Clinical guidelines on isoniazid preventive therapy for patients with silicosis in South Africa

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ABSTRACT
Clinical guidance on the treatment of latent tuberculosis in people with silicosis is provided. This guideline, developed during a workshop held in July 2013, is particularly applicable to resource-constrained, tuberculosis endemic settings and has been aligned with World Health Organization and South African National Department of Health guidelines for the treatment of latent tuberculosis infection. Major changes from the previous guideline include 1) utilization of tuberculin skin testing to guide treatment of latent tuberculosis; and 2) the increase of the duration of isoniazid treatment to 36 months.

Keywords: isoniazid, latent tuberculosis, silicosis, lower-middle income countries, mining

BACKGROUND
According to the Global Tuberculosis Report of 2012, South Africa has the highest incidence of tuberculosis (TB) in the world with an estimated annual incidence rate of 993 per 100 000. The prevalence of HIV infection in incident TB cases is estimated at 65%.1 Reducing the burden of TB is one of the Millennium Development Goals2 and a national priority for South Africa as outlined in the National Development Plan, the Health Sector’s Negotiated Service Delivery Agreement 2010 – 2012, and the National Strategic Plan 2012 – 2016 for the Department of Health.3–5

Silicosis has been identified as an independent risk factor for TB. Gold miners and foundry workers with silicosis have three-fold and 10-fold higher incidence rates of TB, respectively, compared to nonsilicotic workers;6 and, in some settings, patients with silicosis and a positive tuberculin skin test (TST) have an estimated 30-fold higher odds of developing TB than the general population.7 Silica exposure, mainly from mining, has resulted in silicosis still being relatively common in South Africa with prevalence rates of 18 – 25% in ex-gold miners.8 A dose-response has been demonstrated between cumulative silica dust exposure and the risk of TB, even in the absence of silicosis.9

It has also been shown that HIV and silicosis increase the risk of TB multiplicatively. Prior to the roll-out of antiretroviral therapy, a TB incidence of 16.1 per 100 person years in people with HIV and silicosis compared to 4.9 in those with HIV but no silicosis was calculated in a large South African cohort study.11 Another large cohort study in four South African mines found the incidence of TB in South African miners to have increased almost five-fold between 1991 and 2004, from 806 to 3 821 per 100 000.12 This is a significantly greater increase compared to the three-fold increase in incidence from 301 to 898 per 100 000 observed in the general population over the same period.13 The prevalence of HIV, silicosis and TB is summarised in Table 1. The high prevalence rates and multiplicative effects of silicosis and HIV, along with the migrant labour the mining industry employs, have played important roles in fuelling the TB epidemic in southern Africa.14

Treatment of latent TB infection (LTBI) has been shown to be an effective intervention in reducing the risk of developing active TB in people living with HIV (PLHIV)17 as well as people with silicosis.18 Isoniazid preventive therapy (IPT) is associated with very low rates of adverse events,19 and no significant increase in isoniazid resistance has been demonstrated with its administration.20,21 Due to the high burden of TB amongst mine workers, along with the double risk-burden of silicosis and HIV, short course (three month duration) chemoprophylaxis has been found to be of limited use in preventing TB,22 whereas longer term treatment has been shown to significantly reduce incident active TB.23,24

In light of recent evidence, both in terms of treatment and diagnostics, as well as changes in World Health Organization (WHO) Guidelines in the treatment of LTBI, there was a need to revise the South African National Guideline for the treatment of LTBI in persons with silicosis.
DEFINITIONS
Silicosis is defined as radiologic silicosis with profusion of opacities 1/1 or greater, or massive fibrosis according to the ILO system of classifying radiographs of the pneumoconioses.25

GUIDELINES
Treatment regimen:
Isoniazid monotherapy has been shown to have similar effectiveness but with reduced risk of adverse events compared to combination treatments.17,26,27

Strong recommendation:
Isoniazid:
A daily dose of 5 mg/kg up to a maximum dose of 300 mg daily should be offered to eligible individuals.

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

Duration of treatment is guided by Tuberculin Skin Test (TST) positivity. Persons who are TST positive derive the greatest benefit from IPT, regardless of HIV status or duration of IPT.17,26 Revised WHO guidelines also recommend using TST to decide on duration of treatment for PLHIV, but unavailability of a TST result is not a barrier to access IPT.28

Strong recommendation:
In HIV-negative people with silicosis:

V TST not done IPT for 6 months
V TST negative No IPT indicated
V TST positive IPT for at least 36 months

Notes:
1. In HIV-positive patients with silicosis, follow the national guidelines for PLHIV.29
2. The treating clinician should, whenever possible, perform a TST.
3. Current (2013) national guidelines stating IPT is indicated for TST negative patients are under review.

