Diabetes and Tuberculosis

Reinout van Crevel
Median 30 yrs, 13.5% DM (70% new DM) (3.2% of controls; OR 4.7).

1.5% HIV+

BMI (kg/m²)

TB patients

No DM

DM

Alisjahbana et al, Int J Tub Lung Dis 2006

13.5% DM

1.5% HIV+

10

15

20

25

30

35

40

50

60

70

BMI (kg/m²)

The New England Journal of Medicine
Tuberculosis and diabetes mellitus

- 10.4 million TB cases
- 1/4 world latently infected
- 1.7 million deaths, 95% in LMIC

- 425 million with DM, 50% undiagnosed
- >90% Type II
- 80% living in LMIC
- Increase to 630 million by 2045
- 4 million deaths annually
No. of adults with DM – in 2017 and 2045

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

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

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

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

Africa
- 2045: 151 million
- Increase: 84%
- 2017: 41 million

South East Asia
- 2045: 159 million
- Increase: 15%
- 2017: 183 million

World
- 2045: 629 million
- Increase: 48%
- 2017: 425 million

DM is associated with active TB

- 44 studies from 16 countries
- Prospective: DM ~ 3.6-fold higher TB risk (2.3-5.7)
- Higher in low-income and high-incidence
- Higher in Asia compared to Europe/USA
- Higher for confirmed TB and blood tested DM
- DM accounts for 11% (Nigeria) to 18% (India) of TB in high burden countries

Al-Rifai, Pearson, Critchley, Abu-Raddad. Plos One 2017
TB-DM hotspots

- **South India.** 209 pulmonary TB, ~45 years, BMI ~20
  - 54% diabetes (OGTT, HbA1c), 21% pre-diabetes
  - 25% eu-glycemic  
    *Kornfeld et al, Chest 2016*

- **Kiribati, Pacific.** 275 TB cases, ~37 years, BMI 22.5
  - 37% diabetes (>50% in those >35 years) vs. 18% in matched controls
  - 55% previously undiagnosed DM  
    *Viney et al, TMIH 2015*

- **Southern Texas/ Mexico.** 233 TB cases, ~44 years, 25% obese
  - 37% diabetes, ~ 2-3-fold more compared to background population
  - DM responsible for 25% of TB (versus HIV: 5%)
    *Restrepo, Bull WHO 2011*
Higher TB risk with poor glycemic control

Prospective cohort Taiwan (n=123,000); baseline fasting blood glucose

- FBG > 7.2 mmol/L (≥130 mg/L)
- aHR 1.06 for every 10 mg/L increase, P<0.001

Lee et al, Plos Med ‘16

Validation in smaller studies in Denmark, UK, Hong Kong
• English primary care data 2010-2015 (>85,000 DM patients, >150,000 controls)
• Consistently higher risk of infection compared to non-DM, higher risk with higher HbA1c
• 24% of TB among DM patients in UK is a result of poor glycemic control

_Critchley J, Diabetes Care 2018_
Different biological mechanisms may account for increased TB susceptibility, disease severity, early deaths, treatment failure and TB recurrence in DM.
Dyslipidemia?

DM and TB-DM patients: pro-atherogenic lipid profile

In vitro (macrophage infection):
- oxLDL leads to foam cell formation
- higher *Mtb* CFU in macrophages
- Cytokines / Ag-presentation capacity down
- through lysosomal cholesterol accumulation
DM: worse TB outcome, more resistance

- More deaths during treatment
- More TB treatment failure
- More recurrent TB
- Stronger relations in poor countries

