Nolungile: 7% vs 8%), hence both Xpert MTB/RIF & TB culture are used in routine PTB diagnosis
- Xpert MTB/RIF is not a *Mycobacterium tuberculosis* specific test but identifies all mycobacteria within the *Mycobacterium tuberculosis* complex
- Xpert MTB/RIF is currently unable to identify INH-mono-resistant TB strains; this is currently done by the Hain line probe assay.

General principles for investigating suspected PTB

- A single Xpert MTB/RIF performed as part of workup for childhood TB
- The Xpert MTB/RIF test may be requested on any one of the following specimen types: a respiratory tract specimen (e.g. spontaneously produced sputum, induced sputum or tracheal aspirate), a gastric lavage aspirate (gastric washings) or a gastric aspirate (where no fluid is instilled in the stomach).
- Xpert MTB/RIF, when performed, will replace smear microscopy.
- Repeat Xpert MTB/RIF testing is not recommended for evaluating sputum conversion; this should be done by sputum culture
Children <13 years of age

- Submit a **single** respiratory tract or gastric (lavage) aspirate specimen (minimum volume = 2ml) for screening by Xpert MTB/RIF and TB culture.

- Request Xpert MTB/Rif, culture and susceptibility testing on the request form.

- If the Xpert MTB/RIF result is positive for MTB complex that is **rifampicin susceptible**, the TB culture will be completed, and where positive, processed by Hain line probe assay to identify INH-monoresistant isolates. **Further diagnostic specimens should not be sent to the laboratory**

- If the Xpert MTB/RIF result is positive for MTB complex that is **rifampicin resistant**, the TB culture will be completed and processed by Hain line probe assay and second-line drug susceptibility testing (DST). **A second (backup) specimen should be sent for TB culture** to maximize the chance of obtaining a viable isolate that can be used for second-line DST. Ideally, the second specimen should be obtained before the child is commenced on anti-TB therapy.

- If the Xpert MTB/RIF result is either negative for MTB or positive for MTBC but indeterminate for rifampicin, **a second specimen should be submitted for TB culture** to maximize the chance of confirming the diagnosis of TB. This second specimen should be obtained before the child is commenced on anti-TB therapy.
Adolescents ≥13 years of age

- For these adolescents the standard recommended screening approach for adults should apply. In the Western Cape this requires that 2 samples be sent simultaneously to the laboratory. One-respiratory tract specimen will be screened by Xpert MTB/RIF only (i.e. not cultured). The second specimen be processed by MGIT culture in the following situations:

  1. Indeterminate rifampicin Xpert MTB/RIF result,

  2. HIV-infected adolescents with a MTB-negative Xpert MTB/RIF result (thus the HIV status must be indicated on the request form),

  3. Adolescents who test rifampicin resistant on Xpert MTB/RIF

- If the Xpert MTB/Rif is negative, and culture is required for any other reason (such as adolescents who are being retreated for TB or who have been in contact with drug-resistant infectious TB cases), a second sample must be submitted and culture requested.
Xpert MTB/RIF for extra-pulmonary samples

- Xpert MTB/RIF will be performed on the following extrapulmonary specimens:
  - CSF samples
  - Lymph node aspirates, other tissue aspirates and pus aspirates
- Xpert MTB/RIF will NOT be performed on clear (non-purulent) pleural, pericardial or peritoneal fluids, on urine, or on stool samples
- Only one Xpert MTB/RIF assay will be performed per patient and specimen type. In other words, a patient may have an Xpert MTB/RIF on both a sputum and an extra-pulmonary sample (unless one is known to be positive – see point 3), but Xpert MTB/RIF will not be performed on two sputum (or two of the same extra-pulmonary samples)
- If a patient has a positive Xpert MTB/RIF from any site, no further Xpert MTB/RIF testing will be performed on any other specimen, regardless of specimen type. For example, a patient with a positive Xpert MTB/RIF from a sputum will not have an Xpert MTB/RIF performed on the CSF sample.
- The samples listed in point 1 will be processed for both Xpert MTB/RIF and TB culture, in order not to waste the sample, or subject the patient to repeated invasive specimen collection if the Xpert MTB/RIF is negative. If specimen volumes are too small to perform both tests, Xpert MTB/RIF will be performed in preference.
- Xpert MTB/RIF testing will replace microscopy.
  - If the Xpert MTB/RIF assay shows rifampicin resistance, a second (backup) specimen should be sent to the laboratory (if at all possible) for TB culture to maximise the chance of isolating the organism and being able to perform 2nd line susceptibility testing
Diagnosis of childhood TB by Host RNA expression signatures: Risk Scores and Sensitivity and Specificity in the Kenyan Validation Cohort, According to Diagnostic Group.

