Cohorts of MDR-TB patients treated with new drugs

Lorenzo Guglielmetti
DISCOVERY OF ANTI-TB DRUGS

Before 1940
- PAS
- STREPTOMYCIN
- PNX
- Vit. D

40s
- ETHAMBUTOL
- RIFAMPICIN
- CAPREOMYCIN

50s
- ISONIAZID
- PIRAZINAMIDE
- CYCLOSERINE
- ETHIONAMIDE
- KANAMYCIN

60s
- Other Rifamycins
- Re-purposed drugs

After 1970

1946
- MONOTHERAPY

1952
- ASSOCIATION therapy

1970
- SHORTCOURSE therapy
MDR-TB TREATMENT

- **LONG**
  - 20 to 24 months according to WHO

- **POORLY TOLERATED**
  - 14600 pills + injections + adverse events

- **UNEFFECTIVE**
  - Favourable outcomes from 64% (MDR) to 40% (XDR)

- **EXPENSIVE**
  - MDR-TB: 23,272 €; XDR-TB: 93,962 €

NEW ANTI-TB DRUGS

- Isoniazid
- Prothionamide
- Ethionamide
- Cycloserine
- Terizidone
- Meropenem
- Imipenem
- Amoxicillin/clavulanic acid
- Ethambutol
- Bedaquiline

- Mycolic acid biosynthesis
- Inhibition of peptidoglycan synthesis
- Cell wall synthesis
- ATP synthase
- Mycobactin (decreased iron uptake)
- Membrane destabilisation

- PA-824
- Delamanid
- Rifampicin
- Rifabutin
- Linezolid
- Sutezolid
- AZ05847
- Amikacin
- Kanamycin
- Capreomycin
- Clarithromycin
- PAS
- Clofazimine

- Inhibition of folic acid synthesis
- Inhibition of protein synthesis
- Ribosome
- DNA gyrase
- Inhibition of RNA synthesis

- Reactive species

2012 (FDA)
2013 (EMA)
2014 (EMA)

BEDAQUILINE (Bdq)

- Diarylquinoline
- Selective inhibitor of the mycobacterial ATP synthase complex
- PK: good oral bioavailability, $C_{\text{MAX}}$: 5h, terminal elimination half-life: 5.5 months
- Dosage: 400 mg/d for 14 d, then 200 mg thrice/w
BDQ: PRE-CLINICAL DATA

- Bactericidal and sterilizing activity in mice\(^1\)
- Synergic activity with pyrazinamide\(^2\)
- PK characteristics compatible with once a week administration\(^3\)
- Potential to shorten DS-TB\(^4\) and latent TB treatment\(^5\)

Figure 19: Changes in \( \log_{10} \) Sputum CFU Counts From Baseline Over Time With 95% CI

Rustomjee et al, AAC 2008.
BDQ: CLINICAL EVIDENCE (EBA)

Figure 19: Changes in log_{10} Sputum CFU Counts From Baseline Over Time With 95% CI

Rustomjee et al, AAC 2008.
Diacon et al, AAC 2013
BDQ: CLINICAL EVIDENCE (RCT)

**C208 Stage 1**

- **Phase IIb**
- Bdq + OBR vs. placebo + OBR
- MDR-TB only
- Low HIV rate

**C208 Stage 2**
BDQ: CLINICAL EVIDENCE (C208 Stage 1)

Proportion of Culture-Positive Patients

Days to Culture Conversion

Placebo (N=23)

TMC207 (N=21)

N=44

Diacon et al, NEJM 2009
BDQ: CLINICAL EVIDENCE (C208 Stage 2)

N=160

Primary endpoint (difference in TtC): p < 0.0001

Median time to culture conversion was 12 weeks in the BDQ group and 18 weeks in the placebo group.

p-value from Cox proportional model adjusting for strata

Diacon et al, NEJM 2014
BDQ: CLINICAL EVIDENCE (C208 Stage 2)

