TB & HIV: The Terrible Twins

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Epidemiology of HIV-Related Tuberculosis

- One third of the world's population is infected with *MTB*
- ~ 9 million new cases of active TB in 2010

SA >500/100000 vs. US 4/100000

Global TB Report 2014
Epidemiology of HIV-Related Tuberculosis

- Worldwide, 14.8% of TB patients are HIV co-infection
- TB is the most common cause of death among patients with AIDS responsible for about a third of AIDS deaths

Sub-Saharan Africa: ~50-80% of Patients with TB are HIV coinfected.

Global TB Report 2014
TB and HIV

- TB is essentially an Immunologic disease with host tissue damage occurring during immune response to MTB.
- HIV by “interfering” with the immune system alters the response to TB and fuels TB.
- Converts TB into an “new” disease almost unrecognizable by clinicians familiar with TB in the pre-HIV era.
- Understanding the interactions between TB and HIV is critical to the management of both HIV and TB.
Outline of Presentation

- Impact of TB on HIV
- Impact of HIV on TB

- Presentation of TB in coinfected
- Diagnosing TB in the coinfected
- Treatment of TB in the coinfected

- Timing of ART in TB
- Immune Reconstitution Inflammatory Syndrome
Impact of TB on HIV

- TB increases risk of HIV progression and death esp. with untreated HIV disease
- Immune activation → increases expression of HIV co-receptors on CD4 cells -CCR5 and CXCR4- increase substrate for viral infection and virus production
- TB coinfection associated with higher HIV viral loads

Impact of HIV on TB

- HIV mimics TB.
- Alters pathogenesis of TB
- Causes rapid progression from infection to disease
- Alters clinical presentation.
- Alters radiological appearance.
- Affects diagnostic tests.
  - Smear, culture
  - Histology
- Affects treatment: drug toxicity, drug interactions,
- Response to treatment- paradoxical reactions.
- Higher relapse of TB (~4 increased)
- Increased mortality (~4 fold)
- Impacts on response to treatment (regression of symptoms)

< 50% of cases diagnosed ante mortem
HIV

Decreased CMI

Rapid progression to Disease

↑extrapulmonary involvement

atypical radiographic manifestations

Paucibacillary Disease
## Risk of TB Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Increase in risk of TB disease</th>
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<tbody>
<tr>
<td>HIV/AIDS</td>
<td>113-170</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.1</td>
</tr>
<tr>
<td>“old TB” on CXR</td>
<td>13.6</td>
</tr>
<tr>
<td>CRF</td>
<td>25</td>
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<tr>
<td>Other conditions</td>
<td>3-16</td>
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</table>
TB and AIDS

Without HIV lifetime risk of TB in infected person is ~ 10%

With HIV lifetime risk is 50%
Risk of TB is increased at **ALL** stages of HIV infection

- HIV affects CD4 cells both quantitatively and qualitatively
- TB risk doubled in the first year after HIV seroconversion
- Following effective immune reconstitution with ART the risk remains above the background risk of the general population.

Symptoms of TB in HIV

Cardinal symptoms are same irrespective of HIV status

- Cough
- Fever
- Night sweats
- Weight loss

sensitivity ~70-80%  - 20% no symptoms but has TB
specificity ~ 50%  - 50% symptoms but no TB

Low specificity due to other OIs with similar symptoms
Symptoms of TB in HIV

How reliable is the absence of symptoms to exclude TB: Important to exclude TB prior to initiating ART or IPT

Meta analysis of a symptom screening tool in HIV in RLS:
  – Prevalence 5% ⇒ NPV 97.7%
  – Prevalence 20% ⇒ NPV 90%

Symptoms are usually due to an immune response

Asymptomatic subclinical TB not uncommon in regions of high co-infection

Active TB may be missed by symptom screen alone.

Clinical Presentation of TB

- Varies widely - generally similar to HIV uninfected
- Presentation often reflects level of immunosuppression
- Earlier in HIV → classic reactivation-disease
- Advanced immunosuppression similar to primary TB
Impact of HIV on Organ system involvement by TB

HIV positive
HIV negative

Percent (%)

Pulm Dx
Extra-Pulm Dx
Both

Organ System involvement is related to level of immunosuppression

Common Sites of Extrapulmonary TB

- **Lymph node disease:**
  - peripheral - cervical > axillary > inguinal
  - central - mediastinal > hilar, intra-abd.

- **Disseminated disease**

- **Serositis - pleural, pericardial > ascites**

- **CNS - meningitis, tuberculoma**

- **Soft tissue abscesses**
The chest radiograph is the cornerstone of diagnosis for pulmonary TB.

