Policy Brief: A guideline on isoniazid preventive therapy for patients with silicosis in southern Africa

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Background

Silicosis is common in southern Africa and individuals with silicosis are at high risk of developing tuberculosis (TB), particularly in settings with high background rates. Studies from Hong Kong have quantified the annual risk of TB in silicotic subjects at approximately 3-5% per annum[1,2]. The American Thoracic Society (ATS) has estimated the risk of tuberculosis in silicotics to be 30 times greater than in unexposed individuals[3]. Southern African studies have shown high rates of TB in silica exposed gold miners associated with silica dust exposure[4, 5, 6] and increasing risk of TB with increasing severity of silicosis[5,6]. These high rates were before the HIV epidemic and it has been shown that risks of TB due to silicosis and HIV infection combine multiplicatively.[7] Consequently, TB prevalence is very high in groups of workers with high rates of silicosis and HIV; 3000 per 100 000 not uncommon in South African gold miners[8]. Silicosis is associated with increased TB case fatality rates[9].

There is clearly an urgent need for interventions to prevent tuberculosis in people with silicosis. Isoniazid preventive therapy is a recommended intervention in silicotics because:

1. Isoniazid is the safest drug for treating latent TB[3] and serious side-effects of isoniazid preventive treatment are rare.
2. Although the evidence for IPT in TB prevention in southern Africa is limited, it is of proven value in individuals at a similar level of risk from other conditions, such as HIV[3,10].
3. IPT has been shown to reduce TB risk in silicotics in Hong Kong[1].
4. Although the initial protection of IPT may diminish over time the risk of TB is so high that even a short-term benefit may be worthwhile.
5. Drug resistance associated with INH mono-therapy is low[11]

Silicosis is defined here as radiologic silicosis with profusion of opacities 1/1 or greater according to the ILO system of classifying radiographs of the pneumoconioises[12].

Eligibility criteria

Inclusion

- Individuals with silicosis of ILO 1/1 or greater
- All age groups
- No active TB

Tuberculin skin testing not required

In some settings T-cell assays have replaced tuberculin skin testing in the diagnosis of latent TB, but the value of these tests has still to be established in high-incidence regions such as southern Africa.[13]

Exclusion

- Active TB. Confirmed or suspected.
- TB treatment within the past five years
- Previous adverse drug reaction to INH
- History of underlying liver disease
- Regular alcohol use exceeding 28 units per week (men) or 21 units per week (women)
- Symptomatic peripheral neuropathy
- Pregnancy and up to 3 months post-partum

HIV testing

All silicotics being considered for IPT should be routinely offered HIV testing if their HIV status is unknown. HIV-infected individuals should be referred for evaluation for antiretroviral therapy.

Exclusion of active TB prior to IPT

Silicotics with features suggestive of active TB should be investigated for active disease prior to starting IPT. Features suggestive of active TB include (1) a cough for longer than two weeks duration, unexplained weight loss, or fever or drenching night sweats; or (2) an abnormality on the chest radiograph which is either strongly suggestive of TB, or is new or worsened compared with a previous routine radiograph. Chest radiography is recommended in the evaluation of TB in silicotics before starting IPT. But if unavailable, active TB can be excluded on the basis of symptoms, sputum microscopy and culture.

Isoniazid preventive therapy regimen

Isoniazid

A daily dose of 5 mg/kg up to a maximum dose of 300mg daily should be offered to eligible individuals. 180 doses should be taken, which is 6 months of treatment, but 180 doses taken within 9 months of starting treatment is acceptable.

Pyridoxine

Pyridoxine (25mg daily) should be given to all individuals who are prescribed isoniazid for the duration of their isoniazid course.

Monitoring and management of adverse drug events

Isoniazid side effects

Adverse effects of isoniazid should be sought actively at every clinic visit. The main serious adverse effects of isoniazid are:

hepatitis: clinical hepatitis is rare (case fatality among patients with hepatitis estimated at or below 1 in 1000)[14]. The risk is highest 4-8 weeks after starting treatment. In clinical trials of IPT among HIV-infected individuals in Africa, there have been few reports of clinically significant hepatitis[15].

hypersensitivity: this may manifest as fever, skin eruptions or haematological abnormalities. Rarely, a lupus-like syndrome may occur, which is reversible if INH is discontinued.

peripheral neuropathy: risk factors include poor nutrition or heavy alcohol intake. It can be prevented by administration of the vitamin pyridoxine.

central nervous system toxicity: this is uncommon but may manifest as memory loss, psychosis or seizures, and caution is proposed for individuals with a history of convulsions.

Management of adverse drug events.

Hepatitis

Patients with symptoms suggestive of hepatitis should stop isoniazid immediately, visit the treating facility as soon as possible and have ALT measured.

Neuropathy

INH should be permanently stopped if the patient reports new symptoms of peripheral neuropathy . (See Patient education below.)

Hypersenitivity

If a new rash appears, treatment should be stopped temporarily while the rash is evaluated. If due to isoniazid, then stop IPT permanently.

Rarer adverse events

Treatment should be stopped if the patient develops convulsions or psychosis.

Criteria for discontinuation of IPT

INH should be permanently discontinued in the event of the following:

- discontinuation of IPT for 90 days or more
- pregnancy, or intention to become pregnant
- adverse events requiring discontinuation of isoniazid (as above)
- active TB
- commencement of TB treatment

Delivery of isoniazid preventive therapy

Staff delivering the IPT programme need regular reinforcement on the need to educate patients at every visit and to seek symptoms of active TB and side effects of treatment by active questioning. The patient needs to consult the attending health care provider every month while on IPT. To ensure monthly visits, only one month's supply of isoniazid should be dispensed at each visit. At every monthly visit, patient education on the symptoms of adverse reactions to isoniazid should be given. Monthly attendance for consultation and pill refill should be noted in the patient records.

Patient education (Note: health services need to translate instructions and symptoms into the common local languages using generally understood terms)

Prior to starting IPT and at each monthly visit, patients need to be educated about the IPT programme. Symptoms of active TB and the potential side-effects of isoniazid need to be discovered by active questioning. The drug should be discontinued immediately if there are reported symptoms of:

Hepatitis (such as malaise, reduced appetite, yellowing of sclera, nausea, vomiting, right upper quadrant pain, dark urine or pale stools)

TB (such as cough, unexplained loss of weight or drenching night sweats).

Neuropathy (such as tingling [pins and needles] or burning sensations in hands or feet, or weakness in hands or feet)

A new skin **rash**

Patients should be warned to avoid bouts of heavy alcohol consumption

Women patients should be informed that they should postpone pregnancy until after completing the IPT programme.

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