Multi-Drug Resistant TB: A Primer to Patient Care and Treatment
Phoenix, Arizona
February 20, 2008

Treatment of MDR TB
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February 20, 2008

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Arizona February 2008

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Have germs, will travel…
Migrating populations in the 1990s

Compared to 1960-75, four-fold increase in migration

Source: Population Action International 1994

Objectives

• Identify those at risk for drug resistance
• Prescribe treatment regimens for drug resistant disease that prevent amplification of resistance
• Correctly manage treatment problems
  – toxicity, adherence, failure,
• Management of contacts of drug resistant TB
Patients at Risk of Drug Resistant TB

- History of prior treatment for TB or exposure to patient with relapse
- Birth or residence in country with high incidence of drug resistant TB
- Treatment failure
- Relapse and history of poor adherence
- Clinical deterioration during 4 drug therapy

Countries of Birth of Foreign-born Persons Reported with TB
United States, 2005

- Mexico (25%)
- Philippines (11%)
- Other Countries (38%)
- Guatemala (3%)
- Haiti (3%)
- China (5%)
- India (7%)
- Viet Nam (8%)
Primary MDR TB in U.S.-born vs. Foreign-born Persons, United States, 1993–2005*

% Resistant

1993 1995 1997 1999 2001 2003 2005

*Updated as of March 29, 2006.

Note: Based on initial isolates from persons with no prior history of TB.

MDR TB defined as resistance to at least isoniazid and rifampin.

Classification of Drug Resistance

• Primary:
  – Drug Resistance in Patient Not Treated
    • Result of transmission in community of drug resistant disease
      – Chronic non treated patients
        » Untreatable
        » Defaulted on therapy and cannot be found
  – These patients usually have primary TB which is less extensive
    • Treatment duration usually 18 months
    • Good outcomes more likely
Classification of Drug Resistance

• Acquired
  – Drug Resistance in Patient with Prior Therapy
    • Result of poorly functioning public health program
      – Non-adherence
      – Incorrect regimens
  – These patients usually have recurrent
disease, often bilateral, with lung damage and
  cavities
  – Treatment more difficult, longer, outcomes not
    as good as with primary drug resistant TB

Management Should Avoid Amplification of Resistance

• Standard Therapy is designed to protect
against monotherapy until drug resistant
patterns known.
  – Ethambutol is especially beneficial for
    protecting rifampin if there is INH resistance
• Management of drug resistance
  – Always plan to protect against further
    resistance developing
    • Never add a single drug to a failing regimen
Primary Isoniazid Resistance in U.S.-born vs. Foreign-born Persons
United States, 1993–2005*

*Updated as of March 29, 2006.

Note: Based on initial isolates from persons with no prior history of TB.

DX and Management of Treatment Failure

- Treatment failure: “Patients whose sputum cultures remain positive after 4 months of treatment are considered to have failed treatment”

- “Patients with treatment failure should be assumed, until proven otherwise, to have drug-resistant organisms and be treated with multiple agents that they have not received before.

- A single drug should never be added to failing RX

- It is “prudent to add at least 3 new drugs”

  » MMWR Treatment of Tuberculosis 2003; 52
Case Study

• Consult requested 7/27/05
  – 42 yo male with drug susceptible PTB
  – Remains AFB smear and culture positive 3.5 months post start of tx.

• HPI
  – Hospitalized 03/05 with c/o productive cough, SOB, fever, chills, night sweats, 18 lb wt. loss
  – 3/18/05: PPD positive (25 mm)
  – 3/21/05: CXR showed extensive BUL infiltrates with possible cavitation
  – AFB smear positive (>10/HPF); culture eventually grew M.Tb susceptible to first-line agents

Case Study

• Other: HIV (-), ETOH (+), tobacco (+), illicit drugs (-), no comorbid medical conditions
• 3/19/05: tx. initiated with standard RIPE regimen
  – 4/11/05: EMB dc’ed after susceptibility results became available; dosing changed to BIW
• Adherent with DOT; no missed doses
• 5/10/05 and 6/9/05: CXR’s repeated and showed little improvement
Case Study

• Clinical improvement: afebrile, night sweats resolved, cough diminished (only at night), 6 lb. wt. gain, energy level improved but not normal
• Drug susceptibilities repeated on 4/21/05 isolate and remained fully susceptible to first-line agents

