Multi-Drug and Extensively Drug Resistant Tuberculosis

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Disclosures

None
Tuberculosis is a *Social Disease*

With a *Medical Aspect*

Sir William Osler, 1902
WHO High-Burden Countries

Countries in the three high-burden country lists for TB, TB/HIV and MDR-TB being used by WHO during the period 2016–2020, and their areas of overlap

- Bangladesh
- DPR Korea
- DR Congo
- Ethiopia
- India
- Indonesia
- Kazakhstan
- Kenya
- Mozambique
- Myanmar
- Nigeria
- Pakistan
- Philippines
- Russian Federation
- South Africa
- Thailand
- Ukraine
- Uzbekistan
- Viet Nam

MDR-TB

TB

TB/HIV

- Angola
- Azerbaijan
- Belarus
- Kyrgyzstan
- Papua New Guinea
- Peru
- Republic of Moldova
- Somalia
- Tajikistan
- Ukraine
- Zimbabwe

DPR Korea, Democratic People’s Republic of Korea; DR Congo, Democratic Republic of the Congo; HIV, human immunodeficiency virus; MDR, multidrug-resistant; TB, tuberculosis; UR Tanzania, United Republic of Tanzania; WHO, World Health Organization.

* Indicates countries that are included in the list of 30 high TB burden countries on the basis of the severity of their TB burden (i.e. TB incidence per 100 000 population), as opposed to the top 20, which are included on the basis of their absolute number of incident cases per year.
Nomenclature for Drug Resistant Tuberculosis Cases

- Drug Resistant Tuberculosis
- Multi-Drug Resistant Tuberculosis (MDR-TB)
- Rifampin Resistant Tuberculosis (RR-TB) (New definition as of May 2016)
- Pre-XDRTB (Resistant to INH, Rif, and either quinolone OR a second line injectable but not both)
- Extensively-Drug Resistant Tuberculosis (XDR-TB)
DEFINITION OF MDRTB

Multi–drug resistant tuberculosis (MDRTB) is defined as a strain of *M. tuberculosis* which is resistant to AT LEAST isoniazid AND rifampin.
MDRTB

• In 2016 there were an estimated 490,000 new cases of MDRTB worldwide and an estimated 240,000 deaths from MDR/RR-TB in 2016.

• Only about 22% of the estimated 580,000 cases of MDRTB were treated.

• India, China and the Russian Federation accounted for 47% of the 490,000 (MDR-TB) and 110,000 (RR-TB) cases in 2017 report.
TB stats

- India accounts for more than ¼ of the world’s TB cases and deaths.
- Treatment success rate for MDR-TB (2014 cohort) \( \textbf{54\%} \)
- Treatment success rate for extensively drug-resistant (2014 cohort) \( \textbf{30\%} \)
- At least 35 countries in Africa and Asia have introduced shorter regimens for treatment of MDR-TB or RR-TB with high success rates (87-90\%)
TB Stats

• Standardized regimen of 9-12 months is recommended by WHO for all patients (excluding pregnant women) with pulmonary MDR/RR-TB that is NOT resistant to second-line drugs

• At least 89 countries have started using bedaquiline and 54 countries have started using delamanid by June 2017
Primary MDR-TB, United States, 1993–2016*

* As of June 21, 2017.

**Note:** Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.
Primary MDR-TB Among U.S.-Born versus Non-U.S.-Born Persons, United States, 1993–2016*

* As of June 21, 2017.

**Note**: Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.
XDR-TB* Case Count, Defined on Initial DST,† by Year, 1993–2016§

* XDR-TB, extensively drug-resistant TB.
† DST, drug susceptibility test.
§ As of June 21, 2017.

