



# Childhood Tuberculosis: Diagnosis, Treatment and Prevention of TB in HIV-infected Children

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## Tuberculosis Worldwide

Mortality

High

Moderate

None or low



# The Problem

- One million new TB cases in children < 15 years old annually (WHO)
  - 11% of annual burden of cases
- Frequency depends on local TB/HIV epidemic, age structure, diagnostic tools, Rxn, contact investigation
- Children present with TB at any age
- Transmission to a child, results from close infected adult or adolescent contact
- TB infection → Gohn focus → regional adenopathy
- CMI halts disease progression, not functioning in HIV+

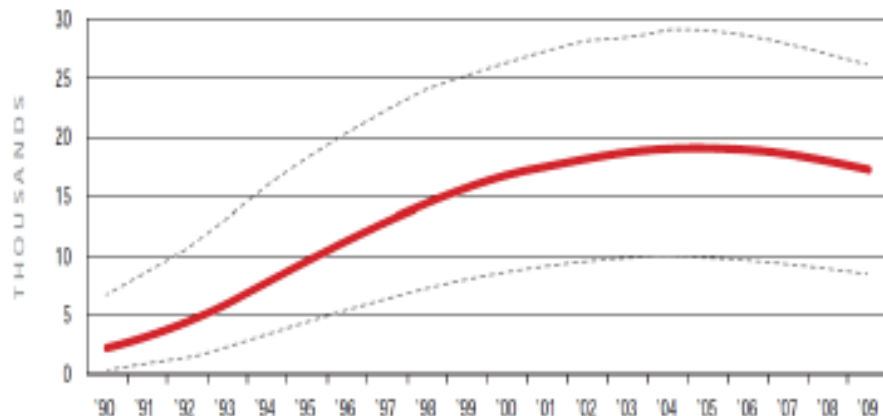
# Children Living with HIV in Latin America and the Caribbean

