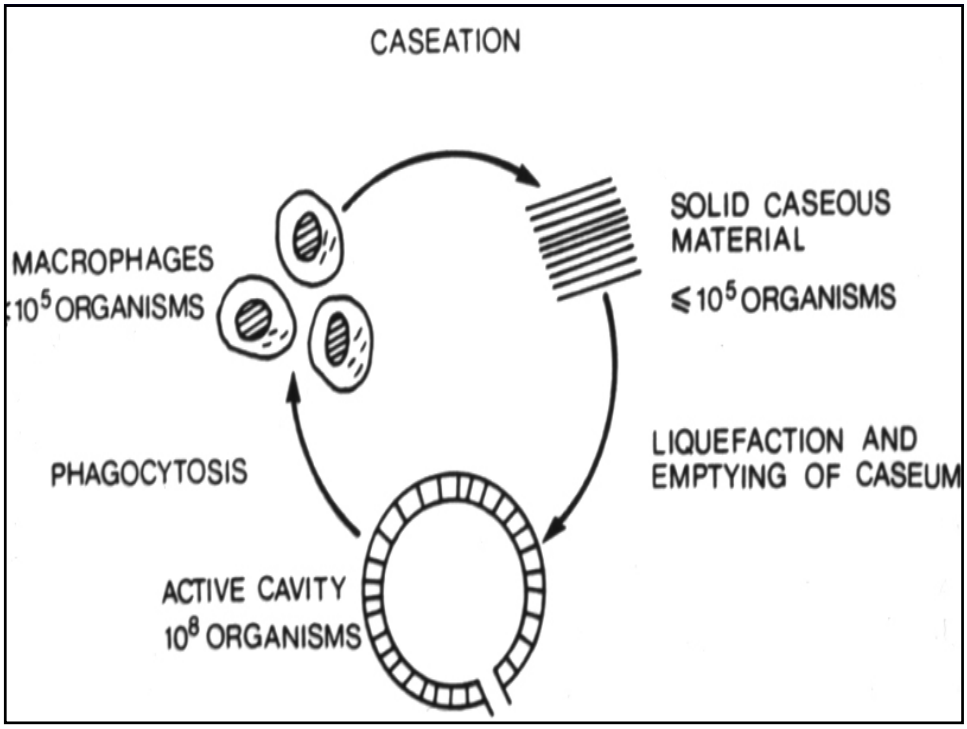
TUBERCULOSIS TREATMENT: MEDICATIONS & REGIMENS

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
- **D**irectly **O**bserved **T**herapy: 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)IsoNicotinyl Hydrazine or isonicotinic acid hydrazide

- **INH available as 100 mg and 300 mg tablets for oral administration**
- **INH empirical formula: C6H7N3O**
- **MOLECULAR WEIGHT: 137.14.**

MECHANISM OF ACTION

- **INH INHIBITS SYNTHESIS OF MYCOLIC ACIDS**
- **MYCOLIC ACID IS ESSENTIAL COMPONNT OF BACTERIAL CELL WALL**
- **INH IS BACTERIOCIDAL 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 NEUROPATHEY (ALCOHOLICS, DIABETICS)

USUALLY PRECEDED BY PARESTHESIAS OF FEET & HANDS

PYRIDOXINE INDICATED FOR PATIENTS WITH CONDITIONS WHERE PERIPHERAL NEUROPATHY COMMON: DIABETES, UREMIA, ALCOHOLISM, AIDS

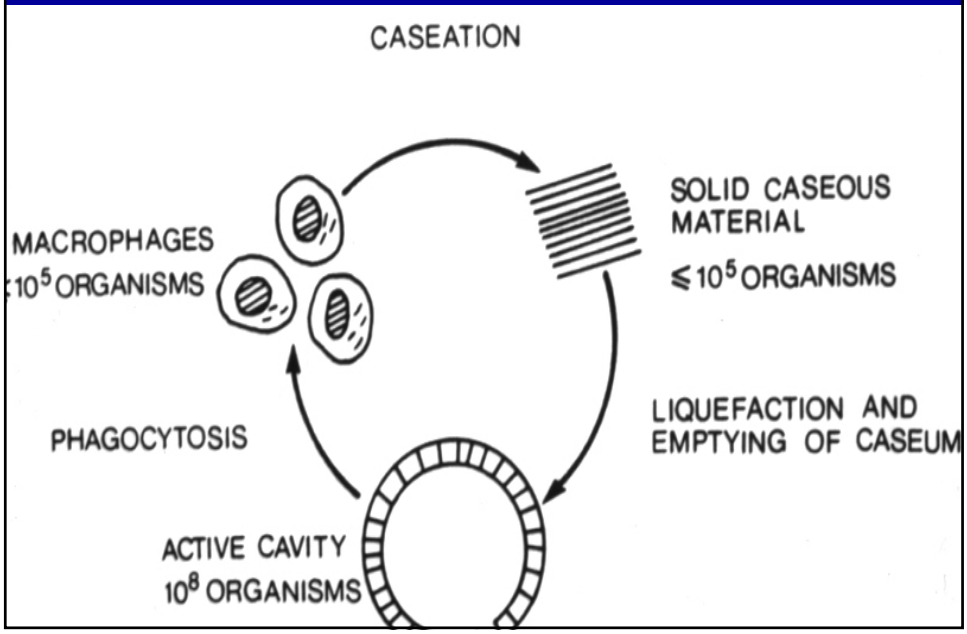
- Pyridoxine indicated for pregnant women on INH

