DISCLOSURE slide

• Nothing to disclose
• CASE history PT 1  slides made by Emily Schaaf MD during her fellowship rotation at Childrens Hospital 2015
• I have her permission to show these slides on our mutual pt
HIV and TB coinfection

- Case reports will illustrate difficulty in diagnosis of TB with HIV
- Complications of IRIS with Antiretroviral therapy
- Review global burden of HIV and TB in children
Case History

• 10 year old girl who flew with her father from Ethiopia to the US 2 days prior to admission

• Two days before her flight, she began having fevers, chills, and right leg/hip pain.
  – She was seen by a doctor in Ethiopia and given a shot in the buttock for this pain.

• Shortly after arriving in the US, she was brought to Minneapolis Children’s Hospital.
Past Medical History

• Treated with frequent courses of antibiotics for bronchitis
• Severe episode of chicken pox 1-2 years ago which left significant scars
• Has not been hospitalized or had any blood transfusions
• Vaccination status unknown – record from Somalia shows 1 MMR vaccine given
Social/Family History

• Social History:
  – Had been living with her mother and 2 younger siblings (ages 2 and 9) initially in Somalia, then in Ethiopia. Her father was in the US working since 1996, but goes back and forth.
  – Her mother died of liver cancer in 1/2015 in Ethiopia (9 months earlier)
  – She stayed with her aunt until her father was able to arrange to fly back to Ethiopia to bring her and her 2 siblings back to the US

• Family History:
  – Mother treated for pulmonary TB in 2012 with 3 medications via observed therapy
    • Other children were checked for TB by sputum samples at that time
    • Infant (younger brother) was breastfeeding at the time, and he received TB treatment as well
    • Father reports he was screened for TB when he arrived in the US in 1996
  – No family members with HIV.
  – Mother was admitted to a hospital in Ethiopia where she was diagnosed with liver cancer.
Physical Examination

- Exam:
  - General: alert, comfortable, thin appearing, no distress.
  - HEENT: normal
  - Neck: supple with no lymphadenopathy
  - CV: RRR without murmur
  - Pulm: Crackles heard in middle lung fields.
  - Abd: Normal. No hepatosplenomegaly.
  - GU and back: normal
  - Ext: reluctant to abduct or externally rotate right hip. Otherwise normal exam of lower extremities.
  - Skin: hyperpigmented scars over body from healed varicella
  - Neuro: normal
Case History

• Admitted to the hospital

• Lab testing:
  – Rapid malaria detection assay and blood smear negative
  – CBC: WBC 10.7 with 61%N, 5%bands, 30% L, 9%M
  – ESR 13. CRP elevated at 23.7 mg/dL
  – UA normal
  – Blood and urine cultures no growth

• Imaging:
  – X-rays of right hip, pelvis, tibia, fibula, foot: normal
  – CXR performed
Enlargement of the right hilum is nonspecific and may relate to underlying lymph node enlargement or infiltrate. TB is in the differential.
Hospital Course

• Started ampicillin for community acquired pneumonia

• MRI spine, pelvis and right lower extremity obtained:
  – normal with no osteomyelitis, mass or abnormality
  – Findings consistent with recent injection in buttock

• By the next day, her hip and leg pain went away completely and did not recur.
ID consultation

• RML pneumonia, with right hilar enlargement
• Risk for TB given maternal history of pulmonary TB and recent death from liver cancer

• 3 hypertonic saline induced sputum samples for AFB stain and culture
• PPD
• Quantiferon
• HIV testing, hepatitis B serology
• Negative pressure room
Area of right lower lobe consolidation in conjunction with right hilar and mediastinal lymphadenopathy and multiple bilateral subcentimeter pulmonary nodules. A granulomatous inflammatory or infectious process such as tuberculosis is a consideration -mildly prominent aortocaval lymph nodes, nonspecific
Hospital Course

- Continues on ampicillin
- Fevers resolve. Hip pain remains fully resolved.
- Feels back to normal.
- Respiratory viral PCR panel shows rhinovirus and RSV
- Collecting 3 induced sputum samples

- HIV Ag/Ab combo: reactive
- CD4 count 33 (2%)
Hospital Course

• HIV RNA PCR: **55,800 copies/mL**

• Discussed with her father
  – Unknown how she could have acquired HIV
  – Mother’s death 9 months earlier in Ethiopia was attributed to liver cancer, but possibly HIV?
  – He and other 2 children will come to clinic for testing
TB evaluation

