Tuberculosis, HIV, Diabetes

- Overlapping epidemics
- More frequent TB disease
- Atypical clinical aspects
- More severe TB disease
- Interfere with therapy, specially in HIV + patients
TB and HIV Data

- Worldwide, 10.4 million people with TB disease in 2016
- Top five countries (56% of cases): India, Indonesia, China, Philippines, Pakistan
- Around 13% (1.03 million) estimated to be HIV-positive
- 1.3 million TB deaths in 2016; 374 000 in HIV infected individuals. 85% in the WHO Africa and South-East Asia region
- However,
  - the number of people dying from HIV-associated TB peaked at 570 000 in 2004 and had fallen to 374 000 in 2016 (a 34% decrease)
  - Decrease of TB incidence by an average of 1.5% per year since 2000, being now 18% lower than in 2000

WHO, Global Tuberculosis Report, 2017
HIV Prevalence in Adults and Tuberculosis Notification Rates

Nunn, Nat Rev Immunol, 2005
Prevalence of HIV among adults aged 15 to 49, 2017
By WHO region

Prevalence (%) by WHO region

- Eastern Mediterranean: 0.1 [<0.1–0.1]
- Western Pacific: 0.1 [<0.1–0.2]
- South-East Asia: 0.3 [0.2–0.4]
- Europe: 0.4 [0.4–0.4]
- Americas: 0.5 [0.4–0.6]
- Africa: 4.1 [3.4–4.8]

Global prevalence: 0.8% [0.6–0.9]

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

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Estimated TB incidence rates, 2017

Incidence per 100,000 population per year:
- 0–24
- 25–99
- 100–199
- 200–299
- ≥300
- No data
- Not applicable
Estimated HIV prevalence in new and relapse TB cases, 2017
Countries in the 3 high burden country list for TB, TB/HIV and MDR-TB in the period 2016-2020
Evolution of TB deaths

Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000–2017. Shaded areas represent uncertainty intervals.
Tuberculosis in Patients Dying in Zambia

125 autopsies on patients who died in University Hospital in Lusaka, Zambia, 2012-13

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=125)</th>
<th>HIV + (n=101)</th>
<th>HIV – (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB (all forms)</td>
<td>78 (62%)</td>
<td>66 (66%)</td>
<td>12 (50%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Extrapulmonary*</td>
<td>35 (28%)</td>
<td>33 (33%)</td>
<td>2 (8%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Pulmonary only</td>
<td>43 (34%)</td>
<td>33 (33%)</td>
<td>10 (42%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* All also had pulmonary tuberculosis

26% of tuberculosis were not diagnosed ante-mortem

Many Groups are at Higher Risk for HIV Infection and TB Infection

- Foreign born
- Prisoners
- Homeless/marginally housed
- Drug Users
- Racial/ethnic minorities
- Recent contact to TB
- Lower socio-economic status
Tuberculosis and Diabetes

- **Pathophysiology** – diabetes, especially when poorly-controlled, causes relative immunocompromise and increases likelihood of reactivation of TB
- **Epidemiology** – dramatic increase of diabetes
- **Demographics** – diabetes disproportionately affects lower socioeconomic groups and ethnic minorities that also have higher prevalence of TB
- **Hidden epidemic** – estimated that ¼ of people with diabetes don’t know they have it
### DM Burden
- 422 million people living with DM in 2015
- 3.7 million people died of DM in 2012
- Prevalence increased from 4.7% in 1980 to 8.5% in 2014

### TB Burden
- 10.4 new tuberculosis cases worldwide in 2016
- 1.3 million people died of TB in 2016
Map 3.2 Estimated total number of adults (20-79 years) living with diabetes, 2017

- <100 thousand
- 100-500 thousand
- 500 thousand-1 million
- 1-2 million
- >2 million
Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)

- **North America & Caribbean**
  - 2045: 62 million
  - 2017: 46 million
  - Increase: 35%

- **Middle East & North Africa**
  - 2045: 82 million
  - 2017: 39 million
  - Increase: 110%

- **Europe**
  - 2045: 67 million
  - 2017: 58 million
  - Increase: 16%

- **South & Central America**
  - 2045: 42 million
  - 2017: 26 million
  - Increase: 62%