## Principles of treatment

### Aim: To cure the child & prevent emergence of drug-resistant TB

### Principles
- Combination therapy to which the bacillus is sensitive
- Short-course regimens comprising both bactericidal and sterilizing activity
- Start with an induction phase to achieve a rapid reduction of the organism load
- Continuation phase: to ensure effective eradication of dormant and intermittently metabolizing (persistent) bacilli, thus preventing disease relapse
- Optimise adherence & minimise adverse effects
### Treatment of new cases of childhood TB

<table>
<thead>
<tr>
<th>TB diagnostic category</th>
<th>Anti-TB regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive phase</td>
</tr>
<tr>
<td>HIV-negative children and no INH resistance</td>
<td></td>
</tr>
<tr>
<td>Smear-negative PTB; Intrathoracic lymph node TB; or Tuberculous peripheral lymphadenitis</td>
<td>2HRZ</td>
</tr>
<tr>
<td>Extensive PTB; Smear-positive PTB; or severe forms of extrapulmonary TB (other than TBM, miliary TB &amp; osteoarticular TB)</td>
<td>2HRZE</td>
</tr>
<tr>
<td>HIV-infected children or high INH prevalence or both</td>
<td></td>
</tr>
<tr>
<td>Smear-positive PTB; Smear-negative PTB with or without extensive parenchymal disease; or All forms of EPTB except TBM and osteoarticular TB</td>
<td>2HRZE</td>
</tr>
<tr>
<td>All children</td>
<td></td>
</tr>
<tr>
<td>Tuberculous meningitis (TBM) / Miliary TB</td>
<td>2HRZEt</td>
</tr>
<tr>
<td>HIV-infected children with TBM</td>
<td>2HRZEt*</td>
</tr>
<tr>
<td>Osteoarticular TB</td>
<td>2HRZE</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Individualized regimens</td>
</tr>
</tbody>
</table>

* All drugs given at twice the standard doses
### Approach to TB therapy & ART

<table>
<thead>
<tr>
<th>Infants and children diagnosed with TB &amp; HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any child with active TB disease should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of CD4 count and clinical stage</td>
</tr>
<tr>
<td>• HIV-infected TB patients with profound immunosuppression (CD4 count ≤200 cells/µL or &lt;15%) or MDR-TB should start ART immediately within the 1st two weeks of initiating TB treatment</td>
</tr>
<tr>
<td>• In HIV-infected children with TB meningitis the start of ART should be delayed by a minimum of 2 weeks, ideally 4-6 weeks</td>
</tr>
<tr>
<td>• The preferred first-line ART regimen for infants &amp; children &lt; 3 years of age who are taking a rifampicin-containing regimen for TB is 2 NRTIs + LPV/r but add RTV to 1:1 ratio LPV:RVT to achieve full therapeutic dose for the duration of TB treatment</td>
</tr>
<tr>
<td>• The preferred first-line ART regimen for children &gt; 3 years of age who are taking a rifampicin-containing regimen for TB is 2 NRTIs + EFV</td>
</tr>
</tbody>
</table>

Adapted from DOH of South Africa, April 2015
### Approach to TB therapy & ART (2)

<table>
<thead>
<tr>
<th>HIV-infected infants &amp; children who develop TB on ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all children, anti-TB therapy should be started immediately upon the diagnosis of TB; ART should continue</td>
</tr>
</tbody>
</table>

