Management of Latent Tuberculosis Infection in Immunocompetent Household Contacts

Latent Tuberculosis Infection Working Group

Tuberculosis Control Coordinating Committee of

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Background

The risk of development of tuberculosis (TB) after recent exposure is well known.[1,2] In a population based study involving 26,542 contacts without treatment of latent TB infection (LTBI) and followed up for up to 12 years, 180 developed TB of which 88% occurred within 2 years.[2] The TB rates for household, close non-household and causal contacts were 2836, 637 and 226 per 100,000 respectively. In another local study screening of 4661 close contacts, the cumulative risk of developing active TB within 5 years was 1.91%. Index smear positivity was a risk factor.[3] Though the TB rate among close contacts in Hong Kong is low probably due to good medical infrastructure with prompt diagnosis and treatment of TB, screening of smear-positive household contacts is still one of the important strategies for local TB control.[4,5]

1. Screening

2.1 Introduction

Various guidelines are available to guide physicians to manage LTBI in their own countries with different disease burden.[6-9] The World Health Organization (WHO) also issued a consolidated guideline for reference in 2020.[10] According to previous studies, history of household contact[2] and index smear positivity[3] were found to be the two important risk factors for development of active TB.

2.2 Guideline statements

2.2.1 All household contacts of tuberculosis patients should be identified during contact tracing.

2.2.2 Active TB should be excluded by symptoms screening/physical examination and chest X-ray (CXR)

2.2.3 For household contacts aged under 65 of smear-positive index tuberculosis patients but without evidence of active TB and past history of TB treatment (for at least two or more months), screening of LTBI would be offered.

1.2.4 Screening of LTBI by tuberculin skin test (TST) (using a cutoff of 5 mm, 10 mm and 15 mm induration for household contacts aged under 1, aged 1-11 and aged >=12 respectively) or Interferon Gamma Release Assay (IGRA) can be done where appropriate.

1.2.5 Sequential testing of TST followed by IGRA can be considered in cases with borderline TST result or those aged >=12 years old with TST of 5 mm to 14mm.

1.3 **Rationale**

Studies have shown that close TB contacts are at an increased risk of TB.[1,2] A local study reported that the risk of development of TB in Hong Kong was low but index smear positivity was found to be a risk factor.[3] Hence, screening LTBI for household contacts of smear positive index would be a useful measure for TB control.

As the baseline TST positivity rate is high among the elderly[11] and there is also an increased risk of hepatotoxicity with treatment of LTBI,[12-14] LTBI screening and preventive treatment are not routinely offered for those aged 65 or above.

In general for those aged 12 or above, TST of 15mm or more is regarded as positive. In a local study analysing data of 1,049 household contacts aged 5 to 64 with smear positive index, T-spot.TB gave a significantly higher positivity rate of and better association with exposure time than TST at the 15mm cut-off.[15] Using TST cut-off of 15mm, 56% of future TB cases were missed. Recently, a pilot programme in TBCS was conducted. For those household contacts aged >=12 with TST falling between 5 to 14mm, IGRA was offered as a sequential test. The pilot programme is still ongoing and may provide information on whether TST followed by sequential testing of IGRA in borderline TST clients would be a useful adjunct for LTBI screening.

2. Regimens for Treatment of LTBI

3.1 Isoniazid (H) monotherapy

3.1.1 **Guideline statement**

Isoniazid given for 6 months (6H) or 9 months (9H) can be considered.

3.1.2 **Rationale**

The safety and efficacy of isoniazid for treatment of LTBI are well established.[16,17] In a cost-effectiveness analysis, 24 weeks of isoniazid was more cost-effective than 12 or 52 week regimens.[18] Therefore, 6H is currently recommended for the treatment of LTBI for immunocompetent

household contacts, but 9 months of isoniazid may also be considered especially among HIV-infected subjects and other immunocompromised persons.

3.1.3 **Implementation**

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)
- >= 16 years or adults: 300mg daily

3.1.4 **Limitation**

Adherence is a concern, especially for the 9H regimen. Clinical trials have also shown that the risk of hepatotoxicity increased with increasing age.[12-14]

3.2 Rifampicin (R) monotherapy

3.2.1 **Guideline statement**

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

(iii). Adherence problem for treatment of LTBI is anticipated especially in paediatric contacts

3.2.2 **Rationale**

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.[19] Similar efficacy and better adherence were also observed in paediatric patients.[20,21]

3.2.3 **Implementation**

- Adults and children : 10mg/kg daily (max. 600mg)

2.2.4 Limitation

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. Drug-drug interactions with in particular immunosuppressives or anti-retroviral therapy may limit its use.