- **Africa**
  - 2045: 41 million
  - 2017: 16 million
  - Increase: 156%

- **South East Asia**
  - 2045: 151 million
  - 2017: 82 million
  - Increase: 84%

- **Western Pacific**
  - 2045: 183 million
  - 2017: 159 million
  - Increase: 15%

- **WORLD**
  - 2045: 629 million
  - 2017: 425 million
  - Increase: 48%
Total Number of Adults with Diabetes by Region

Ogurtsova, Diabetes Res Clin Prac, 2017
Diabetes and Tuberculosis - the converging pandemics

- TB “high burden” by WHO (n=22)
  80% of TB cases in 2008

- China
- India
- Brazil
- Bangladesh
- Indonesia
- Pakistan
- Russia

- Diabetes
  Ten Countries with highest number of people with diabetes in 2010

Global Prevalence of Diabetes

Estimated new TB cases (all forms) per 100,000 population

- < 24
- 25-49
- 50-99
- 100-299
- ≥300
- No estimate
HIV kills TB-specific CD4 cells and impairs macrophages activation

Reduced numbers of lung-homing CD4 cells

Defective granuloma formation

Loss of control of infection

Geldmacher, Curr Opin HIV AIDS 2012
Normoglycemic vs. Hyperglycemic

Natural history of tuberculosis

• Primary TB infection occurs when tubercle bacilli are inhaled and settle in the lung of immunologically naive hosts
• Local and disseminated disease is controlled in most individuals
• In average, 10% of subjects will develop the disease:
  – 5% in the first years, 5% throughout whole life
  – Risk is increased in case of altered immune fonctions
• Reinfection can occur, specially with immune deficiency
Risk Factors for Progression from LTBI to Active Disease.

**Table 2. Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Disease.**

<table>
<thead>
<tr>
<th>Risk Factor and Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced, untreated HIV infection</td>
<td></td>
</tr>
<tr>
<td>Moss et al.(^10)</td>
<td>9.9 (8.7–11)</td>
</tr>
<tr>
<td>Pablos-Méndez et al.(^16)</td>
<td>9.5 (3.6–25)</td>
</tr>
<tr>
<td>Close contact with a person with infectious tuberculosis(^\dagger)</td>
<td></td>
</tr>
<tr>
<td>Ferebee(^17)</td>
<td>6.1 (5.5–6.8)</td>
</tr>
<tr>
<td>Radiographic evidence of old, healed tuberculosis that was not treated</td>
<td></td>
</tr>
<tr>
<td>Ferebee(^17)</td>
<td>5.2 (3.4–8.0)</td>
</tr>
<tr>
<td>Treatment with ≥15 mg of prednisone per day(^\ddagger)</td>
<td></td>
</tr>
<tr>
<td>Jick et al.(^18)</td>
<td>2.8 (1.7–4.6)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td></td>
</tr>
<tr>
<td>Pablos-Méndez et al.(^16)</td>
<td>2.4 (2.1–2.8)</td>
</tr>
<tr>
<td>Treatment with TNF-α inhibitor</td>
<td></td>
</tr>
<tr>
<td>Askling et al.(^19)</td>
<td>2.0 (1.1–3.5)</td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td></td>
</tr>
<tr>
<td>Pablos-Méndez et al.(^16)</td>
<td>1.7 (1.5–2.2)</td>
</tr>
<tr>
<td>Weight ≥10% below normal</td>
<td></td>
</tr>
<tr>
<td>Palmer et al.(^20)</td>
<td>1.6 (1.1–2.2)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Bates et al.(^21)</td>
<td>1.5 (1.1–2.2)</td>
</tr>
</tbody>
</table>

\(^*\) Relative risk was calculated as described in Horsburgh.\(^5\) CI denotes confidence interval, HIV human immunodeficiency virus, and TNF tumor necrosis factor.

\(^\dagger\) Relative risk was calculated for the first 3 years after exposure.