Make adjustments to ART regimens as needed to decrease the potential for toxicities and drug interactions;
- If on a regimen of 2 NRTIs + EFV no adjustment is required
- If on a regimen containing LPV/r, consider adding RTV to 1:1 ratio LPV:RVT to achieve full therapeutic dose
- If on another regimen e.g. salvage regimen, then an individualised decision is required

Adapted from DOH of South Africa, April 2015
Co-treating HIV infection & TB

**LPV/r-based regimens during TB treatment**
- Adults studies: Boosted LPV/r or double dose LPV/r may overcome the effects of rifampicin on LPV metabolism\(^1\)
- LPV/r boosted with additional RTV maintained LPV \(C_{\text{min}} > 1\) mg/ml in 13/15 children aged 7 mo -3.9 yrs\(^2\)
- Boosted LPV/r associated with good 6 & 12 months VL outcomes\(^3\)
- No data on boosted LPV/r in children aged < 6 months
- Double-dose LPV/r results in sub-optimal [LPV]: pre-dose [LPV] was ↓ in 80% of children with TB & 12/20 (60%) had \(C_{\text{min}} < 1\) mg/ml\(^4\)

**EFV-based regimens during TB treatment**
- EFV \(C_{\text{min}}\) was similar during & after TB medication in 15 children, baseline median age: 6.3 years\(^5\)
- Comparison of 40 children with TB and 41 children without TB confirmed that an increased dose of EFV is not required during rifampicin co-treatment\(^6\)
- Paradoxical efavirenz toxicity in patients with CYP2B6 LOF and / or NAT2 LOF polymorphisms\(^7\)

Co-treating HIV infection & TB (2)

• **Triple NRTI-containing regimens**
  - SA: virological failure in 7/15 children after 24 weeks of ART\(^1\)
  - USA: 3 NRTIs associated with delayed virologic control (< 1 log\(_{10}\) VL drop after 12wks in 86%) and poor longer term virologic control (> 400 copies/ml in 44% after 24 weeks & in 69% after 48 weeks)\(^2\)
  - Italy: Children suppressed on PI-containing regimen and switched to 3 NRTIs: 19/20 maintained VL <50 c/ml for 96 wks\(^3\)
  - No studies evaluating 3 NTRIs in TB-co-infected children

• **Rifabutin-containing TB regimens**
  - Rifabutin administered at 5mg/kg three times per week achieved sub-optimal exposure compared to adults receiving 150mg daily and was associated with severe transient neutropaenia
  - A suspension generated from 150mg capsules\(^4\)

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1 Bobat R, et al. 4\(^{th}\) IAS Conference, 2007, TUPEB053
2 Neely M, et al. 17\(^{th}\) CROI, February 2010; Poster #879
## Duration of TB treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment failure, aRR (95% CI)</th>
<th>p</th>
<th>Relapse, aRR (95% CI)</th>
<th>p</th>
<th>Death during TB treatment, aRR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of rifampicin therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Months</td>
<td>1.3 (0.4-0.41)</td>
<td>.67</td>
<td>3.6 (1.1-11.7)</td>
<td>.14</td>
<td>1.8 (1.0-3.1)</td>
<td>.03</td>
</tr>
<tr>
<td>6 Months</td>
<td>1.0 (0.4-2.8)</td>
<td></td>
<td>2.4 (0.8-7.4)</td>
<td></td>
<td>1.0 (0.6-1.6)</td>
<td></td>
</tr>
<tr>
<td>≥ 8 Months</td>
<td>1.0 (reference)</td>
<td></td>
<td>1.0 (reference)</td>
<td></td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Intermittent therapy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Initial phase daily</td>
<td>1.0 (reference)</td>
<td>.02</td>
<td>1.0 (reference)</td>
<td>.002</td>
<td>1.0 (reference)</td>
<td>.42</td>
</tr>
<tr>
<td>Initial phase thrice weekly</td>
<td>4.0 (1.5-10.4)</td>
<td></td>
<td>4.8 (1.8-12.8)</td>
<td></td>
<td>1.3 (0.7-2.3)</td>
<td></td>
</tr>
<tr>
<td>Receipt of ART</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some or all patients</td>
<td>1.0 (reference)</td>
<td>.10</td>
<td>1.0 (reference)</td>
<td>.21</td>
<td>1.0 (reference)</td>
<td>.39</td>
</tr>
<tr>
<td>None or not started</td>
<td>3.8 (0.9-16.4)</td>
<td></td>
<td>3.5 (0.5-26)</td>
<td></td>
<td>0.8 (0.5-1.5)</td>
<td></td>
</tr>
<tr>
<td>Dispersion parameter for model</td>
<td>0.3 (-0.1 to 0.7)</td>
<td></td>
<td>0.22 (-0.04 to 0.53)</td>
<td></td>
<td>0.13 (-0.02 to 0.31)</td>
<td></td>
</tr>
</tbody>
</table>