*Updated systematic review. Huangfu et al. IJTLD 2019*

<table>
<thead>
<tr>
<th>Author/Yr</th>
<th>Design</th>
<th>Population</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez-Gomez A et al. (2015)</td>
<td>Case control</td>
<td>175</td>
<td>2.51 (1.11, 5.67)</td>
</tr>
<tr>
<td>Magee MJ et al. (2015)</td>
<td>Prospective cohort</td>
<td>263</td>
<td>2.27 (1.02, 5.08)</td>
</tr>
<tr>
<td>Fisher-Hoch SP et al. (2008)</td>
<td>Cross-sectional</td>
<td>1436</td>
<td>1.80 (1.13, 2.87)</td>
</tr>
<tr>
<td>Hsu A et al. (2012)</td>
<td>Cross-sectional</td>
<td>139</td>
<td>1.52 (0.59, 3.95)</td>
</tr>
<tr>
<td>Saktiwati AMI et al. (2018)</td>
<td>Retrospective cohort</td>
<td>356</td>
<td>17.90 (3.30, 96.80)</td>
</tr>
<tr>
<td>Rifat M et al. (2014)</td>
<td>Case control</td>
<td>1000</td>
<td>2.56 (1.51, 4.34)</td>
</tr>
<tr>
<td>Bashar M et al. (2001)</td>
<td>Case control</td>
<td>155</td>
<td>5.30 (1.90, 14.70)</td>
</tr>
<tr>
<td>Perez-Navarro LM et al. (2017)</td>
<td>Prospective cohort</td>
<td>507</td>
<td>3.50 (1.80, 7.10)</td>
</tr>
<tr>
<td>Perez-Navarro LM et al. (2015)</td>
<td>Case control</td>
<td>409</td>
<td>3.50 (1.10, 11.10)</td>
</tr>
<tr>
<td>Salindri AD et al. (2016)</td>
<td>Prospective cohort</td>
<td>268</td>
<td>2.51 (1.00, 6.31)</td>
</tr>
<tr>
<td>Min J et al. (2005)</td>
<td>Case control</td>
<td>195</td>
<td>2.68 (1.05, 6.86)</td>
</tr>
<tr>
<td>Hsu A et al. (2012)</td>
<td>Cross-sectional</td>
<td>869</td>
<td>0.95 (0.34, 2.68)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td><strong>2.43 (1.90, 3.12)</strong></td>
</tr>
</tbody>
</table>

*Tegegne, Syst Rev 2018*
TB treatment: TB is different in TB-DM

More drug resistance but also:
- Older
- Heavier (lower concentrations TB drugs?)
- Some studies: more severe TB
- More co-medication (drug-drug interactions; toxicity)
- More kidney function loss / liver steatosis

So maybe:
- Longer TB treatment?
- Dose adjustment or TDM?
- Universal DST (if not all patients tested)
- More close follow-up during treatment?
- Vigilance for higher TB recurrence
DM not a single entity

- Known versus newly diagnosed DM
- Mild versus severe hyperglycemia
- Insulin-dependent or not
- Type 1 or type 2
- Cardiovascular risk profile
- Micro/macro vascular complications yes/no
- Kidney function
- Ethnicity
- Nutritional status
- Level of self-management
- ..
TANDEM – tuberculosis and diabetes mellitus

“The TANDEM Consortium brings together partners with complementary skills in clinical studies, epidemiology, health economics, human genetics and immunology.”
New and known DM among TB

TANDEM consortium (2185 pulmonary TB)
DM defined as HbA1c>7% or >6.5% with confirmatory 2nd test)

69% of DM previously known ("neglected")

