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 697.2 per 100,000 in 1952 to 57.3 per 100,000 in 2018. 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 over 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. In 2018, a local working group was formed to review the management of LTBI in Hong Kong. More resources can be found in the publication titled "Management of latent tuberculosis infection in immunocompetent household contacts".

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] and household contacts [8].

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, namely household contacts aged <65 years old of smear +ve source, silicotics, people living with HIV and patients on immunosuppressant/TNF blocker (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. 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. For patients with silicosis, IGRA is recommended as the test of choice for LTBI while TST is an acceptable alternative [7].

Treatment

1. 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%, 0.3%, 1.2% and 2.3% of treated persons aged <20, 20- 34, 35-49 and 50-64 respectively in field surveillance [9]. 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 [10]. 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 years : 10mg/kg daily (max. 300mg)
- Children aged 5 - <16 years : 5mg/kg daily (max. 300mg)
- Aged >=16 or 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 [11, 12]. There is also no clear evidence to support the use of

chemoprophylaxis for previously fully treated TB patients subsequently put on immunosuppressive therapy.

2. Weekly isoniazid plus rifapentine for 12 doses (3HP)

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 [12].

Rifapentine dosage:

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
> 50.0 kg	900mg

PLUS

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

3. Rifampicin Monotherapy for 4 months (4R)

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

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

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

This alternative regimen is usually well tolerated. Apart from the clinical trial data among silicosis patients [3], recent studies have shown that rifampicin monotherapy for 4 months was not inferior to 9H regimen for the prevention of active TB and was associated with a higher rate of Rx completion & better safety.[14] Similar efficacy and better adherence were also observed in paediatric patients.[15,16] 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.

4. Isoniazid plus rifampicin for 3 months (3HR)

Isoniazid plus rifampicin for 3 months has proven efficacy in the treatment of LTBI [17,18], but adverse effects may be more frequent than isoniazid or rifampicin monotherapy in field application [3].

Rifampicin plus pyrazinamide for two months, though efficacious, has been associated with excess hepatotoxicity, at least among non-HIV infected persons. The regimen is not recommended for treatment of LTBI.

Contacts of multidrug-resistant TB

For contacts of patients with multidrug-resistant TB (resistant to both isoniazid and rifampicin), the pendulum is now swinging towards consideration of preventive treatment in targeted groups.[19-25] WHO suggested consideration of treatment of LTBI in high risk MDR-TB household contacts including children, people on immunosuppressive therapy and people living with HIV.[19] Randomized controlled trials and their analysis are underway for MDR-LTBI treatment. Before the availability of further trial results and if treatment of MDR-LTBI is deemed necessary, a drug regimen basing on the susceptibility results of the index patient may be considered (for example, a later generation fluoroquinolone with or without a second drug if the index patient does not have additional bacillary drug resistance to fluoroquinolones). However, as the recommendation of preventive treatment in MDR-TB contacts is based on very low quality evidence, it should only be done after careful balance of the potential risks and benefits and after thorough discussion and informed consent of the contacts.

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 [26]; 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.

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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 cut-off**
*Household contacts <65 years old of smear +ve source**	Age < 1 year	5 mm
	Age 1 to 11 years	10 mm
	Age >=12 years to 64	15 mm
Silicosis		10 mm
People living with HIV#		5 mm
Immunosuppression/TNF blocker	Before immunosuppression	10 mm
	After immunosuppression	5 mm (if not screened at baseline)

* For close contacts with risk factors for adverse effects from LTBI treatment, (e.g. alcoholic, underlying chronic liver disease, etc), the decision to screen should be made on a case-by-case basis especially for the aged 35-64 group.

For PLHIV with known recent exposures e.g. household contacts, LTBI testing is not needed. Preventive treatment can be offered directly after ruling out active TB.