

VA GREATER LOS ANGELES TUBERCULOSIS PROTOCOLS

TUBERCULIN SKIN TESTING

Revised CDC criteria for classifying 5 TU tuberculin skin test (PPD) as being positive

High risk patients: ≥ 5 mm induration

HIV seropositive (or other profound immunocompromise), abnormal CXR (upper lobe fibronodular lesions), recent contact of patients with infectious TB (household contact or unprotected occupational contact similar in intensity and duration).

Low risk patients: ≥ 10 mm induration

Native of endemic area, IDUs, medically underserved, low-income populations, residents of long-term care facilities; and those with medical conditions that increase the risk of TB.

No risk patients: ≥ 15 mm

All other individuals

LATENT TUBERCULOSIS (PROPHYLAXIS) (Am J Respir Crit Care Med. 2000; 161:S221.).

Risks of reactivation:

Incidence of active tuberculosis with + tuberculin skin test

	Rate per 1,000 person years
Conversion of tuberculin skin test within previous year	13
+ PPD for 1 – 7 years	1.6
HIV+	100
Silicosis	68
Fibrotic lesion on CXR	7.5
Relative rate of active tuberculosis (tuberculin skin test status unspecified)	
General population	1
Underweight by > 5%	2
Diabetes mellitus	3
Gastrectomy	4
Head/neck carcinoma	16
Chronic renal failure/dialysis	18
Silicosis	30
Solid organ transplant	40
Jejunolileal bypass	45

Routine treatment

Treat (prophylax) regardless of age: if PPD positive by previous definitions **and any of the following**

Recent converters: conversion of the tuberculin skin test from negative to positive within the past 2 years

HIV seropositive: CDC recommends universal prophylaxis for all tuberculin-skin test positive HIV infected patients

Abnormal CXR (fibronodular upper lobe lesions)

Recent contacts of patients with infectious TB (household contact or unprotected occupational contact similar in intensity and duration).

Patients with medical conditions that increase the risk of TB: Diabetes mellitus (especially if insulin-dependent), prolonged therapy with > 15 mg prednisone/day or other immunosuppressives, leukemia, lymphoma, injection drug use (increased risk of reactivation even if HIV-negative), end stage renal disease, chronic malnutrition or substantial rapid weight loss (e.g., intestinal bypass surgery, malabsorption, head and neck or other chronic, active carcinoma, gastrectomy).

Treat (prophylax) if age < 35:

Natives of areas endemic for tuberculosis

Medically underserved, low-income populations

Residents of long-term care facilities

Individual assessment of risks and benefits of treatment (prophylax): individuals at low risk for acquisition of tuberculosis who are < 35 and have a PPD of > 15 mm should receive INH unless there are strong countervailing considerations.

Treatment (prophylaxis) options: *See caution note below.* For HIV-seronegative persons, 9 months of daily INH is the preferred treatment; 4 months of daily rifampin is acceptable.

See contra-indications		HIV(-)	HIV(+)-
INH	300 mg qd x 9 months	All	All
	900 mg 2x/wk x 9 months (DOT)	BII	BII
	300 mg qd x 6 months ⁺	BI	CI
	900 mg 2x/wk x 6 months (DOT)	BII	CI
Rifampin*	600 mg qd x 4 months	BII	BIII
Rifampin*/pyrazinamide	600/2000 mg qd x 2 months		AI
	600/4000 mg 2x/wk x 2-3 months (DOT)		CI

A= preferred, B = acceptable, C = offer when A and B cannot be given

I = based on RCT, II = clinical data available, III = expert opinion

* See section on treatment of HIV-infected patients for recommendations regarding the use of rifabutin in persons receiving protease-inhibitors or non-nucleoside reverse transcriptase inhibitors.

