The ‘third wave’ of TB drug development: What’s on the horizon (for patients with or without HIV)

Kelly Dooley, MD, PhD

20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, Other Antivirals
Noordwijk, The Netherlands
15 May 2019
Objectives

• To give you an idea of the drug development pathway for TB drugs, the history, and the pipeline

• To convince you to come work in the TB field, if you are not already
The Problem
State-of-the-state: Global burden of TB disease: 2017

In 2014, TB surpassed HIV as the #1 infectious disease killer worldwide.

In 2017, 10.0M cases

TB is estimated to have killed 1 in 7 of humans who have ever lived.
Preventing tuberculosis in people with HIV—no more excuses

In 2014, tuberculosis eclipsed HIV as the leading infectious killer on earth and it remains the foremost cause of death for people with HIV infection. The risk of tuberculosis doubles after HIV is acquired, skyrockets with falling CD4 counts, and remains substantially elevated even after immune reconstitution with antiretroviral therapy (ART). From the earliest days of the HIV epidemic, it was evident that preventive therapy with isoniazid—a cheap, widely available, well-tolerated drug that has been around for more than 60 years—was protective against tuberculosis in people with HIV infection, and WHO recommended its use as a personal health measure (ie, not as a programmatic imperative) in 1992. Over the past 20 years, numerous clinical trials and observational cohort studies have demonstrated the effectiveness of isoniazid preventive therapy (IPT) in preventing tuberculosis in people with HIV infection in the absence of ART in settings.

In this issue of The Lancet Global Health, Anani Badje and colleagues3 publish the long-term follow-up data from the TEMPRANO study—a randomised, factorial design trial testing the impact of IPT and/or early ART for individuals with HIV infection and CD4 counts of less than 800 cells per μL but above the threshold for initiating treatment during the trial, prior to universal ART being endorsed. The initial results of TEMPRANO found that IPT and early ART each reduced the risk of developing serious HIV events, a large proportion of which were tuberculosis, and that receiving both IPT and early ART provided the best protection from disease. The post-trial phase doubles the duration of observation and shows that 6 months of IPT given early in the course of HIV infection provides a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART over an average of 4.9 years of follow-up.

Chaisson and Golub, Lancet Global Health, 2017
MDR- and XDR-TB: Global Health Emergencies

Multidrug-resistant TB:
*Mycobacterium tuberculosis* resistant to isoniazid and rifampin: 558,000 incident cases in 2017

Extensively drug-resistant TB:
*M. tuberculosis* resistant to isoniazid, rifampin, fluoroquinolones, and injectable agents
Reported in 123 WHO member state countries
## HIV and Tuberculosis Epidemiology

### Global Burden of Tuberculosis, 2017

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>HIV-Infected Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>10.0 million</td>
<td>900,000 (9%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.3 million</td>
<td>300,000 (23%)</td>
</tr>
</tbody>
</table>

WHO Report 2018 Global Tuberculosis Control
## TB Treatment: Global Scientific Agenda

<table>
<thead>
<tr>
<th>Area</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug-sensitive TB</strong></td>
<td>Treatment shortening to ≤ 3 months</td>
</tr>
<tr>
<td></td>
<td>More options for patients</td>
</tr>
<tr>
<td><strong>MDR-TB</strong></td>
<td>Treatment shortening to &lt; 6 months; reduced toxicity</td>
</tr>
<tr>
<td><strong>TB prophylaxis</strong></td>
<td>Highly-safe, ultra-short course treatments for (drug-sensitive) LTBI</td>
</tr>
<tr>
<td></td>
<td>Effective, well-tolerated therapy for MDR-TB contacts</td>
</tr>
<tr>
<td><strong>HIV-TB co-treatment</strong></td>
<td>Regimens that can be used together, avoiding or mitigating drug interactions</td>
</tr>
<tr>
<td><strong>Special unmet medical need</strong></td>
<td>Extrapulmonary TB, specifically regimens for TBM that reduce mortality</td>
</tr>
<tr>
<td><strong>Clinical pharmacology</strong></td>
<td>Optimizing use of the drugs we have</td>
</tr>
</tbody>
</table>
HIV-TB Co-Treatment: Recent adult trials