Ugarte-Gil, Clin Inf Dis 2019
## Diagnostic test

<table>
<thead>
<tr>
<th>Test</th>
<th>Area under ROC curve (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indonesia (649 patients)</strong></td>
<td></td>
</tr>
<tr>
<td>2-steps RPG/POC HbA1c ≥ 6.5%</td>
<td>0.98 (0.96–1.00)</td>
</tr>
<tr>
<td>Point-of-care HbA1c ≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>Full TANDEM score ≥ 12.4</td>
<td>0.97 (0.94–1.00)</td>
</tr>
<tr>
<td>Random plasma glucose ≥ 11.1 mmol/L</td>
<td>0.95 (0.91–0.99)</td>
</tr>
<tr>
<td><strong>Peru (562 patients)</strong></td>
<td></td>
</tr>
<tr>
<td>2-step RPG/POC HbA1c ≥ 6.5%</td>
<td>0.93 (0.89–0.98)</td>
</tr>
<tr>
<td>Point-of-care HbA1c ≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>Full TANDEM score ≥ 12.4</td>
<td>0.95 (0.90–0.99)</td>
</tr>
<tr>
<td>Random plasma glucose ≥ 11.1 mmol/L</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td><strong>Romania (469 patients)</strong></td>
<td></td>
</tr>
<tr>
<td>2-step RPG/POC HbA1c ≥ 6.5%</td>
<td>0.69 (0.56–0.82)</td>
</tr>
<tr>
<td>Point-of-care HbA1c ≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>Full TANDEM score ≥ 12.4</td>
<td>0.69 (0.58–0.79)</td>
</tr>
<tr>
<td>Random plasma glucose ≥ 11.1 mmol/L</td>
<td>0.49 (0.35–0.64)</td>
</tr>
<tr>
<td><strong>South Africa (259 patients)</strong></td>
<td></td>
</tr>
<tr>
<td>2-step RPG/POC HbA1c ≥ 6.5%</td>
<td>0.72 (0.59–0.84)</td>
</tr>
<tr>
<td>Point-of-care HbA1c ≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>Full TANDEM score ≥ 12.4</td>
<td>0.74 (0.61–0.87)</td>
</tr>
<tr>
<td>Random plasma glucose ≥ 11.1 mmol/L</td>
<td>0.60 (0.45–0.76)</td>
</tr>
<tr>
<td><strong>Overall (1939 patients)</strong></td>
<td></td>
</tr>
<tr>
<td>2-step RPG/POC HbA1c ≥ 6.5%</td>
<td>0.81 (0.75–0.86)</td>
</tr>
<tr>
<td>Point-of-care HbA1c ≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>Full TANDEM score ≥ 12.4</td>
<td>0.85 (0.81–0.90)</td>
</tr>
<tr>
<td>Random plasma glucose ≥ 11.1 mmol/L</td>
<td>0.75 (0.70–0.80)</td>
</tr>
</tbody>
</table>

### Overall, conservative definition of diabetes mellitus

<table>
<thead>
<tr>
<th>Test</th>
<th>Area under ROC curve (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-step RPG/POC HbA1c ≥ 6.5%</td>
<td>0.93 (0.87–0.99)</td>
</tr>
<tr>
<td>Point-of-care HbA1c ≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>Full TANDEM score ≥ 12.4</td>
<td>0.95 (0.90–1.00)</td>
</tr>
<tr>
<td>Random plasma glucose ≥ 11.1 mmol/L</td>
<td>0.90 (0.83–0.97)</td>
</tr>
</tbody>
</table>

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**Figure:** Screening TB pts for DM

**Table:** Diagnostic test results for HbA1c screening in different countries.
### Table 6.3: Management of HbA1c or blood glucose at the start of TB treatment

<table>
<thead>
<tr>
<th>HbA1c or FBG at the start of TB treatment</th>
<th>TB patient diagnosed with new DM</th>
<th>TB patient already receiving treatment for DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HbA1c &lt;8% or FBG &lt;10.0 mmol/l (180 mg/dl)</td>
<td>No further immediate action is taken; re-assess blood glucose levels at 2 months and again at the end of TB treatment</td>
<td>No further action is taken; the patient continues on current medication for DM</td>
</tr>
<tr>
<td>If HbA1c ≥8% but less than 10% or FBG ≥10 mmol/l (180 mg/dl) but less than 15 mmol/l (270 mg/dl)</td>
<td>Start metformin 500 mg once a day, re-assess in two weeks and increase the dose to 500 mg twice a day or refer if blood glucose levels have not improved</td>
<td>Intensify current glucose-lowering treatment and re-assess one–two weeks later</td>
</tr>
<tr>
<td>If HbA1c ≥10% or FBG ≥15 mmol/l (270 mg/dl)</td>
<td>Start metformin 500 mg twice a day and seek specialist advice</td>
<td>Seek specialist advice and consider the need for hospital admission for better glucose control</td>
</tr>
</tbody>
</table>
Management of diabetes mellitus during tuberculosis treatment

