Tuberculosis Treatment Regimens: How Good are They and What Does the Future Hold?
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Infectious Diseases Clinic Director, Washington DC VAMC
Associate Professor of Medicine
George Washington University Medical Center
August 2010

THE DREAM
“Our vision is a TB free world: the first children born this millennium will see tuberculosis eliminated in their lifetime.”

The Stop TB Partnership was established in 2000 to realize the goal of eliminating tuberculosis as a public health problem.

Summary
- Framing the problem
- Updates to the current treatment approach
- Investigational regimens using approved drugs
- Investigational agents in clinical development

51 yo man
- 3 months of cough, sweats and weight loss
- Sputum
  - 3+ AFB Smear
- Culture
  - \textit{M. tuberculosis}
What's wrong with our current armamentarium?

- Too long, particularly in extensive or resistant disease
- Too costly in public health manpower
- Too much toxicity
- Too many interactions with current antiretroviral agents
- Poor efficacy against MDR and XDR

Treatment: From Where We've Come

- Hippocrates...
- The sanatorium era, 1840 to 1940, exalted the healing power of rest, fresh air and the sun....
- Collapse therapy

The Era of Chemotherapy

- 1944: Streptomycin
- 1946: PAS
- 1946: Thiacetazone
- 1952: Isoniazid
- 1952: Cycloserine
- 1954: Pyrazinamide
- 1956: Ethionamide
- 1957: Kanamycin
- 1962: Ethambutol

The Era of Chemotherapy: First Line Agents

- 1944: Streptomycin
- 1952: Isoniazid
- 1954: Pyrazinamide
- 1962: Ethambutol
- 1969: Rifampicin (Rifapentine 1998)
Updates to the Current Treatment Approach

Once Weekly Isoniazid and Rifapentine in Continuation Phase?

- HIV negative
- AND absence of cavitary disease
- AND sputum smear negative at end of two months

2003 TB Treatment Statement
Am J Resp Crit Care Med 2003:167;603-662

Extend Therapy to Nine Months
(7 months Continuation Phase)

Sputum Culture Positive at two months and either:
- HIV infection
- Once weekly continuation phase therapy
- Cavitation on initial CXR

2003 TB Treatment Statement
Am J Resp Crit Care Med 2003:167;603-662
INTERMITTENT TB THERAPY
IS ASSOCIATED WITH
ACQUIRED DRUG RESISTANCE AND INCREASED RISK OF RELAPSE
AMONG PATIENTS WITH HIV INFECTION AND ADVANCED IMMUNOSUPPRESSION

Acquired Rifamycin Resistance:
A problem of advanced HIV infection (CD4 cell count < 100) and intermittent therapy
once weekly isoniazid and rifapentine
TBTC Study 22, Vernon Lancet 1999
twice or thrice weekly isoniazid and rifampin
Li CID 2005, Nahid AJRCCM 2007, Khan CID 2010
twice-weekly isoniazid and rifabutin
TBTC Study 23, Burman AJRCCM 2005

MMWR 2002;51:214-5
“For patients with CD4 < 100, daily dosing should be used during the first 2 months of therapy, and thrice-weekly or daily dosing during continuation phase.”

Cytochrome P450 Interactions of Relevance in HIV-TB

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<thead>
<tr>
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<th>1A</th>
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<th>2C19</th>
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| Substrate | etv | Ntv | Ntv | All PI's | rifabutin |
| Inhibitor | atv | efv/etv | efv/etv | ritonavir | All PI's |
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Effect of rifabutin and rifampin on concentrations of protease inhibitors, NNRTI's, integrase inhibitors, (AUC)

IRIS
Immune Reconstitution Inflammatory Syndrome

Starting Antiretrovirals at three Points in Tuberculosis (SAPIT) study
- n = 645 HIV-TB. ART initiation:
  - integrated early (during intensive phase)
  - integrated late (during continuation phase)
  - Sequential (following completion TB Treatment)
- Primary Objective is mortality at 8 weeks, end of treatment and at 18 months
- Sept 2008: Safety Monitoring Committee (SMC) recommended sequential treatment arm to stop immediately due to higher mortality rate.

