TB and Diabetes Mellitus: *Pharmacological aspects of convergence of two epidemics*

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Global TB Epidemic

In 2013, 9 million cases (~ mainly in Asia & Africa).

It is slowly decreased (~ 2% per year).

Mortality decreased by 45% (1990 – 2012) but still, 1.5 million died.

WHO Global TB Report, 2014
Global Diabetes Epidemic

~ 387 million cases in 2014 (prev. 8.3%). ~46% undiagnosed (77% in the low- & middle-income countries)

~ 592 million in 2035. Largest increase (+109%) in Africa

IDF Atlas, 2014
DM and TB

TB decreased 2%
DM increased 20%

DM and TB

TB decreased 2%
DM increased 20%

DM and TB (systematic review)

- More active TB  \((RR: 3.11, 95\% CI 2.27-4.26)\)
- More treatment failure & death  \((RR: 1.69, 95\% CI 1.36-2.12)\)
- More relapse  \((RR: 3.89, 95\% CI 2.43-6.23)\)

Many recent reports

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 Changalucha⁵, Dirk L. Christensen⁵, Harleen M. S. Grewal⁶, Torben Martinussen⁷, Henrik Krarup⁸, Daniel R. Witte⁹, Aase B. Andersen¹⁰ and Henrik Friis¹

- 1250 TB patients
- 16.4% had diabetes
- 50% HIV co-infected
- Patients with DM have higher mortality within the first 3 months
  - 5-fold higher in HIV-negatives (RR: 5.48)
  - 2-fold in HIV positive (RR: 1.95)
• 1262 TB patients
• 29.3% had diabetes
• Patients with DM have more severe TB clinical manifestations & worse treatment outcome
  • delayed sputum conversion (aOR 1.51)
  • treatment failure (aOR 2.93)
  • recurrence (aHR 1.76) and relapse (aHR 1.83)
Effect of DM on TB

- More active TB (RR: 3.11, 95% CI 2.27-4.26)
- More treatment failure & death (RR: 1.69, 95% CI 1.36-2.12)
- More relapse (RR: 3.89, 95% CI 2.43-6.23)

Screening DM patients for TB

Effects of TB on DM

- More glucose intolerance in TB vs. healthy controls
- TB treatment may induce hyperglycemia
- 60% of DM in Indonesian TB patients was newly diagnosed (from screening)

- Screening TB patients for DM

*Dooley KE & Chaisson RE, Lancet Infect Dis, 2009*
Clinical Management of TB-DM

- Should TB treatment be adjusted?
- Should DM treatment be adjusted?
- What about drug–drug interactions?
- Do we need to monitor a TB-DM patient more intensively?
  - What other treatments do TB-DM need?
  - What about lifestyle and smoking?
  - How to adjust counseling & education?
- Where should patients be treated, how to coordinate care?
  - How to continue DM care after TB treatment?
  - ...

Pharmacokinetic aspects
TB treatment in DM patients
Exposure to Rifampicin Is Strongly Reduced in Patients with Tuberculosis and Type 2 Diabetes

Hanneke M. J. Nijland,1 Rovina Ruslami,1 Janneke E. Stalenhoef,2 Erni J. Nelwan,2 Bachti Alisjahbana,3 Ron H. H. Nelwan,2 Andre J. A. M. van der Ven,2 Halim Danusantoso,4 Rob E. Aarnoutse,1 and Reinout van Crevel2

Clin Infect Dis. 2006;43(7):848-54

- 17 TB-DM and 17 age & gender-matched TB-only patients
- in the continuation phase of TB treatment (received 450 mg RIF)
- simple PK curve of Rifampicin

- exposure to Rifampicin was 2 times lower in TB-DM patients
- It was negatively associated with:
  • body weight
  • blood glucose level
  • diabetes status

![Graph showing plasma concentration of rifampicin over time for TB and TB-DM patients.](image)
Intensive phase, after matching for BW

DM is **not associated** with PK of Rifampicin

**most important**
Proper adjustment TB drugs for higher body weight in DM (esp. in the continuation phase)

Ruslami, et. al. AAC, 2010
Pharmacokinetics of Rifampin in Peruvian Tuberculosis Patients with and without Comorbid Diabetes or HIV

Ana Requena-Méndez, Geraint Davies, Alison Ardrey, Oswaldo Jave, Sonia L. López-Romero, Stephen A. Ward, and David A. J. Moore

- 105 TB patients
  - 50 TB, 26 TB-DM, 29 TB-HIV
  - Good adherence, 10mg/kg RIF
  - Sampling at 2 and 6 hrs after drug intake

- DM or HIV comorbidity have no effect on the rate or the magnitude of absorption

- Delayed absorption in Peruvian TB patients:
  - Associated with gender

- Rif conc. is associated with:
  - Delayed absorption
  - Gender
  - And not with the drug dose, BG, age