6.1 Summary statement
6.2 What are the aims and principles of DM management?
6.3 Do these aims and principles apply to the management of persons with DM and TB?
6.4 Who should provide DM care for patients with DM and TB?
6.5 What glucose control target should be aimed for in a patient with DM and TB and how should this be monitored?
6.6 What glucose-lowering drugs should be used in TB patients?
6.7 What should be done for a patient diagnosed with TB in a DM clinic?
6.8 What should be done for a patient diagnosed in a TB clinic who is diagnosed with new DM or who is already receiving treatment for DM?
6.9 What can be done to prevent and/or manage hypoglycaemia?
6.10 How is cardiovascular risk assessed and managed?
6.11 Should cardiovascular risk be assessed and managed in patients with newly diagnosed DM during TB treatment?
6.12 How should DM be managed in patients with HIV-associated TB?
6.13 What should be done at the end of TB treatment?
management of Diabetes

• Aimed at reducing short-term and long-term complications
  
  \textit{(cardiovascular, kidney, eye disease, foot problems)}

• Lifestyle changes
  
  \textit{(diet, exercise, smoking, alcohol..)}

• Glucose control

• Cardiovascular risk management
Glycemic control is difficult in TB-DM

Drug therapy
Side-effects (e.g., vomiting); drug-drug interactions; weight gain during treatment

Active tuberculosis
Inflammation leading to: weight loss; loss of appetite; insulin resistance

Health systems
Access and affordability of health services; collaboration between tuberculosis and diabetes physicians; laboratory facilities; continuous medication supply

Behaviour
Variable food intake; physical activity; treatment compliance

Glucose control - target

- Accepted target HbA1c <7%
- Difficult to achieve in TB
  
  (inflammation, drug interactions, behavior, health systems..)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood (capillary) glucose</td>
<td>&lt;10 mmol/l (&lt;180 mg/dl)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;8%</td>
</tr>
</tbody>
</table>
Should we use insulin or metformin?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metformin</th>
<th>Sulphonyl urea derivates</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug of choice</td>
<td>First choice</td>
<td>Alternative oral drug</td>
<td>Use if HbA1c &gt; 10% or symptomatic hyperglycaemia</td>
</tr>
<tr>
<td>Risk of hypoglycaemia</td>
<td>No</td>
<td>Gliclazide 40–80 mg od</td>
<td>Yes</td>
</tr>
<tr>
<td>Starting dose</td>
<td>500 mg od or bid, titrated to a maximum dose of 2000 mg daily</td>
<td>Glibenclamide 2.5–5 mg od</td>
<td>10 units basal insulin per day</td>
</tr>
<tr>
<td>Interaction with RMP</td>
<td>Not clinically relevant</td>
<td>Glimepiride 1–2 mg od</td>
<td></td>
</tr>
<tr>
<td>Main side effects/toxicity</td>
<td>Gastro-intestinal</td>
<td>Glipizide 5 mg od</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis (rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in reduced kidney function</td>
<td>Dose adjustment if eGFR &lt; 45 ml/min; contraindication if eGFR &lt; 30 ml/min</td>
<td>Increased risk of hypoglycaemia</td>
<td>Can be safely used</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>Recognised benefit</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

HbA1c = glycated haemoglobin; od = once a day; bid = twice a day; RMP = rifampicin; eGFR = estimated glomerular filtration rate.

Clinical management of combined tuberculosis and diabetes

R. van Crevel,*† R. Koesoemadinata,† P. C. Hill,§ A. D. Harries†##
Choice of glucose-lowering drugs

- DM severity (HbA1c)
- TB severity (ambulatory or in-patient)
- Known DM (on treatment) or new DM?
- New TB and new type 2 DM
- Kidney function
- Possibility of self-monitoring
- Service delivery model
- Availability of drugs
- ..
Is glycemic control attainable? And helpful?

Pragmatic clinical trial in TANDEM

- Structured DM management in a TB clinic versus standard care
- Intervention: counseling, more glucose measurements, with adjustment of DM medication according to simple algorithms
- Endpoint: HbA1c; 2nd: TB outcomes, drugs, costs, visits etc
Simple algorithm for glucose control

Intervention arm

- HbA1c ≤ 10%
  - Metformin contraindicated?
    - No
      - Target achieved
      - Check side effects & FBG
    - Yes
      - Metformin
      - Severe side effects (+)
      - Target not achieved
      - Metformin & basal insulin

- HbA1c > 10%
  - insulin
  - Refused insulin
  - Metformin & other orals
Patient education

Anda Mempunyai TB dan Diabetes

- Adanya kejadian dua penyakit TB dan DM pada Anda, ternyata saling berhubungan.
- Penderita DM memang lebih mudah terkena penyakit TB.
- Kerentanan penderita DM disebabkan daya tahan tubuhnya kurang baik untuk bisa mengatasi kuman Mtb.
- Pengelolaan TB dan DM memerlukan perawatan yang lebih besar.
- Karena adanya dua penyakit ini, TB jadi lebih sulit disembuhkan, dan DM juga lebih sulit dikendalikan.
- DM mengakibatkan lebih banyak penderita menjadi mendapat pengobatan.