SAPIT: NEJM Feb 2010

Figure 2: Kaplan–Meier Survival Curves. TB denotes tuberculosis.
CAMELIA: Cambodian Early versus Late Introduction of Antiretroviral Drugs

- Vienna July 2010 International AIDS Conference
- ART two weeks vs eight weeks after beginning TB Treatment
- Primary Outcome: Mortality
  - 59 of the 332 participants who had started HAART at two weeks
  - 90 of the 329 participants who started HAART at eight weeks

The Future

- Investigational regimens using approved drugs
- Investigational agents in clinical development

IDEAL CANDIDATES

- Potency to allow “ultra short course” therapy
- Long half-life to allow for intermittency
- No P450 or other drug drug interactions to allow treatment with rifamycins or antiretroviral therapy
- Low rates of toxicity
- Efficacy and safety in adults and children
- Effective against MDR and XDR

Improving on 2HRZE/4HR Better agents for MDR/XDR TB

- Investigational regimens using approved drugs
  - Fluoroquinolones
  - High Dose rifamycins
  - High Dose rifamycins plus fluoroquinolones
  - Linezolid
- Investigational agents in clinical development
  - TMC207 (Tibotec)
  - PA-824 (TB Alliance)
  - SQ109 (Sequella)
  - OPC-67683 (Otsuka)
  - PNU-100480 (Pfizer)
Fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum Peak</th>
<th>Half life</th>
<th>TB MIC</th>
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<tbody>
<tr>
<td>Ciprofloxacin 750</td>
<td>2.3</td>
<td>4</td>
<td>2.0</td>
</tr>
<tr>
<td>Ofloxacin 400</td>
<td>4.6</td>
<td>7</td>
<td>2.0</td>
</tr>
<tr>
<td>Levofloxacin 500</td>
<td>6.0</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>Sparfloxacin 200</td>
<td>1.3</td>
<td>20</td>
<td>0.5</td>
</tr>
<tr>
<td>Gatifloxacin 400</td>
<td>4.4</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>Moxifloxacin 400</td>
<td>4.5</td>
<td>12</td>
<td>0.5</td>
</tr>
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Moxifloxacin for Treatment Shortening

- Inhibits DNA Gyrase
- No cross-resistance with other TB drugs
- MIC 0.15 to 0.5 ug/ml
- Achieves best concentration to MIC ratio of the fluoroquinolones
- Half life is 10-12 hours
- Commonly used for MDR TB

Miyazaki et al., AAC 1999;43:85-9

Decrease in cfu of M. tuberculosis in lungs of mice

Am J Respir Crit Care Med 2004; 164:421-6
Four Phase II Trials of fluoroquinolones in intensive phase

- **TBTC Study 27**
  - Moxifloxacin replaces ethambutol
- **TBTC Study 28**
  - Moxifloxacin replaces isoniazid
- **Oflotub Consortium**
  - Moxifloxacin replaces ethambutol
- **Johns Hopkins**
  - Moxifloxacin replaces ethambutol

**TBTC Study 27**

Time to culture conversion – moxifloxacin vs. ethambutol

![Graph showing time to culture conversion](image)

- **P=0.02**
- **P=0.003**

**TBTC Study 28: Sputum conversion at 2 months (%)**

![Graph showing sputum conversion](image)

**Proportion of Patients with Negative Cultures by Week**

![Graph showing proportion of patients with negative cultures](image)
Phase III
Fluoroquinolones for Treatment Shortening

**OFLOTUB Consortium Phase II**

Table 6  Patients with negative sputum cultures at 8 weeks

<table>
<thead>
<tr>
<th></th>
<th>7H11 plates</th>
<th>MGT tubes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total patients</td>
<td>Negative culture n (%)</td>
</tr>
<tr>
<td>Control</td>
<td>50</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>GXX</td>
<td>52</td>
<td>46 (77%)</td>
</tr>
<tr>
<td>MMF</td>
<td>44</td>
<td>33 (75%)</td>
</tr>
<tr>
<td>GXX</td>
<td>53</td>
<td>22 (42%)</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>136 (68%)</td>
</tr>
</tbody>
</table>

* GXX vs control, P = 0.155.
* MMF vs control, P = 0.058.

