Manufacturing XDR TB:
Timing of Acquired Resistance to Fluoroquinolones and Second-line Injectable Drugs during MDR TB Treatment in 9 Countries, 2005–2010

Preserving Effective TB Treatment Study (PETTS)

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Conflict of interest disclosure

• I have no, real or perceived, direct or indirect conflicts of interest that relate to this presentation.
XDR TB

Nearly 50% of people with XDR-TB die within two years.

Nearly 85% of people with XDR-TB die within five years.

Preserving Effective TB Treatment Study (PETTS)

- Prospective cohort study of MDR TB in 9 countries, 2005–2010

Countries included:
- South Africa
- South Korea
- Russia
- Thailand
- Taiwan
- Philippines
- Latvia
- Estonia
- Peru
- South Africa
Specific Aims of PETTS

• To determine
  – the frequency of acquired resistance (AR) to second-line drugs (SLD) during treatment of MDR TB
  – the risk factors for AR to SLD
  – the effect of AR to SLD on patient outcomes
  – the timing of AR to SLD
Acquired Resistance (AR) during MDR TB treatment

- Prevalence of baseline resistance to second-line drugs (SLD) is high
  - 43.7% to any SLD; 6.7% XDR

- 30% of patients may AR to SLD during MDR TB treatment
  - 11.2% to FQ, 7.8% to SLI, 8.9% to both FQ and SLI

- Risk of AR increases with baseline resistance to other drugs

- AR is an important predictor of treatment failure or death

Objective

• To determine how quickly acquired resistance to second-line injectable drugs (SLI) and fluoroquinolones (FQ) emerges during treatment of MDR TB
Methods

Baseline Sputum culture

Start of MDR TB treatment

Monthly sputum cultures

End of MDR TB treatment
Methods

* First and last isolate from each patient was tested at CDC for susceptibility to 12 drugs by proportion method on Middlebrook 7H10 agar plates.
Methods

*DST

Baseline
Sputum culture

Start of MDR TB treatment

24-locus MIRU/VNTR genotype

Monthly sputum cultures

Last positive culture

End of MDR TB treatment

*DST

* If DST results changed for SLI or FQ then both isolates genotyped with 24-locus MIRU/VNTR
Methods

24-locus MIRU/VNTR genotype

Matching genotype: ACQUIRED RESISTANCE
Different genotypes: different strains

* Matching MIRU-24 results included isolate pairs that differ by only 1 locus
Methods

For all patients with changing DST results and matching genotypes, all sequential monthly isolates underwent DST.
Methods

MATCHING 24-locus MIRU/VNTR genotype

Baseline Sputum culture

Start of MDR TB treatment

Monthly sputum cultures

End of MDR TB treatment

S

R

0 1 2 3 4 5 6 24

Last positive culture
Time-to-Acquired Resistance (TTAR)

Baseline Sputum culture

1st resistant isolate

Last positive culture

Time-to-Acquired Resistance

S S S R R R R

0 1 2 3 4 5 6

Start of MDR TB treatment

Monthly sputum cultures

End of MDR TB treatment

TTAR = Date of 1st Resistant Isolate – Date of Baseline Sputum culture
Study Population for Analysis of Time-to-Acquired Resistance to FQ and/or SLI

- **832** patients with DST results for baseline & final isolates

- **250** (30%) patients with differences between baseline & final DST result for ≥1 drug were genotyped

- **165** (66%) pairs had matching* MIRU-24 results

- **78** (47%) patients with serial isolates showing a clear change from susceptible to resistant

*Matching MIRU-24 results included 18 isolates that differed in only 1 locus

- **582** patients with same DST results for baseline & final isolates

- **85** patients with different genotypes

- **87** patients without clear AR to FQ or SLI
Clear Acquired Resistance

| S | S | S | S | R | R | R | R | R | R |

OFL
n=79
58/79

KAN
n=56
29/56
Acquired Resistance?

OFL
n=79
58/79
21/79

KAN
n=56
29/56
27/56
Study Population for Analysis of Time-to-Acquired Resistance to FQ and/or SLI

78 patients with serial isolates showing a clear change from susceptible to resistant

58 (74%) patients AR to FQ
29 (37%) patients AR to SLI
9 (12%) patients AR to both FQ and SLI
Number of days from baseline sputum culture to first culture with resistance to FQ and SLI

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<th>Drug Class</th>
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<th>Number patients</th>
<th>Min days</th>
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Time (months) to Acquired Ofloxacin Resistance

Number of patients with AR to Ofloxacin, n = 58

Median = 3 months
IQR = 2–7 months
Time (months) to Acquired Kanamycin Resistance

Number of patients with AR to Kanamycin, n = 29

Median = 4 months
IQR = 2–7 months
Time-to-Acquired Resistance

• Associated with programmatic, social, and clinical characteristics

• Similar to risk factors for
  – Acquired resistance in general
  – Good and bad treatment outcomes

• Time-to Acquired Resistance is dominated by
  – Resistance to other drugs in treatment regimen (accelerates)
  – Effective treatment (decelerates)

Baseline resistance to SLI accelerates TTAR

Time-to-Acquired Resistance to Ofloxacin

- No baseline resistance to SLI
- Baseline resistance to SLI

Months from start of MDR TB treatment
Effective treatment decelerates TTAR

Time-to-Acquired Resistance to Ofloxacin

- Treatment with effective SLI
- Not on treatment with effective SLI

Months from start of MDR TB treatment
Conclusions

• First quantitation of how soon acquired resistance to FQ or SLI emerges during treatment of MDR TB
• Median: 3 months for FQ, 4 months for SLI
• $1/4^{th}$ of AR detectable in 7–8 weeks for FQ, 9–13 weeks for SLI
• $1/4^{th}$ of AR emerged after 6 months, while 10% detected after 15 months
• Timing of AR is accelerated by baseline resistance to other drugs
• Effective treatment regimen decelerated time-to-acquired resistance
Public Health Implications

• Baseline DST results are important to inform an effective MDR-TB treatment regimen

• Susceptibility testing should be repeated at intervals to ensure treatment regimen remains effective
  – Patients in whom cultures remain positive
  – Any other indication treatment may not be effective
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