Gaya Hidup Sehat untuk Diabetis dan Keluarga

1. PINDAH tempat makanan yang sehat dilakukan
   Sama dengan kebijakan diatas, kita harus memperhatikan
   Karena kita kehilangan waktu, kita harus memperhatikan
   Kehilangan waktu, kita harus memperhatikan
   Kehilangan waktu, kita harus memperhatikan
   Kehilangan waktu, kita harus memperhatikan

2. PERSI makanan
   Makanan sehat untuk kebutuhan tubuh
   Makanan sehat untuk kebutuhan tubuh
   Makanan sehat untuk kebutuhan tubuh
   Makanan sehat untuk kebutuhan tubuh

3. BUAH
   Buah-buah yang sehat dan buah-buah yang sehat
   Buah-buah yang sehat dan buah-buah yang sehat
   Buah-buah yang sehat dan buah-buah yang sehat
   Buah-buah yang sehat dan buah-buah yang sehat

4. ALKOHOL
   Alkohol yang sehat dan alkohol yang sehat
   Alkohol yang sehat dan alkohol yang sehat
   Alkohol yang sehat dan alkohol yang sehat
   Alkohol yang sehat dan alkohol yang sehat

5. KELAPA
   Kelapa yang sehat dan kelapa yang sehat
   Kelapa yang sehat dan kelapa yang sehat
   Kelapa yang sehat dan kelapa yang sehat
   Kelapa yang sehat dan kelapa yang sehat

6. MINIM GOENG
   Minum goeng yang sehat dan goeng yang sehat
   Minum goeng yang sehat dan goeng yang sehat
   Minum goeng yang sehat dan goeng yang sehat
   Minum goeng yang sehat dan goeng yang sehat

7. PESAN BURAN
   Pesan Buran yang sehat dan pesan buran yang sehat
   Pesan Buran yang sehat dan pesan buran yang sehat
   Pesan Buran yang sehat dan pesan buran yang sehat
   Pesan Buran yang sehat dan pesan buran yang sehat

8. TEH ATAU KOPI
   Teh atau kopi yang sehat dan teh atau kopi yang sehat
   Teh atau kopi yang sehat dan teh atau kopi yang sehat
   Teh atau kopi yang sehat dan teh atau kopi yang sehat
   Teh atau kopi yang sehat dan teh atau kopi yang sehat
Proportion with HbA1c<8%

Raspati Koesomadinata
Padjadjaran Univ., Indonesia
63-year old woman ...

- New TB and new type 2 DM
- Started on metformin first, then on TB drugs
- first follow up – 1 week after starting TB treatment, no complaints
- 2 weeks after starting TB treatment nausea, adequate drinking
- 3 days later family calls: progressive nausea
- On examination: no jaundice, mild dehydration
- Lab marked elevation of ureum and creatinine level (3.04 mg/dL), elevation of liver function test (AST: 86 IU/L, ALT 52 IU/L), and hyperkalemia. Blood glucose level was 187 gr/dL.