Case Study

• 8/5/05: seen at TCID OPC
  – CT: extensive bilateral disease with multiple cavities in both apices and LLL
  – Serum drug levels
  – Confirmed clinical improvement
  – Repeat drug susceptibilities had been requested on 7/7/05 isolate
  – 7/20/05 sputum specimen reported culture positive
Case Study

- Patients whose sputum cultures remain positive after 4 months of treatment are considered to have failed treatment.
- Patients with treatment failure should be assumed, until proven otherwise, to have drug-resistant organisms and be treated with multiple agents they have not received before.
- Never add a single drug to a failing regimen; add at least 3 new drugs.
Case Study

• Changes to treatment regimen
  – PZA dc’ed
  – INH, RIF, EMB, Levofloxacin daily
  – Amikacin IM TIW
• 7/7/05 isolate reported INH resistant
  – INH dc’ed
• 9/1/05: serum drug level results received
  – INH 900 mg: 2.48 (9-15 mcg/ml)
  – RIF 600 mg: 2.03 (8-24 mcg/ml)

Case Study

• 10/14/05: culture conversion
  – AK dc’ed 12/20/05
• Pt. continues on RIF, EMB, Levofloxacin regimen daily
• Plan to treat for 4 months post culture conversion (mid –February, 2006)
Management of INH Resistance

• INH resistance
  – Rifampin, ethambutol, PZA + INH if only low level resistance daily for 6 months
  – Treatment should be daily 6 – 9 months
  – Rifampin, ethambutol, PZA, given throughout Rx
  – Add fluroquinolone if extensive disease or underlying immunosuppression

• Contacts should have rifampin
  – Adults 4 months
  – Children or HIV + adults, 6 months

Initial Drug Resistance

• 55 year old female; 3 mo history of cough, fever, weight loss, TST negative
  – Rheumatoid Arthritis
    • Prednisone 20 mg twice daily
    • Adalimumab (Humira) stopped three months ago
    • Immigrated from Honduras 10 years ago
    • Worked in egg processing plant and in upholstery factory
  – History of culture negative UTI
    • Treated on multiple occasions with ciprofloxacin
  – Bronchitis treated with levofloxacin
Initial Drug Resistance

• Improved on INH, rifampin, ethambutol and PZA
  – Resolution of fever, decreased cough
  – Cultures convert to negative at 6 weeks

• After 7 weeks of therapy report of resistance to INH and ethambutol

Diagnosis by Smear is Standard of Care in Most of the World

On our border – South and Central America use smear only

Cultures or susceptibility tests rarely done
Protecting Rifampin
Preventing Amplified Drug Resistance

Initial RX: INH, Rifampin, EMB, & PZA.
  – If INH resistance is present:
    • EMB will protect rifampin during initial phase of treatment

Initial RX: INH, Rifampin, & PZA
  – If INH resistance is present:
    • PZA is not active in cavities and rapidly growing lesions so it does not protect rifampin in both the initiation and continuation phase → rifampin monotherapy
    • Culture and susceptibility tests detect INH resistance and allows change in treatment
Initial Drug Resistance

• Re-evaluation prior to starting new regimen
  – Repeat CXR, sputums, and medical evaluation

• Add two, preferably three new drugs
  – Levofloxacin and Capreomycin added

• What should we be worried about?

Initial Drug Resistance

• Possibility of fluoroquinolone and rifampin resistance
  – Repeated courses of ciprofloxacin and levofloxacin
  – Rifampin given with only PZA as active drug

• Treatment with rifampin, PZA, Amikacin Levofloxacin, and ethionamide
  – Plan to stop Amikacin and ethionamide if cultures negative and no further drug resistance, treat at least 9 months
New Immigrant from Uzbekistan

- 30 year old female
- TST positive
- No underlying disease
- No symptoms
- Questionable old abnormality on CXR
- Diagnosed as LTBI
  - Started on INH
  - Non compliant after first three months

TST + Refugee from Uzbekistan
SIX Months Later: Cough and Hemoptysis

Nine Months From Initial Evaluation
Immigrant from Uzbekistan

- Multiple sputum smears and cultures neg
- Public health nurse visits home at 6 am
  - Obtains first am sputum
  - Smear negative
  - Culture positive, INH resistant TB