+ Do not use 6 month INH regimen in HIV+ patients, children, or with abnormal CXR

Treatment goals:

INH qd x 9 months: 270 doses within 12 months

INH qd x 6 months: 180 doses within 9 months

Rifampin/pyrazinamide qd x 2 months: 60 doses within 2 months

Rifampin qd x 4 months: 120 doses within 6 months

Contra-indications to INH:

Previous INH hepatotoxicity

Serious INH allergic reactions

Acute or unstable liver disease (positive hepatitis serology, or past history of cirrhosis or hepatitis does not preclude INH use)

Contra-indications to rifampin/pyrazinamide:

Regimen should not be used in persons with underlying liver disease or prior INH-associated liver injury.

Possible ↑ risk of fatal hepatic injury in HIV seronegative patients. In HIV-sero-positive patients the incidence of abnormal LFTs is similar with use of Rifampin/pyrazinamide and INH alone.

Prophylaxis - MDR *M. tuberculosis*: (MMWR 1992; 41:(RR-11)). Patients with intermediate to high exposure to MDR *M. tuberculosis* should consider MDR preventive therapy if *M. tuberculosis* from the presume source case is 100% resistant to INH and RIF (by the proportion method of susceptibility testing) or if the contact has factors which substantially increase the risk of developing active disease due to *M. tuberculosis*.

Regimens

EMB+PZA

PZA+fluoroquinolone

Duration

HIV-infected, immunosuppressed or non-compliant: 12 months

All others: 6 months

THERAPY OF TUBERCULOSIS

Principles

- Directly observed therapy (DOT) recommended by Los Angeles County Health Department for patients at increased risk for noncompliance, with drug resistance, or prior failure of treatment or relapse. CDC recommends DOT for all patients.
- All successful short term regimens rely upon INH + RIF with PZA during the first 3 months of therapy.
- Fixed drug combinations (Rifamate™, Rifater™) should be used for all patients on self-administered therapy.
- For susceptible isolate, continue four drugs until patient is culture (-) (usually ≤ 2 months).

Regimens Am J Respir Crit Care Med. 1994; 149:1359-1374, MMWR 1993; 42 (RR-7). One of the following therapies should be continued for at least 6 months and 3 months beyond culture conversion.

HIV-infected patients: all should receive DOT

Medications and Doses for Treatment of TB

Rifampin (RFP):

Not recommended: NVP, DLV, NFV, SQV, IDV, APV, or LPV/r (Kaletra™).

No dose adjustment: all NRTIs, EFZ, RTV, SQV/RTV combination

Rifabutin (RFB)

Not recommended: DLV

No dose adjustment: all NRTIs, NVP,

OK with dose adjustment: EFZ, NFV, RTV, SQV, IDV, APV, LPV/r (Kaletra™).

IDV, NFV, LPV/r, or APV, the daily dose of rifabutin should be decreased from 300 mg to 150 mg; the twice-weekly dose of RFB remains at 300 mg.

RTV or RTV/SQV: reduce rifabutin dose to 150 mg qod

EFV: increase dose of RFB to 450 - 600 mg qd or 600 mg 2–3 times/wk.

INH, ethambutol, PZA and streptomycin should be given in standard doses.

Treatment duration:

At least 4 months after last positive culture and resolution of signs and symptoms of tuberculosis (if not accounted for by another disease process).

Rifamycin-based therapy: The minimum duration of short-course RFB-containing TB treatment regimens is 6 months, to complete **a**) at least 180 doses (one dose per day for 6 months) or **b**) 14 induction doses (one dose per day for 2 weeks) followed by 12 induction doses (two doses per week for 6 weeks) plus 36 continuation doses (two doses per week for 18 weeks). For patients not taking protease inhibitors or NNRTIs, rifampin can be substituted for rifabutin.