N=132

Diacon et al, NEJM 2014
BDQ: CLINICAL EVIDENCE (CT)

C209

Phase IIb
Single-arm, open-label
Mostly MDR-TB, 16%
XDR-TB
Low HIV rate

Overall Treatment Phase
18-24 month total MDR-TB treatment

Open Label
24 weeks

OBR + TMC207

Post-Investigational Treatment Phase
2 year follow-up

Optimized Background Regimen (OBR) Alone

TMC207 regimen: 400 mg QD for 14 days, then 200 mg TIW

24 week data available
BDQ: CLINICAL EVIDENCE (C209)

N=205

Pym et al, Eur Resp J 2015
Data from the pooled RCT population ($N = 207$)

Bdq arm:

- Higher incidence of hepatic events (9% vs. 2%)
- Higher incidence of severe adverse events (7% vs. 2%)
- No difference in patients who needed to stop the treatment (4% vs. 5%)

BDQ: QT INTERVAL PROLONGATION

Diacon et al, NEJM 2014.
## BDQ: DEATHS IN C208 AND C209

<table>
<thead>
<tr>
<th>Arm and study</th>
<th>N. of deaths (%)</th>
<th>Timing</th>
<th>TB-related</th>
<th>Related to cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bdq arm (C208 stage 1&amp;2)</td>
<td>12 (12%)</td>
<td>11 out of 12 after stopping Bdq (average 425 days after last dose)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Placebo arm (C208 stage 1&amp;2)</td>
<td>4 (4%)</td>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>C209 study (all Bdq)</td>
<td>16 (7%)</td>
<td>13 out of 16 after stopping Bdq</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

BDQ: “REAL-LIFE” DATA

French cohort\(^1\): N=45, 23 XDR-TB; 80% favorable treatment outcomes, 5 patients QTc>500 ms, 3 severe liver enzyme elevations

South African cohort: N=91, 34 XDR-TB, 54 HIV+; 76% culture conversion at 6 months, 3 pts with QTc>500 ms

Armenian cohort\(^3\): N=60, 25 XDR-TB; 80% culture conversion at 6 months, 4 SAE

2. Ndjeka et al, IJTLID 2015
DELMANANID (Dlm)

- Nitroimidazole, like pretomanid (PA-824)
- Inhibitor of mycolic acid synthesis
- PK: good oral bioavailability – enhanced with food, half-life: 30 hours
- Dosage: 100 mg bid
- Bactericidal activity against *M. tuberculosis*¹
- Sterilizing activity in mice inferred from data on other nitroimidazoles²

² Tasneen et al, AAC 2015.
Diacon et al, IJTLID 2011.
DLM: CLINICAL EVIDENCE (RCT)

Trial 204:
- Phase IIb RCT
- Blinded, controlled
- Mostly MDR-TB
- N=402
- Low HIV rate
- Two Dlm dosages
Of 481 patients who underwent randomization, 402 (83.6%) had cultures that were positive for multidrug-resistant tuberculosis with the use of MGIT at baseline (the modified intention-to-treat population) and were included in the primary efficacy analysis. Of these 402 patients, the proportion who had sputum-culture conversion with MGIT by 2 months in the group of patients who received delamanid at a dose of 100 mg twice daily was 45.4%, as compared with 29.6% in the placebo group (Fig. 2A); this was a significant increase (53%; 95% CI, 11 to 112; P = 0.008). The proportion who had sputum-culture conversion in the 200-mg group was similar (41.9%) and was significantly higher than that in the placebo group (P = 0.04). Results from the secondary analysis of sputum-culture conversion, assessed with the use of solid medium (Fig. 2B), as well as sensitivity analyses of the primary analysis, were consistent with the results of the primary analysis. These analyses included examination of data sets of sputum-culture conversion with the use of last-observation-carried-forward, observed-cases, and per-protocol methods for both MGIT and solid medium, as well as evaluation of the data with the use of various less stringent definitions of sputum-culture conversion, including one routinely used in clinical practice (two consecutive negative cultures obtained 1 month apart) and a single negative culture at 2 months. In addition, a multiple-imputation strategy for dealing with missing sputum-culture results was used. In all cases, the proportion of patients with sputum-culture conversion was higher in the groups receiving delamanid plus the background drug regimen, and in nearly all analyses, the difference was significant.