• Maternal history of pulmonary TB and cause of death not fully certain
• RLL infiltrate with tiny pulmonary nodules
• Hilar and mediastinal lymphadenopathy
• New diagnosis of HIV with CD4 count of 33

• PPD: 0mm
• Quantiferon Gold: negative
• 3 induced sputum AFB smears: negative

What to do next?
Hospital Course

• BAL with AFB stain and culture, MTB PCR, along with bacterial and fungal cultures, and pneumocystis stain.
• BAL done to diagnose and rule out AIDS related Opportunistic pathogens.
• Started empiric TB treatment with rifabutin 300mg x 3 times weekly (lowered dose due to atazanavir interaction),
• Isoniazid 300mg, pyrazinamide 750mg, and ethambutol 600mg
• while awaiting AFB culture results which were negative after 8 weeks
• Started HIV therapy 3 days later in hospital with
  – atazanavir (Reyataz) 200 mg PO daily boosted with (norvir) ritonavir 100 mg PO daily,
  – Tenofovir with emtricitabine (truvada) 300mg-200 mg PO daily
• TMP/SMX prophylaxis three times a week for Pneumocystis
Follow Up

• Has seen Dr Belani for follow up in clinic
  – Father and siblings tested negative for HIV
  – Siblings both had positive Quantiferon testing with normal CXR
  – Both siblings on INH LTBI therapy x 9mos completed
  – Patient has Repeated Quantiferon x 3 and still negative

• AFB cultures negative at 2 months – 4 drug regimen stopped
  – Continued INH for ?LTBI for 1 year

• Continues on her ART Therapy ,adherent  and Viral load undetectable(10/2016 CD4  27% or 477

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<th>Date</th>
<th>HIV RNA PCR</th>
<th>Absolute CD4</th>
<th>CD4 %</th>
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<tr>
<td>10/13/15</td>
<td>55,800</td>
<td>33</td>
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<tr>
<td>11/10/15</td>
<td>143</td>
<td>69</td>
<td>8%</td>
</tr>
<tr>
<td>1/8/16</td>
<td>45</td>
<td>145</td>
<td>8%</td>
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<tr>
<td>1/29/16</td>
<td>Detected, &lt;20</td>
<td>231</td>
<td>11%</td>
</tr>
<tr>
<td>2/25/16</td>
<td>Undetected</td>
<td>312</td>
<td>15%</td>
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</table>
Follow up Imaging

CXR findings improved over the next 2 months
Growing well and gaining weight, in 5th grade
AFB smear and culture

- Obtaining expectorated sputum from children for AFB detection is difficult and is of low yield.
  - 15% or less for microscopic examination
  - 30% or less for culture

- Sputum induction has higher yield than expectorated sputum in children, and is performed via administration of aerosolized saline followed by suctioning.
  - In a study of 250 children (median age 13 months), sputum induction was found to be safe and effective in children as young as one month of age.
  - In two studies, outpatient sputum induction yielded culture results comparable to or better than inpatient gastric aspiration.

- Early morning gastric contents collected from a fasting child contain sputum swallowed during the night.
  - Cultures of gastric aspirate specimens are positive for TB in only 30 to 40% of cases.
  - Smears are even less reliable, with positive results in as few as 10% of cases
QuantiFERON®-TB gold in-tube is not Useful for Diagnosing Active Tuberculosis in HIV/AIDS Patients with Severe Immunodeficiency: Results from Brazil

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Abstract

**Purpose:** To assess interferon gamma release assay (IGRA) and tuberculin skin test (TST) performances in the diagnosis of active tuberculosis (TB) in adults with HIV/AIDS with different degrees of immunodeficiency.

**Methods:** Cross-sectional study conducted with 90 HIV/TB-coinfected adults, São Paulo, Brazil. TB diagnosis was established based on the presence of positive sputum smear, culture, or anatomic-pathological examination. The participants responded to a questionnaire and were submitted to physical examination, chest x-ray (CRX), serum CD4+ and CD8+ T cell count, TST, and IGRA (QuantiFERON®-TB Gold In Tube, Cellestis, Carnegie, Australia).

