Guidelines on
targeted tuberculin testing and
treatment of latent tuberculosis infection

Tuberculosis and Chest Service

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

Background

Directly observed treatment using the standard 6-month short course chemotherapy (DOTS) has been the cornerstone of the local tuberculosis (TB) control strategy for the past few decades. The overall TB notification rate decreased from a peak of 697 per 100,000 in 1952 to 72.5 per 100,000 in 2010. Molecular analysis of clustering patterns of isolated strains suggests that reactivation of remote infection now accounts for around 80%[1] of the local TB cases, likely reflecting the progressive control of recent transmission through successful implementation of DOTS. With the high local burden of TB in the last century, it is estimated that one third of the local population has been previously infected with *Mycobacterium tuberculosis.* The prevalence of such latent TB infection (LTBI) increases steadily with age, and 40% of TB cases now occurs among our elderly. Measures to decrease the risk of reactivation of LTBI are therefore needed to complement DOTS in further reducing the TB morbidity and mortality in Hong Kong.

Screening

Screening tests

Direct identification of individuals who are latently infected with live *Mycobacterium tuberculosis* without active disease is NOT possible. Current immunodiagnostic tests ascertain a state of persistent *M. tuberculosis*-specific immune responses rather than true latent infection. The newer interferon-gamma release assays (IGRA) employing more specific agents are not affected by prior BCG vaccination, in contrast with tuberculin skin test (TST) using non-specific agents in form of purified protein derivatives extracted from the human tubercle bacillus.

Predicting TB risk

Among young individuals with a positive TST identified during TB contact tracing, around 5% will develop active disease in the first five years and another 5% in the rest of their lifetime. The risk is modified by the age of acquiring infection (e.g. being lowest in the age range of 5 to 9 years) [2] and many other host factors (Table 1) [3]. A recent meta-analysis concluded that both IGRA and TST cannot accurately predict the future development of active TB in low/middle-income countries.[4] However, as studies from high income countries were excluded, it is NOT possible to generalize the finding of the meta-analysis to high income areas with a lower risk of ongoing TB transmission. Locally, a tuberculin reaction size of 15mm among primary schoolchildren has been shown to predict subsequent tuberculosis risk [5, 6] and T-Spot.TB (an IGRA) has been shown to outperform TST in predicting subsequent TB risk among silicosis patients [7].

Target groups

Targeted screening of LTBI among identifiable risk groups using either TST or IGRA, followed by treatment of those with a positive test also decrease the risk of TB by up to 90% [3]. Locally, the following four main high risk groups are targeted for screening and treatment to maximize the cost-effectiveness (Table 2). Besides these four groups, other patients at risk of developing active TB disease may also be offered similar screening after assessment on a case-by-case basis, e.g. close contacts aged 35 or above of smear-positive sources. The decision to screen usually means an intention to treat if test positive. The different TST cutoffs as recommended represent an attempt to achieve the best trade-off between sensitivity and specificity for the respective clinical scenarios. IGRA may be used as an alternative or to confirm a borderline TST result, when there is concern over interference by previous BCG vaccination.

Treatment

Isoniazid Monotherapy

Randomized controlled trials have established protective efficacy of isoniazid therapy for 6 to 12 months among non-HIV-infected and HIV-infected subjects with LTBI [3]. Isoniazid-associated hepatitis has been shown to occur in 0.3%, 1.2% and 2.3% of treated persons aged 20- 34, 35-49 and 50-64 respectively in field surveillance [8]. In the International Union Against Tuberculosis (IUAT) Trial, the only study that included direct comparison between 6 and 12 months of isoniazid, the efficacy of the 12-month regimen was better (93% vs 69%) than the 6-month regimen among treatment completers, but the 6-month regimen prevented more tuberculosis cases (2.6 vs 2.1 tuberculosis cases) per case of hepatitis than the 12-month regimen [9]. Six months of isoniazid is therefore recommended for the treatment of LTBI, but 9 months of isoniazid may also be considered, especially among HIV-infected subjects and other immunocompromised persons. The drug is usually given as self-administered therapy at the following daily doses:

- Children aged 5 - <16 years : 5mg/kg daily (max. 300mg)
- Children aged <5 years : 10mg/kg daily (max. 300mg)
- Adults: 300mg daily

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.

While there is no good evidence to suggest that treatment of LTBI with isoniazid will increase the subsequent risk of drug-resistant TB, active TB should be excluded before the initiation of such treatment. The role of prolonged isoniazid therapy among HIV-infected individuals remains controversial as the results are conflicting in two published trials [10, 11]. There is also no clear evidence to support the use of chemoprophylaxis for previously fully treated TB patients subsequently put on

immunosuppressive therapy. Primary isoniazid prophylaxis has not been found effective among HIV-exposed children [12].

Rifampicin Monotherapy for 4 months

Rifampicin alone for 4 months should be considered in the following situations:

1. Past intolerance of, or contraindication to use of, isoniazid

2. Mycobacterium tuberculosis cultured from index patient already known to be resistant to isoniazid

This alternative regimen is usually well tolerated, but clinical trial data on efficacy is currently limited to a single trial among silicosis patients [3]. While some concern remains over possible selection of rifampicin-resistant mutants, especially among HIV-infected individuals, this does not appear to be a problem in its field use in North America. In situations in which rifampin cannot be used, rifabutin can be substituted.