3.3 Short-course regimen with Isoniazid (H) and Rifapentine (P)

3.3.1 **Guideline statement**

(i) Isoniazid and rifapentine given for 12 doses (3HP) weekly may be considered for clients aged >=12.

(ii) It should be administered under directly observed therapy (DOT).

(iii) Adverse events should be monitored closely especially in the older age group.

3.3.2 **Rationale**

Adherence is always a concern in the treatment of LTBI when the benefit cannot be easily perceived. Randomized trials of three months of weekly supervised isoniazid and rifapentine (3HP) were shown to have a higher treatment-completion rate and as effective as 9 months of self-administered isoniazid (9H) in preventing TB in both HIV-infected or non-HIV-infected persons and in children and adolescents. [22-24] The rate of hepatotoxicity was generally low. In a meta-analysis including 15 studies with majority of studies targeted at individuals aged >=12, 3HP was found to be as safe and effective as other recommended LTBI regimens and achieved significantly higher Rx completion rates.[25] However, in a recent report with the use of isoniazid and rifapentine for treatment of LTBI in older Chinese aged 50-69 years, the treatments were terminated early due to unexpected high frequency of adverse effects.[26] The side effects were mostly gastrointestinal, hypersensitivity or allergic reaction and hepatotoxicity was around 1% which was slightly higher than other studies on 3HP. Hence, this regimen should be used with caution in the older age group.

Most of the studies on 3HP were conducted under directly observed treatment (DOT). Two studies with recruitment mainly in US, included patients with 3HP given in form of self-administered therapy (SAT).[27,28] Compared with DOT, SAT showed a comparable completion rate in US but non-inferiority could not be shown in the other countries.[27] Furthermore, data of SAT in adolescents and children were not available. Hence, further

studies may be needed to review the role of SAT for 3HP. In WHO 2020 guideline, daily isoniazid and rifapentine for 1 month (1HP) is also an alternative preventive treatment option for age >=13 years old basing on the results of a study on preventive treatment among people living with HIV (PLHIV).[29] However, similar recommendation has not yet been made in the CDC 2020 guideline. More evidence would be desirable to make it a standard recommendation.

3.3.3 **Implementation**

The efficacy of weekly rifapentine plus isoniazid for 12 doses (3HP regimen) has been established in clinical trials (adults and children aged 2 years or above).

3HP weekly regimen

Rifapentine dosage:

Body 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 aged 12 years or above. Isoniazid 25 mg/kg (round up to nearest 50 or 100 mg; 900 mg max) if 2—11 years old.

Before the availability of more convenient paediatric preparations for dosing of rifapentine, the 3HP regimen will be used as an alternative regimen mainly in persons aged 12 years or above.

Limitation

This regimen will not be used if index is a known case of isoniazid or rifampicin resistance. Drug-drug interaction with rifapentine should be considered.

3.4 Three-month regimen with Isoniazid and Rifampicin

3.4.1 **Guideline statement**

Isoniazid and rifampicin given for 3 months (3HR) daily may be considered, especially in children.

3.4.2 **Rationale**

Studies on 3HR or 4HR were done on children.[30,31] The HR regimens were found to be safe, efficacious and with better adherence when compared with 6 to 9-month isoniazid monotherapy. With respect to the adherence in children, one study showed that comparing with unsupervised LTBI treatment, the overall adherence to supervised LTBI treatment (for 6H and 3HR) for those aged under 5 was better.[31]

3.4.3 **Limitation**

This regimen will not be used if index is a known case of isoniazid or rifampicin resistance. Drug-drug interaction with rifampicin should be considered.

3. Management of LTBI for contacts of multidrug-resistant TB

4.1 Guideline statement

For contacts of patients with MDR-TB, a drug regimen based on the susceptibility results of the index patient may be considered in high risk MDR-TB household contacts including children, people on immunosuppressive therapy and PLHIV, after careful balance of the potential risks and benefits and after thorough investigations to rule out active TB, discussion and obtaining informed consent from the contacts.

4.2 Rationale

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.[10,32-37] WHO suggested consideration of treatment of LTBI in high risk MDR-TB household contacts including children, people on immunosuppressive therapy and PLHIV. 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.

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