## Number of children living with HIV, 1990-2009

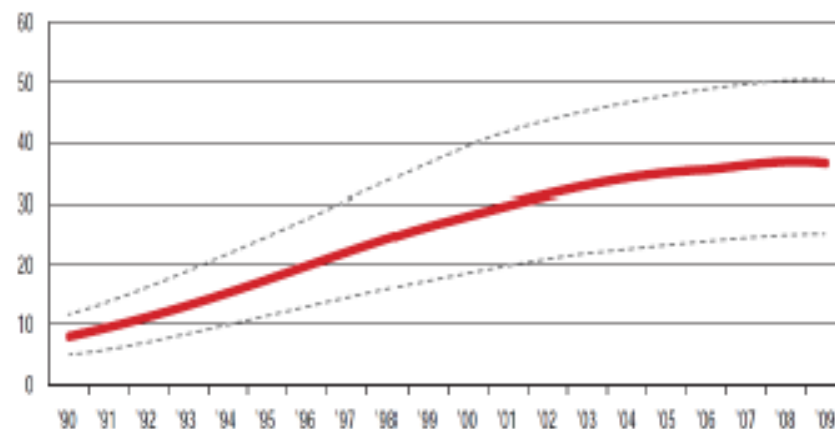
Caribbean

Central America

Number of children living with HIV



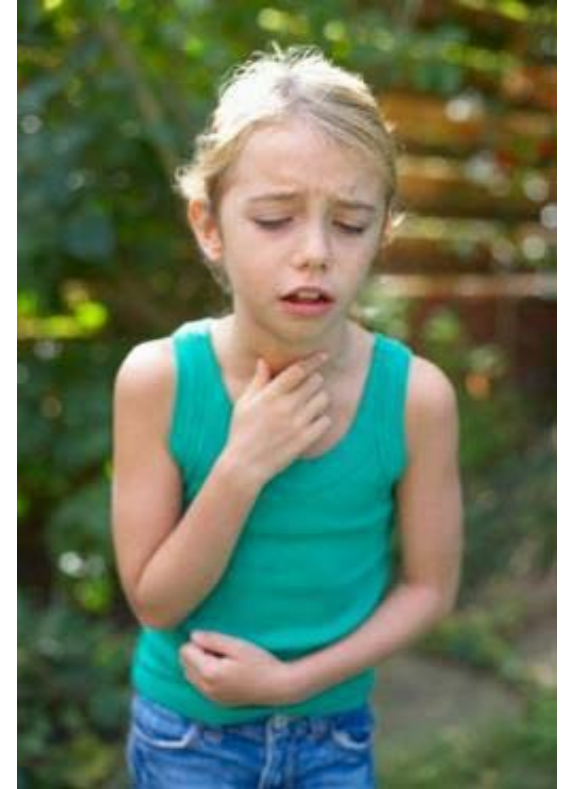
Number of children living with HIV



# **DIAGNOSIS**

# Clinical Presentations in Children

- Pulmonary TB
  - Mostly primary (not reactivation)
  - Uncomplicated
    - Unilateral adenopathy, cervical adenitis
    - Typical primary complex
      - Hilar, mediastinal adenopathy, lung opacity
  - Complicated
    - Lobar/ segmental adenopathy, bronchial compression
    - → atelectasis
    - Unilateral hyperinflation
    - Cavitation (rare)
    - TB bronchopneumonia
- Adenopathy, cervical adenitis
- Meningitis, tuberculomas
- Disseminated TB
- TB effusions
  - Pericarditis, pleuritis, peritonitis
- Spinal TB





# Presentations of TB in Children with HIV

- Depends on stage of HIV
- Early HIV infection
  - TB presentation same as in HIV negative child
- Late HIV infection
  - Disseminated TB common, eg., meningitis, miliary, TB adenopathy
- Older children with TB/HIV
  - Same presentation as in HIV+ adults
- TB/HIV co-infection have longer hospital stays, malnutrition, higher mortality
- High index of suspicion for TB in HIV+ child
- Isolate *M. tuberculosis* from expectorated sputum, lymph node, CSF, effusions, tissue

# Diagnosis of TB in HIV-infected Children



- Children do not produce sputum,
  - sputum, gastric washings usually M. tb-negative
- Careful history
  - Chronic cough > 2-3 weeks
  - Fever > 14 days, excluded common causes
  - Weight loss, failure to thrive
- Contact
  - Older household, caregiver with smear-positive TB
  - Especially HIV-infected adults



# Clinical Examination

- Uncommon, highly suggestive
  - Gibbus, vertebral TB
  - Painless, cervical adenopathy with fistula formation
- Meningitis, not responding to antibiotics
- Pleuritis
- Pericarditis
- Ascites
- Painless adenopathy without fistula
- Painless joint enlargement
- Tuberculin hypersensitivity





# Mantoux Tuberculin Skin Test

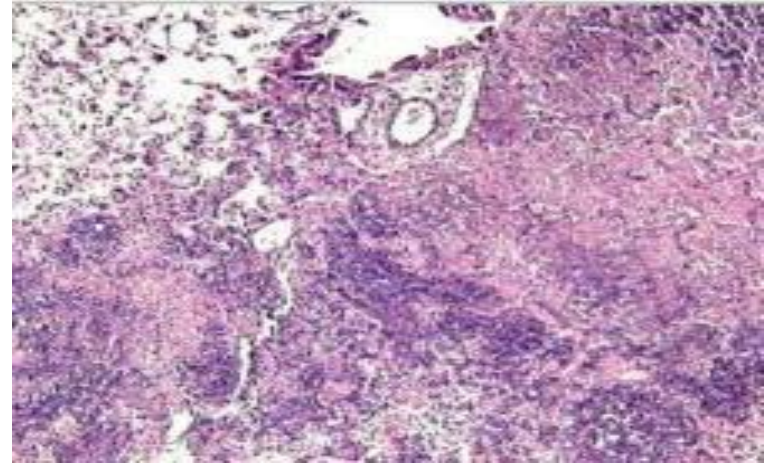


- Mantoux is positive with TB infection
- Mantoux+ with suggestive clinical symptoms is diagnostic of tuberculosis disease
  - Usually, 5 tuberculin units of PPD, trained health care workers administer test
  - High risk cases: TST  $\geq$  5 mm
  - HIV+, close contacts to active TB, malnutrition, CXR suggestive of TB
  - All other children: TST  $\geq$  10 mm induration,
    - Without regard to BCG vaccination status
  - Negative Mantoux does not exclude active TB disease, especially in HIV-infected children



# Bacteriologic Confirmation

- Bacteriologic diagnosis preferable, using available specimens, especially for
  - Suspected drug resistance
  - HIV infection
  - Complicated/ severe cases
  - Uncertain diagnosis
- Sputum in children > 10 years
- Gastric aspirates
- MTB-RIF Xpert rapid dx also applies to children