Low serum INH Levels and Treatment Failure

- In patients treated with once weekly INH/Rifapentine all INH pharmacokinetic parameters lower in pts with failure/relapse
  - Median INH AUC \(_{0-12}\) was 36 in 22 pts with failure or relapse versus 55.9 mcg/hr/ml in 49 with cure.
  - 2 HIV + pts with acquired rifamycin resistance had very low INH levels and pharmokinetic parameters.
- Twice weekly INH/Rifampin AUC were similar in pt with failure/relapse and cure
  » Weiner AJRCCM 2003
Pharmacokinetics: INH + Rifabutin
Acquired Rifamycin Resistance (ARR)

- 102 of the 163 Study 23 patients included, 7/8 with ARR

<table>
<thead>
<tr>
<th></th>
<th>ARR</th>
<th>No ARR</th>
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<tr>
<td>Rifabutin AUC</td>
<td>3.3 ug/ml/hr</td>
<td>5.2 ug/ml/hr</td>
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<tr>
<td>adjusted for CD4</td>
<td>3.0</td>
<td>5.2</td>
</tr>
<tr>
<td>INH AUC</td>
<td>20.6</td>
<td>28.0</td>
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</tbody>
</table>

Weiner. CID 2005

Low Rifabutin Drug Levels Associated with Rifampin Resistance

- Pharmokinetic evaluation of HIV+ patients in rifabutin trial (Rifabutin 300mg/INH 300mg daily)
  - Patients with treatment failure or relapse with acquired rifamycin resistance had significantly lower rifabutin levels measured by area under curve
  - Patients also had significantly lower INH levels
Acquired Rifamycin Resistance
USPHS 23

- INH + rifabutin twice weekly in continuation
- 169 patients enrolled
  - 3 treatment failures + 6 relapses; 9/169 (5.3%)
  - 8/9 (89%) acquired rifamycin resistance
- Risk factors for ARR:
  - Twice weekly RX during first 2 months
  - Low CD4
    - CD4 < 100: 9/73 (12%)
    - CD4 > 100: 0/65 (0%)

» Burman. Am J Respir Crit Care Med 2005

Rifampin Resistant Tuberculosis

- Treatment outcomes poor
- Rifampin the most important drug in the treatment.
- Respond as you would MDR TB
Treatment of Rifampin Resistant TB

• INH, EMB, PZA, Levofloxacin x 12 months; +/- Injectable x 2 months
• INH, EMB, PZA and Streptomycin x 2 months then INH,PZA and Streptomycin x 7-10 months
• INH, PZA and EMB x 18 -24 months

Management of Rifampin Resistance

• Minimum duration of therapy is 12 – 18 mo
• Injectable for 2 – 4 months, at least until culture conversion unless minimal disease
• INH, ethambutol, PZA, and fluroquinolone

One step away from MDR TB!
Principals of Treatment and Management of MDR TB

• DOCUMENT SUSCEPTIBILITY
  – Wait for susceptibility results if possible when dealing with patients with likely extensive drug resistance or multiple treatment failures.

• IF EMPIRIC THERAPY IS NEEDED
  – Design a 6 to 7 drug regimen based on the latest susceptibility tests, drug Rx history and drug resistance in the community.
  – Extra drugs can be stopped later.

Principals of Treatment and Management of MDR TB

• Treat patients with likely drug resistant disease with an adequate number of drugs to prevent emergence of further resistance (amplification of resistance).

• TREAT AS IF IT IS YOUR LAST CHANCE TO CURE!
Principals of Treatment and Management of MDR TB

• Drug selection
  – **At least 3 New drugs** not previously used
  – Those with **proven or suspected** susceptibility
  – **As many bactericidal** drugs as possible
  – Any first line drugs with proven susceptibility
    • Even if part of prior failing regimens

• Limit toxicity as much as possible

Principals of Treatment and Management of MDR TB

• Consider co-existing illness
  – Renal failure
    • Avoid or adjust aminoglycoside
    • Decrease dose of PAS
    • Decrease dose and increase dosing interval to 3 times/week when Cr Cl < 30
      – PZA, Ethambutol, Levofloxin
  – Liver disease
    • INH, rifampin, Ethionamide, PZA potential hepatotoxicity
Principals of Treatment and Management of MDR TB

• Plan an initial 6 drug regimen to start
• Use 3 to 4 bactericidal drugs
  – Levofloxin or Moxifloxin
  – Injectable: Streptomycin, Amikacin or Capreomycin
  – Ethionamide, EMB, PZA, or rifabutin if susceptible
  – Second injectable
  – Support drugs: PAS, cycloserine
  – Linezolid if resistant to all first line and injectable or fluoroquinolone
  – Clofazimine