### Treatment of TB Disease

<table>
<thead>
<tr>
<th>Antiretroviral medication§</th>
<th>Rifamycin*</th>
<th>Trial name/sponsor</th>
<th>Dose adjustments in adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>High-dose rifampicin</td>
<td>RIFAVIRENZ/ANRS</td>
<td>Probably none</td>
</tr>
<tr>
<td>Lower-dose efavirenz</td>
<td>Rifampicin</td>
<td>ENCORE-1 substudy OPTIMIZE project</td>
<td>Likely not necessary</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Rifampicin</td>
<td>REFLATE/ANRS</td>
<td>Increase raltegravir to 800 mg twice daily</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Rifampicin</td>
<td>INSPIRING/ViiV</td>
<td>Increase dolutegravir 50 mg twice daily</td>
</tr>
<tr>
<td>Ritonavir-boosted lopinavir</td>
<td>Rifabutin</td>
<td>ACTG A5290</td>
<td>Decrease rifabutin to 150 mg once daily</td>
</tr>
<tr>
<td>Tenofovir alafenamide (TAF)</td>
<td>Rifampicin</td>
<td>Gilead Sciences</td>
<td>Likely not necessary</td>
</tr>
</tbody>
</table>

### Treatment of TB Infection (LTBI) : See Anthony Podany’s talk, coming up next...

Atwine et al IAS 2017 MOPEB0340 Poster; NCT01986543; Cerrone 2019 CID and Kaboggoza 2019 Open Forum Inf Dz; Grinsztejn et al Lancet ID 2014 14:459; Clinical Infectious Diseases 2019 (in press); in preparation (see also Naiker 2014; Lan 2014); Cerrone JAC 2019, in press.
History
We've come a long way (or have we?)....
How did we get here?

• Something, anything:
  • Streptomycin (MRC, 1946)

• Two is better than one:
  • p-aminosalicylic acid (PAS) plus streptomycin vs. either alone (MRC, 1952)

• Choose a regimen that prevents INH resistance:
  • Isoniazid plus (rifampin, streptomycin, ethambutol, PAS, thiacetazone):
    3 drugs for 2 months, then 2 drugs for 12 months

• Now shorten it up:
  • Pyrazinamide allows shortening of treatment from 9 to 6 months:

• Now remove the injectable:
  • Ethambutol used in place of streptomycin

Why is rifampin special? What is “sterilizing activity”?  

SUMMARY  Model systems were set up in vitro to explore the reasons why rifampin is a better sterilizing drug than isoniazid in short-course chemotherapy of tuberculosis. When the growth rate of *Mycobacterium tuberculosis* strain H37Rv was reduced uniformly by lowering the incubation temperature or the pH of the culture medium, the bactericidal activity of rifampin and isoniazid decreased to a similar extent. However, when a culture was maintained at 8°C and incubated for daily periods of 1 or 6 h at 37°C, rifampin killed more rapidly than isoniazid. Maintenance of control cultures without antimicrobials at 8°C with or without periods at 37°C, had little or no effect on their viability, ability to commence logarithmic growth at 37°C, or to incorporate [¹⁴C]uridine. Old cultures left undisturbed or to which small additions of fresh culture medium were regularly added were killed more rapidly by rifampin than by isoniazid. These experiments supported the view that the special part of the bacterial population that is killed more rapidly by rifampin than by isoniazid during short-course chemotherapy consists of bacilli dormant much of the time but occasionally metabolising for short periods.

AM REV RESPIR DIS 1981; 123:367–371

Dickinson & Mitchison 1981
What can pyrazinamide do: before rifampicin

Are lower doses as effective?

With INH, in patients with advanced disease, no previous treatment:

<table>
<thead>
<tr>
<th>PZA Dosage</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/kg</td>
<td>49/53 (92%)</td>
<td>48/53 (91%)</td>
</tr>
<tr>
<td>20-30 mg/kg</td>
<td>37/52 (71%)</td>
<td>28/42 (66%)</td>
</tr>
</tbody>
</table>

“Therapeutic inferiority was particularly evident at the lowest dosage level of 20 mg/kg”

Pyrazinamide has proven, significant sterilizing activity; dual therapy with INH at high doses results in cavity closure, protection against resistance, cure in most patients

Pyrazinamide for treatment shortening: Pyrazinamide with rifampicin

Adding Z at dose of 35-40 mg/kg in first two months allows for shortening to 6 months

**RELAPSES IN FIRST 6 MONTHS AFTER CHEMOTHERAPY AMONG PATIENTS WITH STRAINS OF TUBERCLE BACILLI DRUG-SUSCEPTIBLE BEFORE TREATMENT**