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

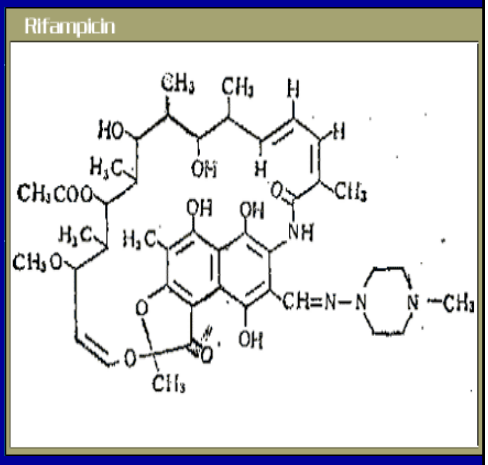
ENABLES SHORT COURSE TREATMENT:

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

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

Combined regimen for treatment of HIV and tuberculosis	PK effect of the rifamycin	Tolerability / toxicity	Antiviral activity when used with rifampin	Recommendation (comments)
Efavirenz-based ART * with rifampin-based TB treatment	Well-characterized, modest effect	Low rates of discontinuation	Excellent	Preferred (efavirenz should not be used during the first trimester of pregnancy)
PI-based ART * with rifabutin-based TB treatment	Little effect of rifabutin on PI concentrations, but marked increases in rifabutin concentrations	Low rates of discontinuation (if rifabutin is appropriately dose-reduced)	Favorable, though published clinical experience is not extensive	Preferred for patients unable to take efavirenz †
Nevirapine-based ART with rifampin-based TB treatment	Moderate effect	Concern about hepatotoxicity when used with isoniazid, rifampin and pyrazinamide	Favorable	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir / tenofovir with rifampin-based TB treatment[10]	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	No published clinical experience	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, no other effects predicted	Anemia	Favorable, but not evaluated in a randomized trial	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz and if rifabutin not available
Super-boosted lopinavir-based ART with rifampin-based TB treatment	Little effect	Hepatitis among healthy adults, but favorable experience, among young children (< 3 years)	Good, among young children (< 3 years)	Alternative if rifabutin not available; preferred for young children when rifabutin not available

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

Non-nucleoside reverse transcriptase inhibitors			
	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Efavirenz	None (some experts recommend 800 mg for patients > 60 kg)	No change (600 mg/day)	Efavirenz AUC ↓ by 22%; no change in rifampin concentration. Efavirenz should not be used during the 1st trimester of pregnancy.
Nevirapine	No change	No change (600 mg/day)	Nevirapine AUC ↓ 37-58% and Cmin ↓ 68% with 200 mg 2x/day dose.
Delavirdine	Rifampin and delavirdine should not be used together		Delavirdine AUC ↓ by 95%
Etravirine	Etravirine and rifampin should not be used together		Marked decrease in etravirine predicted, based on data on the interaction with rifabutin
Single protease inhibitors			
	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Ritonavir	No change	No change (600 mg/day)	Use with caution. Ritonavir AUC↓ by 35%; no change in rifampin concentration. Monitor for antiretroviral activity of ritonavir.
fos-Amprenavir	Rifampin and fos-amprenavir should not be used together		
Atazanavir	Rifampin and atazanavir should not be used together		Atazanavir AUC ↓ by >95%
Indinavir	Rifampin and indinavir should not be used together		Indinavir AUC ↓ by 89%.
Nelfinavir	Rifampin and nelfinavir should not be used together		Nelfinavir AUC ↓ 82%
Saquinavir	Rifampin and saquinavir should not be used together		Saquinavir AUC ↓ by 84%