The minimum duration of non-rifamycin, streptomycin-based TB treatment regimens is 9 months. As with HIV-negative patients, at least 9 months is generally recommended for certain forms of extrapulmonary disease, such as meningioma, bone, and joint TB

Adverse reactions in HIV-infected patients:

Possibly higher predisposition toward isoniazid-related peripheral neuropathy

Rifabutin toxicity: arthralgias, uveitis, and leukopenia

Paradoxical reactions:

Definition: severe or life-threatening clinical manifestations (e.g., uncontrollable fever, airway compromise from enlarging lymph nodes, enlarging serosal fluid collections [pleuritis, pericarditis, peritonitis], sepsis-like syndrome) occurring within several weeks after the concomitant initiation of anti-tuberculous and anti-retroviral therapy in HIV-infected patients.

Treatment: Consider hospitalization and possible a time-limited use of corticosteroids (e.g., prednisone started daily at a dose of 60–80 mg and reduced after 1 or 2 weeks, with the resolution of symptoms as a guide; in most cases, corticosteroid therapy should last no more than 4–6 weeks).

Culture-negative, pulmonary tuberculosis:

INH, RIF, and PZA: daily for 8 weeks followed by 8 weeks of daily INH and RIF or 2-3 times per week. If local rate of INH resistance is $\geq 4\%$ add EMB or SM to initial regimen until culture negativity is demonstrated; rate of INH resistance in Los Angeles County is $\geq 4\%$.

Culture-positive, fully sensitive, pulmonary tuberculosis: Substitution of EMB or SM for PZA during the first 2 months reduces the effectiveness of all regimens.

INH, RIF, EMB, and PZA: daily for 8 weeks followed by 16 weeks of daily INH + RIF. **Preferred regimen at VA Greater Los Angeles Healthcare System.**

INH and RIF: daily for 9 months. If local rate of INH resistance is $\geq 4\%$ add EMB or SM to initial regimen until susceptibility to INH and RIF is demonstrated. Reserve for patients who cannot take PZA.

INH, RIF, PZA, and EMB/SM: daily for 2 weeks followed by 2 times per week for 6 weeks then 2 times per week INH and RIF for 16 weeks. *Denver DOT regimen.*

INH, RIF, PZA and EMB/SM: 3 times per week for 6 months (DOT). Must continue PZA and EMB for all 6 months. SM can be stopped at 4 months if cultures convert to negative.

Pregnancy: INH, RIF and EMB can be safely used. PZA is recommended internationally but inadequate teratogenic data has precluded labeling for use during pregnancy in the USA. SM, CM and KM associated with congenital deafness. No safety data with cycloserine, ethionamide. Prophylaxis may be deferred until the completion of pregnancy.

Extra-pulmonary tuberculosis: duration of therapy same as for pulmonary disease except in infants and children where because of inadequate data 12 months of therapy is recommended for bone/joint infection, meningitis and miliary disease.

INH-resistant tuberculosis

INH, RIF, PZA, and EMB initial management: Stop INH when sensitivity data available. Continue RIF, PZA and EMB for a total of 6 months or until patient is culture-negative for ≥ 4 months, whichever takes longer.

INH, RIF, and EMB initial management: Stop INH when sensitivity data available. Continue RIF, and EMB for a total of 12 months.

INH, and RIF initial management: Stop INH when sensitivity data available. Repeat sensitivity tests, add 2 new drugs (e.g. PZA and EMB).

INH and RIF resistant (multi-drug resistant) tuberculosis: All such patients should be referred to LA TB Control Program (213-744-6160). Isolates are often also resistant to EMB and SM. Give 3 new drugs in addition to original regimen until patient is culture-negative followed by ≥ 12 months of 2 drug regimen. Many authorities recommend 18-24 months of multi-drug therapy after culture conversion. Following recommendations are by Iseman (NEJM. 1993; 329:789).