Principals of Treatment and Management of MDR TB

• Levofloxin or Moxifloxin
  – Both highly bactericidal
  – Both well absorbed
    • Avoid calcium and magnesium containing antacids and supplements, multivitamins, iron, enteral supplements, sucralfate
  – Good penetration to all tissue sites
  – No need to decrease dose of moxifloxin in renal insufficiency
Principals of Treatment and Management of MDR TB

• Which fluoroquinolone?
  - Levofloxin: 750mg/day
    • Extensive experience with long term use and pushing drug levels to 1000 +mg/day
    • Peak level at 12; MIC 1.0 mcg/ml
  - Moxifloxin: 400mg/day
    • Early bactericidal activity rivals rifampin, potentially greater than levofloxin
    • Peak level at 4; MIC 0.25mcg/ml
    • Prolonged half life

Principals of Treatment and Management of MDR TB

• Which injectable?
  - All are bactericidal
    • Streptomycin: document susceptibility, more auditory toxicity, less renal
    • Amikacin: easy to get drug levels
    • Capreomycin: smaller volume if IM injection planned
  - Toxicity depends on total dose
    • 15mg/kg 5 x/week first 4-6 months
    • 15mg/kg 3 x/week next 6 – 8 months
    • Attempt to reach peak serum level of 25
• Dual injectable therapy? (Capreomycin and Amikacin)
  - When extensive drug resistance and extensive disease
PRINCIPALS OF THERAPY
MDR-TB

• Initiate drugs likely to have toxicity slowly over the first one to two weeks of treatment
  – Decrease toxicity
  – Limit psychological intolerance
  – Space out medications initially
    • Ethionamide 250 hs x 3 days, then 250 bid, then 500/250mg
    • PAS 2-4 grams daily x 5 days increasing to 3-4grams bid
    • Cycloserine 250mg x 3 days; then 500mg

Step 1
Begin with any available First line agents to Which the isolate is Susceptible
Add a Fluoroquinolone And an injectable Drug based on susceptibilities

First-line drugs
Pyrazinamide Ethambutol

Fluoroquinolones
Levofloxacin Moxifloxacin

Injectable agents
Amikacin Capreomycin Streptomycin Kanamycin

PLUS One of these PLUS One of these

Step 2
Pick one or more of these
Oral second line drugs
Cycloserine Ethionamide PAS

Step 3
Consider use of these
Third line drugs
Imipenem Linezolid Macrolides Amoxicillin/Clavulanate
Principals of Treatment and Management of MDR TB

- Treat at least 18-24 months after conversion of the culture to negative
- Continue injectable at least 6 - 12 months after conversion of culture to negative
- Shorter therapy for limited, primary or early disease
  - Consistent with the International Standards for TB Control released 3-24-06

Principals of Treatment and Management of MDR TB

- Never add a single drug to a failing regimen
- However a single drug can be added;
  - To augment a weak regimen in the first two to three weeks or after conversion of cultures
  - To augment an oral regimen after D/C of injectable or another drug if patient is responding and cultures are negative
- If culture still positive, add 2 drugs
Principals of Treatment and Management of MDR TB

- Monitor and respond quickly to clinical toxicity
- CBC, LFT'S, TSH, creatinine, calcium,
- Audiological evaluation
- Vestibular toxicity screen
- Visual screen
- Drug levels
  - Assure efficacy and limit toxicity, push meds when regimen weak and disease extensive

Factors Associated with Good Treatment Outcomes for MDR TB

- Younger age
- Absence of cavities
- HIV negative
- Primary disease
- Hospitalization
- Culture conversion by 3 months
- ? Surgery
- Sensitivity to ofloxacin
- No prior therapy with ofloxacin
- Fewer # drugs MTB is resistant to
- More effective drugs in regimen
- Appropriate therapy
New Immigrant from Nepal

- History of TB treated for one year with one drug, unknown type
- Reported normal exit CXR and cleared for immigration to US
- Coughing during flight

Evaluation in US

- Weight loss, malnutrition, (76 lbs)
- Chronically ill
- Abnormal CXR
- Sputum + for AFB
- Treatment: RIPE plus Moxifloxacin

