

Guidelines on tuberculin testing
and treatment of latent TB infection
among immunocompetent household
contacts (aged 1 – 34) of smear-positive
pulmonary tuberculosis patients in Hong Kong

(2005)

Internal guidelines of
the Tuberculosis & Chest Service of
the Department of Health of
the Government of the Hong Kong SAR

Background

1. The Centers for Diseases Control of the United States published a detailed set of guidelines on tuberculin testing and treatment of latent tuberculosis infection in 2000¹.
2. Anti-TB chemoprophylaxis has not been widely practiced in Hong Kong, partly because of the difficulty in interpreting a positive tuberculin response within a community where BCG revaccination was widely practiced, and partly because of potential problems with drug compliance and drug reaction with prolonged course of treatment.
3. A study on a cohort of local children given BCG vaccination at birth from 1978 to 1982 suggested that those who were tuberculin-positive (induration ≥ 10 mm) at an age of 6 to 9 were at a greater risk of developing TB than those who were tuberculin-negative².
4. A higher cut-off point of 15 mm or over is more likely to indicate latent tuberculosis infection (LTBI)^{3,4}. Because of the higher prevalence of LTBI among close TB contacts, a tuberculin test response of 15 mm or over among close TB contacts is more likely to indicate LTBI, irrespective of past BCG vaccination.
5. The average risk of progression from TB infection to disease is approximately 10% for an immunocompetent adult. The short-term risk of developing disease is especially high among those recently infected. Treatment of LTBI has been accorded priority only second to treatment of active TB disease⁵.
6. A daily 12-month regimen of isoniazid was shown to be more effective than a 6-month regimen of isoniazid for preventing TB in persons with fibrotic lung disease⁶. The problems with the former regimen are client acceptance and compliance. Recent data from Centres for Disease Control indicate that only 60% of patients complete at least 6 mo of treatment¹.
7. In United States, isoniazid daily regimen for 9 months is recommended¹ because, in subgroup analyses of several trials, the maximal beneficial effect of isoniazid is likely achieved by 9 months⁷⁻⁹. A 6-mo regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons¹. In some situations, treatment for 6 months rather than 9 months may provide a more favorable outcome from a cost-effectiveness standpoint¹⁰.
8. Despite an earlier favourable report in the use of the 2-month rifampicin plus pyrazinamide regimen in the treatment of latent tuberculosis among the

HIV-infected subjects¹¹, such regimen was associated with a high incidence of hepatotoxicity in a recent local study on the treatment of latent tuberculosis infection among the silicotic subjects¹². There have also been similar reports from other places¹³⁻¹⁷.

9. In a previous study of anti-tuberculosis drug-related liver dysfunction in Hong Kong, age and HBsAg status were found to be the predictors of drug-related liver dysfunction¹⁸. In a retrospective study on TB in older people in Hong Kong, the incidence of liver dysfunction among those patients aged 65 or above was found to be 17.7%, in contrast with only 9.2% among younger patients¹⁹. The recent study by Jasmer et al on the treatment of LTBI also found that patients older than 35 years had a higher risk of grade 3 or 4 hepatotoxicity¹⁷.
10. Isoniazid-associated hepatitis occurs in 0.3% of treated persons from the age of 20 to 34, 1.2% from 35 to 49, and 2.3% of those from 50 to 64²⁰.
11. This set of guidelines is intended to provide general guidance for tuberculin testing and treatment of latent tuberculosis infection among immunocompetent, household contacts aged 1 to 34 inclusive of smear-positive pulmonary tuberculosis patients. Infants <1 are managed differently as detailed in the guidelines for tuberculin testing and treatment of LTBI among infant household contacts of smear-positive tuberculosis patients. For contacts aged 35 or above, such treatment may still be offered after careful assessment on an individual basis if there is documented tuberculin conversion after significant exposure or other exceptional circumstances.

Tuberculin testing of household contacts (aged 1 to 34 inclusive) of smear-positive pulmonary tuberculosis patients

All **household contacts** aged 1 to 34 (i.e. ≥ 1 or < 35) of **smear-positive index tuberculosis patients** will be offered tuberculin test (2 unit RT-23) as part of the contact screening work-up except those with past history of confirmed tuberculosis (i.e. TB requiring treatment and not just lung scars).