**Results:** Characteristics of 90 HIV/TB-coinfected individuals: male (60.0%), white (54.4%), single (57.3%), and average age 39 (±10.8) years with pulmonary TB (45.6%) and average CD4+ T-cell count (198.92 cells/mm3). TST was positive in 25.56%, and IGRA was positive in 65.56%. IGRA performance was better when compared to TST (p<0.001) and was able to diagnose TB with 93.75% probability when CD4+ ≥ 187 cells/mm³; TST showed similar efficacy when CD4+ ≥ 500 cells/mm³.

**Conclusion:** IGRA exhibited better performance for TB disease diagnosis in HIV-infected individuals with severe immunodeficiency when compared to TST. Nevertheless, both tests may exhibit false-negative results in this type of population. Despite the fact that IGRA has better performance than TST in the diagnosis of active TB in patients with HIV/AIDS, the practical utilization of the method seems to be limited and should be considered only for patients with CD4+ ≥ 187 cells/mm³.
Optimizing the Detection of Recent Tuberculosis Infection in Children in a High Tuberculosis–HIV Burden Setting

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Abstract

Rationale: Children who are young, malnourished, and infected with HIV have significant risk of tuberculosis (TB) morbidity and mortality following TB infection. Treatment of TB infection is hindered by poor detection and limited pediatric data.

Objectives: Identify improved testing to detect pediatric TB infection.

Methods: This was a prospective community-based study assessing use of the tuberculin skin test and IFN-γ release assays among children (n = 1,343; 6 mo to <15 yr) in TB-HIV high-burden settings; associations with child characteristics were measured.

Measurements and Main Results: Contact tracing detects TB in 8% of child contacts within 3 months of exposure. Among children with no documented contact, tuberculin skin test and QuantiFERON-TB Gold In-Tube positivity was greater than T-SPOT.TB. Nearly 8% of children had IFN-γ release assay positive and skin test negative discordance. In a model accounting for confounders, all tests correlate with TB contact, but IFN-γ release assays correlate better than the tuberculin skin test (P = 0.0011). Indeterminate IFN-γ release assay results were not associated with age. Indeterminate QuantiFERON-TB Gold In-Tube results were more frequent in children infected with HIV (4.7%) than uninfected with HIV (1.9%), whereas T-SPOT.TB indeterminates were rare (0.2%) and not affected by HIV status. Conversion and reversion were not associated with HIV status. Among children infected with HIV, tests correlated less with contact as malnutrition worsened.

Conclusions: Where resources allow, use of IFN-γ release assays should be considered in children who are young, recently exposed, and infected with HIV because they may offer advantages compared with the tuberculin skin test for identifying TB infection, and improve targeted, cost-effective delivery of preventive therapy. Affordable tests of infection could dramatically impact global TB control.

Keywords: HIV; latent tuberculosis infection; pediatrics; IFN-γ release tests; tuberculin test
• Smear negative pulmonary TB represents 30-60% of all pulmonary TB cases, according to region.
  – In Brazil, 24-30% of cases of pulmonary TB in adults are smear negative.
• Included adult patients with a diagnosis of pulmonary TB and a sputum, induced sputum or BAL culture positive for TB.
• 198 patients
  – 34.8% were smear positive
  – 65.2% were smear negative
• Cough, dyspnea and hemoptysis were less frequent in smear negative patients.
TB-HIV Co-infected Cases: United States and Minnesota, 2005-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of TB-HIV cases in MN:</th>
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<tbody>
<tr>
<td>2005</td>
<td>12</td>
</tr>
<tr>
<td>2006</td>
<td>11</td>
</tr>
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<td>2007</td>
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<td>2011</td>
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<td>7</td>
</tr>
<tr>
<td>2013</td>
<td>7</td>
</tr>
<tr>
<td>2014</td>
<td>6</td>
</tr>
</tbody>
</table>

- Percent coinfection-MN
- Percent coinfection-US

No. of TB-HIV cases in MN:
2005 – 12
2006 – 8
2007 – 12
2008 – 11
2009 – 7
2010 – 6
2011 – 3
2012 – 6
2013 – 4
2014 – 4
# Tuberculosis Cases by HIV Status and Place of Birth, Minnesota, 2010-2014

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>Foreign-Born Cases No. (%)</th>
<th>U.S.-Born Cases No. (%)</th>
<th>Total No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Negative</td>
<td>546 (92)</td>
<td>126 (91)</td>
<td>672 (92)</td>
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<tr>
<td>Positive</td>
<td>21 (4)</td>
<td>2 (1)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Refused</td>
<td>4 (1)</td>
<td>2 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Not Offered</td>
<td>22 (4)</td>
<td>9 (6)</td>
<td>31 (4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>593 (100)</strong></td>
<td><strong>139 (100)</strong></td>
<td><strong>732 (100)</strong></td>
</tr>
</tbody>
</table>