Ischemic bowel? Inferior myocardial infarct?
Metformin-associated lactic acidosis? ...
increased (early) mortality of TB-DM

Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients from Mwanza, Tanzania

Daniel Faurholt-Jepsen¹, Nyagosya Range², George PrayGod³, Kidola Jeremiah³, Maria Faurholt-Jepsen¹, Martine G. Aabye⁴, John Changalucha³, Dirk L. Christensen⁵, Harleen M. S. Grewal⁶, Torben Martinussen⁷, Henrik Krarup⁸, Daniel R. Witte⁹, Aase B. Andersen¹⁰ and Henrik Friis¹

• 1250 pts, 51% HIV+, 17% DM
• death < 3 mths: RR 5.0 in HIV/DM; RR 2.2 in DM

Impact of Diabetes and Smoking on Mortality in Tuberculosis

George W. Reed¹, Hongjo Choi², So Young Lee², Myungsun Lee², Youngran Kim², Hyemi Park², Jongseok Lee², Xin Zhan⁴, Hyeungseok Kang⁵, SooHee Hwang⁵, Matthew Carroll⁶, Ying Cai⁶, Sang-Nae Cho²,³, Clifton E. Barry III⁶, Laura E. Via⁶, Hardy Kornfeld⁷,⁸

• Taiwan, 657 pts, 20% DM, 80% smoking (HIV+ excluded)
• 1-year mortality 6% in non-DM, 13% in DM
• DM plus smoking: one-year TB-ass mortality: HR 5.78
Cardiovascular risk management

• Higher rate (RR 2-5) of early deaths in TB-DM, more in smokers
• Cardiovascular disease leading cause of death for DM
• May explain (early) deaths in TB-DM
• TB itself: more stroke and myocardial infarction
  – Taiwan cohort: 40% more acute coronary syndrome and 50% more stroke

• Four possible interventions
  – Life style
  – Hypertension
  – Lipids (statins)
  – Platelets (aspirin)

*Chung W. IJTLID 2014;18:78
Sheu J, Stroke 2010;41:244*
Table 2  Cardiovascular disease risk assessment and management in patients with diabetes mellitus and active TB disease

<table>
<thead>
<tr>
<th>Cardiovascular risk</th>
<th>Target</th>
<th>The intervention</th>
<th>Specific considerations in TB patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Stop smoking</td>
<td>Counselling</td>
<td>Relevant for TB treatment outcomes and reducing relapse rates of disease</td>
</tr>
<tr>
<td>Obesity</td>
<td>Body mass index &gt; 23 (Asian) or &gt; 25 (other)</td>
<td>Counselling (diet, physical activity)</td>
<td>Often ~10% weight gain as a result of anti-tuberculosis treatment</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>Avoid alcohol intake during anti-tuberculosis treatment</td>
<td>Counselling</td>
<td>Risk of liver dysfunction associated with anti-tuberculosis drugs</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&lt;130/80 mmHg</td>
<td>Antihypertensive treatment</td>
<td>RMP reduces the efficacy of some antihypertensive drugs (calcium channel blockers and ACE inhibitors)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No interaction with thiazide diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACE inhibitors cause cough in 10–15% of patients</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>LDL &lt; 2.6 mmol/l (100 mg/dl)</td>
<td>Statins: 1) for those aged &gt;40 years; 2) for those with previous cardiovascular disease</td>
<td>Rifampicin reduces the efficacy of most statins</td>
</tr>
</tbody>
</table>

Established cardiovascular disease (previous myocardial infarct, stroke, peripheral arterial disease)
Secondary prophylaxis
Aspirin
Statin
Risk of bleeding (e.g., haemoptysis in pulmonary TB)

TB = tuberculosis; RMP = rifampicin; ACE = angiotensin-converting-enzyme; LDL = low-density lipoprotein.

- Successful initiation of TB treatment is priority
- main consideration at start of treatment: secondary prevention
What about TB treatment in TB-DM?
TB is different in TB-DM

Compared to TB without DM:
- Older
- Heavier (lower concentrations TB drugs?)
- Some studies: more severe TB
- More co-medication (drug-drug interactions; toxicity)
- More kidney function loss / liver steatosis
Longer or intensified TB treatment?

- 9 versus 6 months anti-TB treatment
  - lower recurrence rate in DM (HR 0.76 [0.59-0.97]),
  - under conditions of full DOTs (HR 0.69 [0.43-1.11]).

- Lower drug levels in TB? No adequate adjustment for weight?
- Role for higher rifampicin or intensified TB treatment?

Wang, J. Y. et al, CHEST 2014
TB drug levels and therapeutic drug monitoring?