\(^\ddagger\) The drug was taken for 2 weeks or more.
Risk factors for tuberculosis

• Exposure
  • Household contacts
  • Foreign-born from TB endemic regions, ethnic minorities
  • Congregate settings- shelters, prisons, hospitals
  • Poverty, homeless, IV drug users

• Impaired immunity (host factors)
  • Substance abuse: IVDA, Smoking, Heavy ETOH
  • Nutritional status: underweight, Vit D
  • Systemic disease: silicosis, HIV, DM, renal dz; gastric bypass, celiac sprue
  • Immune compromise: HIV, steroids, TNF inhibitors, transplant

• Age
TB as an Opportunistic Infection

• Risk progression from LTBI to TB disease in HIV infected (7-10% annual risk) is much greater than for HIV-negative patients (5%-10% lifetime)

• Increased risk for TB at all levels of immuno-suppression, although relative risk and disease differ in different CD4 ranges

• Increased risk for TB disease begins early after HIV infection
Treatment for LTBI

• Treating LTBI reduces the risk that *M. tuberculosis* infection will develop into TB disease
• Certain groups have higher risk for developing TB disease after infection; should be treated
• Before beginning treatment for LTBI
  – Exclude diagnosis of TB
  – Ensure patient has no history of adverse reactions resulting from prior LTBI treatment
Pathogenesis and Natural History

Wood, Int J Tuberc Lung Dis, 2010
TEMPRANO: Immediate or Deferred ART Initiation ± IPT for African Pts

- Randomized, controlled, unblinded, multicenter (Ivory Coast), 2 x 2 factorial

Pts with HIV infection and CD4+ cell count < 800 cells/mm³ who did not meet WHO criteria for initiating ART* (N = 2056)

- Immediate ART† (n = 515)
- Immediate ART† + IPT‡ (n = 518)
- Deferred ART§ (n = 511)
- Deferred ART§ + IPT‡ (n = 512)

*WHO criteria evolved during the study (updates 2006, 2010, 2013). †ART initiated immediately following randomization. ‡IPT = 300 mg daily isoniazid initiated 1 mo after enrollment and terminated 7 mos after enrollment. §Deferred until meeting WHO criteria for initiating ART.

- Pts in the treatment arms well matched at baseline
  - First-line ART primarily EFV + TDF/FTC (68% to 71%) or LPV/RTV + TDF/FTC (22% to 24%)
- Median duration of follow-up: 29.9 mos

TEMPRANO: Immediate vs Deferred ART Initiation and IPT Delivery for African Pts

Effect of ART on Tuberculosis: Haiti

Kaplan-Meier Estimates of Being Tuberculosis Free

No at risk:

Early 380  
302  
140  
20

Standard 393  
288  
122  
16

p value = 0.0125 by log rank test

Severe, NEJM, 2010
START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial

HIV-positive, ART-naive adults with CD4+ cell count > 500 cells/mm³ (N = 4685)

- Composite primary endpoint: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)
- Mean follow-up: 3 yrs; median baseline CD4+ cell count: 651 cells/mm³; median baseline HIV-1 RNA: 12,759 copies/mL
- Median CD4+ cell count at initiation of ART for deferred group: 408 cells/mm³

Immediate ART
ART initiated immediately following randomization
(n = 2326)

Deferred ART
Deferred until CD4+ cell count ≤ 350 cells/mm³, AIDS, or event requiring ART
(n = 2359)

Study closed by DSMB following interim analysis
## START: Primary Endpoint Components With Immediate vs Deferred ART

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Immediate ART (n = 2326)</th>
<th>Deferred ART (n = 2359)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AIDS-related event</td>
<td>14 (0.20)</td>
<td>50 (0.72)</td>
<td>0.28 (0.15-0.50)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Serious non-AIDS–related event</td>
<td>29 (0.42)</td>
<td>47 (0.67)</td>
<td>0.61 (0.38-0.97)</td>
<td>.04</td>
</tr>
<tr>
<td>All-cause death</td>
<td>12 (0.17)</td>
<td>21 (0.30)</td>
<td>0.58 (0.28-1.17)</td>
<td>.13</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6 (0.09)</td>
<td>20 (0.28)</td>
<td>0.29 (0.12-0.73)</td>
<td>.008</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1 (0.01)</td>
<td>11 (0.16)</td>
<td>0.09 (0.01-0.71)</td>
<td>.02</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>3 (0.04)</td>
<td>10 (0.14)</td>
<td>0.30 (0.08-1.10)</td>
<td>.07</td>
</tr>
<tr>
<td>Non-AIDS–defining cancer</td>
<td>9 (0.13)</td>
<td>18 (0.26)</td>
<td>0.50 (0.22-1.11)</td>
<td>.09</td>
</tr>
<tr>
<td>CVD</td>
<td>12 (0.17)</td>
<td>14 (0.20)</td>
<td>0.84 (0.39-1.81)</td>
<td>.65</td>
</tr>
</tbody>
</table>