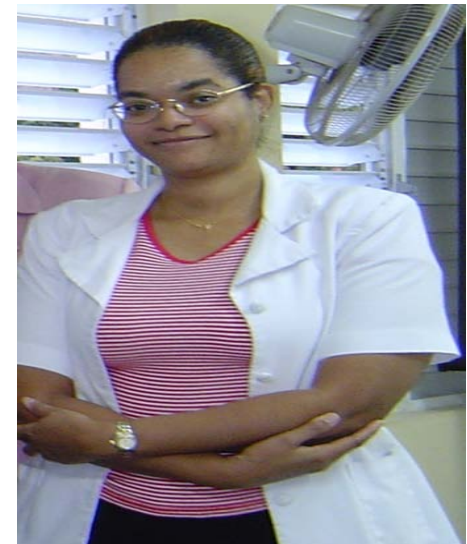
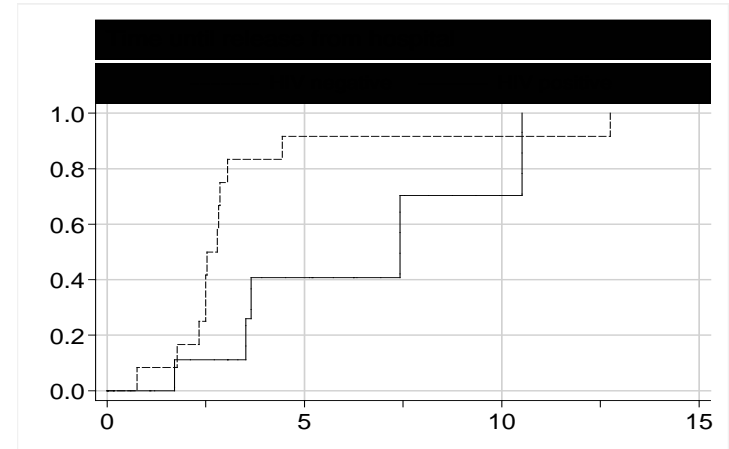
# Investigations for Pulmonary and Extra Pulmonary TB

- CXR changes of TB
  - Persistent lung opacities
  - Collapse consolidation
  - Hilar/mediastinal adenopathy
  - Opacification does not improve after antibiotics
  - Pleural effusions
- Histology, other special investigations (EPTB), CSF for TB meningitis
- PCR, interferon gamma release assay (IGRA), need more research for TB diagnosis in children
- CT, MRI's, bronchoscopy not usually recommended in children



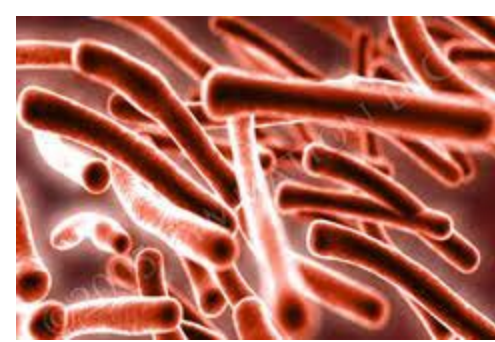
# HIV and TB Co-infections in Jamaican Children

- Significant increase in TB and TB/HIV co-infections at UHWI over four years
- 24 TB cases; All had BCG vaccine
- HIV-infected statistically more likely to be
  - Older
  - Have failure to thrive
  - Digital clubbing
  - Hepatomegaly
  - Splenomegaly
  - Generalized adenopathy
  - Negative Mantoux skin tests
- Appropriate in house-anti-TB Rxn, > 2 mos
- Death more likely and hospital stay longer in HIV infected vs., non-infected
- Household family members with active TB in 12 cases



Geoghagen M, Farr JA, Hambleton I, Pierre R, Christie CDC. *WIMJ*, 2004;53;5:339-345.

# TREATMENT



# Treating Childhood TB/HIV

- New smear negative PTB and less severe EPTB
  - 2 mos INH, RIF PZA plus 4 mos INH, RIF
- New smear positive TB, new smear negative TB with extensive parenchymal involvement, Severe EPTB, or Severe concomitant HIV disease
  - 2 mos INH, RIF, PZA, ETH plus 4 mos INH, RIF
- Miliary TB and TB meningitis: use higher doses
  - 2 mos INH, RIF, PZA, STR plus 4 mos INH, RIF (WHO), or
  - 2 mos INH, RIF, PZA, STR (or ETH) plus 5-7 mos INH, RIF (AAP)
- Previously treated smear positive TB, with relapse, treatment after interruption, treatment failure
  - 2 mos INH, RIF, PZA, ETH, STR plus 5 mos INH, RIF, ETH
- MDR TB
  - Special regimens, after consultation