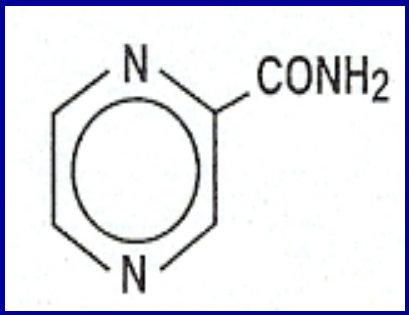
Table 2. (cont.) Recommendations for coadministering antiretroviral drugs with RIFAMPIN – 2007

Dual protease-inhibitor combinations			
	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Saquinavir/ritonavir	Saquinavir 400 mg + ritonavir 400 mg twice-daily	No change (600 mg/day)	Use with caution; the combination of saquinavir (1000 mg twice-daily), ritonavir (100 mg twice-daily), and rifampin caused unacceptable rates of hepatitis among healthy volunteers
Lopinavir/ritonavir (Kaletra™)	Increase the dose of lopinavir / ritonavir (Kaletra ™) – 4 tablets (200 mg of lopinavir with 50 mg of ritonavir) twice-daily	No change (600 mg/day)	Use with caution; this combination resulted in hepatitis in all adult healthy volunteers in an initial study.
"Super-boosted" lopinavir /ritonavir (Kaletra™)	Lopinavir / ritonavir (Kaletra ™) – 2 tablets (200 mg of lopinavir with 50 mg of ritonavir) + 300 mg of ritonavir twice-daily	No change (600 mg/day)	Use with caution; this combination resulted in hepatitis among adult healthy volunteers. However, there are favorable pharmacokinetic and clinical data among young children
CCR-5 receptor antagonists			
	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Maraviroc	Increase maraviroc to 600 mg twice-daily	No change (600 mg/day)	Maraviroc Cmin ↓ by 78%. No reported clinical experience with increased dose of maraviroc with rifampin
Integrase inhibitors			
	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Raltegravir	No change	No change (600 mg/day)	No clinical experience; raltegravir concentrations ↓ by 40-61%

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:
$C_5H_5N_3O$ 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:

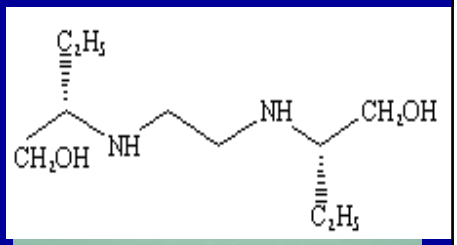
- **HYPERURICEMIA:**
  - PZA inhibits renal excretion of urates
  - All patients have increase in uric acid levels: usually entirely asymptomatic
  - Occasionally causes arthralgias: Offer patient choice of NSAIDS or D/C PZA and treat longer
  - Rarely causes acute gouty arthritis, most often in elderly: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

    CNS TOXICITY:CONVULSIONS & PSYCHOTIC DEPRESSION which can lead to suicidal behavior
  - **ETHIONAMIDE: SEVERE GI NTOLERANCE (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**

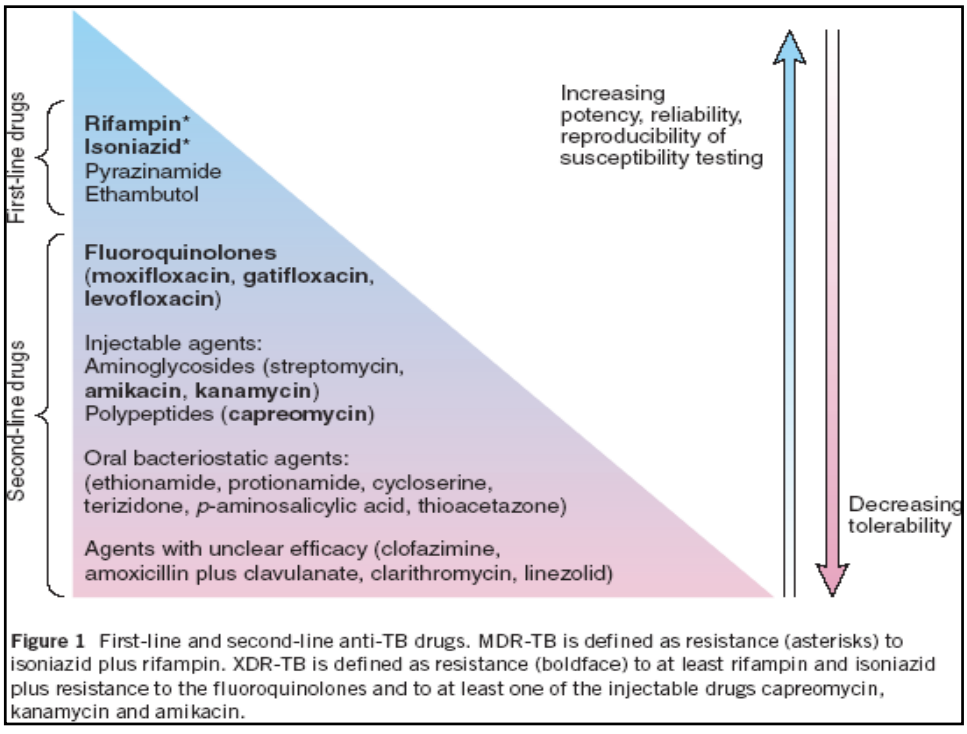
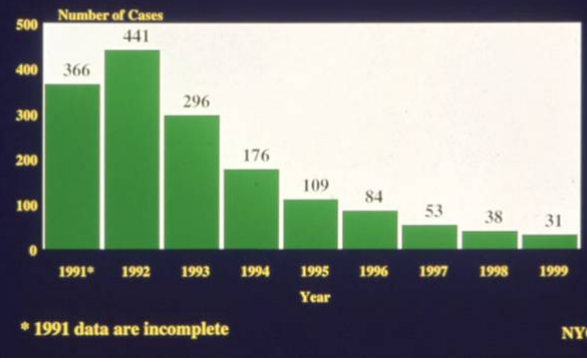