HIV, TB and ART

Lawn, J Infect Dis, 2011
Does ARV reduce Tuberculosis incidence to background rate in HIV + Patients?

A national observational cohort study from England, Wales, and Northern Ireland

Tuberculosis incidence by months on antiretroviral therapy in the national HIV cohort in England, Wales, and Northern Ireland

Gupta, Lancet HIV, 2015
Tuberculosis incidence in national HIV cohort compared with that in background HIV-negative population in 2009

Data shown for patients with HIV receiving antiretroviral therapy and with most recent CD4 count of at least 500 cells per µl

Gupta, Lancet HIV, 2015
Association between DM and TB

• Study in US and foreign-born persons attending the San Francisco Tuberculosis Clinic.

• Between 2005 and 2012:
  – 4371 (19.0%) individuals without evidence of TB infection,
  – 17,856 (77.6%) with latent tuberculosis
  – 791 (3.4%) with tuberculosis.

• The prevalence of diabetes was the highest among individuals with tuberculosis and increased during the study period.

• There was a disproportionate association of TB and DM relative to LTBI and DM among Filipinos in individuals older than 45 years old.

Suwanpimolkul, PLoS ONE 2014
Association between DM and TB

Suwanpimolkul, PLoS ONE 2014
DM is associated with Tuberculosis in Indonesia

Figure: Fasting blood glucose concentrations according to body mass index among TB patients (A) and control subjects (B).

Alisjabanah B, Int J Tuberc Lung Dis, 2006
The prevalence of diabetes and prediabetes in TB and non-TB.

<table>
<thead>
<tr>
<th></th>
<th>TB</th>
<th>non-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.3*</td>
<td>4.7</td>
</tr>
<tr>
<td>Male</td>
<td>64*</td>
<td>4.2</td>
</tr>
<tr>
<td>Female</td>
<td>6.0</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>B Prediabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Male</td>
<td>7.4*</td>
<td>6.1</td>
</tr>
<tr>
<td>Female</td>
<td>7.4</td>
<td>7.1</td>
</tr>
</tbody>
</table>

- **C Diabetes**
  - <30: 1.2, 1.1
  - 30-39: 1.4, 1.4
  - 40-49: 3.4, 3.4
  - 50+: 8.3*, 6.8

- **D Prediabetes**
  - <30: 2.1, 2.1
  - 30-39: 5.8*, 5.8
  - 40-49: 7.1, 7.1
  - 50+: 9.6, 9.6

- **E Diabetes**
  - <18.5: 2.9, 2.9
  - 18.5-23.9: 5.8*, 6.8
  - 24+: 7.7, 7.7

- **F Prediabetes**
  - <18.5: 8.2, 8.2
  - 18.5-23.9: 6.4, 6.4
  - 24+: 9.3*, 9.3

Note: *p < 0.05 for difference with non-TB controls

DM and Tuberculosis

From: Diabetes Mellitus and Latent Tuberculosis Infection: A Systemic Review and Metaanalysis
Is Diabetes a Risk Factor for LTBI?