* Alive at diagnosis
Global HIV and tuberculosis

- In 2014 - 9.6 million new cases of TB
- 1.2 million in HIV infected
- 1.5 million deaths from TB, 0.4 million in HIV
- Worldwide 13% with TB infected with HIV with 31% mortality
- TB is common AIDS defining illness (no.3 in Europe)
- HIV with TB 23/100 Child years in SA vs 1/100 in UK
- TB as a cause of death in HIV children(x3-x6 mortality) underestimated as often not diagnosed
- Risk and Mortality in MDR TB very high in HIV
No one with HIV should die from Tuberculosis

Both can be treated with ARV and Anti TB therapy

• Leading cause of mortality (1000 with HIV & TB die each day)
• Gaps in delivery of care despite decades of knowledge of TB and HIV synergy
• Silos of care in most nations, no comprehensive clinics
• Lack of ARV therapy in TB cases
• Lack of Isoniazid/LTBI chemoprophylaxis in HIV
• No new drug trials for TB in HIV patients vice versa
• 36% reduction with efforts 2004-2011 but not enough
HIV and TB Coinfection

2008 WHO Three (FIVE) I’s strategy

• Intensified Case Finding
• Isoniazid Prophylaxis
• Infection control
• Integrated care for coinfected
• Immediate initiation of antiretroviral therapy

Above Endorsed but not acted upon universally
With few pockets of success – NYC, Baltimore, USA & Rio, Brazil
HIV and TB coinfection

STOP TB Partnership’s Global TB plan 2016-2020
Zero Tuberculosis Deaths By 2050 declaration
Zero TB Cities Project(2014)
WHO END TB strategy 2015

• Mass Scale up of TB screening, diagnosis, and treatment of 90% HIV patients
• ARV treatment for HIV patient at any CD4 count soon after diagnosis
• Better diagnostic strategies to detect Tb in HIV Co infection
• Research on Drug-Drug interaction in TB & ARV therapy
Diagnosis of TB in HIV infection

- Congenital TB more common in infants born to HIV positive mothers with active TB
- Paucity of Clinical symptoms or non specific symptoms in coinfected children
- Atypical Chest XRAY findings, CT more sensitive
- Anergy causing False negative TST and IGRA assay,
- No sputum production can make diagnosis difficult-
- No gold standard only clinical criteria
- Extrapulmonary (60% of cases) and miliary and disseminated TB more common in age < 4 years
Treatment Guidelines HIV and TB CoInfection

- Survival improved if ART started early after TB therapy
- All HIV with active Tb start TB rx immediately
- All HIV with active TB treat
- Start ART –
  - CD4<50 within 2 weeks after TB therapy
  - CD4>/=50 to 200 with severe clinical TB disease within 2-4 weeks
    (CD4>200 moderate recommendation)
  - CD4>50-500 with no severe clinical TB >2-4 weeks delay after TB therapy start but within 8-12 weeks
    (CD4 >500 moderate recommendation)
Treatment Guidelines HIV and TB CoInfection

• HIV Infected pregnant women with active TB start ART soon as possible
• HIV infected children
• In MDR TB cases start ART 2-4 weeks after confirmation of resistance with second line TB therapy
• Rifabutin is preferred with ART,
• As rifampin a potent enzyme inducer is contraindicated (drug interaction with PIs and other ARTs)
• Rifapentine based LTBI regimen also contraindicated with ART
• DOT strongly recommended as in others with active TB
• Ethionamide for CNS TB and ethambutol both indicated in HIV
IRIS and Co-Infection Therapy

Restoration of immune competence by ART with exuberant host response to Tb bacilli/antigens

Unmasking – symptoms of active disease start after ART
  (TB at ART 6.2/100 child yrs, after ART 0-90/100 child yrs)
Paradoxical-worsening of TB clinical symptoms after ART
  (19% in children with low CD4 counts in Thailand 4 weeks after ART)

IRIS- mild, moderate or severe (life threatening)
IRIS not an indication to discontinue ARV or TB therapy
Severe IRIS (CNS TB, etc) use Corticosteroids
IRIS after BCG in 15% of HIV infected
IRIS in Children

