TUBERCULOSIS TREATMENT: MEDICATIONS & REGIMENS

GENERAL PRINCIPLES

• ALWAYS USE AT LEAST 2 DRUGS:
  – Begin with 4 pending sensitivities
  – Natural incidence of spontaneous resistance to any 1 drug = 1 in 10,000 organisms
  – Bacilli resistant to 1 will be killed by others
  – Natural resistance to 2 drugs spontaneously = 1 in 10^{10}

• Prolonged Length of Rx: 6-9 months DEPENDING UPON REGIMEN
• Directly Observed Therapy: ALL SHOULD BE
Treatment: First Line Drugs

1. ISONIAZID = INH
   - Bacteriocidal against dividing organisms
   - Dose = 300mg = one pill = well absorbed
   - Good CNS penetration
   - Can be used during pregnancy
ISONIAZID (INH) or isonicotinyl Hydrazine
or isonicotinic acid hydrazide

- INH available as 100 mg and 300 mg tablets for oral administration
- INH empirical formula: C6H7N3O

MECHANISM OF ACTION
- INH INHIBITS SYNTHESIS OF MYCOLIC ACIDS
- MYCOLIC ACID IS ESSENTIAL COMPONENT OF BACTERIAL CELL WALL
- INH IS BACTERICIDAL AGAINST ACTIVELY GROWING INTRACELLULAR & EXTRACELLULAR ORGANISMS
- INH RESISTANT *M. tuberculosis* organisms develop rapidly when INH monotherapy administered
CLINICAL PHARMACOLOGY

• PEAK BLOOD LEVELS W/IN 1 - 2 hrs AFTER ORAL ADMINISTRATION
• PEAK BLOOD LEVELS DECLINE TO 50% W/IN 6 HOURS; 50-70% OF DOSE EXCRETED IN URINE IN 24 HOURS
• DIFFUSES READILY INTO ALL BODY FLUIDS (cerebrospinal, pleural, and ascitic fluids), TISSUES, ORGANS & EXCRETA (saliva, sputum, and feces)
• PASSES THROUGH PLACENTA & INTO BREAST MILK IN CONCENTRATIONS COMPARABLE TO THOSE IN PLASMA

INH TOXICITY: HEPATIC

CHEMICAL vs. CLINICAL HEPATITIS

20% patients have rise in transaminases; resolves without stopping INH; usually occurs within first 1-3 months of RX.
• Rise in transaminase >5 times normal is significant and INH should be stopped
• Toxicity is age related:
  <35 = 0.3%; >65 = 4%
INH TOXICITY: NEUROPATHY

UNCOMMON; DOSE-RELATED
OCCURS MOST OFTEN IN MALNOURISHED & THOSE PREDISPOSED TO NEUROPATHY (ALCOHOLICS, DIABETICS)
USUALLY PRECEDED BY PARESTHESIAS OF FEET & HANDS
PYRIDOXINE INDICATED FOR PATIENTS WITH CONDITIONS WHERE PERIPHERAL NEUROPATHY COMMON: DIABETES, UREMIA, ALCOHOLISM, AIDS
• Pyridoxine indicated for pregnant women on INH

2. RIFAMPIN (RMP):
ENABLES SHORT COURSE TREATMENT

• BACTERIOCIDAL
• Dose = 600mg = (2) 300mg capsules = well absorbed
• Good CNS penetration if meninges inflamed
• Can be used in pregnancy
**ENABLES SHORT COURSE TREATMENT:**
6-9 months vs. 18-24 months w/out RMP

**RMP: MECHANISM OF ACTION**

- Inhibits DNA-dependent RNA polymerase in susceptible strains of bacteria
- Absorption: Almost completely absorbed
CLINICAL PHARMACOLOGY

• C max is 1 to 4 hr (oral)
• Absorption decreased 30% if taken w/food
• Distribution: Diffuses well into most body tissues and fluids, including CSF
• Crosses placenta & distributes into breast milk
• Protein binding is 89%.