From: Diabetes Mellitus and Latent Tuberculosis Infection: A Systemic Review and Metaanalysis
Diabetes is consistently a risk factor for developing active TB

Study | Sample Size | RR       | 95% CI
--- | --- | --- | ---
Cohort | Cases/Pop |     |     |     |
John, 2001 [32] | 166/1251 | 2.24 | (1.38, 3.65) |
Summary |     | 3.11 | (2.27, 4.26) |
Heterogeneity: |     | I² =39% (0%,81%) |
Case-control | Cases/Cntrs |     |     |     |
Mori, 1992 [34] | 46/46 | 5.20 | (1.22, 22.1) |
Buskin, 1994 [35] | 151/545 | 1.70 | (0.70, 4.30) |
Rosenman, 1996 [36] | 148/290 | 1.16 | (0.58, 2.32) |
Pablos-Mendez, 1997 [8] | 5290/37366 | 1.61 | (1.50, 1.73) |
Brassard, 2006 [31] | 386/38600 | 1.50 | (1.15, 1.90) |
Coker, 2006 [37] | 334/334 | 7.83 | (2.37, 25.9) |
Jick, 2006 [33] | 497/1966 | 3.80 | (2.30, 6.10) |
Perez, 2006 [11] | 3847/66714 | 1.65 | (1.50, 1.81) |
Heterogeneity: |     | I² =68% (34%,85%) |
Other* | Cases/Pop |     |     |     |
Ponce-de-Leon, 2004 [9] | 581/21230 | 6.00 | (5.00, 7.20) |
Dyck, 2007 [25] | 1118/791673 | 0.99 | (0.80, 1.23) |
Heterogeneity: |     | I² =99% (99%,100%) |

Effect of DM on the Risk of developing TB

• Prospective cohort study: 17 715 Taiwanese persons
• DM significantly associated with TB
• Risk of TB increased as the number of complications of DM increased (P = .0016), with >3-fold risk if ≥2 DM-related complications (OR 3.45; 95% CI, 1.59–7.50).
• Similarly, the risk increased among those with higher Diabetes Complications Severity Index scores (P = .0002).

Baker, CID, 2012
Severity of diabetes increases the risk for TB

42,000 adults >65 years old from Hong Kong*

Diabetes with HbA1C≥7 compared to <7; odds for developing active PTB were 3.63 (1.79-7.33)*

Improve Screening !
TB and HIV Screening

Globally in 2016, 57% of notified TB patients had a documented HIV test result, up from 55% in 2015 and a 19-fold increase since 2004. In the WHO African Region, where the burden of HIV-associated TB is highest, 82% of TB patients had a documented HIV test result. A total of 476,774 TB cases among HIV-positive people were reported and of these, 85% were on antiretroviral therapy (ART).

The highest proportion of HIV-positive cases among those tested for HIV was the WHO African Region (34%). Overall, the percentage of TB patients testing HIV-positive has been falling globally since 2008. This decline is evident in all WHO regions with the exception of the WHO European Region, where the proportion of TB patients testing HIV-positive has increased from 3% in 2008 to 15% in 2016.
Percentage of new and relapse\textsuperscript{a} TB cases with documented HIV status, 2004–2017, globally and for WHO regions\textsuperscript{b}

\textsuperscript{a} The calculation is for all cases in years prior to 2015.

\textsuperscript{b} Countries were excluded if the number with documented HIV status was not reported to WHO.
Global numbers of notified new and relapse cases known to be HIV-positive (black), number started on antiretroviral therapy (blue) and estimated number of incident HIV-positive TB cases (red), 2004–2016. Shaded areas represent uncertainty bands.

WHO, 2017 report
HIV is not diagnosed in TB; ART cannot be started

FIGURE 7.2 Percentage of TB patients with known HIV status, 2004–2011

Globally, Only 40% TB cases HIV status known
Screening for diabetes in new TB patients can be highly effective (India)

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Number of TB patients whose DM status was ascertained [a]</th>
<th>Number with previously known DM [b]</th>
<th>Number of DM newly diagnosed [c]</th>
<th>Additional Yield [c/(b+c)*100]</th>
<th>Number needed to screen (NNS) [(a−b)/c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Smear Positive Pulmonary TB</td>
<td>307</td>
<td>87</td>
<td>70</td>
<td>45%</td>
<td>3.1</td>
</tr>
<tr>
<td>New Smear Negative Pulmonary TB</td>
<td>37</td>
<td>4</td>
<td>7</td>
<td>64%</td>
<td>4.7</td>
</tr>
<tr>
<td>New Extra-pulmonary TB</td>
<td>128</td>
<td>15</td>
<td>21</td>
<td>58%</td>
<td>5.3</td>
</tr>
<tr>
<td>Relapse</td>
<td>35</td>
<td>12</td>
<td>8</td>
<td>40%</td>
<td>3.3</td>
</tr>
<tr>
<td>Treatment after Failure</td>
<td>19</td>
<td>7</td>
<td>2</td>
<td>22%</td>
<td>6.0</td>
</tr>
<tr>
<td>Treatment after Default</td>
<td>26</td>
<td>3</td>
<td>7</td>
<td>70%</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Overall, number of TB patients needed to screen (with HbA1c) in order to detect one new case of diabetes was just 4.
Screening for DM in persons with TB

