CURE-TB Strategy and the Stratified Medicine Trial Design

September 9th, 2019
INTERTB Meeting
St. George’s Hospital, University of London

Rada Savic, Patrick Phillips, and Payam Nahid
On behalf of the CDC-TBTC CURE-TB protocol team
Cancer versus Consumption

A brief journey through the approaches to patient care in cancer of the lung and TB of the lung

Deidentified images courtesy of
Khai Vu, MD
Associate Professor
Department of Radiology and Biomedical Imaging
Zuckerberg San Francisco General Hospital
University of California, San Francisco
An Oncology Program
View of Patient Care
Four patients with newly diagnosed adenocarcinoma of the lung
AdenoCA-Stage 1
Posterior right hilar mass
AdenoCA Stage 2
Right upper lobe para-mediastinal mass (Blue arrow)
Right hilar adenopathy (orange arrow)
AdenoCA Stage 3
Right apical mass (Blue arrow)
Bilateral hilar adenopathy (Green arrows)
AdenoCA-Stage 4
Left upper lobe nodule (Blue arrow)
Contralateral para tracheal adenopathy (Orange arrow)
Bilateral neck LAD (green arrows)
Using CT, PET, bronchoscopy, biopsies and tissue pathology, among other techniques, stages are confirmed.
Lung Cancer Stages and Treatments

- **Stage 1: Localized**
  - Surgery, +/- chemotherapy

- **Stage 2: Larger (> 5 cm) or spread to local lymph nodes**
  - Surgery, +/- chemotherapy

- **Stage 3: Locally advanced**
  - Chemotherapy and radiation, +/- surgery

- **Stage 4: Advanced/metastatic**
  - Chemotherapy +/- palliative radiation

Barbie, Health and Medicine, 2013
A TB Program View of Patient Care
Smear/ Culture / Xpert confirmation
Diagnosis: Active TB
Plan: 2HRZE/4HR
Smear/ Culture / Xpert confirmation
Diagnosis: Active TB
Plan: 2HRZE/4HR
Smear/ Culture / Xpert confirmation
Diagnosis: Active TB
Plan: 2HRZE/4HR
We’ll extend treatment when we need to, but does this apply to contemporary regimens?

• Iterative trials have reduced the duration of rifamycin-based regimens giving us an evidence base on which to extend treatment for defined periods of time, applied on case by case basis, as needed (still not a great approach).

• But what about new regimens and new trials? 2HPZE/2HP (S31)? BPaL regimen (NixTB)? Or entirely new chemical entities for pan-TB regimens developed for 2 months? or 3 months? Will we know whether extension is safe, tolerable and effective? When to use it? For how long to extend?

• And do we ever seek to reducing duration? If so, when? By how much?
What proportion of patients are cured with the 6-month standard regimen for drug-susceptible pulmonary TB?

<table>
<thead>
<tr>
<th>Proportion</th>
<th>Regimen</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>99%</td>
<td>SHRZ/HR</td>
<td>Fox, 1981</td>
</tr>
<tr>
<td>95-99%</td>
<td>SHRZ/HR(Z)</td>
<td>FDA guidance for pulmonary TB trials, 2013</td>
</tr>
<tr>
<td>96%</td>
<td>SHR</td>
<td>EA/BMRC Study R 1972</td>
</tr>
<tr>
<td>95.1% (PP)</td>
<td></td>
<td>RIFAQUIN, Jindani et al. 2014</td>
</tr>
<tr>
<td>92%</td>
<td></td>
<td>NIRT, Jawahar et al. 2013</td>
</tr>
<tr>
<td>92% (PP)</td>
<td></td>
<td>REMoxTB, Gillespie et al. 2014</td>
</tr>
<tr>
<td>88.7% (PP)</td>
<td></td>
<td>OFLOTUB Phase III, Merle et al. 2014</td>
</tr>
<tr>
<td>85.6% (MITT)</td>
<td></td>
<td>RIFAQUIN, Jindani et al. 2014</td>
</tr>
<tr>
<td>84% (MITT)</td>
<td></td>
<td>REMoxTB, Gillespie et al. 2014</td>
</tr>
<tr>
<td>82.8% (MITT)</td>
<td></td>
<td>OFLOTUB Phase III, Merle et al. 2014</td>
</tr>
</tbody>
</table>

MITT = Modified Intention-To-Treat; PP = Per Protocol

**Terms and Conditions**

Composite endpoints may include non-TB-related outcomes.