RIFAMPIN TOXICITY

• Most common adverse reaction = GI upset
• Can cause cholestatic jaundice
• Skin rash
• Thrombocytopenia (rare)
• Bonded to inactive dye which is excreted in urine, sweat, tears: Colors these fluids orange

• MAJOR PROBLEM WITH RMP IS DRUG-DRUG INTERACTION
Rifampin

- **Induces hepatic microsomal enzymes: P450 system;** accelerates metabolism of many drugs making them less effective or ineffective when rifampin is being given:
  - Methadone
  - Coumadin
  - Estrogen: Oral Contraceptives
  - Glucocorticoids
  - Digitoxin
  - Anti-arrhythmic agents (quinidine, verapamil, mexiletene)
  - Theophylline
  - Anti-convulsants
  - Cyclosporin

**PROTEASE INHIBITORS**

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**Table 1. Recommendations for regimens for the concomitant treatment of tuberculosis and HIV infection**

<table>
<thead>
<tr>
<th>Combined regimen for treatment of HIV and tuberculosis</th>
<th>PK effect of the rifamacin</th>
<th>Tolerability / toxicity</th>
<th>Antiviral activity when used with rifamcin</th>
<th>Recommendation (comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz-based ART* with rifampin-based TB treatment</td>
<td>Well-characterized, modest effect</td>
<td>Low rates of discrimination</td>
<td>Excellent</td>
<td>Prohibited (contraindicated during the first trimester of pregnancy)</td>
</tr>
<tr>
<td>PI-based ART* with rifampin-based TB treatment</td>
<td>Limited effect of rifampin on PI resistance, concomitant increases in trough concentrations</td>
<td>Low rates of drug resistance (rifampin in appropriate dose range)</td>
<td>reversible, though published concern of hepatitis is not extensive</td>
<td>Prohibited for patients unable to tolerate rifampin</td>
</tr>
<tr>
<td>Nevirapine-based ART with rifampin-based TB treatment</td>
<td>Moderate effect</td>
<td>Concern about hepatotoxicity when used with nevirapine, efavirenz, and pyrazinamide</td>
<td>reversible</td>
<td>Alternative for patients who cannot take efavirenz and/or nevirapine</td>
</tr>
<tr>
<td>Zidovudine + lamivudine + abacavir / dicitrile / nevirapine with rifampin-based TB treatment</td>
<td>50% decrease in plasma, possible effect on abacavir not evaluated</td>
<td>Anemia</td>
<td>No published clinical experience</td>
<td>Alternative for patients who cannot take dicitrile and/or nevirapine</td>
</tr>
<tr>
<td>Zidovudine + lamivudine + abacavir / dicitrile / efavirenz with rifampin-based TB treatment</td>
<td>50% decrease in plasma, no other effect evaluated</td>
<td>Anemia</td>
<td>reversible, but not evaluated</td>
<td>Alternative for patients who cannot take efavirenz and/or dicitrile</td>
</tr>
<tr>
<td>Zidovudine + lamivudine + abacavir with rifampin-based TB treatment</td>
<td>50% decrease in plasma, possible effect on abacavir not evaluated</td>
<td>Anemia</td>
<td>early faileboxability, but drug combination is less effective than rifampin-based regimen to persons not taking abacavir</td>
<td>Alternative for patients who cannot take abacavir and/or dicitrile</td>
</tr>
<tr>
<td>Nuprolampedicolate-based ART with rifampin-based TB treatment</td>
<td>Little effect</td>
<td>Hepatitis among healthy adults, but favorable experience, among young children (≤ 3 years)</td>
<td>Good, among young children (≤ 3 years)</td>
<td>Alternative if dicitrile not available, preferred for young children when rifampin use available</td>
</tr>
</tbody>
</table>
Table 2. Recommendations for coadministering antiretroviral drugs with RIFAMPIN – 2007