Was this a good idea?
Recent Immigrant from Nepal

- Culture positive for M Tb
  - Initial: resistant to INH, rifampin, ethambutol (5.0 ug/ml), rifabutin,
  - Treatment: Amikacin, Moxi, EMB, Cycloserine
  - Susceptible to ethionamide, levofloxacin, amikacin, ethambutol (7.5 ug/ml)

Should we worry about fluoroquinolone resistance?
Fluoroquinolone resistance

- Susceptibility testing performed on isolates of all culture-confirmed TB cases between 1/98-3/02
  - 55 patients; 19 received fluoroquinolone monotherapy prior to initiation of anti-TB drugs
  - 2/55 had some resistance to fluoroquinolones;
    - both were among the 19 (11%) previously treated who were HIV infected with CD4 < 50
- Conclusion: Incidence of fluoroquinolone resistance high, particularly among patients previously treated with fluoroquinolones


Recent Immigrant from Nepal

- Patient improves clinically
  - Gains 25 pounds
  - Cough nearly resolves, fever and night sweats gone
  - Sputum smears and cultures convert at 12 weeks
  - Last positive culture
    - New intermediate resistance to Moxifloxacin
Role of Surgery in the Treatment of MDR TB

- Indications
  - Extensive pulmonary disease
  - Extensive drug resistance
  - Prolonged positive cultures
  - Failure of therapy
  - Hemoptysis

MDR TB Case History (1)

- 47 y.o. female with cough, fever, wt loss x 1 yr
- Had TB 3 years ago – Rx in Mexico x 6 mo
- Using accessory muscles of respiration, bilateral clubbing, < 10% IBW
- HIV negative
- Diabetic HbA1c > 10
MDR TB Case History (2)

• AFB + >10/hpf
• Started Trial 28 (4/30/07)
  – Moxi, EMB, PZA, rifampin
• Clinical improvement
• 5/28/07
  – Resistant: INH & RIF
• Three new drugs added
  – Amikacin-ethionamide-PAS

MDR TB Case History (3)

• One month later culture
  – New resistance to ethambutol and ofloxacin (5/28)
  – New resistance to ethionamide (6/4)
  – Received report of PZA resistance on initial culture!
• Clinical improvement
  – 3 lb weight gain, ↓ cough and fever
  – AFB + < 1/hpf
• Moxi, EMB, PZA, Amikacin, Ethionamide, PAS
Key Questions

• What if any modifications to the regimen should be considered at this point?
• Is there complete cross resistance between fluoroquinolones?
• How often does fluoroquinolone resistance occur?

Clinical Pearls

• Evaluate sputum cultures monthly in MDR TB
• Repeat susceptibility studies on new positive cultures if > 2 mo or if possibility of compromised regimen
• Use serum drug levels to maximize therapy and limit toxicity
• Pts < 10% IBW at risk of relapse
• Cross resistance to Moxifloxin is not complete
• Always use 5 to 6 good drugs, (injectable and FQN)
Management of Contacts of MDR TB

• Use 2 drugs to which the infecting organism has demonstrated susceptibility (Ethambutol, levofloxacin, Moxifloxin and PZA)
• Treat for 6 months or observe without treatment (HIV-negative)
• Treat HIV-positive persons for 12 months
  • Follow for 2 years regardless of treatment
  • CXR and clinical evaluation

Management of Contacts of MDR TB

• Regimens with PZA have been reported in observational studies and case reports to have high rates of hepatotoxicity
  – 18% and higher
  – Some with significant toxicity
    • Hospitalization
• My personal bias is to use fluoroquinolone and ethambutol when possible
  – Monitor visual toxicity
  – Even in kids this is my choice
Infectiousness of MDR TB

- Varying degrees of transmission reported
- Clearly MDR TB is transmissible
  - Nosocomial Outbreaks in NYC in 1990s
  - High incidence of MDR TB in Eastern Europe and Soviet Union
  - Outbreaks in correctional setting
  - South Africa
- HIV infection markedly increases transmission

When Can Isolation of an MDR TB Patient be Discontinued?

