TUBERCULOSIS TREATMENT: MEDICATIONS & REGIMENS

TREATMENT: 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 BACTEROICIDAL AGAINST ACTIVELY GROWING INTRACELLULAR & EXTRACELLULAR ORGANISMS
- INH RESISTANT *M. tuberculosis* organisms develop rapidly when INH monotherapy administered
CLINICAL PHARMACOLOGY

- Peak blood levels within 1-2 hours after oral administration.
- Peak blood levels decline to 50% within 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
MID 27

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

<table>
<thead>
<tr>
<th>Combined regimen for treatment of HIV and tuberculosis</th>
<th>PK effect of rifampin</th>
<th>Tuberculosis / miliary</th>
<th>Antiviral activity when used with rifampin</th>
<th>Recommendation (comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz-based ART* withrifampin-based TB treatment</td>
<td>Weak, numerically, modest effect</td>
<td>Low rates of discrimination</td>
<td>Excellent</td>
<td>Preferred (efavirenz should not be used during the first trimester of pregnancy)</td>
</tr>
<tr>
<td>PI-based ART* with rifampin-based TB treatment</td>
<td>Little effect on rifampin concentration, but marked increases in rifampin concentrations</td>
<td>Low rates of discrimination (rifampin is appropriately dose-adjusted)</td>
<td>Potentially, through published clinical experience in not uncommon</td>
<td>Preferred but patients unable to take statins ?</td>
</tr>
<tr>
<td>Nelfinavir-based ART with rifampin-based TB treatment</td>
<td>Moderate effect</td>
<td>Concern about hepatotoxicity when used with nelfinavir, efavirenz and protease inhibitors</td>
<td>Frequent</td>
<td>Alternative for patients who cannot take efavirenz and/or rifampin not available</td>
</tr>
<tr>
<td>Zidovudine / lamivudine / abacavir / nevirapine with rifampin-based TB treatment</td>
<td>50% decrease in zidovudine, no other effects predicted</td>
<td>Anemia</td>
<td>No published clinical experience</td>
<td>Alternative for patients who cannot take efavirenz and/or rifampin not available</td>
</tr>
<tr>
<td>Zidovudine / lamivudine / abacavir / nevirapine with rifampin-based TB treatment</td>
<td>50% decrease in zidovudine, no other effects predicted</td>
<td>Anemia</td>
<td>Frequent, but not excluded in a randomized trial</td>
<td>Alternative for patients who cannot take efavirenz and/or rifampin not available</td>
</tr>
<tr>
<td>Zidovudine / lamivudine / abacavir / nevirapine with rifampin-based TB treatment</td>
<td>50% decrease in zidovudine, no other effects predicted</td>
<td>Anemia</td>
<td>Early experience, but no discrimination in less effective than efavirenz-based regimen in process not taking statins</td>
<td>Alternative for patients who cannot take efavirenz and/or rifampin not available</td>
</tr>
<tr>
<td>Stop boosted protease-based ART with rifampin-based TB treatment</td>
<td>Little effect</td>
<td>Hepatitis among healthy adults, but favorable experience, among young children (&lt; 3 years)</td>
<td>Good, among young children (&lt; 3 years)</td>
<td>Alternative if efavirenz not available, preferred for young children when rifampin not 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 experts recommend 800 mg for patients &gt; 40 kg)</td>
<td>No change (600 mg/day)</td>
<td>Efavirenz AUC + 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 (600 mg/day)</td>
<td>Nevirapine AUC + 15-59% and Cmax + 68% with 200 mg 2/day dose.</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Delavirdine and delavirdine should not be used together</td>
<td>Delavirdine AUC + by 59%</td>
<td>Delavirdine AUC + by 59%</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Lopinavir and lopinavir should not be used together</td>
<td>Lopinavir AUC + by 59%</td>
<td>Method decrease in ritonavir predicted, based on data on the interaction with rifampin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Single protease 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>Ritonavir</td>
<td>No change</td>
<td>No change (600 mg/day)</td>
<td>Use with caution. Ritonavir AUC + by 59% no change in rifampin concentration. Monitor for antiretroviral activity of ritonavir.</td>
</tr>
<tr>
<td>5x-Hydroxytegrin</td>
<td>Teplanavir and 5x-hydroxytegrin should not be used together</td>
<td>Teplanavir AUC + by 59%</td>
<td>Teplanavir AUC + by 59%</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Teplanavir and atazanavir should not be used together</td>
<td>Atazanavir AUC + by 59%</td>
<td>Atazanavir AUC + by 59%</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Teplanavir and indinavir should not be used together</td>
<td>Indinavir AUC + by 59%</td>
<td>Indinavir AUC + by 59%</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Teplanavir and nelfinavir should not be used together</td>
<td>Nelfinavir AUC + by 59%</td>
<td>Nelfinavir AUC + by 59%</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Teplanavir and saquinavir should not be used together</td>
<td>Saquinavir AUC + by 59%</td>
<td>Saquinavir AUC + by 59%</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 400 mg twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Use with caution, the combination of saquinavir (1000 mg twice-daily), ritonavir (300 mg twice daily) and rifampin caused unacceptably high levels of hepatic enzymes in healthy volunteers.</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra®)</td>
<td>Increase the dose of lopinavir/ritonavir (Kaletra®) 4 tablets (200 mg of lopinavir with 50 mg of ritonavir) twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Use with caution, this combination resulted in hepatic enzymes in all adult healthy volunteers in a clinical study.</td>
</tr>
<tr>
<td>“Super-powered” lopinavir/ritonavir (Kaletra®)</td>
<td>Lopinavir/ritonavir (Kaletra®) 2 tablets (200 mg of lopinavir with 50 mg of ritonavir) twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Use with caution, this combination resulted in hepatic enzymes in all adult healthy volunteers. However, there are favorable pharmacokinetic and clinical data among youth children.</td>
</tr>
</tbody>
</table>