<table>
<thead>
<tr>
<th>Non-nucleoside reverse transcriptase inhibitors</th>
<th>Recommended change in dose of antiretroviral drug</th>
<th>Recommended change in dose of rifampin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>None (some reports recommended 600 mg for patients &gt;40 kg)</td>
<td>No change (600 mg/day)</td>
<td>Efavirenz AUC is by 22%; no change in rifampin concentration. Efavirenz should not be used during the 1st trimester of pregnancy.</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>No change</td>
<td>No change (400 mg/day)</td>
<td>Nevirapine AUC is 32-56% and Cmax is 69% with 200 mg 2x/day dos.</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Delavirdine and rifampin should not be used together</td>
<td>Delavirdine AUC is by 55%</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Atazanavir and rifampin should not be used together</td>
<td>Atazanavir AUC is by 45%</td>
<td></td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>Isavuconazole and rifampin should not be used together</td>
<td>Isavuconazole AUC is by 50%</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Nelfinavir and rifampin should not be used together</td>
<td>Nelfinavir AUC is 0.28x</td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Saquinavir and rifampin should not be used together</td>
<td>Saquinavir AUC is by 64%</td>
<td></td>
</tr>
</tbody>
</table>

Single protease inhibitors

<table>
<thead>
<tr>
<th>Recommended change in dose of antiretroviral drug</th>
<th>Recommended change in dose of rifampin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ritonavir</td>
<td>No change (600 mg/day)</td>
<td>Use with caution. Ritonavir AUC is by 55%; no change in rifampin concentration. Monitor use antiretroviral activity at ritonavir.</td>
</tr>
<tr>
<td>lopinavir</td>
<td>Lopinavir and ritonavir should not be used together</td>
<td>Lopinavir AUC is by 45%</td>
</tr>
<tr>
<td>indinavir</td>
<td>Indinavir and ritonavir should not be used together</td>
<td>Indinavir AUC is by 50%</td>
</tr>
<tr>
<td>nefartinavir</td>
<td>Nelfinavir and ritonavir should not be used together</td>
<td>Nelfinavir AUC is 0.28x</td>
</tr>
<tr>
<td>saquinavir</td>
<td>Saquinavir and ritonavir should not be used together</td>
<td>Saquinavir AUC is by 64%</td>
</tr>
</tbody>
</table>

Table 2. (cont.) Recommendations for coadministering antiretroviral drugs with RIFAMPIN – 2007

<table>
<thead>
<tr>
<th>Dual protease-inhibitor combinations</th>
<th>Recommended change in dose of antiretroviral drug</th>
<th>Recommended change in dose of rifampin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir/ritonavir</td>
<td>Saquinavir 400 mg + ritonavir 200 mg twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Use with caution; combination of saquinavir (400 mg twice-daily) and ritonavir (400 mg twice-daily), and saquinavir caused unmeasurable rise of hepatitis among healthy volunteers</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kalera®)</td>
<td>Increase the dose of lopinavir/ritonavir (Kalera) 300 mg twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Use with caution; combination resulted in hepatotoxic in all adult healthy volunteers in an initial study.</td>
</tr>
<tr>
<td>&quot;Super-hived&quot; lopinavir/ritonavir (Kalera®)</td>
<td>Lopinavir/ritonavir (Kalera) 300 mg twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Use with caution; combination resulted in hepatotoxic in adult healthy volunteers. However, there are favorable pharmacokinetic and clinical data among young children.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>CCR-5 receptor antagonists</th>
<th>Recommended change in dose of antiretroviral drug</th>
<th>Recommended change in dose of rifampin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>Increase maraviroc to 400 mg twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Maraviroc Cmax is by 76%. No reported clinical experience with increased dose of maraviroc with rifampin</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Integrase inhibitors</th>
<th>Recommended change in dose of antiretroviral drug</th>
<th>Recommended change in dose of rifampin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>No change</td>
<td>No change (600 mg/day)</td>
<td>No clinical experience; Raltegravir concentrations 4x by 40-41%</td>
</tr>
</tbody>
</table>