<table>
<thead>
<tr>
<th>Duration of Chemotherapy (months)</th>
<th>Regimen</th>
<th>Patients Assessed (no.)</th>
<th>Total (no.)</th>
<th>(%)</th>
<th>Relapses *</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>SHR</td>
<td>150</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SHRZ/S₂H₂Z₂</td>
<td>90</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SHRE/S₂H₂E₂</td>
<td>86</td>
<td>16</td>
<td>19</td>
<td>0</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S₃H₃R₃Z₃/S₂H₂Z₂</td>
<td>74</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>SHRZ/S₂H₂Z₂</td>
<td>88</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SHRE/S₂H₂E₂</td>
<td>87</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S₃H₃R₃Z₃/S₂H₂Z₂</td>
<td>89</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Hong Kong Chest Service/BMRC (1978) Am Rev Resp Dis: controlled trial of 6-month and 8-month regimens...
Used at ‘minimally effective dose’ because of narrow therapeutic margin- solely to prevent resistance

Ethambutol Partitioning in Tuberculous Pulmonary Lesions Explains Its Clinical Efficacy

Matthew Zimmerman, a Jodi Lestner, a,b Brendan Prideaux, a Paul O’Brien, a Isabela Dias-Freedman, a Chao Chen, a Jillian Dietzold, b Isaac Daudelin, a Fırat Kaya, a Landry Blanc, a Pei-Yu Chen, a Steven Park, a Padmini Salgame, a Jansy Sarathy, a Véronique Dartois a

Public Health Research Institute, New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, New Jersey, U.S.A.; Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, United Kingdom; Department of Medicine, Division of Infectious Disease, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA.

ABSTRACT Clinical trials and practice have shown that ethambutol is an important component of the first-line tuberculosis (TB) regime. This contrasts the drug’s rather modest potency and lack of activity against nongrowing persistor mycobacteria. The standard plasma-based pharmacokinetic-pharmacodynamic profile of ethambutol suggests that the drug may be of limited clinical value. Here, we hypothesized that
Drug-Sensitive TB: The Role of Individual Drugs in “Short Course” Therapy

**INH:** Early **bactericidal** activity, rapid reduction in organism burden

**Rifampin:** Unique **sterilizing** activity against “persisters”, key contributor to cure without relapse

**Pyrazinamide:** Sterilizing activity in **acidic environments** over the first 2 months, allowing for shortening of treatment

**Ethambutol:** **Prevents resistance** to other antibiotics
### New (2018) Standard-Duration (18-24mo) MDR Rx

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Levofloxacin or moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td>B</td>
<td>Clofazimine</td>
</tr>
<tr>
<td></td>
<td>Cycloserine or terizidone</td>
</tr>
<tr>
<td>C</td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Imipenem-cilastin or meropenem (plus clavulanic acid)</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
</tr>
<tr>
<td></td>
<td>Ethionamide or prothionamide</td>
</tr>
<tr>
<td></td>
<td>p-aminosalicylic acid</td>
</tr>
</tbody>
</table>

- **Include all 3** (unless they can’t be used)
- **Add both** unless they can’t be used
- **Add to complete the regimen** and when medicines from Groups A and B cannot be used

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Levofloxacin or moxifloxacin</td>
<td>Generally well-tolerated</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
<td>QT prolongation</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Bone marrow suppression, peripheral neuropathy</td>
</tr>
<tr>
<td>B</td>
<td>Clofazimine</td>
<td>Skin discoloration, ichthyosis</td>
</tr>
<tr>
<td></td>
<td>Cycloserine or threidone</td>
<td>CNS toxicity</td>
</tr>
<tr>
<td>C</td>
<td>Ethambutol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
<td>Mild QT prolongation</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipenem-cilastin or meropenem (+ clavulanic acid)</td>
<td>IV formulation</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>Deafness, vestibular dysfunction, kidney toxicity</td>
</tr>
<tr>
<td></td>
<td>Ethionamide or prothionamide</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>p-aminosalicylic acid</td>
<td>GI toxicity, hypersensitivity, drug-induced lupus</td>
</tr>
</tbody>
</table>