# Management of HIV-related TB

- Cotrimoxazole prophylaxis
  - Daily, prolongs survival and reduces respiratory infections and hospitalizations
  - All HIV+ children with advanced immune-suppression should be placed on cotrimoxazole
- Antiretroviral therapy
  - In HIV+ child, priority is to commence anti-TB drugs
  - Many drug-drug interactions between ARV's and RIF
  - Similar adverse reactions in anti-TB drugs and ARV's
  - When to start, not optimally determined for children
  - Consider degree of immune-suppression and child's progress during anti-TB Rxn

# Timing of ART after anti-TB Treatment with Rifampin-containing regimen

- Extra Pulmonary TB
  - Start ART 2-8 wks after anti-TB treatment
- Pulmonary TB and lymph node TB
  - If clinical Mnx:
    - Start ART 2-8 wks after anti-TB Rxn or
    - Delay ART until anti-TB Rxn completed
  - CD4 values available
    - Severe/advanced immune deficiency
      - Start ART 2-8 wks after anti-TB Rxn
    - Mild or no immune deficiency
      - Delay ART until anti-TB Rxn is completed
- ART's:
  - < 3 years -- Triple NRTI 1<sup>st</sup> line regimen d4T /AZT + 3TC+ ABC, or 2 NRTI's + NVP
  - > 3 years: triple NRTI 1<sup>st</sup> line d4T/ AZT + 3TC +ABC, or standard 1<sup>st</sup> line 2 NRTI's + EFV





# Special Considerations

- Immune reconstitution
  - Exacerbation of symptoms, signs, CXR manifestations after anti-TB therapy
  - Self limited, consider steroids
- Steroids for TB meningitis, miliary TB, airway obstruction by TB lymph glands, pericarditis
  - Improves survival, reduces mortality
  - Taper the dose after 4 weeks

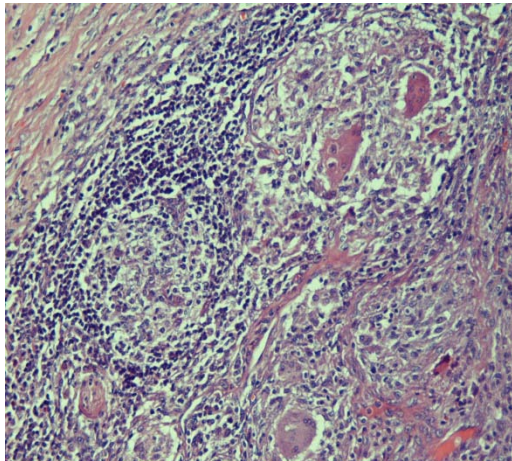
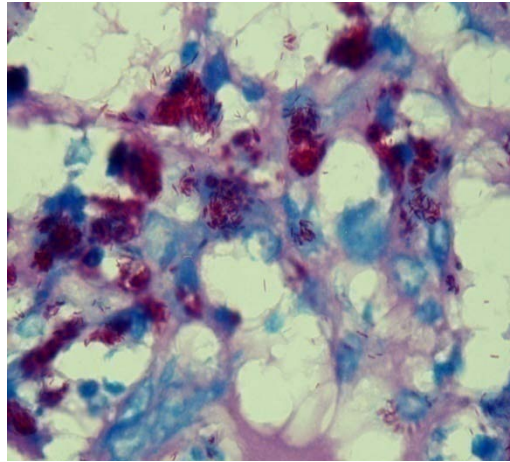
# Adherence

- Educate children and caregivers about TB and importance of completing therapy
- Support for care giver/family, record doses on Rxn card
- Treatment should be free, give fixed dose drugs
- Hospitalise children with severe TB for intensive management
  - Meningitis
    - Local vasculitis, tuberculoma, raised ICP and hydrocephalous
  - Miliary TB
  - Respiratory distress
  - Spinal TB
  - Severe adverse events, eg., hepatotoxicity
  - Adherence questionable

# Monitoring During Treatment

- Symptom assessment
- Adherence
- Adverse events, eg., LFT's, haematology, rashes, IRIS
- Weight and medication adjustment for wt. gain
- Adherence and reviewing treatment card
- Followup sputum for AFB smear microscopy (if +)
  - Followup CXR's not routine, slow recovery
  - Non-response → drug-resistance, complications, non-adherence, other?