Note: XDR-TB is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.
WHO MDR-TB 2017 REPORT

Percentage of new TB cases with MDR/RR-TB

Percentage of previously treated TB cases with MDR/RR-TB

* Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before 2002 are not shown.
MDRTB

Ilya Pitalev/Kommersant Photo via Getty Images

2016 WHO Report

WHO fact sheet 2015
## New Grouping of MDR-TB Drugs 2016

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>Second-line injectable</td>
<td>Other Core Second-line</td>
<td>Add-on agents</td>
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<tr>
<td>Levofloxacin</td>
<td>Amikacin</td>
<td>Ethionamide/Prothionamide</td>
<td>D1: Pyrazinamide</td>
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<tr>
<td>Moxifloxacin</td>
<td>Capreomycin (Streptomycin)</td>
<td>Cycloserine/Terizidone</td>
<td>Ethambutol</td>
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<tr>
<td>Gatifloxacin</td>
<td>Kanamycin</td>
<td>Clofazimine/Linezolid</td>
<td>High-dose INH</td>
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</tbody>
</table>

D2: Bedaquiline
Delamanid
D3: *P*-aminosalicylic acid
Imipenem/meropenem
Amoxacillin/Clavulanate (Thioacetazone)
# Short Course Standardized Regimen for MDR-TB

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive</th>
<th>Continuation</th>
<th>Number</th>
<th>Cum. %</th>
<th>Treatment Success %</th>
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<tbody>
<tr>
<td>1</td>
<td>3KCOEHZP</td>
<td>12 OEHZP</td>
<td>59</td>
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<tr>
<td>2</td>
<td>3(+)KCOEHZP</td>
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<tr>
<td>3</td>
<td>3(4)KCOEZP</td>
<td>12 OEZP</td>
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<td>8.2</td>
<td>57.1</td>
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<td>66.7</td>
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<td>12 OHEZC</td>
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<td>84.2</td>
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<td>6</td>
<td>4(+)KCGEHZP</td>
<td>5 GEZC</td>
<td>206</td>
<td>48.2</td>
<td>87.8</td>
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<td>427</td>
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</table>

C = clofazimine, E = ethambutol, G = gatifloxacin, H = isoniazid, K = kanamycin, O = ofloxacin, P = prothionamide, Z = pyrazinamide

3(4) = minimum of 3 mos, prolonged to 4 months if no conversion by end of 3 mos
3(+) = minimum of 3 mos, prolonged until conversion achieved
4(+) = minimum of 4 mos, prolonged until conversion achieved

Short Course Standardized Regimen for MDR-TB

WHO 2011 MDRTB Treatment Recommendations for Optimized Background Regimen (OBR)

- Treatment with a fluoroquinolone should be used (strong)

- A later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional)

- Ethionamide (or prothionamide) should be used (strong)

- (4) second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent) as well as pyrazinamide, should be included in the intensive phase (conditional)

- Regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used (conditional)

- Treatment duration for 24 months
Building a Treatment Regimen with 2016 Update

### Step 1
- **Group A (one)**
  - Levofloxacin
  - Moxifloxacin
  - Gatifloxacin

### Step 2
- **Group B (one)**
  - Kanamycin
  - Amikacin
  - Capreomycin

### Step 3
- **Group C (two)**
  - Ethionamide/Prothionamide
  - Clofazimine
  - Cycloserine/Terizidone
  - Linezolid

### Step 4
- **Group D1**
  - Pyrazinamide (include)
  - Ethambutol*
  - High-dose INH*

- **Group D2**
  - Bedaquiline
  - Delamanid

- **Group D3**
  - Imipemem/Meropenem
  - Amoxacillin/Clavulanate
  - P-aminosalicylic acid

≥5 likely effective including 4 core drugs, PZA and consider*
Short(er) Course Regimen for MDR-TB

<table>
<thead>
<tr>
<th>Initial Phase (7 drugs)</th>
<th>Continuation Phase (4 drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin*</td>
<td></td>
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<tr>
<td>Ethambutol</td>
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<tr>
<td>Pyrazinamide</td>
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<td>Clofazimine</td>
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<tr>
<td>Prothionamide</td>
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</tr>
<tr>
<td>Isoniazid*</td>
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<tr>
<td>Kanamycin</td>
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</table>

*High dose

months

0  1  2  3  4  5  6  7  8  9+

Property of Presenter
Not for Reproduction
WHO Policy Recommendation
Shorter Course MDR-TB Regimen

Recommendation:

In patients with RR or MDR-TB
• who have not been treated with second-line drugs and
• in whom resistance to FQNs and SLI agents has been excluded or is considered to be highly unlikely

a shorter MDR-TB regimen of 9-12 mos may be used instead of a conventional regimen