Resistance Pattern	Regimen	Duration
INH, SM, PZA	RIF, PZA, EMB, AMI	6 - 9 months
INH, EMB (\pm SM)	RIF, PZA, Oflox, (\pm AMI)*	6 - 12 months
INH, RIF (\pm SM)	PZA, EMB, Oflox, (\pm AMI)*	
INH, RIF, EMB (\pm SM)	PZA, Oflox, (\pm AMI)* + 2 other drugs ⁺	24 months after conversion [#]
INH, RIF, PZA, EMB (\pm SM)	Oflox, (\pm AMI) + 3 other drugs ⁺	24 months after conversion [#]

* Substitute capreomycin if there is resistance to AMI, KM and SM. Injectable agents are usually continued for 4 - 6 months if toxicity does not intervene.

+ Choose among ethionamide, cycloserine or aminosalicylic acid. Role of clofazimine and amoxicillin-clavulanate is ill-defined

Strongly consider surgery.

Definition of failure

Culture-positive at 2 months: re-evaluate for resistance and adherence. Strongly consider DOT.

Culture-positive at 5-6 months: Repeat sensitivity testing. Mandatory DOT, continue same drugs or add 3 new drugs.

Relapse management: Patients with susceptible isolates who relapse following treatment with INH and RIF based regimens generally have disease due to sensitive drug.

MONITORING

Clinical follow-up: Monthly visits to determine adherence to regimen and symptoms of toxicity. Q 2 week monitoring for persons receiving rifampin/pyrazinamide – give these patients no more than a 2 week supply of medication. Patients should stop RIF-PZA immediately and seek medical attention for abdominal pain, emesis, jaundice or other hepatitis symptoms.

Baseline Laboratory tests: LFTs, serum creatinine, CBC, pregnancy test, CXR; check uric acid in patients receiving PZA. Baseline visual acuity, red-green color discrimination (Snelling test) with high-dose (> 15 mg/kg/d) EMB therapy. Baseline auditory function with SM therapy. Offer HIV testing to all patients.

Follow-up laboratory tests

LFTs: Discontinuation therapy if AST/ALT increase to > 5 times the baseline value, or AST/ALT greater than normal and accompanied by symptoms of hepatitis or a serum bilirubin greater than normal.

RIF/PZA (monitor at baseline and every 2 weeks in ALL patients receiving this regimen) – see **cautionary notes regarding this regimen**.

INH: Monitor LFTs monthly under the following conditions. If LFTs are stable for 3 months may reduce frequency to q 2-3 months.

Baseline ALT \geq 5X ULN or evidence of chronic liver disease

Age > 35

Daily alcohol use

Injection drug use

Post-pubertal Black or Hispanic women

Treatment with PZA or INH+RIF

Pregnant or < 6 months post-partum

Previous hepatic disease or dysfunction

Renal function: Patients treated with SM or KM require monthly BUN and creatinine.

Vestibular function: assess clinical assessment at least monthly; formal testing every 2 months with streptomycin treatment

Audiograms: assess clinical assessment at least monthly; formal testing monthly with kanamycin treatment, every 2 months with streptomycin.

Eye test: Snelling monthly in patients treated with >15 mg/kg/d EMB or if visual complaints develop

Sputum AFB:

Repeat culture monthly until culture negative

Expected response for susceptible isolates, adherent patient: 85% culture-negative at 2 months, > 90% culture-negative at 3 months.

CXR: less important than clinical and sputum response. Check film at completion of therapy.