If bacillary isoniazid monoresistance is discovered in the index patient after LTBI treatment with isoniazid is initiated in an infected contact, switching to rifampicin therapy should be considered, subject to a continuing need for LTBI treatment. A similar consideration applies to isoniazid intolerance necessitating withdrawal of isoniazid in an infected contact, but caution should be exercised in case of significant drug-induced hepatotoxicity as rifampicin is also potentially hepatotoxic (see Management of hepatotoxicity below). Careful balance of risks and benefits would be required, and expert consultation should be sought where necessary.

Isoniazid plus rifampicin for 3 months

Isoniazid plus rifampicin for 3 months has proven efficacy in the treatment of LTBI, but adverse effects may be more frequent than isoniazid or rifampicin monotherapy in field application [3].

Weekly rifapentine plus isoniazid for 12 doses

The efficacy of weekly rifapentine plus isoniazid for 12 doses has recently been established in two clinical trials, one among predominantly non-HIV-infected subjects [13] and the other among HIV-infected individuals [11].

RPT 900 mg once-weekly x 12 doses (3 months) for persons weighing > 50.0 kg. For persons weighing < 50.0 kg, the following doses will be given:

Weight	Dose
10.0-14.0 kg	300 mg
14.1-25.0 kg	450 mg
25.1-32.0 kg	600 mg
32.1-50.0 kg	750 mg

PLUS

INH 15 mg/kg (round up to nearest 50 or 100 mg; 900 mg max) once weekly x 12 doses if > 12 years old. INH 25 mg/kg (round up to nearest 50 or 100 mg; 900 mg max) if 2—11 years old.

Rifampicin plus pyrazinamide for two months, though efficacious, has been associated with excess hepatotoxicity, at least among non-HIV infected persons.

Contacts of multidrug-resistant TB

For contacts of patients with multidrug-resistant TB, expert opinions differ on whether to treat, with at least two drugs or just a fluoroquinolone, and for how long, despite some encouraging preliminary results on the use of fluoroquinolone-containing regimens recently. Close clinical observation for two years is normally recommended locally, except when specific clinical circumstances require otherwise.

If bacillary resistance to isoniazid PLUS rifampicin is discovered in the index patient after LTBI treatment with isoniazid is initiated in an infected contact, it would be appropriate to discuss with the patient as to whether to complete the remaining course of isoniazid treatment. As about half of the active tuberculosis diseases to be observed among such contacts are caused by drug-susceptible tubercle bacilli locally [14], isoniazid treatment is likely to offer some degree of protection, mainly against the development of drug-susceptible TB. Careful balance of risks and benefits would be required, and expert consultation should be sought where necessary.

Evaluation and Monitoring

Clinical evaluation and chest x-ray examination should be undertaken to exclude active TB before the initiation of treatment for LTBI. Care should also be exercised to exclude extrapulmonary TB, especially TB lymphadenopathy commonly occurring in neck area. Sputum examination should be conducted on clinical or radiological suspicion of active TB. Baseline blood tests should be performed on any clinical indications suggesting an increased risk of drug toxicity, e.g. advanced age, 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 months of delivery), persons with a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis), persons who use alcohol regularly, patients who are concurrently on other potentially hepatotoxic medications and others who are at risk for chronic liver disease. Patients should be clearly informed of the potential side effects and advised to report them promptly.

Patients will be followed up at least monthly during treatment. At all treatment visits, patients will be assessed clinically for adverse side effects. For those who are HBs Ag-positive, with abnormal baseline LFT or otherwise at risk of hepatic disease, LFT should be checked serially AND as required according to clinical suspicion.

Management of hepatotoxicity

If patient has asymptomatic biochemical liver dysfunction with ALT < 3 X upper limit of normal (ULN) and bilirubin < 2 X ULN, 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.

Treatment should be stopped when i) ALT exceeds three times ULN, in the presence of EITHER relevant symptoms (e.g. anorexia, nausea, vomiting, epigastric distension, right upper abdominal discomfort, malaise and weakness) OR hyperbilirubinemia with total bilirubin exceeding two times ULN; or ii) ALT exceeds five times ULN irrespective of symptoms [15]; or iii) other clinical evidence of hepatitis. After stopping treatment, LFT will be repeated weekly until ALT returns to normal. Based on consideration of the risk versus benefit ratio, treatment is generally NOT resumed after significant hepatotoxicity.

References

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Table 1: Incidence / relative risk of active TB for selected risk factors

	Incidence of Disease among tuberculin-positive subjects (per 1000 person-years)	Relative Disease Risk
Recent TB infection		
Infection <1 yr past	12.9	
Infection 1–7 yr past	1.6	
Old TB scar	2.0–13.6	
HIV infection	35.0–162	
Injection drug use		
HIV seropositive	76.0	
Other	10.0	
Smoking		
Current smokers		2.63
Ex-smokers		1.41
Never Smokers		1.00
Passive smoking		1.49
Body Mass Index		
>=30		0.38
25-<30		0.58
23-<25		0.74
18.5-<23		1.00
<18.5		2.11
Silicosis	68	30
Diabetes mellitus (DM)		
DM vs no DM		1.8–4.1
HBA1c>=7%vs <7%		3.1
Chronic renal failure		10.0–25.3
Gastrectomy		2–5

Jejunoileal bypass	27–63
Renal Transplant	37
Heart Transplant	20-74
Head and neck carcinoma	16

Table 2: Target groups for LTBI screening and recommended TST cutoffs for a positive test

Target group		**TST cutoff**
Household contacts (esp. < 35 years old) **of a smear+ source**	Age > 1 yr:	15mm
	Age < 1 yr:	5mm
Silicosis		10mm
HIV-infected		5mm
Immunosuppression/TNF blocker	Before immunosuppression:	10mm
	After immunosuppression:	5mm*

* if not screened at baseline, or > baseline when there is a new indication to screen