## New-ish (in 2016): WHO Short-Course MDR-TB Rx

<table>
<thead>
<tr>
<th>Phase</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-month intensive phase</td>
<td>High-dose INH* Prothionamide/ethionamide* Kanamycin/amikacin Moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Ethambutol* Pyrazinamide* Clofazimine</td>
</tr>
<tr>
<td>5-month continuation phase</td>
<td>Moxifloxacin Ethambutol* Pyrazinamide* Clofazimine</td>
</tr>
</tbody>
</table>

*Resistance likely for many MDR patients

Why It’s Tricky
Principles of Antimycobacterial Chemotherapy

TB is a complex disease: metabolic/anatomic compartments

- Metabolic state of bacteria may vary by lesion type
- Need for prolonged therapy (months) to completely eradicate infection (because of “persisters”)
- Drug activity may be different depending on microenvironment
- TB is both an intracellular and extracellular disease
Lesion PK and activity

Strydom 2019 PLoS Medicine
## Baseline characteristics, on-treatment culture status and adherence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of unfavorable outcomes/ number of study participants (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>85/913 (9)</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;90 and &lt;100%</td>
<td>37/230 (16)</td>
<td>2.4 (1.6–3.6)</td>
</tr>
<tr>
<td>≤90%</td>
<td>16/43 (37)</td>
<td>5.9 (3.3–10.5)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>98/999 (10)</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>40/187 (21)</td>
<td>3.1 (2.0–4.6)</td>
</tr>
<tr>
<td>Month 2 culture status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>93/922 (10)</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>45/264 (17)</td>
<td>1.8 (1.3–2.7)</td>
</tr>
<tr>
<td>BMI (per 5 kg m$^{-2}$ decrease)</td>
<td></td>
<td>1.5 (1.0–2.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30/347 (7)</td>
<td>Reference</td>
</tr>
<tr>
<td>Male</td>
<td>108/839 (13)</td>
<td>1.5 (1.0–2.4)</td>
</tr>
</tbody>
</table>

Imperial (2018) Nature Medicine
Preclinical assessment
Clinical PK-safety

Phase 1 trials (individual drug X)
- Single dose, Multiple dose
- Safety and PK studies

Animal model studies
(Drug X alone and in combinations)
- PK/PD Assessments
- Bactericidal activity (microbiology)
- Sterilizing activity (stable cure, no relapse)
- Drug distribution

Preclinical:
- PK/PD driver
- Pharmacologic sanctuaries

Human:
- ADME, basic PK with variability
- Maximal tolerated dose
- Human hepatocyte studies - identify DDI
- Food effect

Phase 2A
Early Bactericidal Activity (EBA) trial
- Individual drug X
- Or Drug X in combination
- Dose-Ranging 7-14 days
- 15-20 patients/arm
- Outcome: Sputum colony forming units over time with treatment
- Deliverable: Evidence of single drug microbiologic effect; Dose to take forward

Phase 2B/C
Multidrug treatment trial
- Combination therapy
- Limited number of doses of X 8 weeks
- 60-75 patients/arm
- Outcome: Sputum culture conversion to negative at 8 weeks
- Deliverable: Safety, comparative early microbiologic activity, go/no-go for Phase 3

Drug-drug interaction studies
- With ART, with other TB drugs

Phase 3
Confirmatory trial
- Combination therapy
- Single dose of X
- Full course of treatment
- 500-1000 patients/arm
- Outcome: Failure/relapse
- Deliverable: Noninferiority compared to standard treatment

Registration/Use
- Who did not respond, and why?
- PK-microbiology-relapse
- PK-disease state-resistance

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Clinical Efficacy & Safety
Lo, fear not...

**THE LANCET Infectious Diseases**

## Adult trials (DS-TB)

<table>
<thead>
<tr>
<th>TB Research Area</th>
<th>Key studies in Adults</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
</table>
| Drug-sensitive TB Treatment shortening | • HIGHRIF1: Rifampin max tolerated dose (max 40 mg/kg)  
• HIRIF: Higher-dose rifampicin (max 1200)  
• RIFASHORT: Higher-dose rifampicin (to 1800), 4 months  
• MAMS-TB-01: High-dose rifampicin +/- moxifloxacin | • II  | • Completed  |
|                  | • TBTC 31/A5349: High-dose RPT +/- moxifloxacin                                        | • III | • Fully enrolled |
| Optimizing rifamycins | • SUDOCU (PanACEA): BDM+STZ vs. $R_{high}$, $H_{high}$, $E$ vs. $R_{high}$, $HZE$ vs. SOC | • IIC | • Planning   |
| Regimens involving new drugs | • SImpliciTB: BDQ+Pretomanid+MFX+PZA, 4 months  
• APT: pretomanid+INH+PZA+RBT or RIF, 12 weeks  
• TRUNCATE-TB: multiple 2 month regimens  
• Clo-FAST (ACTG A5362): Clofazimine + RPT+ HZE, 13-17 weeks  
• CRUSH-TB (TBTC): BDQ+MFX+PZA+ RBT or DLM, 4 months | • III | • Enrolling  |
|                  |                                                                                       | • II  | • Enrolling  |
|                  |                                                                                       | • III | • Enrolling  |
|                  |                                                                                       | • IIC | • Planning   |
|                  |                                                                                       | • IIC | • Planning   |