A computerized register should be kept of all **household contacts** (of any age) of **smear-positive index tuberculosis patients** (including cases notified from outside sources). For contacts aged 1 to 34, besides chest x-ray, tuberculin testing will also be offered for targeted screening. If the client agrees to tuberculin testing, BCG history should be obtained. The number of previous BCG scars should be recorded while the test is being administered. The tuberculin reaction (in mm) should also be recorded in the register when they are read 48 to 72 hours later. In mobile clinics, where there may be difficulty in arranging the tuberculin testing, the relevant contacts should be offered the options of having CXR examination in the mobile clinic or both CXR and tuberculin test in the closest full-time chest clinic. Irrespective of tuberculin status, all contacts should be given health education on early recognition of symptoms suggestive of TB.

All household contacts with tuberculin reaction ≥ 15 mm should be interviewed by the public health unit. They will be told that they are likely to have been infected by TB and the life-time risk of developing TB disease later is approximately 10%. They should be referred to see a doctor, preferably, within the same session. The attending doctor should examine the CXR taken for contact screening and discuss treatment for LTBI with the contact if it is appropriate. Irrespective of whether these strongly tuberculin-positive close contacts are put on treatment, they should be offered annual follow-up for two years. During the follow-up visits, CXR will be offered, unless the patient is pregnant.

For those contacts with tuberculin reaction ≤ 14 mm, they should be offered an

appointment for tuberculin retesting after 3 months, unless their last contact with the infectious source was over eight weeks ago. Smear-positive patients will be regarded as non-infectious for the usual community settings if they have been on effective treatment with the standard four-drug regimen for two or more weeks, unless drug resistance is suspected. For those agreeing for retesting but failing to return on scheduled date, a reminder will be sent by either telephone or mail.

Treatment of latent tuberculosis infection among tuberculin strongly positive household contacts of smear-positive pulmonary tuberculosis patients

In view of a considerable risk of developing tuberculosis after infection, treatment of latent tuberculosis infection with isoniazid should be considered, irrespective of previous BCG vaccination, if all of the following conditions are met:

1. Subjects aged 1 to 34 (below 35)
2. Household contacts of patients with smear-positive pulmonary tuberculosis
3. Strongly positive tuberculin skin test response defined as an induration ≥ 15 mm in response to 2 units of PPD RT23 or documented tuberculin conversion (an increase of the tuberculin reaction size by 10mm or above on repeat testing).

However, such treatment is not appropriate for confirmed cases of active tuberculosis and may not be appropriate in the following situations:

1. Clinical suspicion of active pulmonary tuberculosis
2. Clinical suspicion of extrapulmonary tuberculosis
3. History of receiving more than two months of continuous anti-tuberculosis treatment in the past
4. Past intolerance of, or contraindication to use of , isoniazid
5. Poor general condition
6. Symptomatic hepatitis or alanine transaminase (ALT) above the upper limit of normal on at least 2 occasions separated by 2 weeks or known case of liver cirrhosis at enrollment
7. Alcoholism (habitual alcohol drinkers with alcohol **dependence**), even if alcohol use will be discontinued during treatment
8. Concurrently taking other medications commonly associated with clinically significant liver injury
9. Reluctance and / or inability to take medications or attend for follow-up
10. *Mycobacterium tuberculosis* cultured from index patient already known to be resistant to isoniazid

Decision on targeted testing and preventive treatment should be made after discussion with patients. While contacts should be fully informed of the risk of contracting and developing TB, asymptomatic individuals with LTBI do not pose an immediate public health hazard. Their informed choice should therefore be respected.

Special situations

This set of guidelines is not intended for the management of HIV-infected or other immunocompromised contacts. For such situations or for other contacts in whom the risk of the disease is particularly high or the consequence of disease particularly grave, a lower cut-off value for the tuberculin response may have to be used. Reference should be made to other relevant guidelines for up-to-date information, e.g. the latest ATS recommendations and the local guidelines prepared by the Scientific Committee on AIDS for HIV-infected contacts.