• Every patient with TB over the age of 18 should be screened for DM
  – A fasting plasma glucose > 125 mg/dl = DM
  – A random plasma glucose > 200 mg/dl = DM
  – A Hemoglobin A1c > 6.5% = DM

• Abnormal glucose values should be repeated in patients who have no symptoms of DM
Clinical Presentation in HIV Patients

• Presentation depends on immune state
• Extra-pulmonary disease occurs in 40 to 80%
• CNS TB develops in 5 to 10% of HIV + patients (< 2% of HIV – patients)
• Bacteremia more frequent
## Clinical presentation

<table>
<thead>
<tr>
<th></th>
<th>Late HIV (CD4 &lt; 200)</th>
<th>Early HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulm / Extra pulm</td>
<td>50/50</td>
<td>80/20</td>
</tr>
<tr>
<td>Chest X ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lymph node</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>- Lower lobes</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>- Cavitation</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Anergy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Smear +</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Clinical Characteristics of TB Associated with DM

• A population-based study in adults diagnosed with TB between 2000 and 2013 in Barcelona.
• Of 5849 TB patients, 349 (5.9%) had DM.
• Factors associated with DM were:
  – being Spanish-born (OR 1.46, 95%CI 1.11-1.96),
  – age ≥40 years (OR 6.08, 95%CI 4.36-8.66),
  – cavitary patterns on chest X-ray (OR 1.42, 95%CI 1.08-1.86),
  – experiencing more side effects due to anti-tuberculosis treatment (OR 1.86, 95%CI 1.28-2.64)
  – hospitalization at the time of diagnosis (OR 1.8, 95%CI 1.40-2.31).

Moreno Martinez, Int J Tuberc Lung Dis 2015
Clinical Characteristics of TB Associated with DM

Detection rates of chest radiograph signs between three groups.

Notes: Group I: HbA1c level <7%; Group II: HbA1c level from 7% to 9%; Group III: HbA1c level >9%. *p<0.05 compared with Group I, *p<0.05 compared with Group II.
The impact of diabetes on tuberculosis infection

Hodgson et al, Immunology 2015, 144:171
Influence of HIV on TB Evolution

WHO, 2015 report
Tuberculosis and Death in UK in HIV + Patients

HR for death for TB/HIV co-infected persons: 4.77

Zenner, Thorax, 2015
Outcome in TB associated with DM

- Prospective study in Southern Mexico
- The prevalence of DM among 1262 Pts with pulmonary TB was 29.63% (n=374)
- Pts with DM and pulmonary TB had:
  - More frequent cavities of any size (aOR 1.80)
  - Delayed sputum conversion (aOR 1.51)
  - Higher probability of treatment failure (aOR 2.93), recurrence (aHR=1.76) and relapse (aHR=1.83)
- Most of second episodes among Pts with DM were due to bacteria with the same genotype but in 5/26 (19%), reinfection with a different strain occurred

Jimenez-Corona, Thorax, 2013
All cause mortality increased in diabetics during TB treatment (compared to non-diabetics)

Fielder, 2002 [38] USA 13/22 (59%) 29/152 (19%) 3.80 (1.42, 10.16)
Oursler, 2002 [48] USA 8/18 (44%) 14/106 (13%) 6.70 (1.57, 26.52)
Dooley, 2009 [12] USA 6/42 (14%) 20/255 (8%) 6.50 (1.11, 38.20)
Wang, 2009 [56] Taiwan 13/74 (18%) 11/143 (8%) 5.20 (1.77, 15.25)
Summary 4.95 (2.69, 9.10)