Key: MFX=moxifloxacin, PZA=pyrazinamide, INH=isoniazid; RBT=rifabutin; RIF=rifampin; BDQ=bedaquiline; RPT=rifapentine; DLM=delamanid
The Second Wave
# Second Wave Drugs

<table>
<thead>
<tr>
<th></th>
<th>Bedaquiline</th>
<th>Delamanid</th>
<th>Pretomanid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Diarylquinoline</td>
<td>Nitroimidazole</td>
<td>Nitroimidazole</td>
</tr>
<tr>
<td><strong>MOA</strong></td>
<td>ATP synthase inhibitor</td>
<td>Ketomycolate synthesis inhibitor</td>
<td>Cell wall synthesis inhibitor; toxic reactive nitrogen species</td>
</tr>
<tr>
<td><strong>Indication/regulatory</strong></td>
<td>FDA 2012, EMA 2013 MDR-TB; 24 weeks</td>
<td>EMA 2014 MDR-TB, 24 weeks</td>
<td>FDA review 2019 coming XDR TB with LZD+BDQ</td>
</tr>
<tr>
<td><strong>Pediatrics</strong></td>
<td>WHO recommended to age 6</td>
<td>WHO recommended to age 3</td>
<td>Not tested yet in children</td>
</tr>
<tr>
<td><strong>PK quirks</strong></td>
<td>CYP3A substrate</td>
<td>Metabolized by albumin</td>
<td>CYP3A minor pathway</td>
</tr>
<tr>
<td></td>
<td>Long terminal half-life</td>
<td>Low bioavailability</td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Moderate QT effects</td>
<td>Modest QT effects</td>
<td>Unknown; liver</td>
</tr>
<tr>
<td><strong>HIV Co-Rx</strong></td>
<td>EFV and PI and CYP3A</td>
<td>--</td>
<td>EFV DDI</td>
</tr>
<tr>
<td><strong>Current trial landscape</strong></td>
<td>Short-course MDR 4-month drug-sensitive</td>
<td>MDR prophylaxis</td>
<td>Short-course MDR 4-month drug-sensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-course MDR</td>
<td></td>
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</tbody>
</table>

*Sutezolid also a second wave drug, under re-development*
### Key studies in Adults

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A5312: INH dose-finding EBA</td>
<td>II</td>
<td>Enrolling</td>
</tr>
<tr>
<td>LIN-CL001: Linezolid EBA/safety, dose-finding (DS-TB)</td>
<td>II</td>
<td>In f/u</td>
</tr>
<tr>
<td>OptiQ: Levofloxacin dose-finding</td>
<td>II</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Trial 213: Delamanid + OBR vs. placebo + OBR x 6 months</td>
<td>III</td>
<td>Completed</td>
</tr>
<tr>
<td>STREAM Stage 1: 4MCEZHKPro/5MCZE (9 months) vs. SOC</td>
<td>III</td>
<td>Completed</td>
</tr>
<tr>
<td>STREAM Stage 2: SOC vs. MCEZHKPro (9 mo) vs. BLCEZHKPro (9 months, all-oral) v. BLCZHK (6 months, incl injectable)</td>
<td>III</td>
<td>Enrolling</td>
</tr>
<tr>
<td>NC-005: B-Pa-M-Z</td>
<td>II</td>
<td>Completed</td>
</tr>
<tr>
<td>SimpliciTB: B-Pa-M-Z</td>
<td>III</td>
<td>Enrolling</td>
</tr>
<tr>
<td>NIX-TB: B-Pa-LZD x 6 months (XDR-TB)</td>
<td>III</td>
<td>In f/u</td>
</tr>
<tr>
<td>ZeNIX-TB: B-Pa-LZD (LZD dose/duration finding)</td>
<td>III</td>
<td>Enrolling</td>
</tr>
<tr>
<td>A5343: bedaquiline + delamanid added to OBR x 6 months</td>
<td>II</td>
<td>In f/u</td>
</tr>
<tr>
<td>A5356: D+LZD+OBR (all-oral) vs. D+OBR</td>
<td>II</td>
<td>Planning</td>
</tr>
<tr>
<td>NExT-5001: LzBlvZ(H or Eth or Ter) vs. SOC</td>
<td>II/III</td>
<td>Enrolling</td>
</tr>
<tr>
<td>MDR-END: D+Lvf+Lzd+Z vs. SOC</td>
<td>II</td>
<td>Enrolling</td>
</tr>
<tr>
<td>TB-PRACTECAL: BPaMLz v BPaLzC v BPaLz vs. SOC</td>
<td>II/III</td>
<td>Enrolling</td>
</tr>
<tr>
<td>endTB: 9BLzMZ v 9BLzClvZ v 9BLzDLvZ v 9DCMZ v SOC</td>
<td>III</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>