(conditional recommendation, very low certainty in the evidence)
Worldwide use of Shorter MDR-TB Treatment Regimens

Countries that had used shorter MDR-TB treatment regimens by the end of 2016
## Treatment Success*

### Shorter vs. Conventional Regimens

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Shorter MDR-TB Regimen (N=1116)</th>
<th>Conventional MDR-TB Regimen (N = 5850)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>90.3%</td>
<td>78.3%</td>
</tr>
<tr>
<td>PZA susceptible; FQN susceptible</td>
<td>96.8%</td>
<td>83.5%</td>
</tr>
<tr>
<td>PZA resistant; FQN susceptible</td>
<td>88.8%</td>
<td>81.4%</td>
</tr>
<tr>
<td>PZA susceptible; FQN resistant</td>
<td>80.0%</td>
<td>64.4%</td>
</tr>
<tr>
<td>PZA resistant; FQN resistant</td>
<td>67.9%</td>
<td>59.1%</td>
</tr>
</tbody>
</table>

*Treatment success – cure or completed

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WHO 2016 Update
Eligibility For Short-course Regimen for MDR-TB in Europe

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<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>SLID</th>
<th>FQ</th>
<th>Pto/Eto</th>
<th>E</th>
<th>Z</th>
<th>N</th>
<th>%</th>
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<td>80</td>
<td>41</td>
<td>25</td>
<td>48</td>
<td>64</td>
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<td>France</td>
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<td>37</td>
<td>33</td>
<td>64</td>
<td>60</td>
<td>67</td>
<td>48</td>
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</table>

*16 countries in Europe

Lange C, et al. AJRCCM 2016;194:1029
May 2016 WHO MDRTB Short Course Treatment for MDR-TB/RR-TB

- Exposure to >1 second-line medicines in the shorter MDR-TB regimen for >1 month
- Intolerance to >1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Extrapulmonary disease
- At least one medicine in the shorter MDR-TB regimen not available in the programme

**Shorter MDR-TB regimen**
- Intensive phase: Duration: 4-6 months, Composition: 4 second-line drugs
- Continuation phase

**MDR/RR-TB regimens**
- Intensive phase: Duration: Up to 8 months, Composition: 4 or more second-line drugs
- Continuation phase

If any of the above conditions apply, the shorter regimen is not feasible, and the patient should be treated with the individualised regimen.
Shorter Course MDR-TB Regimen
Implementation Considerations

• Patients should be tested for susceptibility to FQNs and SLI agents before starting the regimen
• WHO recommends that MTBDR susceptibility tests be used as the initial direct test instead of phenotypic culture-based DST
• In settings in which laboratory capacity for DST to FQN and SLI agents is not yet available, treatment decisions would need to be based on likelihood of resistance
• Clofazimine and high-dose INH may be difficult to procure in some countries.
• Development of an active pharmacovigilance program
MDRTB

PREVENT SELECTION OF RESISTANT BACTERIA

– PRESCRIBE AN ADEQUATE REGIMEN
– ASSURE COMPLIANCE
Prior partial gastrectomy contributed to medication malabsorption
CAUSES OF MDRTB

- Primary (Initial) Resistance
- Secondary (Acquired) Resistance
  - Malabsorption (Surgery/HIV)
  - Poor adherance to medical regimen
  - Inadequate treatment regimen
MDRTB

IF YOU DON’T SUSPECT DRUG RESISTANCE YOU DEFINITELY WON’T FIND IT!
NEVER, NEVER, NEVER

ADD A SINGLE DRUG TO A FAILING REGIMEN
### Anti-Mycobacterial Drug History

**Organism ID:** MDR TB  
**Drug Susceptibility:** ETA/SM/KM/AK/CS/PAS  
**Drug Resistance:** INH/RIF/EMB

<table>
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<tr>
<th>Date</th>
<th>8/88</th>
<th>4/90</th>
<th>7/90</th>
<th>9/90</th>
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<th>9/92</th>
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<td>+/-</td>
<td>NJH</td>
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**Comments:** 8 months FUO  
Resp failure  
7 etiology  
Began on Biweekly RX  
i/c/cough  
N/V/malaise with SM  
CT chest RUL cavity
What about Vitamin D?