An additional key secondary analysis assessed differences among the groups with respect to time to sputum-culture conversion. For this analysis, Kaplan-Meier curves representing the time to conversion according to culture medium type (Fig. 3) showed a 10% separation between delamanid groups and the placebo group by day 36 with MGIT. By the end of the 2-month treatment period, the difference in sputum-culture conversion between the delamanid groups and the placebo group was significant (P = 0.001 for the comparisons of the 100-mg and 200-mg doses of delamanid with placebo; the same trend was observed with the use of solid medium (P = 0.0004 and P < 0.0001, respectively, by the log-rank test). In a Cox regression analysis of sputum-culture conversion, including study-dose assignment and the presence or absence of cavitation on chest radiography (a stratifiable variable), the hazard ratio for increased time to conversion to a negative sputum culture as assessed with the use of MGIT was 0.58 (95% confidence interval [CI], 0.39 to 0.89) in the 100-mg group and 0.63 (95% CI, 0.42 to 0.96) in the 200-mg group. The hazard ratio for increased time to conversion to a negative sputum culture as assessed with the use of solid medium was 0.54 (95% CI, 0.36 to 0.81) in the 100-mg group and 0.44 (95% CI, 0.29 to 0.64) in the 200-mg group.
DLM: CLINICAL EVIDENCE (RCT)

b) Completion of Trial 204

Delamanid
Trial 204 (2 months of treatment)

WHO OBR
Intensive phase (6–8 months; ≥4 months after SCC)

Completion of the intensive phase of treatment

Trial 208
Completion of Trial 208 (6 months of treatment)

Continuation phase (12–18 months; ≥16 months after SCC)

Observational Study 116 (24 months)

Completion of observation

Completion of the continuation phase of treatment
Minimum 4 weeks; more than 4 months in one third of patients
DLM: CLINICAL EVIDENCE (RCT)
### DLM: CLINICAL EVIDENCE (Trial 208)

#### Table 2

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Long-term treatment</th>
<th>Short-term treatment</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>143 (74.5; 67.7-80.5)</td>
<td>126 (55.0; 48.3-61.6)</td>
<td>269 (63.9; 59.1-68.5)</td>
</tr>
<tr>
<td>Cured</td>
<td>110 (57.3; 50.0-64.4)</td>
<td>111 (48.5; 41.8-55.1)</td>
<td>221 (52.5; 47.6-57.4)</td>
</tr>
<tr>
<td>Completed</td>
<td>33 (17.2; 12.1-23.3)</td>
<td>15 (8.5; 3.7-10.6)</td>
<td>48 (11.4; 8.5-14.8)</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>49 (25.5; 19.5-32.3)</td>
<td>50 (25.9; 23.4-31.7)</td>
<td>152 (36.1; 31.5-40.9)</td>
</tr>
<tr>
<td>Died</td>
<td>2 (1.0; 0.1-3.7)</td>
<td>19 (8.3; 5.1-12.7)</td>
<td>21 (5.0; 3.1-7.5)</td>
</tr>
<tr>
<td>Failed</td>
<td>32 (16.7; 11.7-22.7)</td>
<td>26 (11.4; 7.6-16.2)</td>
<td>58 (13.8; 10.6-17.4)</td>
</tr>
<tr>
<td>Defaulted</td>
<td>15 (7.5; 4.4-12.6)</td>
<td>58 (25.3; 19.8-31.5)</td>
<td>73 (17.3; 13.8-21.3)</td>
</tr>
</tbody>
</table>