**Key:** Lz=LINEZOLID; Lf=LEVOFLOXACIN; D=DELAMANID; B=BEDAQUILINE; Pa=PRETOMANID; C=CLOFAZIMINE; Z=PYRAZINAMIDE
The Third Wave
Target Regimen Profiles (TRP): What are we aiming for?

- TRPs prioritize regimen characteristics
- TRP takes into account the needs of patients, care providers and policy-makers
- Target audience includes pharmaceutical industry, research institutions, PDPs, donors, NGOs & civil society organizations
- TRPs for
  - Rif susceptible TB regimens
  - Rif Resistant TB regimens
  - “Pan TB” regimens*

*Drug-resistant organisms may behave differently from drug-sensitive organisms, aside from response to drug X or Y
2019 Global New TB Drug Pipeline

Discovery
- Diarylthiazoles
- DprE1 Inhibitors
- Direct InhA Inhibitors
- Mtb energy metabolism
- Macrolides
- Mycobacterial Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, Clp, PKS13
- Oxazolidinones
- Squaramides

Preclinical Development
- Early Stage Development
  - CPZEN-45*
  - TBAJ-587
  - Spectinamide
  - TBAJ-876 - 1810*
  - GSK-286*
  - TB-47*
  - Sanfetrinem
  - S-004992*

GMP/GLP Tox.
- Phase 1
  - SPR720*
  - TBI-223
  - BTZ-043*
  - TBI-166
  - Macozinone* (PBTZ-169)
  - GSK-656* (070)
  - TBA-7371*
  - Conteozolid

Clinical Development
- Phase 2
  - OPC-167832*
  - Telacebec* (Q203)
  - Delpazolid (LCB01-0371)

- Phase 3
  - Bedaquiline*
    (TMC-207)
  - Delamanid*
    (OPC-67683)
  - Pretomanid*
    (PA-824)

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

1 New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = new to Phase since Oct 2018

www.newtbdrugs.org
Updated: March 2019
Breaking it down, by class, drugs in clinical testing—oxazolidinones, widening the therapeutic margin

| **Oxazolidinone** - Protein synthesis inhibitor, binds bacterial 23s rRNA of 50S subunit to prevent formation of 70S initiation complex |
|---|---|---|
| **Sutezolid, PNU-100480** | Sequella, Inc, TB Alliance | In mice, shortens standard treatment by one month, activity superior to linezolid Safety and tolerability up to 1000 mg in humans Highly active primary metabolite (PNU-101603) at higher concentration than parent Phase 2 data: No heme/neuro AE, 14% patients with ALT elevation NCT01225640 (2, complete) SUDOCU (2, proposed) STEP (2c, proposed) |
| **Delpazolid, LCB01-0371** | LegoChem Biosciences, Inc. | Phase 1: tolerated to 1200mg twice daily (though decline in heme values for daily doses>800mg), NCT02836483 (2, enrolling) |
| **Contezolid, MRX-4** | MicuRx Pharmaceuticals, Inc. | Broad gram-positive activity, comparable to linezolid; MRX-1 in phase 3 trials in China for skin/soft tissue, MRX-4 (prodrug of MRX-1) being studied in US NCT03033329 (1, complete) |
| **TBI-223** | TB Alliance, Institute of Materia Medica | Lower activity on mammalian mitochondrial protein synthesis (MPS); no evidence in vitro of CYP induction, Success in mice with BPa-TBI223 (replace linezolid); No hematologic/marrow toxicity in 14 and 28 day rat studies NCT03758612 (1, pending) |
**DprE1 inhibitors - completely new drug class**