Upper-lobe infiltrates and cavities typical of reactivation TB is seen with higher CD4 counts (>350 cells/μL).
Reactivation (Post-Primary/Secondary) TB
Reactivation (Post-Primary/Secondary) TB
The chest radiograph is the cornerstone of diagnosis for pulmonary TB.

Primary disease characterized by intrathoracic lymphadenopathy & lower-lobe infiltrates is seen with more immunosuppression (CD4 <100).
AIDS/TB Chest X-ray

Bilateral hilar/mediastinal LAN
RML Infiltrate

Pleural Effusion
PCP: 6 days into Cotrimoxazole
Pathology of Miliary TB

Lung

Spleen
The chest radiograph is no longer the cornerstone for diagnosis of PTB.

Chest radiographs may appear normal in up to 21% of culture-positive TB with CD4 <50.

Role of the CXR in diagnosing TB

- Sensitive ~76%
- Specificity ~68%  

Risk of over or under diagnosing

When should do CXR:
- Complications: pneumothorax, effusion, hemoptysis.
- Coexistent lung disease.
- Smear negative patient with strong suspicion of TB.
Diagnosing TB

- Symptoms
- Signs
- Ancillary Investigations:
  - CXR
  - Hb
  - Albumin
  - ESR
  - CRP

Sensitive but not specific
Unhelpful for diagnosis
Helpful for monitoring response to Rx
Diagnosing TB: Detect organism or DNA

- Microscopy
- Culture
- PCR based assays
AFB Smear- Microscopic examination for AFB

- Historically mainstay for the diagnosis of TB
- High specificity
- Rapid turn around time
- Low sensitivity - non-cavitary Dx & HIV (~ 35%)
- Require a minimum of 10,000 AFB/ml of sputum for smear to be positive
Culture

- Makes definitive diagnosis of TB
- Detects fewer AFB: limit 10-100 org/mL (100-1000x more sensitive than smear)
- Time to positivity depends on org. load- median time 3/52
- Expensive, need skill technologists, infrastructure
- Estimated ~ 15% of reported TB cases are culture negative
  - 1 MGIT culture identifies 71% cases
  - 2 MGIT increase yield to 88% (17% increase)
  - 3 MGIT identifies 98% cases (10% more cases)

Depends on the number of times the culture is repeated.
Culture- Important diagnostic tool in paucibacillary Disease

When should you culture:

- TB suspects with negative GeneXpert test
- To confirm GeneXpert showing rifampicin resistant
- To check susceptibility to other drugs
- Patient failing treatment despite RIF susceptible- high suspicion of resistance to other drugs

National Tuberculosis Management Guidelines 2014
2 different molecular based tests available

- The Gene Xpert (GXP)
- The Line Probe assay
Gene Xpert

- Automated PCR based
- Replaced sputum smear as rapid screening tool
- Allows for rapid diagnosis in SND processing time ~ 2 hours.
- Uses sputum - minimal pre-processing prior to loading instrument
- Validated for CSF, gastric aspirate, L/N aspirate and tissue (i.e. pleural biopsy)
- Instrument is a closed system → low risk for contamination, minimal expertise required, low risk for human error.
- Detects TB & RIF
Gene Xpert

- Not a monitoring tool – high false positive in previously treated TB- 27% GXP positive after 6/12 ATT
- Cannot identify XDR TB
- Detects a minimum of ~130 org/ml sputum
## Gene Xpert

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<tr>
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<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Smear positive disease</td>
<td>98.2%</td>
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</tr>
<tr>
<td>Smear negative disease – one sample</td>
<td>72.5%</td>
<td>99.2%</td>
</tr>
<tr>
<td>Smear negative disease – 3 samples</td>
<td>90.2%</td>
<td></td>
</tr>
<tr>
<td>Rifampicin Susceptibility</td>
<td>97.6%</td>
<td></td>
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<tr>
<td>Rif resistance</td>
<td>98.1%</td>
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NEJM 2010; 363: 1005
Line Probe Assay

- Approved for direct testing on smear positive specimens and isolates from solid and liquid culture for smear neg.
- PCR based – identifies MTB and specific mutations that confer RIF and INH resistance
- Results within 48 hours in the lab & 7 days in health facilities.
- Used as guide whilst awaiting phenotypic tests- 6-8wks
- Labour intensive, prone to contamination, human error, highly trained staff, special equipment & infrastructure
SA TB programme

Approach to the diagnosis of TB centered on GXP due to the high burden of HIV and MDR-TB
ALL PEOPLE WITH SYMPTOMS OF TB
Collect one spot specimen (sputum; gastric washing/lavage; lymph node fine needle aspirate; pleural biopsy; cerebro spinal fluid).
Sputum collection must be under supervision