Martineau et al; J Steroid Biochem Mo Biol; 2007
Wejse et al; Am J Resp Crit Care Med; 2009
Maratineau et al; Lancet; 2011
“An ounce of prevention is worth a pound of cure”

- Case fatality rate
- Administration of therapy
PAS granules

Must be taken with acidic beverage
“An ounce of prevention is worth a pound of cure”

- Case fatality rate
- Administration of therapy
- Duration of therapy
“An ounce of prevention is worth a pound of cure”

• Case fatality rate
• Administration of therapy
• Duration of therapy
• Toxicity of medications
“An ounce of prevention is worth a pound of cure”

- Case fatality rate
- Administration of therapy
- Duration of therapy
- Toxicity of medications
- Cost
Cost of Drug Therapy for MDRTB

Capreomycin 1 gm IV TIW x 6 months 2,500
Moxifloxacin 400 mg po QD x 2 yrs 11,600
Ethionamide 500 mg po QD x 2 yrs 5,500
Cycloserine 500 mg po QD x 2 yrs 8,200
PAS 4 gms po BID x 2 yrs 6,500
Ethambutol 800 mg QD x 2 yrs 5,000

Levothyroxin 100 mcg po QD x 1.5 yrs 240
Pyridoxine (Vit. B6) 50 mg po QD x 2 yrs 60

$ 39,600

Bedaquiline 400mg/day x 2wks → 200mg 3x/week x 22 weeks
High income country $ 30,000
Middle income country $ 3,000
Low income country $ 900
New WHO 2016 Treatment Guidelines for MDRTB/ RR-TB

• 9-12 months of treatment that is NOT resistant to second-line drugs (Except for pregnant women)
• All RR-TB cases are to be treated with a MDR-TB regimen, regardless of isoniazid susceptibility
• Clofazimine and Linezolid are now recommended as core second-line medicines
• PAS is an add-on agent
• MACROLIDES ARE NO LONGER INDICATED
Permission to use photo
Left bronchopleuralcutaneous fistula
MDRTB SURGICAL MANAGEMENT

V/Q scan
Post-op
apical air cap
MDRTB SURGICAL MANAGEMENT

NJC outpatient visit. C/O “gurgling” in left chest with nausea and vomiting
MDRTB SURGICAL MANAGEMENT

Herniation of intestine through left hemidiaphragm
Pt. underwent emergent transthoracic repair of the hernia and continues to do well. She completed 2 years of medical therapy post-operatively and remains disease free.
MDRTB Pre-op
Surgery for Pulmonary TB Disease

“VATS” Approach

- Thoracoscopic Lobectomy/Pneumonectomy
  - Two 1 cm incisions
  - One 4 cm “utility” incision
  - No rib spreading
- Operation otherwise identical to open approach
- Double lumen tube
- No epidural catheter
- Prior surgery not absolute contraindication
TB infection on chest wall
Thoracoplasty


Permission to use photo
Pre-op 7/26/2006
Disseminated TB of sacrum 40 days after surgical debridement (12/06)
Disseminated TB rib 20 days surgical debridement (11/23/06)
MDRTB without surgery
MDRTB without surgery
• The need for new therapies to treat multidrug-resistant (MDR) tuberculosis is great

• The new compound TMC207, a diarylquinoline that inhibits mycobacterial ATP synthase, shows promising activity against MDR tuberculosis

• In this study involving 47 patients, the administration of TMC207, as compared with placebo, resulted in a shorter time to sputum-culture conversion and a significant increase in the proportion of patients achieving culture conversion to negative
Observations

1. Of the 10 deaths in the bedaquiline group, 8 patients converted.

2. The 2 patients who did not convert died from a TB-related cause.

3. Of the 8 who converted:
   - 4 relapsed:
     - 3 died from TB-related causes (1 from hemoptysis)
     - 1 discontinued and died from MVA
   - 4 did not relapse but died from non-TB related causes

4. Two deaths in the placebo group did not convert and died from TB-related causes.
Bedaquiline and Delamanid Use By Country as of 6/2017