**TABLE 3 Multivariate regression model of the independent association of various variables with exposure to rifampin**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proportional difference</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_max (6 h)</td>
<td>0.71^b</td>
<td>0.55–0.93</td>
<td>0.012</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.91^c</td>
<td>1.42–2.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rifampin dose received</td>
<td>1.05</td>
<td>0.96–1.14</td>
<td>0.299</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>0.98</td>
<td>0.71–1.37</td>
<td>0.926</td>
</tr>
<tr>
<td>DM</td>
<td>0.99</td>
<td>0.71–1.37</td>
<td>0.931</td>
</tr>
</tbody>
</table>

AAC, 2012 May; 56(5): 2357–63
- 206 samples form 54 TB patients (with and without DM)
- NONMEM

- DM: ↗ absorption rate constant (ka) & ↗ Vd of rifampicin
- BMI: ↗ clearance of rifampicin

- TB-DM patients → lower rifampicin conc.
So, DM and PK of TB drugs…

- **Diabetes status?**
  - (-): Ruslami et al, AAC, 2007 and Mendez et al. AAC, 2012

- **Blood glucose level?**
  - (+): Nijland et al. CID 2006,
  - (-): Ruslami et al, AAC, 2007 and Mendez et al. AAC, 2012

- **Body weight? → drug dose/kg?**

- **Gender?**
  - (+) Mendez et al. AAC, 2012, McIlreron, AAC, 2006
DM management in TB patient
Glycemic control in TB-DM patients

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

Inflammation
- weight loss
- loss of appetite
- insulin resistance

Health systems
- access / affordability of health services
- collaboration of TB and DM physicians / clinics
- laboratory facilities
- continuous medication supply

Behaviour
- variable food intake
- physical activity
- treatment compliance

Riza AL, et.al. Lancet Diab Endocrinol, 2014
Glycemic control — in TB-DM patients - is problematic

- Rifampicin-induced hyperglycemia (reversible)
  - Rifampicin augments intestinal absorption of glucose or reduces insulin sensitivity.

- Rifampicin interferes most oral DM drugs
  and this effect shows large inter-individual variation

Drug (dose) adjustment – risk of hyper/hypoglycemia
<table>
<thead>
<tr>
<th>Antidiabetic drug</th>
<th>Change in exposure (AUC)</th>
<th>Metabolic enzymes</th>
<th>Transporters</th>
<th>Additional comments or citations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
<td>no effect anticipated</td>
<td>None</td>
<td>--</td>
<td>no published studies</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>strong decrease</td>
<td>CYP2C9</td>
<td>OATP2B1, P-gp, MRP1, BCRP</td>
<td>*</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>-39%</td>
<td>CYP2C9</td>
<td>--</td>
<td>*</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>-70%</td>
<td>CYP2C9</td>
<td>--</td>
<td>*</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>-34%</td>
<td>CYP2C9</td>
<td>--</td>
<td>*</td>
</tr>
<tr>
<td>Glipizide</td>
<td>-22%</td>
<td>CYP2C9</td>
<td>--</td>
<td>*</td>
</tr>
<tr>
<td><strong>Sulphonylureas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Biguanides</strong></td>
<td>Metformin</td>
<td>possible interference</td>
<td>None</td>
<td>OCT1,2,3, MATE 1-2, PMAT, P-gp</td>
</tr>
<tr>
<td><strong>Meglitinide analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>-57%, -31%, -50%</td>
<td>CYP3A4, OATP1B1</td>
<td>--</td>
<td>*</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>-24%</td>
<td>CYP2C8, CYP2C9,</td>
<td>--</td>
<td>*</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>-54%, -65%</td>
<td>CYP3A4, CYP2C8</td>
<td>P-gp</td>
<td>*</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>-54%</td>
<td>CYP2C8</td>
<td>--</td>
<td>*</td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide, Exenatide</td>
<td>no effect anticipated</td>
<td>None</td>
<td>--</td>
<td>no published studies</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>-76% in saxagliptin, -27% total moiety exposure</td>
<td>CYP3A4</td>
<td>P-gp</td>
<td>A9</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>no effect anticipated</td>
<td>Minor (CYP3A4, CYP2C8)</td>
<td>hOAT3, OATP4, C1, P-gp</td>
<td>*</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>No effect anticipated</td>
<td>None</td>
<td>P-gp</td>
<td>*</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>-40%</td>
<td>Minor (CYP3A4)</td>
<td>P-gp</td>
<td>product inform</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>-22%</td>
<td>None (phase II metabolism)</td>
<td>--</td>
<td>product inform</td>
</tr>
</tbody>
</table>

Riza AL, et.al. Lancet Diab Endocrinol, 2014
Metformin for TB-DM patients?