Figure 1 First-line and second-line anti-TB drugs. MDR-TB is defined as resistance (asterisks) to isoniazid plus rifampin. XDR-TB is defined as resistance (boldface) to at least rifampin and isoniazid plus resistance to the fluoroquinolones and to at least one of the injectable drugs capreomycin, kanamycin and amikacin.

Multidrug-resistant Tuberculosis New York City, 1991 - 1999



XDR TUBERCULOSIS: DEFINITION

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

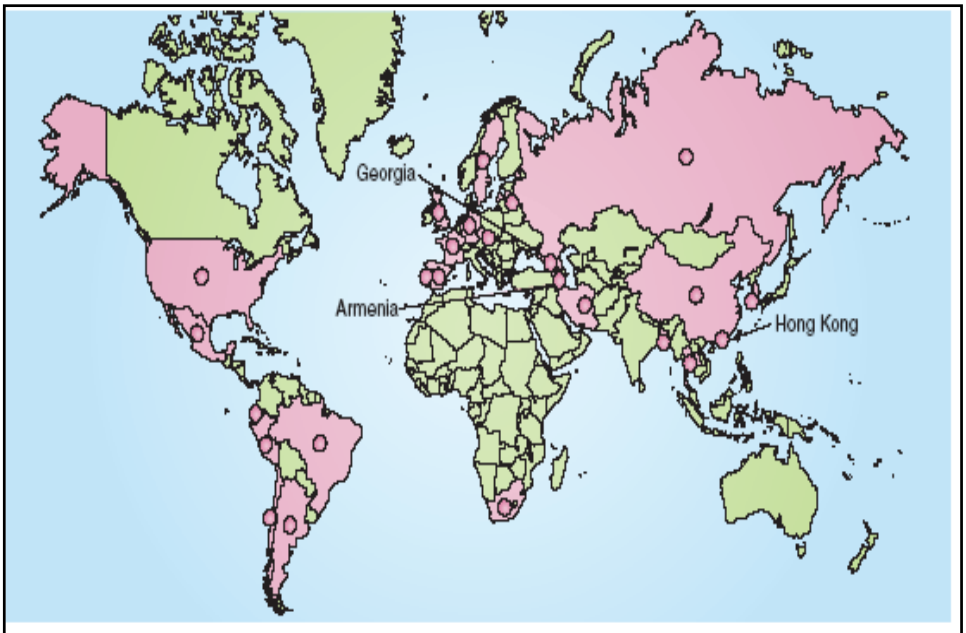
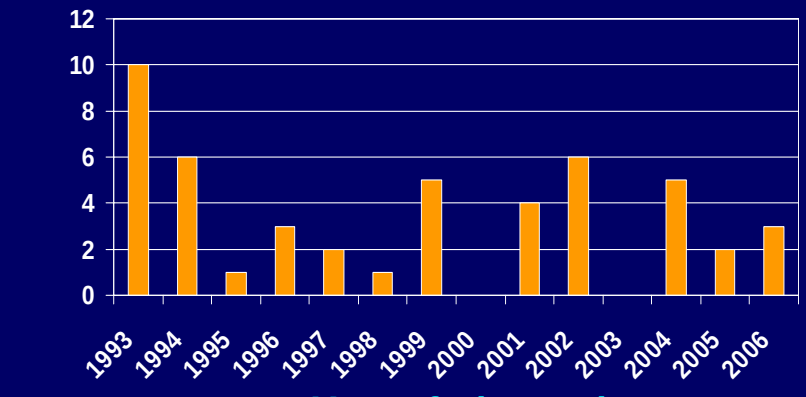