MGT = mycobacteria growth indicator tube; GXX = gatifloxacin; MMF = moxifloxacin; GXX = ofloxacin.

Rustomjee et al. IJLTD/Feb 2008

**OFLOTUB Consortium Phase III**

in collaboration with WHO/TDR

- 2 HRZG / 2 HRG
- Gatifloxacin replaces ethambutol and treatment shortening
- 2 HRZE / 4 RH

1035 patients/arm. Enrollment 2006-2008
Bénin, Guinée, Kenya, Sénégal, South Africa
D Mitchison and C Lienhardt
Year 1 Analysis anticipated 2010

**ReMOXTB**

Rapid evaluation of Moxifloxacin in tuberculosis

- 2MRZE / 2MR
- Moxi replaces isoniazid and treatment shortening
- 2HRZM / 2HRM
- Moxi replaces ethambutol and treatment shortening
- 2HRZE / 4HR

500 patients/arm. Enrolling 2008
European & Developing Countries Clinical Trial Partnership (EDCTP) / MRC
Global Alliance for TB Drug Development (GATB)/Gates Foundation
S Gillespie
The Tuberculosis Research Council (TRC) Indian Council of Medical Research

- 2GHRZ3 / 2GHR3
  - thrice weekly gati replaces ethambutol and shortening

- 2MHRZ3 / 2MHR3
  - thrice weekly moxi replaces ethambutol and shortening

- 2HRZE / 4HR
  2009: DSMB recommended suspension at interim analysis due to higher relapse rates in gati and moxi arms.

Ongoing: daily gatifloxacin and moxifloxacin trial.

**HIGH DOSE RIFAMYCINS**

**OPTIMIZING RIFAMPIN DOSING**

- Pharmacodynamic simulations (free drug/MIC)
  of RPT vs. RIF in the mouse model

Activity of enhanced-dose rifapentine in the mouse model

PLOS Medicine 2007: 4: e344

TBTC Study 29 Phase II Schema

Sputum smear+ PTB suspect

Sputum culture conversion at 8 weeks

ATS/CDC/IDSA-recommended continuation phase regimen

High Dose Rifampin Program

APRIORI PROJECT, Martin J Boeree, Tanzania

- Phase I: Max tolerated dose to 2000, 2400...
- Phase IIa: n=50 per arm
  - Daily 600 vs 900 vs 1200
- Phase IIb: n= 200 per arm
  - Daily 600 vs 1200 vs ??

TBTC Study 26
Treatment of Latent TB Infection

- Compares weekly observed
  - isoniazid 900 plus rifapentine 900 for 12 weeks
  - To standard daily self administered
    - isoniazid for 9 months
- June 2001 to January 2008
- Enrollment completed in HIV-negative adults with sample size of 8000 achieved
- Continues to enroll children and patients with HIV infection
HIGH DOSE RIFAMYCINS PLUS FLUOROQUINOLONES

![Graph showing log10CFU in Lung with data points for different regimens.]

Two month mouse data
Rosenthal, Nuermberger, Grosset et al, AJRCCM July 2006

Hopkins Phase II Trial of Moxifloxacin and High Dose Rifapentine

- 2 weeks MRZE / 6 weeks MP15ZE
  Moxi replaces INH and rifapentine replaces rifampin:
- 8 weeks HRZE

Johns Hopkins University Center for Tuberculosis Research
Federal University of Rio de Janeiro
Hospital Universitario Clementino Fraga Filho
NIAID ICIDR grant

Phase III Rifaquin Study
St. George's Hospital / EDCTP

- 2HRZE / 4HP1
  - Continuation phase weekly 1200 mg rifapentine
- 2MRZE / 2MP1
  - Moxifloxacin replaces isoniazid
  - continuation phase weekly 1200 mg rifapentine and treatment shortening
- 2HRZE / 4HR
  1250 patients, Durban, Cape Town, Ndola, Harare, Maputo, Tanzania