Investigators and protocol team not responsible for variable responses in the trial, or for the actions or inactions of regimens. Fees may apply.
A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis


Nature Medicine 24, 1708-1715 (2018) | Download Citation
CURE-TB Strategy – Stratified Medicine for TB Care

Bringing stratified medicine to TB – a paradigm shift in overall objectives in TB care

1. Reduce duration (and toxicity, cost, to programmes and patients)
   • Treatment for severe disease may be longer, but a significant proportion of TB patients with less severe disease can be cured with shorter durations

2. Enhancing cure rates for severe TB
   • Achieve higher cure rates than is currently reported in the field and trials for TB overall, unfavourable outcomes are dominated by severe forms of the disease.
   • Stratification of risk using simple markers allows for programmatically relevant strategies.

3. Patient-centered approach
   • Selecting regimen with greater precision for burden of disease

4. Alternative to “One Size Fits All” approach
   • Patients in different risk groups receive different durations (or compositions) of regimens, but if stratification not feasible, ”one-size-fits-all” still available.
Epidemiologic model supports impact of enhancing efficacy over tx shortening

<table>
<thead>
<tr>
<th>Regimen characteristic</th>
<th>Values modeled for novel RS TB regimen</th>
<th>Values modeled for novel RR TB regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>• Minimal: 94%</td>
<td>Minimal: 76%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 97%</td>
<td>Intermediate: 88%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 99%</td>
<td>Optimistic: 94%</td>
</tr>
<tr>
<td><strong>Barrier to resistance</strong></td>
<td>• Minimal: 5%</td>
<td>Minimal: 10%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 0.8%</td>
<td>Intermediate: 5%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 0%</td>
<td>Optimistic: 0.8%</td>
</tr>
<tr>
<td><strong>Preexisting novel-regimen resistance</strong></td>
<td>• Minimal: 10%</td>
<td>Minimal: 15%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 3%</td>
<td>Intermediate: 5%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 0%</td>
<td>Optimistic: 0%</td>
</tr>
<tr>
<td><strong>Medical contraindications</strong></td>
<td>• Minimal: 11%</td>
<td>Minimal: 11%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 5%</td>
<td>Intermediate: 5%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 0%</td>
<td>Optimistic: 0%</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>• Minimal: 6 mo</td>
<td>Minimal: 20 mo</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 4 mo</td>
<td>Intermediate: 9 mo</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 2 mo</td>
<td>Optimistic: 6 mo</td>
</tr>
<tr>
<td><strong>Tolerability/ease of adherence</strong></td>
<td>• Minimal: 0%</td>
<td>Minimal: 0%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 25%</td>
<td>Intermediate: 25%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 50%</td>
<td>Optimistic: 50%</td>
</tr>
</tbody>
</table>

![Graph showing annual rifampin-resistant TB mortality per 100,000 adults over years after novel rifampin-resistant TB regimen's introduction]

CURE-TB Strategy Trial
Stratified Medicine for Treatment of Drug-Susceptible TB: A randomized, open-label, controlled phase 3 clinical trial
Towards Stratified Medicine
The CURE-TB Strategy
CURE-TB Strategy Trial Hypotheses

A) Rifapentine-based regimen duration stratified based on baseline markers

• In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, with duration stratification based on baseline markers, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.

B) Rifapentine-based regimen duration stratified based on baseline and on-treatment markers

• In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, with duration stratification based on baseline markers with treatment extension based on on-treatment markers, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.
CURE-TB Strategy Trial Hypotheses

A) Rifapentine-based regimen duration stratified based on baseline markers

- In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, with duration stratification based on baseline markers, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.

B) Rifapentine-based regimen duration stratified based on baseline and on-treatment markers

- In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, with duration stratification based on baseline markers with treatment extension based on on-treatment markers, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.
Design

• Build on results of TBTC S31
• An international, multicenter, randomized, controlled, open-label, 3-arm, phase 3 superiority trial (including strata-level non-inferiority tests).

• **Population**: Patients aged 10 years and older with newly diagnosed, previously untreated pulmonary tuberculosis

• **Number of Sites**: Multiple international sites of the Tuberculosis Trials Consortium.