- 363 patients, 130 with DM
- TDM for slow-responders and all DM patients (at 2 weeks)
- Dose-adjustment according to drug-levels
- Pre-post analysis (64 vs 66 TB-DM pts)
- Time to sputum culture-conversion down from 62 to 42 days
- culture negative TB-DM at 2 months up from 50% to 80%
diabetes and genotypic drug-resistance

“The TANDEM Consortium brings together partners with complementary skills in clinical studies, epidemiology, health economics, human genetics and immunology.”
DM associated with genotypic resistance

Mutations conferring resistance to:

- Isoniazid
- Rifampicin
- Ethambutol
- Streptomycin
- Pyrazinamide
- Ethionamide
- Fluoroquinolones
- Kanamycin
- Any first-line drug
- Any resistance
- MDR-TB
- Primary MDR
- Acquired MDR

OR (95% Confidence Interval)

- Combined
- Indonesia
- Peru

Carolien Ruesen
Underlying mechanism?..
Prevention of TB among people with DM?

- diabetes ~ latent TB (odds ratio 1.2 in systematic review)
- diabetes ~ more progression of LTBI to active TB?

<table>
<thead>
<tr>
<th></th>
<th>DM patients</th>
<th>TB household contacts</th>
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</thead>
<tbody>
<tr>
<td>Active TB</td>
<td>4.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Latent TB (IGRA)</td>
<td>38.6%</td>
<td>68.6%</td>
</tr>
<tr>
<td>Ratio active-latent</td>
<td>1:8</td>
<td>1:57</td>
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</tbody>
</table>

Koesoemadinata et al. Tr Royal Soc Trop Med H 2017

Follow up of those without TB after median 3.4 years:
At least 17% had died (28% loss/refusal)
TB incidence (17.1; 95% CI 5.25-29.00 / 1000 person-years) among those with LTBI; 3.6 fold higher compared to DM / no LTBI

Preventive treatment of latent Tuberculosis Infection among people with Diabetes Mellitus ("PROTID")

- first phase 3 RCT globally
- 6000-7000 DM screened for TB and LTBI
- 3000 DM/ LTBI included RCT: 3HP vs placebo
- Quality of care (gaps in care, guidelines etc)
- Epidemiological & economic modeling

Makarere Univ, Kampala, Uganda
KCMC, Moshi, Tanzania
Mbeya Medical Research Unit, Tanzania
SGUL and King’s College, London
Radboud, Netherlands
Funding from EDCTP

Similar study will be proposed for Indonesia / The Philippines (PROTID-Asia)
In conclusion: DM and TB

- Increased TB risk, especially with high HbA1c
- Higher risk of infection and disease reactivation
- More severe TB, more drug resistance, worse TB outcomes
- More (vascular?) early deaths
- Lower host defence + more inflammation / immunopathology
- Heterogeneity of both DM and TB-DM

- Global increase in DM prevalence will affect TB control
- need for screening, clinical management and new interventions
DM care often substandard

- in ‘the South’ or those at highest TB risk in ‘the North’
- access
- retention
- glycemic control
- insufficient $1^0 / 2^0$ prevention cardiovascular disease
- TB as a “2nd chance” for DM patient?
- 6 mths is short. How to sustain the engagement of a TB-DM patient with the health system?

Cascade of care

Syndemics 2

Non-communicable disease syndemics: poverty, depression, and diabetes among low-income populations

Emily Mendenhall, Brandon A Kohrt, Shane A Norris, David Ndetei, Dorairaj Prabhakaran

The co-occurrence of health burdens in transitioning populations, particularly in specific socioeconomic and cultural contexts, calls for conceptual frameworks to improve understanding of risk factors, so as to better design and implement prevention and intervention programmes to address comorbidities. The concept of a syndemic, developed by medical anthropologists, provides such a framework for preventing and treating comorbidities. The term

Lancet 2017; 389: 951–63
This is the second in a Series of three papers about syndemics
See Editorial page 881
- **UNPAD Bandung, Indonesia**: Bachti Alisjahbana, Rovina Ruslami, Raspati Koesoemadinata, Nanny NM Soetedjo, Prayudi Santoso, Lidya Chaidir
- **UMFCV Craiova, Romania**: Mihai Ioana, Nicolae Panduru, Anca Riza
- **UPCH Lima, Peru**: Cesar Ugarte
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