Xpert positive
Rifampicin susceptible

Treat as Drug Susceptible TB
Start on Regimen 1

If patient has Pulmonary TB
Collect one spot sputum specimen for microscopy

If smear positive
Conduct contact screening/source investigation

Xpert positive
Rifampicin unsuccessful

Treat as Drug susceptible TB
Start on Regimen 1

Collect one spot specimen for microscopy, LPA, or culture and DST

Xpert positive
Rifampicin resistant

Refer to MDR-TB treatment initiation site
Conduct contact screening/source investigation
ALL PEOPLE WITH SYMPTOMS OF TB

Collect one specimen (sputum, gastric washing, lavage, lymph node fine needle aspirate, pleural biopsy).
Sputum collection must be under supervision

**Sputum negative**

Consider the HIV status of the patient

**If HIV positive**

- Hi risk look hard
- Re-assess the patient clinically
- Do a chest x-ray (if available)
- Collect another specimen for culture and LPA or DST

**X-ray findings consistent with TB**

- Treat as Drug susceptible TB
  - Start Regimen 1
- Follow up and review LPA/ DST results

**If drug susceptible TB**

- Continue treatment
- Start treatment if not already on treatment
- Conduct contact screening/ source investigation

**If drug resistant TB**

- If on Regimen 1, stop treatment
- Refer to MDR-TB treatment initiation site
- Conduct contact screening/ source investigation

**If HIV negative**

- Treat with antibiotics
- Re-assess the patient after one week

**If well and asymptomatic**

- No further follow up is required
- Advise to return when symptoms recur

**If HIV negative**

- Treat with antibiotics
- Re-assess the patient after one week

**If still symptomatic and sick**

- Consider other diagnosis
- Refer to hospital for further investigation
Treatment

- 6/12 standard therapy adequate
- Longer treatment may ↓ relapse – no RCT
- ART is recommended during TB therapy regardless of the CD4 cell count - ↓ mortality, ↓ HIV progression.
- Overlapping toxicities & drug-drug interactions with ARVs requiring dose modification, alternate regimens and alternate rifamycins.
TB while on ART

- Use standard first line treatment:
  - TDF/3TC/EFV
  - EFV is preferred over NVP
- On LPV/r second line ART:
  - Double dose LPV/r
Toxicities

- S/E twice as common in HIV coinfected (26 vs. 13%)
  - hepatotoxicity,
  - Peripheral Neuropathy
  - Vomiting
  - Arthralgia
  - Rash

- Peripheral neuropathy – INH, stavudine, didanosine

- DILI - INH, rifampin, pyrazinamide, NRTIs, NNRTIs, and PIs.

Timing of ART in TB

- CD4 ≤ 50 - ART within 2wks of TB treatment
  - Reduced AIDS progression and mortality

Immediate ART arm (CD4 < 50)
Immediate ART arm (CD4 ≥ 50)
Early ART arm (CD4 < 50)
Early ART arm (CD4 ≥ 50)

Immediate within 2/52
Early: 8-12 weeks

ART 8-12/52 CD4<50
ART within 2/52 CD4<50
Immediate/early ART: CD4≥50

Figure 2. Time to New AIDS Defining Illness or Death
NEJM 2011; 365:1482–1491.
Timing of ART in TB

- **CD4 >50** - ART after intensive phase of TB treatment.
  - Reduced overlapping toxicity, reduce risk of IRIS

- **Early ART requires**
  - Coordination between TB and HIV care
  - Vigilance for drug toxicities
  - Adherence to high pill burden
  - Vigilance for IRIS

What is IRIS?

Aberrant manifestation of immune reconstitution → pathogen specific inflammatory response triggered by:

- Initiation HAART
- Re-initiation HAART
- Change to more active HAART

Two forms: Paradoxical, Unmasking
Paradoxical IRIS

Clinical deterioration while on effective ATT

Development of new or worsening clinical symptoms or signs of TB

- Fever, night sweats, weight loss
- Respiratory symptoms
- Enlarged lymph nodes
- Worsening radiologic features
- New or worsening CNS manifestations
Paradoxical IRIS

Associated with:
- Low CD4
- High viral load
  - Short interval between TB Rx and ART initiation - 2-3 months of ART

Diagnosis of exclusion: other O/Is, poor adherence, MDR

Managed symptomatically, severe IRIS consider prednisone

ART continued as far as possible.

TB IRIS is seldom fatal
Unmasking IRIS

New diagnosis of TB after initiation of ART in a patient who, prior to commencing HAART, had no features to suggest TB.

Sub-clinical or unrecognised infections “unmasked” by the emergence of pathogen-specific immune responses.
Conclusion

- HIV has converted TB into a more complex disease
- Impacts virtually all aspects of the disease
- Diagnostic challenges → resort to molecular methods for rapid diagnosis
- Management complicated by drug interactions, overlapping toxicities
- Response to treatment confounded by IRIS
- Despite all, TB in the coinfected can be cured