Risk factors for IRIS- (seen usually in first 90 days of Rx)

• CD4<50
• C4 increase on ART
• Decrease in viral loads on ARV
• Severity of TB disease
• <30 day interval between TB Therapy and ARV
• Symptoms- Fever, lymphadenopathy, Pleural effusion, Respiratory distress, Cerebral tuberculosis exacerbation (with increased ICP)
CASE report 2 - TB and AIDS with IRIS

- 8 yr old female from Zambia arrived on tourist visa in 1998
- Admitted Xmas 1999 with fever weight loss, chills and cough
- Persistent cough from sept treated as Asthma in school clinic as no insurance
- PPD Positive
- Diagnosed with Bilateral Cavitary TB and ileal Tb and splenic lesions
- head CT normal
CASE report IRIS

- HIV ab Positive
- HIV RNA PCR 500,000 copie/ml
- CD4 absolute count 32
- Anemic, hyopalbuminemic
- Hospitalised for 5 months in Isolation room
- TB treatment started 12/28/1999
- HIV treatment started 1/22/2000
TB and AIDS with IRIS

- Sputum smear positive for 5 months until May 2000, INH resistant Mtb
- Treatment for TB started 12/27/99 IV amikacin x 40 days, PO INH, RIF, EMB, PZA
- HIV treatment 1/22 Nelfinavir, Stavudine and Lamivudine
- Rifabutin started 1/22, rifampin discontinued
- TB medications x 18 mos emb, pza and Rifabutin
Case Report 2 IRIS

- HIV viral Load <400 12/2000
- CD4= 444 2000 /27%
- High fevers after ARV started with development of bilateral cervical adenopathy
- Needle aspiration –afb smear positive,culture negative 5/2000
- Fevers resolved
- Spontaneous drainage from cervical nodes june 2000 with cheesy material rt and later left side
Case Report 2 with IRIS

• Multiple surgical excision both rt and left side neck for debridement, excision of nodes in 2000, 2001
• Reconstruction of extensive keloid scars 2009
• Residual Hypoglossal nerve damage during excision and infection/inflammation
• Lymph node cultures all negative for Mtb
• Now a 25 yr old college graduate with full time job
Paradoxical reaction

• The incidence of paradoxical reactions in the recent literature in non HIV infected cases is 6-30%, with 60-80% of these in extrapulmonary and disseminated TB with median time of onset at 60 days after initiation of anti TB therapy. Similar to IRIS in HIV infected

• Due to ? Lower baseline lymphocyte counts at initial diagnosis of Tb with surge in lymphocyte count at time of Paradoxical reactions

• Surgical intervention in 60%, or recurrent aspiration and/or steroids
LTBI and HIV Coinfection

Remember ARV may unmask LTBI-Conversion of TST or IGRA assay-negative to positive

HIV strongest risk factor or progression from LTBI to Active disease

• Criteria for positive TST in HIV is >/=5 mm
• LTBI Rx irrespective of age in HIV
• After Excluding TB disease(CXR, biopsy, BAL, sputum, cultures)
• LTBI Rx also in Pregnant women and children with HIV
• INH and rifapentine NOT recommended for LTBI RX with ART
• Rifampin NOT recommended
• Rifabutin with dose adjustment can be used ,no clear guidelines
LTBI and HIV coinfection

- INH 10mg/kg /dose daily x 9 months (270 doses) in children and adults with HIV with Vitamin B6 supplementation is preferred
  (or twice weekly INH DOT (76 doses ) in HIV infected adults )

Monitoring on LTBI therapy

- (check for Hepatitis B & C coinfection
- Baseline Liver function tests (AST, ALT, Bilirubin)
- Monthly evaluation for adherence, adverse effects and symptoms of TB disease and hepatitis (on Isoniazid)
- Discontinue INH if LFT’s 3X normal (monitor with CXR)
Prevention

- BCG vaccine-Live attenuated M bovis strain
- Given at birth in most countries (not USA)
- Global efficacy about 50% (protection against for severe disseminated and CNS TB)
- Can decrease TB risk in adulthood by 70% in some studies
- Dissemination of BCG (BCGosis) in 1% of HIV positive
- 15% with IRIS after BCG
- **WHO now recommends NO BCG vaccine in HIV infection**
- (15 fold increase in TB in France & Sweden in children of immigrant parents after BCG universal vaccination stopped)
- 12 New vaccines in development (needed asap)
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