MID 27
3. PYRAZINAMIDE (PZA)

- Bactericidal in acid environment (macrophages)
- Dose = weight dependent = 25-30 mg/kg: **PATIENT MUST BE WEIGHED**
- Main role in sensitive disease is to reduce length of treatment from 9 months to 6 months
- Do not use in pregnancy: no teratogenicity data

PZA structural formula:
C5H5N3O  M.W.123.11
MECHANISM OF ACTION
UNKNOWN

• PZA MAY BE BACTERIOSTATIC OR BACTERIOCIDAL AGAINST *M. tuberculosis* DEPENDING ON CONCENTRATION OF DRUG ATTAINED AT SITE OF INFECTION
• IN VITRO & IN VIVO DRUG IS ACTIVE ONLY AT SLIGHTLY ACIDIC pH

CLINICAL PHARMACOLOGY

• Well absorbed from GI tract
• Peak plasma concentrations in 2 hours
• Widely distributed in body tissues including lungs, liver and CSF when meninges inflamed
• 10% bound to protein
• Half-life (t ½)=9-10 hours in patients with normal renal function but may be prolonged in pts with renal insufficiency
• 70% of oral dose excreted in urine w/in 24 hours, mainly by GFR
PYRAZINAMIDE TOXICITY:

• HYPERURICEMIA:
  – PZA inhibits renal excretion of urates
  – All patients have increase in uric acid levels: usually entirely asymptomatic
  – Occasionally causes arthralgias: Offer patient choice of NSAIDS or D/C PZA and treat longer
  – Rarely causes acute gouty arthritis, most often in elderly: STOP PZA

• HEPATIC:
  – Increase in transaminases
    Chemically similar to isoniazid

4. ETHAMBUTOL (EMB)

• Most important function is prevention of resistance
• Used in drug resistance and when INH or RMP cannot be used (INH hepatotoxicity or RMP drug-drug interactions)
• Bacteriostatic
• Can use in pregnancy
• Primarily excreted by kidney so must adjust dose in renal insufficiency
ETHAMBUTOL

- Dose = weight dependent = 15-25 mg/kg: WEIGH PATIENT
- Toxicity more likely with higher dose
- Poor CNS penetration
- Can use in pregnancy

CLINICAL PHARMACOLOGY

- EMB at 25 mg/kg attains peak serum levels 2 to 4 hours after administration
- Following oral administration of EMB approximately 50 percent of initial dose excreted unchanged in the urine w/in 24 hours
- No drug accumulation observed w/ consecutive single daily doses of 25 mg/kg in patients with normal kidney function
- BUT marked accumulation in patients with renal insufficiency: TOXICITY
ETHAMBUTOL TOXICITY=
RETROBULBAR NEURITIS

- Blurred vision=initial symptom
- Red-green color blindness common and may be picked up earlier with testing
- Dose related: <1% of those receiving 15 mg/kg; recommended dose is 15-25 mg/kg
- CHECK VISUAL ACUITY & COLOR VISION AT BASELINE AND MONTHLY: ISHIHARA

TREATMENT REGIMENS:
ALL SHOULD BE DOT
IMMUNOCOMPETENT & DRUG SENSITIVE

- 6 Months total: FIRST 2 MONTHS=INITIATION OR INTENSIVE PHASE
  -2 months H/R/Z/E + 4 months H/R daily for entire 6 months
  -2 months H/R/Z/E daily + 4 months H/R BIW
  -TIW for entire 6 months: 2 months H/R/Z/E +4 months H/R
- 9 Months total: 9 months H/R without PZA: Pregnant women, Elderly if PZA intolerant, & M.bovis (PZA resistant)
- Drop EMB when sensitivities known
EXTEND CONTINUATION PHASE
3 MONTHS IF:

