Using new antiretroviral agents and dosing with TB treatment

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Outline of presentation

• Overview of TB Epidemiology
• Brief overview of TB diagnosis and treatment
• New Drugs and drug sensitive TB (DS TB)
• New Drugs and drug resistant TB (DR TB)
• Case study
Status of TB world-wide

**Burden of disease**

- In 2015, there were an estimated 10.4 million new TB cases worldwide
- 386 000 in South Africa
- 1.0 million (10%) among children.
- PLHIV accounted for 1.2 million (11%) of all new TB cases.
- Six countries accounted for 60%
  - India
  - Indonesia
  - China
  - Nigeria
  - Pakistan
  - South Africa
Status of MDR-TB world-wide

Burden of disease

- In 2015, of the estimated **580,000** people eligible for MDR-TB treatment, only **125,000** (~ 1 in 5) were started on treatment.
- Overall, the outcomes of MDR/RR-TB patients in the 2013 cohort:
  - **52%** were successfully treated
  - **17%** died,
  - **15%** were lost to follow-up
  - **9%** were determined to be treatment failure
  - **7%** had no outcome information

Data Source
Where does TB occur?
TB diagnosis in HIV infected persons

People living with HIV should be systematically screened for active TB at each visit to a health facility

• TB screening questions
  – Cough of any duration
  – Night sweats
  – Weight loss
  – Fever
If screen positive

- Use Xpert MTB/RIF test as a primary diagnostic test
- CXR can be considered
- No symptom, TB unlikely
- Consider IPT
Treatment of drug sensitive TB

- Two main drugs for treatment of DS TB
  - Isoniazid
  - Rifampicin
- Treatment taken 6 months by mouth
- Treatment very successful
  - >90% cure for patients who take their medication
- If resistance to rifampicin occurs treatment
  - takes much longer
  - more side effects does not work as well
Rifampicin

- Potent selective inducer of drug metabolism.
- Causes a proliferation of the smooth endoplasmic reticulum and an increase in the cytochrome P-450 content.
- Studies and case reports have demonstrated that rifampicin accelerates the metabolism of several drugs, including:
  - Oral anticoagulants
  - Oral contraceptives
  - Glucocorticoids
  - Digoxin
  - Quinidine
  - Methadone
  - Hypoglycaemic
  - Barbiturates
## Rifampicin induction

<table>
<thead>
<tr>
<th>Enzyme/transporter</th>
<th>ARV substrate</th>
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<tbody>
<tr>
<td>CYP3A4 (55.1-fold)</td>
<td>PIs, NVP</td>
</tr>
<tr>
<td>CYP2B6 (8.8-fold)</td>
<td>EFV, NVP</td>
</tr>
<tr>
<td>P glycoprotein (3.5-fold)</td>
<td>PIs, TAF</td>
</tr>
<tr>
<td>BCRP</td>
<td>TAF</td>
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<tr>
<td>UGT1A1</td>
<td>Raltegravir, Dolutegravir</td>
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</table>
In the old days........

• PK studies in patients with TB show no significant effect with EFV
• Package insert says AUC reduced 26% (n=12, no P value given)
• Standard FDC was given
But now to the new

Raltegravir & rifampicin

Graph showing plasma concentration over time for different doses of Raltegravir with and without rifampin.
ANRS REFLATE: EFV- vs RAL-based ART in TB

- Multicenter, randomized, open-label phase II trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

Lancet Infect Dis 2014;14:459
REFLATE – VL outcomes
Dolutegravir & rifampicin

![Graph showing Dolutegravir concentration over time for different dosing regimens.]

- **AUC<sub>0-24</sub>**: DTG 50 mg/d = 32.1
- **DTG 50 mg 12 hourly + rif**: 42.6

*JAIDS 2013; 62:21*
Dolutegravir adjusted doses in TB

• Absorption is saturable, so doubling the daily dose is not an option

• Clearance is increased and estimated $C_{\text{min}}$ is about the same as IC90

• Therefore 12 hourly dosing is likely to be necessary

• INSPIRING study will assess PK of DTG 12 hourly in patients with TB & evaluate efficacy (not powered versus comparator though)

• Need an adequately powered RCT of virologic efficacy of DTG 12 hourly (plus 2 NRTI) against the current standard of care (EFV, TDF, FTC) in patients with TB
Tenofovir Alafenamide vs TDF: Pharmacokinetics