≥ 6 months of Dlm treatment

≤ 2 months of Dlm treatment

**DLM: CLINICAL EVIDENCE (Trial 208)**

### Table 2

Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

| Treatment outcome  | Long-term treatment ≥ 6 months of Dlm treatment | Short-term treatment ≤ 2 months of Dlm treatment | All patients
|--------------------|-----------------------------------------------|-----------------------------------------------|-----------------
| Favourable         | 143 (74.5; 67.7-80.5)                          | 126 (55.0; 48.3-61.6)                         | 269 (63.9; 59.1-68.5) |
| Cured              | 110 (57.3; 50.0-64.4)                          | 111 (48.5; 41.8-55.1)                         | 221 (52.5; 47.6-57.4) |
| Completed          | 33 (17.2; 12.1-23.3)                           | 15 (6.6; 3.7-10.6)                            | 48 (11.4; 8.5-14.8)  |
| Unfavourable       | 49 (25.5; 19.5-32.0)                           | 103 (45.0; 38.4-51.7)                         | 152 (36.1; 31.5-40.9) |
| Died               | 2 (1.0; 0.0-3.7)                               | 19 (8.3; 5.1-12.7)                            | 21 (5.0; 3.1-7.5)    |
| Failed             | 32 (16.7; 11.7-22.7)                           | 26 (11.4; 7.6-16.2)                           | 58 (13.8; 10.6-17.4) |
| Defaulted          | 15 (7.8; 4.4-12.6)                             | 58 (25.3; 19.8-31.5)                          | 73 (17.3; 13.8-21.3) |

**Long-term mortality:**

6 (2.9 %) in long-term Dlm vs. 31 (12.0 %) in short-term Dlm

Data from Trial 204 (N = 481) at 8 weeks of treatment:

Dlm-containing arms (N=321) and placebo arm (N=160)

• No difference in SAE (11.2% vs. 8.8%)
• No difference in patients who had to stop the treatment (3.1% vs. 2.5%)
• No difference in hepatic-related side effects

Gler et al, NEJM 2012.
DLM: QT INTERVAL PROLONGATION

Arms with Dlm at 100 mg bid (recommended dose)

- QTc prolongation: 9.9% (Trial 204) and 9.1% (Trial 208) in Dlm arms, 3.8% in placebo arm
- Mean QTcF increase: 12.1 ms
- Increased QTcF>500ms in Dlm vs. placebo arms
- No clinically significant arrhythmias

Gler et al, NEJM 2012; Gupta et al, IJTLI 2015.
DLM: “REAL-LIFE” EVIDENCE

- One case report
- A cohort of children treated with Dlm under CU program: N=19, 13 achieved culture conversion at interim analysis, 1 SAE with renal impairment and QTc>500 ms

1. Esposito et al, Eur Resp J 2014
Adult (≥18 y.o.) patients with pulmonary MDR-TB

- when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide cannot be designed;

- when there is documented evidence of resistance (or intolerance) to any fluoroquinolone or second-line injectable drug (*just for Dlm*)

Treatment duration: 24 weeks.
DLM: ADDITIONAL INDICATION

Presence of risk factors for poor treatment outcome:

- Advanced/extended disease
- HIV coinfection
- High sputum bacillary load
- Low BMI
- Comorbidities (i.e. diabetes mellitus)
- ...
• One published case (no SAE)¹

• French cohort²
  
  • N=45 (XDR-TB=23)
  
  • 33/45 >24 wks Bdq treatment, 15 Bdq for all treatment
  
  No difference in safety data (SAE, cardiologic, hepatic) between the two groups

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¹ Lewis et al, Eur Resp J 2016.
SPECIAL POPULATIONS: PEDIATRIC USE

- **Bdq (use in <18 y.o. is off label)**
  - PK/safety study planned; no pediatric formulation; dose: 6 mg/kg loading, then 3 mg/kg
  - Few children treated by MSF, promising safety

- **Dlm (use in >6 y.o. and >20 kg permitted through CU)**
  - Good PK/safety data in >6 y.o.; pediatric formulation being developed; 100mg twice daily if >35kg; 50mg twice daily if 20-35kg; in general 3-4 mg/kg
  - One case series\(^1\) (children 8-17 y.o.) with good results

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\(^1\) Esposito et al, Eur Resp J 2014
Drug-drug interactions!