• **Study Duration**: Duration per participant is approximately 18 months.
CURE-TB Strategy Trial in DS-TB
(Phase 3, Superiority, Pragmatic Trial to Cure All)

Eligibility criteria (including GeneXpert)

Eligible DS-TB patients

Regimen randomization

Randomization

2HRZE/4HR

HPZE: Strategy 1

HPZE: Strategy 2

Strata 1: Low Risk

8 weeks

8 weeks +8 weeks

Fixed duration: 6 months WHO/CDC Standard

Strata 2: Moderate Risk

16 weeks

16 weeks +8 weeks

Strata 3: High Risk

24 weeks

24 weeks +8 weeks

Stratify

Eligible DS-TB patients

Stratify Randomization

Baseline Risk Markers

Strategy 1: Baseline Risk Markers

Strategy 2: Baseline/On Treatment Markers, with option to extend treatment by 8 weeks

H: Isoniazid, R: Rifampicin, P: 1200mg Rifapentine, Z: Pyrazinamide, E: Ethambutol
CURE-TB Strategy Protocol Development Progress
Topics addressed

• Leverage the systems, CRFs, protocol and experience of Study 31.
• CURE-TB proceeding regardless of S31 regimens meeting non-inferiority margins.
  • Impacts decisions around shortest duration feasible (e.g., 2 months versus 3 months)
• Design with S31 Regimen 2 (i.e., HPZE) for now.
• Define the all regimens by doses, not just duration, making up missed doses.
• Increase pragmatic features including the eligibility criteria
  • But acknowledging this is a first for testing stratified medicine principles in TB.
• Adherence measurement and enhancement is essential
  • DOT or other highly reliable approaches will be needed
Topics addressed

• Eligibility criteria:
  • HIV CD4 >100 threshold debated and remains
  • 12 years threshold reduced to 10 years
  • Lowered weight threshold from 40kg to 35kg

• For stratification markers, keep simple – smear grade or Xpert Ct, chest X-ray, HIV test, CD4 count, BMI, and sex

• For stratification system, use an algorithmic approach rather than table based approach. The TBTC systems for S31 can randomize and define strata assignments centrally.
Topics being addressed

• Focus on strategy 1 only, using baseline markers, dose counted, with duration possibly extended based on microbiology and adherence?

• Risk stratification algorithm development and refinement

• Can cycle thresholds be proxy for smear at baseline?

• In place of culture data, can cycle threshold be used for decision making on extension of continuation phase (most relevant to shortest regimen)?

• HIV ARV choice, should PK/DDI substudy to be built in for DTG with P1200mg daily?

• Configuring outcome definitions to be better fit for purpose for stratified medicine CURE-TB
Summary

• Lessons can be learned from the oncology field in stratifications of care
• A rich and robust evidence base now exists in TB to merit the conduct of a clinical trial to test stratified medicine approach to treating patients with greater precision than one-size-fit-all.
• Continued development of regimens with a one-size-fits-all viewpoint will continue to bring risk of failing to meet non-inferiority, driven by participants with highest burden of disease.
• Patient-centered at its core, stratified medicine allows for meaningful reductions in duration and toxicities for patients with minimal burden of disease, and maximally enhanced cure rates, reduced morbidity, transmission and drug resistance in patients with high burden disease
• Design of stratified medicine trials is underway, using field-friendly, immediately implementable tools for stratification.
CURE-TB Protocol Team

Rada Savic (Co-Chair)          Barbara Seaworth
Payam Nahid (Co-Chair)         Harriet Mayanja-Kizza
Patrick Phillips (Trial Methodology)  Lindsay McKenna
Susan Dorman                  Madeleine Lourens
April Pettit                   Phan Ha
Bob Belknap                    Nguyen Viet Nhung
John Johnson                   Neil Martinson
Tony Garcia-Prats              DCC Protocol Members
Jennifer Green
Marjorie Imperial
Alvaro Schwalb
Mark Weiner
Alicia Wright

DCC Protocol Members
Erin Bliven-Sizemore
Rosanna Boyd
Kia Bryant
Anne Purfield

With thanks to Katya Kurbatova, Kim Hedges, Lakshmi Peddareddy, and Yan Yuan for DCC contributions