<table>
<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 600 mg twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Maraviroc Cmax + by 74%. No reported clinical experience with increased dose of maraviroc with rifampin</td>
</tr>
</tbody>
</table>

<table>
<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 + by 40-60%</td>
</tr>
</tbody>
</table>
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 within 24 hours
- No drug accumulation observed with 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 therapeutict-toxic window
    CNS TOXICITY: CONVULSIONS & PSYCHOTIC DEPRESSION which can lead to suicidal behavior
  – ETHIONAMIDE: SEVERE GI 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
XDR TUBERCULOSIS: DEFINITION

• RESISTANT TO INH & RMP
• RESISTANT TO FLUOROQUINOLONES
• RESISTANT TO 1 OF THE INJECTABLE DRUGS: AMIKACIN, KANAMYCIN OR CAPREOMYCIN

Figure 2: Countries with confirmed XDR-TB cases thus far (pink). From the World Health Organization, http://www.who.int/tb/xdr/xdr_jan.pdf (accessed 22 January 2007).
XDR TB Counted Cases defined on Initial DST† by Year, 1993–2006*

Case Count

Year of Diagnosis

*Reported incident cases as of 7/18/07
†Drug Susceptibility Test

FIGURE. Number of reported cases of extensively drug-resistant tuberculosis (XDR TB)* — United States, 1993–2006

*XDR TB defined as resistance to at least isoniazid, rifampin, any fluoroquinolone, and at least one second-line injectable drug (kanamycin, amikacin, 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

Nishi Gandhi, Anthony Mull, A Willem Sturm, Robert Pauwels, Thokozani Govender, Unasho Lala, 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 1539 patients. We detected MDR tuberculosis in 221 patients, 67% of whom had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 95% (145 patients) for MDR and 96% (306) 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. 52 of 53 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis (IQR 8–37) 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)