<table>
<thead>
<tr>
<th><em>DprE1 inhibitor</em> - Inhibits decaprenyl-phosphoribose epimerase (DprE1) involved in cell wall arabinan biosynthesis</th>
<th><strong>OPC-167832</strong></th>
<th>Otsuka Pharmaceutical Development &amp; Commercialization, Inc.</th>
<th>Activity against replicating and dormant intracellular bacilli; Active in acute and chronic murine models; No antagonism with other TB drugs; Additive effect with Dlm exceeding RHZE</th>
<th>NCT03678688 (1-2, enrolling)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BTZ043</strong></td>
<td>University of Munich, Hans-Knöll Institute, Jena, German Center for Infection Research (DZIF)</td>
<td>Superior to INH at 2 months in mice (6 month pending) No antagonism with existing drugs, apparent synergy in vivo with Bdq-Rif Low level CYP450 interaction</td>
<td>NCT03590600 (1, enrolling)</td>
<td></td>
</tr>
<tr>
<td><strong>Macozinone, PBTZ169</strong></td>
<td>iM4TB-Innovative Medicines for Tuberculosis, Bill &amp; Melinda Gates Foundation, Nearmedic Plus LLC</td>
<td>Highly active against replicating bacteria; No antagonism with RHZE, synergy in vitro with Bdq, Ctz, Dlm, sutezolid Prior formulation with good tolerability, bactericidal activity against DS TB at 640mg</td>
<td>NCT03776500 (1, pending)</td>
<td></td>
</tr>
<tr>
<td><strong>TBA-7371</strong></td>
<td>TB Alliance</td>
<td>Efficacy in vitro and in mice Phase 1 trial complete on food effect, optimal dose, DDI, PK, PD as single dose or multiple doses</td>
<td>NCT03199339 (1, complete)</td>
<td></td>
</tr>
</tbody>
</table>
Also keep an eye out for...

<table>
<thead>
<tr>
<th>Imidazopyridine amide - Inhibits qcrB subunit of cytochrome bc₁ complex</th>
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<tbody>
<tr>
<td><strong>Q203, Telacebec</strong></td>
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<thead>
<tr>
<th>Oxaborole - Inhibits leucyl-tRNA synthetase (LeuRS), protein synthesis inhibitor</th>
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<tbody>
<tr>
<td><strong>GSK 070, GSK3036656</strong></td>
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SPR720- gyrase B inhibitor

TBAJ-587- new diarylquinoline

*oral carbapenem program as well
Summary

• Exciting time to be in TB drug development– many new compounds in clinical testing

• Challenging, though
  • Multidrug regimens must be bactericidal, sterilizing, robust to emergence of resistance, safe to use together
  • One size does not fit all
  • HIV-TB co-treatment
Acknowledgements (TNTC)

- Johns Hopkins University
  - **Center for TB Research**
    - Richard Chaisson, Eric Nuermberger, (Susan Dorman), Jonathan Golub, Amita Gupta, Grace Barnes, Kristina Bigelow, Liz Tucker, Dalin Rifat, Elisa Ignatius
  - **Division of Clinical Pharmacology**
    - Lisa Wolf, Mark Marzinke, Ethel Weld, Charles Flexner, (Omamah Alfirisi)
- **Clinical Trials Networks**
  - Tuberculosis Trials Consortium/CDC
  - AIDS Clinical Trials Group
  - IMPAACT Network

- **Partners**
  - TB Alliance, Sanofi, ViiV, Janssen, Otsuka, Pfizer
  - UCSF (Rada Savic) – pharmacometrics
  - Elin Svensson, Mats Karlsson
  - NIRT, BJGMC, UNC/Malawi Project
  - Stellenbosch, DTTC, UCT, UCTLI

- **Funding**
  - R01FD004794 (FDA)
  - R01HD074944 (NICHD)
  - R01AI111992 (NIAID)
  - R01FD005724 (FDA)
  - TBTC/CDC, ACTG/DAIDS
  - UNITAID
Thank you.