# Isoniazid-resistant Disseminated *M. tuberculosis* in a Jamaican Infant with HIV/AIDS



**I Singh-Minott, RB Pierre, O Olugbuyi, J Dunkley-Thompson, D Haughton, CDC Christie. *West Indian Med J* 2008;57(3):298-302.**

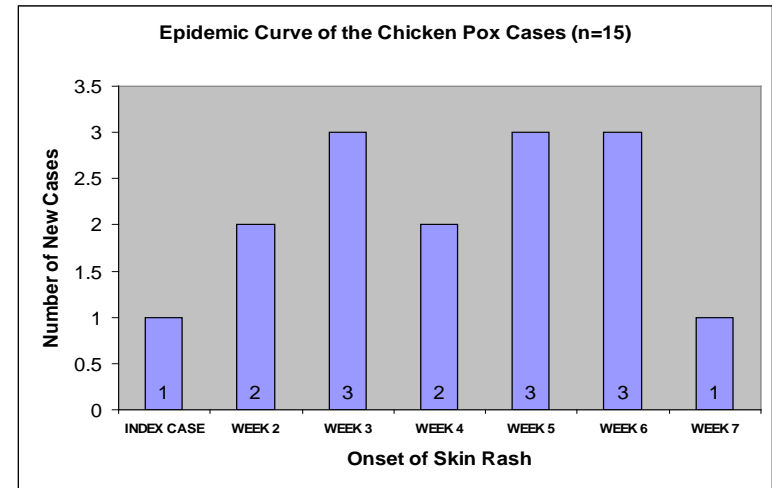
**PREVENTION**

# Child Contact

- Newly infected children with TB at high risk for miliary TB, meningitis if no preventive Rxn
- Close contact screening and management, adults family member, day-care contact with infectious TB
- Mantoux skin test-positive children:
  - If well (no symptoms, Normal CXR and growth), give INH preventive therapy x 6 months
  - If unwell, evaluate and treat for TB, if present
- Mantoux skin test negative children:
  - If well, IPT x 2 months, repeat Mantoux skin test
  - If positive at 2 months, continue IPT for 6-9 months
  - If negative at 2 months, discontinue IPT

# Tuberculosis, Scabies and Chicken Pox Outbreaks in an Orphanage for Children with HIV/AIDS in Jamaica

- Concurrent outbreaks of tuberculosis (N=4), chicken pox (N=15), scabies (N=14) among 24 children residing in an AIDS orphanage
- Emphasizes need for:
  - Immunizations
  - Screening of staff and clients
  - Infection control
  - Education



Geoghagen M, Pierre R, Evans-Gilbert T, Rodriguez B, Christie CDC.  
*WIMJ*, 2004;53;5:346-351.

# Intensive Case Finding and Prevention in Children with HIV – TB Screening

- Children living with HIV who do not have poor weight gain, fever, or current cough -- are unlikely to have active TB
- Children living with HIV who have poor weight gain, fever, or current cough, or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of age.
  - ***Strong Recommendation, low quality of evidence***



# INH Regimen and Duration

- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom screening and have no contact with a TB case should have 6 months of IPT (10 mg/kg/day)
- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB should receive 6 months of IPT, if the evaluation shows no TB disease
  - ***Strong recommendation, moderate evidence***
- All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional 6 months
  - ***Conditional recommendation, moderate evidence***

# BCG lymphadenitis and Immune Reconstitution Syndrome in HIV-infected Children on Antiretroviral Therapy in Jamaica

- Three children with HIV infection developed BCG adenitis **after** initiation of highly active antiretroviral therapy (HAART)
- All “rapid progressors” with severe HIV/AIDS
- “Immune reconstitution syndrome”
- BCG vaccination should continue, per WHO policy



# BCG Vaccination in Children

- HIV-infected children who received BCG vaccine at risk for disseminated BCG disease
- Vaccinate:
  - HIV-uninfected children in high prevalence HIV+ populations
  - Infants born to women with unknown HIV status
  - HIV-exposed infants, asymptomatic, unknown HIV status
- Do not vaccinate:
  - Known HIV+ children, asymptomatic
  - Unknown HIV status in symptomatic children
  - Known HIV infected children, symptomatic

Are we going to see

# THE END OF TB

in our lifetimes?

*A call from the millennium children of the Eastern Mediterranean Region*



Thank you