- CYP450 inducers: efavirenz (contraindicated with Bdq)
- CYP450 inhibitors: protease inhibitors, ritonavir (contraindicated with Bdq, little effect on Dlm)¹

...but good results from the South African cohort, where HIV-positive patients frequently received Lpv/r

¹ Mallikaarjun et al, AAC 2016
SPECIAL POPULATIONS:
PREGNANCY

- Bdq: animal reproduction studies have failed to demonstrate a risk to the fetus, no data in pregnant women (FDA pregnancy category B)

- Dlm: teratogenic in reproductive toxicity studies in animals, no data in humans
BDQ-DLM
CONCOMITANT USE

• The association is now allowed by manufacturers
• Not recommended by the WHO (sequential use)
• Two published case reports¹,²
• Should be considered in selected patients, and in presence of appropriate monitoring conditions

OPEN QUESTIONS

• Role of new drugs in new treatment regimens for MDR/XDR-TB

• New drugs and shortened MDR-TB treatment
ASSOCIATIONS WITH NEW DRUGS (EBA STUDIES)

Promising EBA results have been shown with the following drug associations:

- Bdq + PA-824 + Z\(^1\) (2 weeks)
- PA-824 + Mfx + Z\(^2\) (2 weeks)
- PA-824 + Mfx + Z\(^3\) (8 weeks)