No definitive data exist concerning treatment of contacts who have been exposed to patients with probable or confirmed isoniazid-resistant TB. Rifampicin alone for 4 months^{1,21} is an acceptable alternative and may be offered after careful assessment and discussion with the patient. In situations in which rifampin cannot be used, rifabutin can be substituted.

For contacts of patients with multidrug-resistant tuberculosis (resistant to both isoniazid and rifampicin), the problem has not been evaluated in prospective studies, and consensus is lacking. These patients are unlikely to benefit from treatment with isoniazid and rifampicin. There is, as yet, insufficient evidence to allow recommendation of preventive treatment on a regular basis. Use of a regimen containing other agents active against *M. tuberculosis* should be considered if treatment of latent tuberculosis infection is to be given. Decision has to be made on a case-to-case basis in full consultation with the patient, and after careful balance of the potential risks and benefits.

Pretreatment Investigations

1. Baseline blood tests for patients aged 16 or above or on any clinical indications, e.g. patients whose initial evaluation suggests a liver disorder, patients infected with HIV, pregnant women and those in the immediate postpartum period (i.e., within 3 mo of delivery), persons with a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis), persons who use alcohol regularly, and others who are at risk for chronic liver disease:
 - a. Complete blood picture (CBP),
 - b. Liver function test (LFT) including albumin and total protein,
 - c. Renal function test (RFT)
 - d. Hepatitis B surface antigen (HBsAg)
2. Sputum examination: two sputum sample collected on two different days are collected for acid-fast bacilli (AFB) smear and culture for mycobacteria.
3. Urinalysis for glucose and protein

Chemoprophylaxis Regimen

Six-month course of daily isoniazid (6H) with 180 doses in total.

- Children aged ≤ 16
Isoniazid 5mg/kg daily (max. 300mg)
- Adults
Isoniazid 300mg daily (a lower dose of 200mg daily may be considered for patients with chronic renal failure)

(Pyridoxine supplementation at 10 mg daily should be considered for those with malnutrition or at risk of neuropathy, e.g. diabetes mellitus, habitual alcohol use, chronic renal failure, and HIV infection.)

Patient Education and Dispensing of Medication

The drug should be dispensed on a monthly basis with a drug calendar. Health education and counselling will be provided before treatment and at each monthly visit. Patients should be clearly informed of the potential side effects and advised to report them

promptly. They should be encouraged to comply with the prescription and record every consumed dose in the calendar honestly. The monthly drug calendar is to be returned in the next follow-up visit. Help of relatives should be enlisted if available.

Monitoring

1. All patients will be followed up at least monthly during treatment.
2. At all treatment visits, patients will be assessed clinically for adverse side effects. For those HBsAg-positive, with abnormal baseline LFT or otherwise at risk of hepatic disease, LFT should be checked biweekly at 2, 4 and 6 weeks, and 2 months. Any other investigation will be done according to clinical suspicion. Treatment should be withheld according to the management of drug-induced hepatitis protocol.
3. The drug calendar will be reviewed at each visit to assess compliance with treatment.
4. Treatment will be terminated for any adverse drug reactions that entail treatment interruption for more than 1 month.
5. If the patient fails to complete the 180 doses of treatment within 6 months, treatment may be extended to allow completion of the regimen, up to a maximum of 3 more months.
6. CXR, sputum and / or other investigations will be checked upon clinical suspicion. If active TB develops during treatment of LTBI, chemoprophylaxis must be replaced by appropriate anti-TB treatment.
7. After treatment, all patients should be offered follow-up at 1 year (from date of tuberculin test) and 2 year. During the follow-up visits, CXR will be offered, unless the patient is pregnant.

Management of drug-induced liver dysfunction

If patient has asymptomatic biochemical liver dysfunction with ALT < 3 X the upper limit of normal and bilirubin < 2 X the upper limit of normal, treatment may be continued under close clinical and biochemical monitoring. LFT has to be monitored every 2 weeks or more frequently as appropriate until ALT returns to normal.