- Control blood glucose through several mechanisms
- no hypoglycemic effect
- relatively cheap
- widely available.
Metformin for TB-DM patients?

- Control blood glucose through several mechanisms
- no hypoglycemic effect
- relatively cheap
- widely available.

GI side effects:
- Nausea, bloating, vomitus, diarrhea
- Taste disturbance
- B12 deficiency
- Lactic acidosis (in kidney disorder)
Pharmacokinetics of metformin

Inter individual variability
- Pharmacokinetics
- Glycemic response

Pharmacokinetics:
- $T_{\text{max}}$: 3hrs
- Minimal FDI & DDI
- Not metabolized
- Urine excretion ($t\frac{1}{2}$: 5 hrs)
- Clearance: 510+120 ml/min

Transporters involved:

Adapted from Graham et al. 2011

Large inter individual variability of transporters expression
Rifampicin – Metformin interaction

**Study in rats:** PXR agonist pregnenolone-16-carbonitrile:
- ✶ AUC Metformin due to increase expression of
  - OCT1 (in the liver)
  - OCT2 (in the kidney)

**Study in healthy volunteers:** Rifampicin (PXR agonist in human)
- Metformin exposure ➕ 13%
- glucose lowering effect of metformin ➕
  - Max BG level ➖ 41%, and AUC ➖ 51%
- OCT1 in peripheral ➕ 4 x (& hepatic uptake is also ➕)
- OCT2 is not detected (in the kidney)

*Maeda T, et al., Drug Metab Disp, 2007*

*Cho SK et al., Clin Pharm Ther, 2011*

The specific effects of rifampicin on metformin pharmacokinetics and on the clinical response in actual TB–DM patients
The specific effects of rifampicin on metformin pharmacokinetics and on the clinical response in actual TB–DM patients

Metformin-Rifampicin Interaction Study in TB-DM patients
TANDEM: Tuberculosis and Diabetes Mellitus

www.tandem-fp7.eu
### The Facts...

- 15% TB also with DM
- TB-DM: Poor outcome
- Little is known about why worse outcome of TB in DM
- Even less known about basic mechanism for susceptibility

### Questions...

1. How to screen?
2. How to manage?
3. What is the basis for the poor outcome?
4. What is basic mechanism for susceptibility?
TANDEM: Methodology
Pragmatic trial in TANDEM

Objective:
- To evaluate the effect of enhanced glycemic monitoring of DM during TB treatment on clinical & microbiological outcomes.

Study design:
- 350 TB-DM patients across the sites (Romania, Peru, and Indonesia)
- Randomization for the clinical monitoring strategies
  - Normal practice (standard)
  - More intensive monitoring (intensive)
“Standard” vs. “Intensive”

**Standard**
- Normal practice at the site
- Information gathering & sampling at 2 time points (mo. 2 and 6)

**Intensive**
- Patient education - counseling
- More frequent glucose monitoring → adjust anti-diabetes meds - algorithms
- SMBG
Algorithms for glucose control

- Flow-chart A₁ (previously known DM)
- Flow-chart A₂ (newly diagnosed DM)
- Flow-chart B (not optimal with metformin)
- Flow-chart C (contraindication to metformin)
Intensive arm:

A1. Previously known DM

1. more frequent BG monitoring,
2. more intensive the adjustment of DM medications
3. keep metformin as long as possible.
Pharmacokinetic sub-study

METRICS

- Drug-drug interaction (Rifampicin-Metformin)
- Bioequivalence approach

- 27 TB-DM pts. on RH and Metformin

- Effect of Rifampicin on:
  - PK of metformin
  - Efficacy of metformin (glucose AUC)
  - Expression of the relevant transporters
While doing this study...

- Managing side effect is challenging
  - Metformin + Rifampicin together → vomitus

- Vomitus → PK sampling & BG sampling not reliable anymore
- Some adjustments needed
Future research
- LTBI screening and prophylaxis indicated for DM?
- More MDR-TB → Drug-drug interaction between second-line TB drugs and anti diabetic drugs?
- Newer anti TB drugs…?
- What is actually the cause of poorer treatment outcome of TB in TB-DM patients?
- Possible benefit and operational issues of more intensified DM monitoring and treatment in TB patients → Insulin? Metformin?
- ...?
- The convergence of TB and DM epidemics lead to an increased incidence of TB, especially in TB-endemic countries.

- DM also leads to more TB treatment failure, death and relapse

- Need for DM screening in TB (and TB in DM?)

- Glycemic control is difficult in TB (rifampicin..)
  - Drug-drug interaction
  - Augment of adverse effect
  - Role of metformin, insulin

- Many remaining questions related to optimal management

- Both at level of individual patient and of health systems
Acknowledgement

- TB Research Center, Unpad, Bandung, Indonesia
- Radboud UMC, Nijmegen, The Netherlands
- TANDEM consortium