Heterogeneity I-squared = 0% (0, 85)
Weights are from random effects analysis
TB/HIV Co-infection: Principles of Treatment

• Standard course in susceptible disease (4 drugs for 2 months and 2 drugs for 4 months)
• Increase to 9 months if suboptimal response (culture + after 2 months)
• Longer courses (9 to 12 months) in disseminated disease and some extra-pulmonary sites (skeletal TB, CNS TB)
• If using regimens without INH or a rifamycin, duration should be 12 to 15 months
Interactions of Rifamycins with ART: The P450 system

- Isoform CYP 3A is induced by NNRTIs
- Isoform CYP 3A is inhibited by protease inhibitors
- Rifamycins induce CYP 3A
  - Rifampin > rifapentine > rifabutin
  - Rifampin is not metabolized by CYP 3A: level not affected by other drugs
  - Rifabutin is metabolized by CYP 3A: level is affected by other drugs that affect CYP 3A
Protease Inhibitors and Rifampin

• Rifampin will reduce the level of Pis by 75-90%
  – Super-boost or double dose of LPV/r may be used but can induce hepatotoxicity

• Rifabutin may be substituted for rifampin but:
  – Need to reduce the dose to avoid rifabutin toxicity (uveitis, cytopenia)
  – If patient interrupts ARV treatment, the dosage of rifabutin will not be sufficient
Interactions between ARV and Rifamycins: Dose Adjustments

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
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<tr>
<td>Efavirenz</td>
<td>EFV 600mg, increase to 800mg if &gt; 60 kg</td>
<td>Increase rifabutin to 450 – 600 mg daily</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Risky</td>
<td>No dose adjustment (300mg daily)</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Not recommended</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Do not co-administer</td>
<td>Increase rilpivirine ?</td>
</tr>
<tr>
<td><strong>PI/r</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Do not co-administer</td>
<td>Decrease rifabutin to 150 mg OD or every other day</td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Consider to increase to raltegravir to 800mg bid</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Increase dolu to 50mg bid</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>Nucleosides</strong></td>
<td></td>
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</tr>
<tr>
<td>Enfuvirtide</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>
Tuberculosis and HAART

The NEW ENGLAND JOURNAL of MEDICINE
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Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

Francois-Xavier Blanc, M.D., Ph.D., Thim Sok, M.D., Didier Laureillard, M.D., Laurence Borand, Pharm.D., Claire Rekacewicz, M.D., Eric Nerrienet, Ph.D., Yoann Madec, Ph.D., Olivier Marcy, M.D., Sarin Chan, M.D., Narom Prak, M.D., Chhindamony Kim, M.D., Khemarin Kim Lak, M.D., Chanroeurn Hak, M.D., Bunnet Dim, M.D., Chhun Im Sin, M.D., Sath Sun, M.D., Bertrand Guillard, M.D., Borann Sar, M.D., Ph.D., Sirenda Vong, M.D., Marcelo Fernandez, M.D., Lawrence Fox, M.D., Ph.D., Jean-Francois Delfraissy, M.D., Ph.D., and Anne E. Goldfeld, M.D., for the CAMELIA (ANRS 1295–CIPRA KH001) Study Team.

Integration of Antiretroviral Therapy with Tuberculosis Treatment


Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis


CAMELIA (Cambodia)  SAPIT (South Africa)  STRIDE (multicontinent)
Tuberculosis and HAART

Havlir, NEJM, 2011
Tuberculosis and HAART: Camelia

Kaplan–Meier Survival Estimates According to Study Group.


No. at Risk
- Earlier-ART group: 332, 278, 192, 101, 4
- Later-ART group: 329, 256, 168, 87, 3

No. of Deaths
- Earlier-ART group: 0, 46, 56, 57, 59
- Later-ART group: 0, 63, 85, 90, 90