TB meningitis: A recent study suggested that the standard short intensified regimen should be administered for 9 months\(^3\)

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1. WHO & IUATBLD, Guidance for national tuberculosis & HIV programmes, 2010 (near-final draft)
• Incidence of IRIS: 10 – 20%
• Highest risk period for TB IRIS: 1st 100 days of ART
• Definitions
  – Unmasking of new TB disease
  – Paradoxical worsening of established disease
• Manifestations
  – Swinging fever
  – Worsening lymphadenitis
  – Worsening pulmonary infiltrates, respiratory failure
  – Worsening pleuritis, pericarditis, ascites
  – Intracranial tuberculomas, TBM
  – Disseminated skin lesions
  – Hepatosplenomegaly, soft tissue abscesses
• Treatment
  – Expectant
  – Glucocorticosteroids

**Post-exposure prophylaxis (PEP)**

- Post-exposure INH prophylaxis prevents progression to disease

- **Indications:**
  - HIV uninfected children aged 0-5 years
  - HIV-infected children irrespective of their age

- **Dosing instructions:** INH 10 mg/kg body weight/day for 6 months

- **Drug-resistant TB contact:** prophylaxis depends on the resistance pattern of the TB isolate
**PEP for child contacts of DR-TB**

- INH mono-resistant contacts: Rifampicin 10-15 mg/kg/day x 4 months
- Rifampicin mono-resistant contacts: INH 10 mg/kg/day x 6 months
- MDR-TB: Levofloxacin 15-20 mg/kg/day, INH 15-20 mg/kg/day & Ethambutol 15-25 mg/kg/day x 6 months
- Pre-XDR-TB or XDR-TB: INH 15-20 mg/kg/day x 6 months
- Importance of follow-up to detect the development of active TB
INH prophylaxis

• IPT uptake in children in Cape Town
  – Missed opportunities: 117/182 (64.3%) of children who developed culture-confirmed TB did not receive IPT\(^1\)
  – IPT & drug-resistant contacts\(^2\)

• IPT pre-exposure trial in infants
  – Phase II/III trial [PACTG 1041]: INH 10-20mg/kg/day vs placebo
  – INH-treated (n=273, med age=97d), placebo (n=274, med age=95d)
  – 31.5% were on ART at baseline, and 98.9% during study
  – 1\(^\circ\) end point: TB disease or death within 96-108 wks of randomization: 19.0% and 19.3% in INH and placebo groups respectively reached 1\(^\circ\) end point, p=0.93
  – Conclusion: IPT did not improve disease-free survival in infants enrolled at 3-4 months of age\(^3\)

\(^1\) Schaaf HS, et al. BMC Infect Dis 2007;7:140
INH prophylaxis (2)

IPT pre-exposure trial in children beyond infancy

- RCT (INH [10mg/kg/day] vs placebo)\(^1\)
  - n=263 > 8 wks of age [median age: 24.7 months]: 9% on ART
  - median follow-up: 5.7 mo [IQR: 2.0-9.7]
  - All-cause mortality was lower in INH arm (8% vs 16%, HR=0.46, CI:0.22-0.95, p=0.015)
  - Incidence of TB was lower in INH arm (3.8% vs 9.9%, HR=0.28, CI:0.1-0.78, p=0.005)

- Efficacy of IPT in children on ART: A recent cohort analysis suggested that IPT may offer additional protection\(^2\)

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