Definition of symptomatic hepatitis:

It is defined as the presence of symptoms of hepatitis, such as malaise, reduced appetite,

nausea, vomiting, yellowing of sclera, lethargy and/or right upper quadrant discomfort, together with the presence of liver dysfunction irrespective of the severity of the biochemical abnormalities.

Management of drug-induced hepatitis:

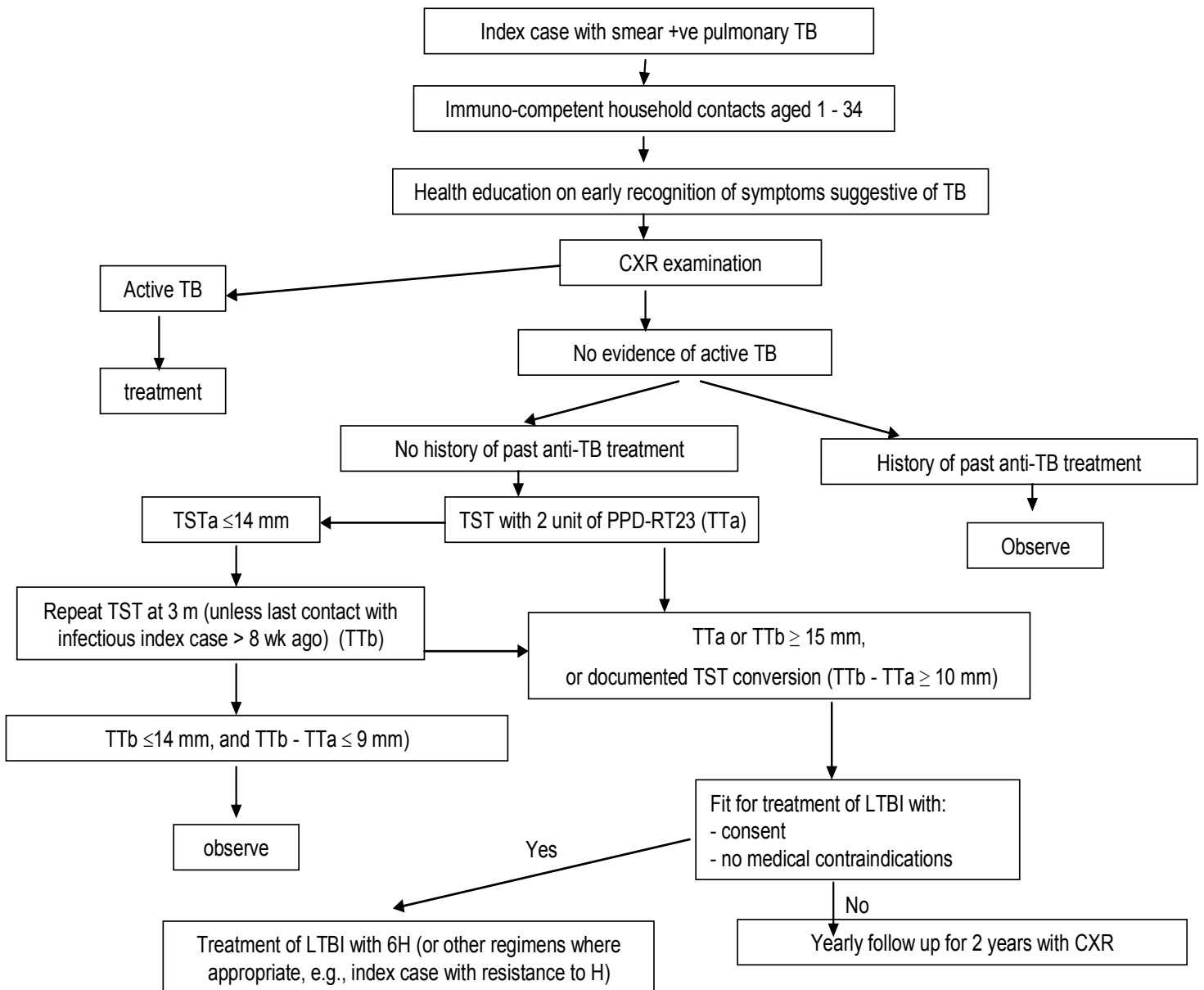
Treatment should be stopped and not resumed for any of these findings:

1. ALT > normal range when accompanied by symptoms of hepatitis, or
2. ALT > 3 X the upper limit of normal range in an asymptomatic person,
3. Serum bilirubin > normal range when accompanied by symptoms of hepatitis
4. Serum bilirubin > 2 X the upper limit of normal in an asymptomatic person.

After withholding treatment, LFT will be repeated weekly until ALT returns to normal.

Figure 1

Tuberculin testing and treatment of LTBI among immunocompetent household contacts (aged 1 to 34) of smear positive pulmonary TB patients



References

1. Targeted tuberculin testing and treatment of latent tuberculosis infection. CDC Morbidity and mortality weekly report *MMWR* 2000 ; Vol. 49, No. RR-6.
2. Leung CC, Tam CM, Chan SL, Chan-Yeung M, Chan CK, Chang KC. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. *Int J Tuberc Lung Dis* 2001;5:717-23.
3. Edwards LB, Acquaviva FA, Livesay VT et al. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. *Am Rev Respir Dis* 1969;99:1-132.
4. Chee CB, Soh CH, Boudville IC, Chor SS, Wang YT. Interpretation of the tuberculin skin test in Mycobacterium bovis BCG-vaccinated Singaporean schoolchildren. *Am J Respir Crit Care Med*. 2001;164:958-61.
5. Hopewell PC. Targeting Tuberculosis Prevention (Editorial). *Am J Resp Crit Care Med* 2000;162:2017-2018.
6. International Union Against Tuberculosis, Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis. *Bull World Health Organ*. 1982; 60: 555 – 564.
7. Ferebee, S. H., and F. W. Mount. 1962. Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. 85:490–521.
8. Comstock, G. W., and S. H. Ferebee. 1970. How much isoniazid is needed for prophylaxis? *Am. Rev. Respir. Dis*. 101:780–782.
9. Comstock, G. W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int. J. Tuberc. Lung Dis*. 3:847–850.
10. Snider, D.E., Jr., G. J. Caras, and J. P. Koplan. 1986. Preventive therapy with isoniazid: costeffectiveness of different durations of therapy. *J.A.M.A*. 255:1579–1583.
11. Gordin F, Chaisson RE, Matts JP, Miller C, De Lourdes Garcia M, Hafner R, et al. Rifampicin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. *JAMA* 2000; 283: 1445 – 1450.
12. Leung CC, Law WS, Chang KC. et al. Initial experience of a randomized controlled trial on the treatment of latent tuberculosis infection among silicotic subjects in Hong Kong: two months of rifampin and pyrazinamide versus six months of isoniazid. *Chest* 2003; 124: 2112-8.
13. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. *JAMA* 2000; 283: 1445 – 1450.
14. CDC. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection—New York and Georgia, 2000. *MMWR* 2000;50:289–91.
15. American Thoracic Society. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations-United States, 2001. *Am J Respir Crit Care Med* 2001;164:1319-20.
16. Centers for Disease Control. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide treatment for latent tuberculosis infection. *Morb Mortal Wkly Rep* 2002 Nov 8; 51(44): 998-9.
17. Jasmer RM, Saukkonen JJ, Blumberg HM, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med* 2002;137:640-7.
18. Wong WM, Wu PC, Yuen MF, et al. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. *Hepatology* 2000; 31(1): 201-206.
19. Leung CC, Yew WW, Chan CK, et al. Tuberculosis in older people: a retrospective and comparative study from Hong Kong. *J Am Geriatr Soc* 2002; 50 (7): 1219-26
20. Kopanoff DE, Snider DE, Caras GJ. Isoniazid-related hepatitis: A US Public Health Service cooperative surveillance study. *Am Rev Respir Dis* 1978;117:991.

21. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three anti-tuberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992; 145:36-41.