P=0.004 by log-rank test
Tuberculosis and HAART

Abdoul Karim, NEJM, 2011
## Tuberculosis and HAART

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>ARV timing</th>
<th>IRIS</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanc</td>
<td>N = 661 Median CD4 = 25</td>
<td>2 vs 8 wks</td>
<td>HR 2.51 for early ARV</td>
<td>HR for death 0.62 (for early ARV)</td>
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<tr>
<td>Havlir</td>
<td>N = 809 Median CD4 = 77</td>
<td>Median of 10 vs 70 days</td>
<td>Early 11% Late 5%</td>
<td>Death rate: overall 12.9% vs 16.1% (NS) CD4&lt;50: 15.5% vs 26.6% (p=0.02)</td>
</tr>
<tr>
<td>Abdool Karim</td>
<td>N = 642 Median CD4 = 150</td>
<td>Median of 21 vs 97 days</td>
<td>HR of 2.62 for early ARV</td>
<td>AIDS or death: no difference overall CD4&lt;50: 8.5 vs 26.3 per 100 py (p=0.06)</td>
</tr>
</tbody>
</table>
ART

Viral suppression

(CD4 rise)

Restoration of pathogen-specific immunity

Regression or prevention of opportunistic infections

Inflammatory reactions days to months after starting ART = IRIS

IRIS = Immune Reconstitution Inflammatory Syndrome
IRD = Immune Restoration Disease
PaCents on TB treatment

Paradoxical TB-IRIS

ART

ART-associated TB

Unmasking TB-IRIS

Patients not on TB treatment
Paradoxical TB-IRIS characteristics

• Incidence 8 – 54% (15.7% in meta-analysis)
• Onset of symptoms: Median 14 days from ART start
• Focal and systemic inflammatory features
  – Fever, tachycardia, weight loss
• Hospitalisation in up to 48%
• Median duration 2-3 months
• Mortality infrequent
  – Meta-analysis 3.2% (substantially higher if CNS IRIS)

Worsening pulmonary infiltrate and cavitation due to TB-IRIS
Pericardial tamponade due to paradoxical TB-IRIS

On TB treatment prior to ART

3 weeks on ART
(1 litre drained at pericardiocentesis)
Major TB-IRIS risk factors

- Low CD4 count
- Short interval between TB treatment and ART
- Disseminated TB

Lawn AIDS 2007;21:335
Meintjes Lancet Infect Dis 2008;8:516
Burman IJTLD 2007;11:1282
Immune Reconstitution Inflammatory Syndrome

Müller, Lancet ID, 2010
IRIS: Timing

TB-associated IRIS in South Africa
- 160 patients receiving treatment for TB at the time HAART was initiated
- Median CD4 68
- IRIS in 12% overall, 32% in those who started HAART within 2 months of TB treatment

Graph showing the risk of TB-IRD among patients stratified by baseline CD4 cell count and by the interval between TB diagnosis and initiation of ART (days)
When to start ART after recent diagnosis of TB?

3 recent large RCTs (SAPIT, STRIDE, CAMELIA)
SAPiT IRIS incidence
(IRIS cases/100 person years)
Treatment of TB in persons with DM

• Ensure that TB treatment is appropriately adjusted in persons with DM
  – Check creatinine for diabetic nephropathy
  – May need to adjust frequency of PZA and EMB administration
  – Give B6 to prevent INH induced peripheral neuropathy
Metformin and Risk of Active Tuberculosis in Pts with T2DM

Lin SH, Respirology, 2018

(---) Compared group,
(—) without metformin use,
(−−−) with metformin use.
HIV and TB: Key Points

- TB is the most common manifestation of HIV infection in high TB prevalence areas, consider in HIV positive immigrants
- HIV is the strongest known risk factor for progression from LTBI to TB disease
- Presentation of TB is atypical and TB is more severe in advanced HIV infection
- All HIV+ should be screened for LTBI
- All HIV+ with TB should be started on ART; management is complicated by drug interactions and by IRIS
Tuberculosis and Diabetes: Key Points

• People with diabetes have a 2-3 times higher risk of developing TB disease compared to people without diabetes.
• Diabetes must be screened in every subject with TB
• People with TB and coexisting diabetes have 4 times higher risk of death during TB treatment and higher risk of TB relapse after treatment.
• People with TB and coexisting diabetes are more likely to be sputum positive, to have lung cavitations and take longer to become sputum negative.
• Diabetes may adversely affect TB treatment outcomes by delaying the response time to treatment.
• Diabetes may interfere with the activity of TB medications
• Toxicity of TB medications should be carefully monitored