- Criteria more stringent
  - Rapid bactericidal effect of INH not present
- CDC recommends continuing isolation in the hospital setting until three consecutive cultures are negative
- Some experts recommend continuing isolation in hospital for the duration of stay
  - Risk of breakthrough + culture
  - Risk of treatment failure
Outbreak of XDR TB Raises Important Ethical Questions

- Treatment of non compliant patients
- Protection of health care workers

South Africa: “Patients Flee TB Patients” NY times 3-7-07

- 100 patients walked out of a hospital in S Africa when 8 patients with XDR TB were brought in by paramedics wearing head to toe protection
  - Lack of adequate infection control in most third world countries –
    - Those with the most MDR TB
S Africa “Doctors Say it Might Be Necessary to Detain TB Patients”
Associated Press 1-23-07

• Benefits are stopped when a patient is hospitalized
  – Many leave treatment
  – Proposal to pay patients during treatment
• Consideration of detainment

Reports of XDR TB

• November 3, 2006; 303 cases in S Africa
• March 2007; 205 cases in KwaZulu-Natal
• 5.4 million HIV positive in S Africa
• February 2007, Antiretroviral Conference
  – Estimated 600 cases XDR TB
  – Estimated 27,000 are infected each year
    • 16,000 die
A Globally Accepted Path Forward

• INTERNATIONAL STANDARDS FOR PATIENT CARE
  • March 2007
Diagnosis: Key Points

• Describes need for examination of patients with cough for 2-3 weeks or more
• Emphasizes requirement for microbiological evaluation for suspected pulmonary and extra pulmonary sites; de-emphasizes radiography as a tool for diagnosis.
• Describes a rigorous approach to diagnosis of smear negative tuberculosis (including children).

Standards for Treatment

• Standard 7: Any practitioner treating a patient for TB is assuming and important public health responsibility, therefore
  – Prescribe appropriate regimen
  – Be capable of assessing the adherence of patient
  – Be capable of addressing poor adherence
Standards for Treatment

• Standard 14: An assessment of likelihood of drug resistance should be obtained for all patients
  – History of prior treatment
  – Exposure to Possible drug resistance source case
  – Community prevalence of drug resistance

• Patients who fail therapy should always be assessed for drug resistance

• If likely drug resistance, perform culture and drug susceptibility promptly

Standards for Treatment

• Standard 15: Patients with drug resistant TB, especially MDR TB should be treated with specialized regimens containing second-line antituberculosis drugs.
  – At least 4 drugs to which the organisms are known or presumed to be susceptible should be used
  – Treatment for at least 18 months
  – Consultation with a provider experienced in treatment of patients with MDR TB
Standards for Treatment

- Standard 15 (continued)
- Specialized regimens
  - Standardized treatment regimens
    • Based on representative drug resistance surveillance or history of drug use in the country
  - Empiric treatment regimens
    • Used while DST results are pending
    • Recommended to avoid deterioration & transmission
  - Individualized treatment regimens
    • Based on DST profiles and drug history of patient

Chronic MDR TB
Extensive Drug Resistance

- 56 y.o. male, treated age 37, relapsed 2002
  - Positive smear after 5 months of Rifater
    • Ciprofloxacin 2 ½ months led to negative smears
- Relapsed 2003, smear remained + after Rifater, EMB and Ciprofloxacin for 6 months
- All treatment was in private sector
- 2005: Cough, SOB, wt loss, destroyed lung
  - Referred to Binational Project
Chronic MDR TB
Extensive Drug Resistance

- 2005: Referred to Binational Project
  - Resistance: INH, Rifampin, Rifabutin, Strep, PZA, EMB, Ethionamide, Levofloxacin and Imipenem
  - Susceptible: Amikacin, Capreo, Cycloserine, PAS, Linezolid
  - Intermediate: Moxifloxacin 1.0 microgram/ml
- Treatment: Amikacin, Capreo, Moxifloxin 800mg, PAS and Linezolid 600mg
  - Culture conversion at 3 months
  - A long way still to go
Summary

• Preventing MDR TB must be the goal
• Current treatment options can be successful in > 90% of patients but are costly and time consuming
• Successful therapy requires DOT, case management & expert consultation
• Current MDR patients have increasing drug resistance
• New therapies are needed

Possible New Treatment Options?

• Newer Fluroquinolones
• Oxazolidinones: Linezolid
• Nitroimidazoles: PA-824
• Nitro-imidazo oxazole: OPC 67683
• Diarylquinoline: TMC207 “J”
• Lupin LL 3858
• Inhaled aminoglycosides
• Gamma interferon/other immunotherapies
THEY ALWAYS COME BACK

Do It Right The First Time!