**Plasma TFV**
- Mean TFV Concentration, ng/mL (SD)
- Time (h)
- E/C/F/TDF (n=29)
- E/C/F/TAF (n=36)

**Intracellular TFV-DP**
- Geometric mean (95% CI)
- E/C/F/TDF (n=14)
- E/C/F/TAF (n=21)

Lancet 2015; 385: 2606–15 (suppl app)
Tenofovir Alafenamide

- TAF is a substrate of the drug transporters P-glycoprotein, OATP1B1, OATP1B3 and BCRP; and also (minimal) CYP3A4
- When co-administered with cobicistat (an inhibitor of P-gp, OATP1B1, OATP1B3, BCRP and CYP3A4) the dose of TAF is reduced from 25 mg to 10 mg (versus modest 23% ↑AUC for TDF, requiring no dose adjustment).
- Rifampicin induces CYP3A4, P-gp, and BRCP; and inhibits (!) OATP1B1 and OATP1B3 – the nett effect is unknown (package insert: co-administration not recommended)
- Urgent need for a PK study with rifampicin, endpoint intracellular tenofovir-DP
Definitions of TB Drug Resistance

- **Drug Sensitive**
  - Rifampicin
  - Isoniazid

- **Multi drug resistant**
  - Rifampicin
  - Isoniazid

- **Pre-XDR**
  - Rifampicin
  - Isoniazid
  - Fluoroquinolone
  - Amikacin or kanamycin or capreomycin

- **Extensively drug resistant**
  - Rifampicin
  - Isoniazid
  - Fluoroquinolone
  - Amikacin or kanamycin or capreomycin
New Drugs and drug resistant TB (DR TB)

• Standard Treatment for MDR TB
• KM, Moxifloxacin, INH, Ethionamide, PZA, ethambutol, clofazamine
• No drug interactions with
  – EFV
  – DTG
  – Ral
  – PI
New kids on the block for MDR TB

- Bedaquiline: novel agent, ATPase inhibitor
- Used for XDR, preXDR and MDR TB toxicity.
- Over 4000 courses given in the NTP
- Cannot be used with EFV
- Options
  - NVP
  - LPVr
  - DTG
  - RPV
New kids on the block for MDR TB

- Delaminid: Nitroimidazole
- Recently launched by NDoH
- no ART interactions
- Not for use with BDQ yet
Case study

• 33 year old female patient, nurse
• On FDC (TFE) for three years
• Diagnosed in pregnancy
  – Nadir CD4+ 450
  – Virally suppressed after 6 months
  – Current CD4+ 325/ VL LDL
• Presents for a routine visit
• Asks to change to new drug- started working night shifts in a mine hospital
Routine visit

She complains of a cough for the last three days. She has not lost weight and dose not have a fever.

a) Start her on moxifloxacin
b) Start her on Augmentin
c) Send of a sputum specimen for AFB
d) Send of a sputum specimen for GeneXpert
e) Do routine bloods and review in 6 months
Routine visit

She complains of a cough for the last three days. She has not lost weight and does not have a fever.

a) Start her on moxifloxacin
b) Start her on Augmentin
c) Send of a sputum specimen for AFB microscopy
d) **Send of a sputum specimen for GeneXpert**
e) Do routine bloods and review in 6 months
Results of GeneXpert

- MTB detected, Rif sensitive
  a) Refer to local clinic for TB treatment
  b) Repeat the test, it cannot be correct!
  c) Do a Chest Xray
  d) Do a smear and start HREZ
Results of GeneXpert

- MTB detected, Rif sensitive
  a) Refer to local clinic for TB treatment
  b) Repeat the test, it cannot be correct!
  c) Do a Chest X-ray
  d) Do a smear and start HREZ
What next?

- Her smear is 2+, you book her off work for at least month, start her TB treatment.
- She comes back for her two month check up. Smear is now negative
- “But doctor”, she says “I am back at work. I feel well but next month I am going on night duty. I still feel dizzy at night with my FDC. I want to go on the new, fancy drug”
What are your options?

a) Tell her to stop consulting Dr GOOGLE.

b) Put her on double dose LPVr and TDF/FTC until she has finished her TB treatment.

c) Put her on twice daily dose of DTG with TDF/FTC once a day.
Conclusions

• TB is a real and present danger in South Africa
• At this stage, we are stuck with rifampicin for DS TB
• New drugs have some interactions but can be overcome.