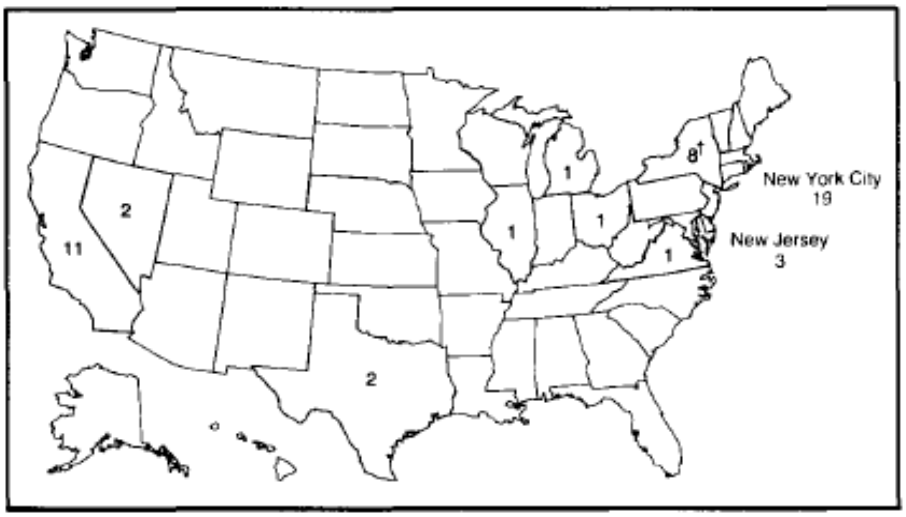
Figure 2 Countries with confirmed XDR-TB cases thus far (pink). From the World Health Organization, http://www.who.int/tb/xdr/xdr_jan.pdf (accessed 22 January 2007).

XDR TB Counted Cases defined on Initial DST† by Year, 1993–2006*



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

FIGURE. Number of reported cases of extensively drug-resistant tuuberculosis (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

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, 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, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 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. 52 of 53 patients with XDR tuberculosis 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.

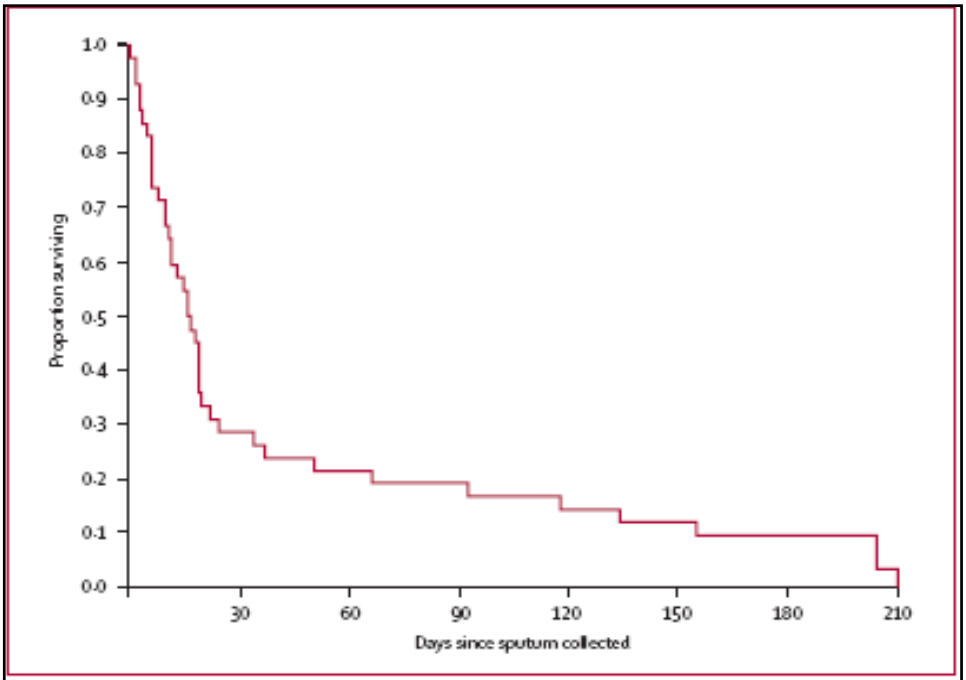


Figure: Survival after sputum collection in patients with XDR tuberculosis with confirmed dates of death (n=42)