Linezolid in MDR TB

- Oxazolidanone
- Daily therapy reduces marrow but not neurologic toxicity and ototoxicity
- EBA: day 0-1 EBA, no extended EBA (day 2-14)
- TBTC Study 30: LiMiT 2010 enrolled, n=43
- Pfizer MDR Study: October 2008, n=50
- NIH XDR Study in Korea, n=60
INVESTIGATIONAL AGENTS

- TMC207 (Tibotec)
- PA-824 (TB Alliance)
- SQ109 (Sequella)
- OPC-67683 (Otsuka)
- PNU-100480 (Pfizer)

Johnson and Johnson R20790
Tibotec: TMC207

- Diarylquinoline (DARQ):
- Inhibits ATP Synthase
- 3A4 substrate (rifampin decreases AUC 48% and Cmax 57%)
- and 2E1 and 2C9 inducer
- Half life of 24 hours and MIC of 0.06
- Time dependant killing, single dose results in days over MIC
- "J" alone at four weeks equivalent to HRZ at 8 weeks


Bactericidal activity of daily J 25mg/kg alone in mice

Science 2005;307:223-7

Phase II, Sputum Smear Positive MDR TB
TMC207-C208 Trial Design

Diacon NEJM June 2009
Nitroimidazopyran: Pa-824
Chiron Corporation, GATB

- Derivative of metronidazole, MIC is 0.125 \( \mu g/ml \)
- Inhibits protein synthesis and cell wall mycolate synthesis
- In Phase I association with increase in creatinine: decline in creatinine secretion at the tubular level without decline in renal function
- Mouse: In continuation phase PA-824 alone performs as well as HR, good sterilizing activity
- Potential short course MDR cure, PA-824/Moxi/PZA
- Human: EBA and PK of PA-824 in Smear-Positive Tuberculosis Patients: lowest dose provides maximal EBA.

Nuernberger AAC 2006, 2008
Ginsburg AAC Sep 2009, Diacon, AAC August 2010

CFU counts in the lungs of mice treated with PA-824 (PA) during continuation phase

Initiation of treatment

Log 10 CFU count

Days

control
2RHZ/4RZ
2RHZ/4H
2RHZ/4PA
4-2RHZ/4M

Nuernberger AAC 2006, 2008

CFU counts after 2 months of treatment

Ginsburg et al
**SQ109**
Sequella Inc, Rockville, MD

- Ethambutol congener / novel structure diamine
- Developed in partnership with NIH
- Concentrates in lung and spleen
- High potency and long half-life (61 hours)
- Effective in murine models and against MDR strains
- Synergy with rifampin
- Phase I clinical trials completed 2009
- In vitro synergy with TMC 207 and with rifampin
- Reddy AAC July 2010
- Murine Model SQ 641, capuramycin analog

**OPC 67683**
Otsuka Pharmaceuticals

- Dihydroimidazo-oxazoles
- Phase II Trial: Safety, Efficacy and PK of Four Oral Doses
- Phase II MDR Trial: optimized background regimen (OBR) plus:
  - 100 mg OPC-67683 BID
  - 200 mg OPC-67683 BID
  - placebo BID

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**PNU-100480**

- Oxazolidonone
- Murine: Williams… Grosset AJRCCM 2009
- Phase I: Wallis JID Epub Jul 2010
  - Antimycobacterial activity superior to 300 mg linezolid

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**Working Group TB Drug R&D Projects by Stage of Development**

Courtesy of Barbara Laughon
Summary

- In addition to more resources, improved diagnostics and improved access to care, simpler and more effective TB therapy is needed.
- We have made small improvements in the current treatment approach.
- There is hope that high dose rifamycins and/or fluoroquinolones may allow shortening of therapy.
- Investigational agents in clinical development hold promise for treatment of MDR and XDR tuberculosis and ultimately for ultra short course therapy for fully susceptible tuberculosis.
- ‘The Pipeline’ holds further promise.

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- M. Boeree, A Diacon
- D McNeely, LG Geiter, G Horwith
- J Grosset, J Rosenthal and E Neurmerger

TB Trials Consortium