ANTI-TUBERCULOUS THERAPEUTIC AGENTS

Combination Preparations

Rifamate: 300 mg rifampin/150 mg INH

Rifater: 120 mg rifampin/50 mg INH/300 mg PZA

Adult Dosages

Drug	Daily	2 times/week	3 times/week
INH	5 mg/kg; max 300	15 mg/kg; max 900	15 mg/kg; max 900
RIF	10 mg/kg; max 600	10 mg/kg; max 600	10 mg/kg; max 600
Rifabutin	300 mg*	300 mg ⁺	
Rifapentine	600 mg q week		
PZA	15-30 mg/kg; max 2 gm	50-70 mg/kg; max 4 gm	50-70 mg/kg; max 3 gm
EMB	15-25 mg/kg; max 2.5 gm	50 mg/kg;	50 mg/kg; max 2.5 gm
SM	15 mg/kg; max 1 gm	25-30 mg/kg; max 1.5 gm	25-30 mg/kg; max 1 gm
KM	15-30 mg/kg		
Ofloxacin	400 mg bid		
Cipro	750 mg bid		
PAS	150 mg/kg; max 12 gm		
ETH	15-20 mg/kg; max 1 gm		
CYC	15-20 mg/kg; max 1 gm		

Dose adjustment with NNRTIs and protease inhibitors

	Rifampin	Rifabutin
Nevirapine (NVP)	OK if no other choices	No dose adjustment
Delavirdine (DLV)	Contra-indicated	Contra-indicated
Efavirenz (EFV)	↑ EFZ to 800 mg qd	↑ RFB to 450 qd or 600 mg 2-3x/wk
Nelfinavir (NFV)	Contra-indicated	↓ RFB* (150 mg qd or 300 mg 2-3x/wk); ↑ NFV to 1000 mg q 8h
Ritonavir (RTV)	Avoid if RTV is the only PI	↓ RFB to 150 mg qod; usual RTV usual SQV, IDV, APV, fos-APV, or ATV if any dose of RTV used as boosting agent
Saquinavir (SQV)	Contra-indicated	Not recommended
SQV + RTV	Contraindicated, hepatotoxic	Probably OK; ↓ RFB to 150 mg 2-3x/wk

Indinavir (IDV)	Contra-indicated	↓ RFB* (150 qd, 300 2-3x/wk); ↑ IDV (1000 mg q 8h)
Amprenavir (APV)/fos-APV	Contra-indicated	↓ RFB* to 150 qd, 300 2-3x/wk; = APV
Lopinavir/rtv	↑ RTV to 400 mg qd	↓ RFB to 150 mg qod; = LPV/r
Atazanavir	Contra-indicated	↓ RFB to 150 mg qod or tiw; = ATV

Pharmacology

Food interactions: ↓ absorption of INH and rifampin with food

Drug interactions: ↓ INH absorption with antacids (but ddl has no effect).

GLA INFECTION CONTROL

Intensity of exposure: Concentrations of infectious droplet nuclei/ft³ of expired air ranges from 1/11,000 to 1/70. Average patient exhales 18 ft³ of air per hour. Thus the risk of infection per 1 hour of exposure ranges from 1 in 400 to 1 in 600.

Duration of infectiousness: 3 negative sputum AFB smears on consecutive days in a patient on anti-tuberculous therapy indicates an extremely low potential for transmission of infection. A negative culture virtually assures that there is no potential for infection.

Quarantine: generally clear and convincing data are necessary to prove danger and thus to justify commitment.

Policy:

The Infectious Diseases Consultation Service will consult on and follow all patients hospitalized with suspected or known infectious (S/KI) tuberculosis.

Patients being treated for S/KI tuberculosis require 3 negative AFB smears before release into the general hospital population or into a hospice, nursing home, board and care facility, domiciliary, substance abuse treatment unit, dormitory, jail or home environment with previously unexposed individuals (especially immunocompromised persons and children under age 5). Patients with known MDR *M. tuberculosis* should remain in respiratory isolation for duration of hospitalization in view of tendency for treatment failure or relapse.

If a patient attempts to leave the Medical Center against medical advice (AMA), the physician or nurse shall notify the Infection Control Unit and/or other identified personnel immediately who will notify the local Health Department. Patients who are deemed to be a public health hazard (i.e., clinical and laboratory evidence of infectious tuberculosis and documented smears and repeated non-compliance with treatment), may be placed on a Public Health Order of Isolation by the Los Angeles County Health Department. Regardless, no patient may be held against his or her will without an additional specific court order to this effect.

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