• CAVITARY DISEASE & POSITIVE SPUTUM CULTURE AFTER 2 MONTHS INITIAL PHASE
• ASSOCIATED WITH INCREASED RELAPSE IN CLINICAL TRIALS
• EXTENDED CONTINUATION PHASE DECREASED RELAPSE IN SILICOTUBERCULOSIS FROM 20% TO 3%
• HIV INFECTED PATIENT WITH SPUTUM CULTURE STILL POSITIVE AT 2 MONTHS

MDRTB: DEFINITION=
Resistance to Both INH & RMP

• CANNOT TREAT WITH EITHER INH OR RMP
• NEED 6-9 Month of injectable + 3 oral agents to which organism sensitive for total 24 months treatment after culture conversion
• Second line drugs necessary
• Poor prognosis: >50% treatment failure
• Old data published from National Jewish Center in Denver; referral center for secondary drug resistance
SECOND LINE DRUGS

• INJECTABLES:
  – STREPTOMYCIN
  – AMIKACIN
  – KANAMYCIN
  – CAPREOMYCIN

• ORAL AGENTS
  – QUINOLONES: LEVOFLOXACIN OR MOXIFLOXACIN
  – CYCLOSERINE
  – ETHIONAMIDE
  – P-aminosalicylic acid (PAS)

INCREASING TOXICITY & SIDE EFFECTS

• ORAL AGENTS:
  – CYCLOSERINE: narrow therapeutictoxic window
    CNS TOXICITY: CONVULSIONS & PSYCHOTIC DEPRESSION which can lead to suicidal behavior
  – ETHIONAMIDE: SEVERE GI N TOLERANCE (VOMITING);
    HEPATOTOXICITY similar to INH
INJECTABLES

• **AMIKACIN**: NEPHROTOXIC
• **STREPTOMYCIN**: NEUROTOXIC TO VIII NERVE
  - Both auditory and vestibular ototoxicity
  - Partial or total irreversible deafness may continue to develop after drug is stopped
  - Other features of neurotoxicity include paresthesia, twitching, and seizures.
  - Teratogenic: Contraindicated during pregnancy
• **KANAMYCIN**: SIMILAR TO STREPTOMYCIN
• **CAPREOMYCIN**
Multidrug-resistant Tuberculosis
New York City, 1991 - 1999

* 1991 data are incomplete

Number of Cases

Year
366 441 296 176 109 84 53 38 31


- MDR, US-born
- MDR, Non-US born

Extracellular drug resistance: The resistance to isoniazid or rifampin plus resistance to any four of the following: ethambutol, kanamycin, capreomycin, and any second-line AMR drugs (e.g., amikacin, kanamycin, capreomycin).
XDR TUBERCULOSIS: DEFINITION

- RESISTANT TO INH & RMP
- RESISTANT TO FLUOROQUINOLONES
- RESISTANT TO 1 OF THE INJECTABLE DRUGS: AMIKACIN, KANAMYCIN OR CAPREOMYCIN
Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Nefertir Gandhi, Anthony Wells, A Willem Storm, Robert Fournier, Thabisini Govender, Umesh Laloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

Summary

Background: The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

Methods: We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

Results: From January, 2005, to March, 2006, sputum was obtained from 1530 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 35% (165 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR tuberculosis had never been previously treated for tuberculosis; 67% (28 of 42) had a recent hospital admission. All 44 patients with XDR tuberculosis who were tested for HIV were co-infected. Of 53 patients with XDR tuberculosis, 5 died, with median survival of 16 days from time of diagnosis (IQR 6–37) among the 42 patients with confirmed dates of death. Genotyping of isolates showed that 39 of 46 (85%, 95% CI 74–95) patients with XDR tuberculosis had similar strains.
Figure: Survival after sputum collection in patients with XDR tuberculosis with confirmed dates of death (n=42)