## PLANNED RCTs WITH NEW DRUGS

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Design</th>
<th>Study Population</th>
<th>Comparator</th>
<th>Experimental Arm/s</th>
<th>Sample Size</th>
<th>Sponsor</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otsuka 213</td>
<td>Double blind, RCT Phase III</td>
<td>MDR-TB (no XDR-TB)</td>
<td>OBR + placebo</td>
<td>OBR+ Dlm</td>
<td>511</td>
<td>Otsuka</td>
<td>Completed / analysis ongoing</td>
</tr>
<tr>
<td>STREAM II</td>
<td>Open-label, RCT Phase III</td>
<td>R-resistant, FQ- and SLI-susceptible</td>
<td>- WHO SOC</td>
<td>- Bdq + Lfx + Cfz + E + Z for 40 weeks; hH + Pto for 16 weeks</td>
<td>1155</td>
<td>IUATLD</td>
<td>Recruiting</td>
</tr>
<tr>
<td>endTB</td>
<td>Open-label, RCT (Bayesian) Phase III</td>
<td>R-resistant, FQ-susceptible</td>
<td>WHO MDR/XDR-TB SOC</td>
<td>- Bdq+Lzd+Mfx + Z - Bdq+Cfz+Lzd+Lfx +Z - Bdq+Dlm+Lzd+Lfx +Z - Dlm+Cfz+Lzd+Lfx +Z - Dlm+Cfz+Mfx + Z for 36 weeks</td>
<td>750</td>
<td>MSF, PIH</td>
<td>Not started</td>
</tr>
</tbody>
</table>
## PLANNED RCTs WITH NEW DRUGS (2)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Design</th>
<th>Study population</th>
<th>Comparator</th>
<th>Experimental arm/s</th>
<th>Sample size</th>
<th>Sponsor</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEXT</td>
<td>Open-label, RCT Phase III</td>
<td>R-resistant, FQ- and SLI-susceptible</td>
<td>WHO MDR/XDR-TB SOC</td>
<td>Lzd + Bdq + Lfx + Z + (Eto or hH or Tzd) for 6 to 9 months</td>
<td>300</td>
<td>University of Cape Town</td>
<td>Enrolling</td>
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<tr>
<td>MDR-END</td>
<td>Open-label, RCT Phase II</td>
<td>Rifampicin-resistant, FQ-susceptible TB patients</td>
<td>WHO MDR/XDR-TB standard of care</td>
<td>Dlm + Lzd + Lfx + Z for 9 to 12 months</td>
<td>238</td>
<td>Seoul National University Hospital</td>
<td>Enrolling</td>
</tr>
<tr>
<td>STAND</td>
<td>Open-label, partially randomized, controlled, Phase III</td>
<td>R-resistant, FQ- and Z-susceptible</td>
<td>DS-TB control arm: Mfx + Pa + Z</td>
<td>MDR-TB experimental arm: Mfx + Pa + Z for 26 weeks</td>
<td>1500 (including DS-TB cases)</td>
<td>Global TB Alliance</td>
<td>On hold; to resume soon</td>
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<tr>
<td>Nix-TB</td>
<td>Open-label, non randomized, uncontrolled Phase III</td>
<td>XDR-TB, failed MDR, drug intolerance</td>
<td>No control</td>
<td>Bdq + Pa + Lzd for 6 to 9 months</td>
<td>200</td>
<td>Global TB Alliance</td>
<td>Enrolling</td>
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</table>
Thank you...
EXTRA SLIDES
<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment arm</th>
<th>Category</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>208-4041</td>
<td>BDQ</td>
<td>Non-responder; converted; discontinued</td>
<td>Alcohol poisoning</td>
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<tr>
<td>208-4153</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>TB-related illness</td>
</tr>
<tr>
<td>208-4224</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>TB-related illness</td>
</tr>
<tr>
<td>208-5069</td>
<td>BDQ</td>
<td>Non-responder; converted; discontinued</td>
<td>Cirrhosis, hepatitis, anaemia</td>
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<tr>
<td>208-4399</td>
<td>BDQ</td>
<td>Responder; converted</td>
<td>Cerebrovascular accident</td>
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<tr>
<td>208-5067</td>
<td>BDQ</td>
<td>Responder; converted</td>
<td>Peritonitis and septic shock</td>
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<tr>
<td>208-4378</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>Motor vehicle accident</td>
</tr>
<tr>
<td>208-4464</td>
<td>BDQ</td>
<td>Non-responder; failure to convert</td>
<td>TB-related illness</td>
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<tr>
<td>208-4155</td>
<td>Placebo</td>
<td>Non-responder; failure to convert</td>
<td>TB-related illness</td>
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</tbody>
</table>

Deaths during long-term survival follow-up of prematurely withdrawn subjects

<table>
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<tr>
<th>Subject</th>
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<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>208-4127</td>
<td>BDQ</td>
<td>Non-responder; failure to convert</td>
<td>TB-related illness</td>
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<tr>
<td>208-4145</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>TB-related illness</td>
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<td>208-4378</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>Motor vehicle accident</td>
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<td>208-4155</td>
<td>Placebo</td>
<td>Non-responder; failure to convert</td>
<td>TB-related illness</td>
</tr>
</tbody>
</table>
• Case with sequential acquisition of resistance to Bdq ($Rv0678$ mutation) and Dlm ($FbiA$ mutation)

1. Bloemberg et al, NEJM 2015
• *Rv0678* (and *pepQ*) mutations confer Cfx cross-resistance

• *Rv0678* mutations found in 6.1% of MDR-TB patients not exposed to Bdq/Cfx\(^1\)

• Clinical significance of *Rv0678* mutations associated with different Bdq MICs is unknown

DRUG RESISTANCE TO NEW DRUGS (3)

• Bdq-resistant strains found in 4/209 (1.9%) MDR-TB patients tested at the NRL in France:
  ▪ 2 patients were not previously exposed to Bdq/Cfz
  ▪ 1 patient had been exposed to Bdq before (Rv0678 mutation)
  ▪ 1 patient acquired resistance during treatment (Rv0678 mutation)

Veziris N, personal communication.