Countries that had used bedaquiline for the treatment of M/XDR-TB as part of expanded access, compassionate use or under normal programmatic conditions by the end of June 2017

Countries that had used delamanid for the treatment of M/XDR-TB as part of expanded access, compassionate use or under normal programmatic conditions by the end of June 2017

* Data shown reflects country reporting supplemented with additional information from pharmaceutical manufacturers.
Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

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Delamanid Use – WHO Recommendations 2016

• May now be used in patients age 6 and older and may be used in HIV infected patients
  – It is not currently recommended in pregnancy, breast feeding or children

• Do no use if corrected QT is >500ms

• It must be used in conjunction with WHO OBR
  – PZA, quinolone, second line injectable, plus 2 bacteriostatic agents (ethionamide, PAS, cycloserine)

• Use in first 6 months of treatment

• No current standardized DST for Delamanid

• No current recommendation for use of BOTH delamanid and bedaquiline in a treatment regimen

• Recommended dose of Delamanid is 100mg BID
New Drugs/Regimens

The global development pipeline for new anti-TB drugs and regimens, August 2017

<table>
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<th>Phase I(^a)</th>
<th>Phase II(^a)</th>
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<td>PBTZ169(^b)</td>
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<td>Rifapentine – Moxifloxacin for drug-susceptible TB (TB Trial Consortium Study 31/A5349)</td>
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\(a\) New drug compounds are listed first, followed by repurposed drugs and then by regimens.

\(b\) New chemical class.

Source: Adapted from the Stop TB Partnership Working Group on New TB Drugs pipeline. More information on these products and other ongoing projects can be found at http://newtbdrugs.org
Current Treatment Trials

• endTB trial- Started in 2017 to compare several regimens for treatment of MDR-TB or XDR-TB with the current longer regimen recommended by WHO. The regimens include bedaquiline or delamanid (or both), moxifloxacin or levofloxacin, and pyrazinamide plus linezolid or clofazimine (or both), in various combinations
Current Treatment Trials

- **MDR-END trial** - Looking at a 9-12 month regimen of delamanid, linezolid, levofloxacin and pza for MDR-TB patients WITHOUT resistance to fluoroquinolones.

- **NeXT trial** – Testing a 6-9 month injection-free regimen of bedaquiline, ethionamide or high-dose isoniazid, linezolid, levofloxacin and pza for MDR-TB, compared with the short regimen of 12 months recommended by WHO.
Current Treatment Trials

- **NIX-TB trial** - 6-month combination of bedaquiline, pretomanid and linezolid (all oral agents) in patients with XDR-TB and treatment-intolerant MDR-TB.
- **ZeNix trial** – Exploring lower doses and sorter durations of linezolid to minimize toxicity
- **TB Alliance** – Phase IIc trial of bedaquiline, pretomanid, moxifloxacin and PZA (BPaMZ).

In the phase IIb study of the BPaMZ regimen showed almost 100% culture conversion at 2 months in patients with MDR-TB
STREAM Trial

Regimen A

WHO-approved MDR-TB Regimen

Regimen B

KM+INH+PTO+
MFX+CFZ+EMB+PZA

Regimen C

INH+PTO+
BDQ+LFX+CFZ+EMB+PZA

Regimen D

KM+INH+BDQ+
LFX+CFZ+PZA

MFX+CFZ+EMB+PZA

BDQ+LFX+CFZ+EMB+PZA

BDQ+LFX+CFZ+PZA

0 8 16 28 40

Weeks

Intensive phase

Continuation phase

Current Treatment Trials

• **STREAM trial** – Stage 1 is comparing a 9-month regimen for MDR-TB with longer regimens of 18-24 months. Patients with rifampicin-resistant pulmonary TB and no evidence of resistance to fluoroquinolones or kanamycin are eligible.

• **TB-PRACTECAL trial** - Phase II/III trial to evaluate the safety of 6-month regimens that contain bedaquiline, pretomanid and linezolid, with or without moxifloxacin or clofazimine, for the treatment of adults with MDR-TB or XDR-TB.
Bull Moose near Walden, Colorado