People with silicosis who are TST negative should not receive IPT as it has been shown that there is no significant reduction in the incidence of active TB for these individuals through the administration of chemoprophylaxis.17

Interferon-gamma release assays (IGRAs) have been developed as an alternative to TST testing and have been adopted by the Centers for Disease Control and Prevention (CDC) to replace TST under certain circumstances.30 The WHO does not recommend the use of IGRAs in resource-constrained settings.31 IGRAs cannot distinguish between active and latent TB and results may be influenced if assays are performed soon after a TST.32,33

Inclusion and exclusion criteria for IPT:
All persons should receive HIV testing and counselling and, if HIV positive, IPT and ART should be given according to the South African National Antiretroviral Treatment Guidelines.29

Box 1. Notes on exclusion and exclusion criteria for IPT

1. Pregnancy is not an exclusion criterion for IPT
2. Unavailability of TST is not an exclusion criterion for IPT

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Table 1. Prevalence of HIV, silicosis and tuberculosis in South African gold miners

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>27%</td>
</tr>
<tr>
<td>Silicosis</td>
<td>18.3 – 19.9%</td>
</tr>
<tr>
<td>LTBI</td>
<td>89%</td>
</tr>
<tr>
<td>Undiagnosed Active TB</td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td>2.3%</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

### Adverse event Management guideline

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Management guideline</th>
</tr>
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| Peripheral neuropathy | • All patients initiated on IPT should receive 25 mg of pyridoxine daily to help prevent peripheral neuropathy.  
• Patients should be advised on nutrition and reducing alcohol consumption. |
| Hepatitis          | • Clinical hepatitis is rare but can be fulminant and fatal. If isoniazid-induced hepatitis is suspected:  
• stop isoniazid treatment immediately and conduct liver function tests  
• refer patient for specialist care  
• Risk factors for isoniazid-induced hepatitis include age, under-nutrition, heavy alcohol consumption and pregnancy. The more serious outcomes can be avoided if symptoms are recognised early and isoniazid discontinued.  
• Clinically, isoniazid-induced hepatitis is indistinguishable from viral hepatitis. Clinical features include nausea, vomiting and anorexia, right upper quadrant tenderness, pale stools, dark urine and jaundice. |
| 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. If the only symptom is mild itching, patient can be treated with antihistamines and followed-up.  
• Severe hypersensitivity reactions (fever, generalized skin rash) are an indication to stop isoniazid therapy immediately. |
| Seizures           | • Convulsions are a rare (~0.02%) adverse event associated with isoniazid therapy and usually a result of overdose.  
• Patients with isoniazid-associated convulsions should be screened for other potential causes, including isoniazid overdose. |
| Drug interactions  | • Clinically significant drug interaction with isoniazid can occur with the following:  
• antacids, benzodiazepines, carbamazepine, disulfiram, hydralazine, levodopa, paracetamol, phenytoin, prednisone, theophylline, valproic acid and warfarin. |

**Inclusion criteria**
- Individuals with silicosis of ILO 1/1 or greater, or massive fibrosis
- No evidence of active TB

**Exclusion criteria**
- Active TB confirmed or suspected
- Previous adverse drug reaction to isoniazid
- History of underlying liver disease
- o liver function tests, such as ALT, are not required to enter IPT
- Regular alcohol use, o exceeding 28 units per week (men) or 21 units per week (women)
- Symptomatic peripheral neuropathy

**Exclusion of active TB prior to IPT**
- All patients should be screened for active TB and offered HIV counselling and testing
- If no evidence of active TB is found, IPT should be initiated
- Active TB should be excluded prior to starting IPT on symptoms and chest radiograph. If a person has any of the following symptoms or signs, he/she should be investigated fully for TB:  
  - night sweats, fever, coughing for more than 24 hours and reported weight loss (or measured weight loss of > 5%); or  
  - chest radiography features consistent with TB
- If radiography is unavailable, active TB can be excluded on the basis of symptoms and Xpert or culture results
- People with silicosis with one or more symptoms, or a
new or changing chest radiographic lesion, should be investigated for TB by collecting a spot-sputum specimen for Xpert or culture

- Undiagnosed TB among HIV-positive people with silicosis is very high. Therefore, active TB in HIV-positive people with silicosis should be excluded, based on symptoms, radiography and the collection of one spot-sputum specimen for testing with GeneXpert
- Symptomatic HIV-infected people with silicosis who have a negative Xpert test should follow the Department of Health guidelines for PLHIV

Criteria for discontinuation of IPT:
INH should be permanently discontinued in the event of the following:

- Adverse events requiring discontinuation of isoniazid
  - isoniazid-induced clinical hepatitis
  - severe hypersensitivity to isoniazid
- Diagnosis of active TB
  - isoniazid monotherapy should be stopped and appropriate TB treatment initiated

MONITORING AND MANAGEMENT OF ADVERSE EVENTS
Adverse events resulting from isoniazid are rare. Box 2 summarises common and serious adverse events and provides guidelines on management.

DELIVERY OF ISONIAZID PREVENTIVE THERAPY
Prior to starting IPT, patients need to be educated about the IPT programme, symptoms of active TB and the potential side-effects of isoniazid. Staff delivering the IPT programme require 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. Patients need to consult the attending health care provider every month while on IPT.

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 provided. Monthly attendance for consultation and pill refill should be noted in the patient record. Appropriate enablers and/or incentives should be considered within the resources of the treating service. Individual enablers may include mechanisms to limit inconvenience to patients (e.g. short waiting times), refreshments while waiting to see clinic staff, and personalised message reminders for visits and treatment. Small incentives may be appropriate at intervals in the IPT programme. See Box 3.

CONCLUSION
IPT is effective and safe for the treatment of LTBI. Together with intensified case finding and infection control, IPT forms part of the WHO strategy to reduce the burden of TB. People with silicosis are at increased risk of developing active TB and must be offered IPT. It is advised that all persons receive TST prior to initiating IPT and those with TST positive results should be placed on IPT for 36 months. Patient education is paramount.
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORSHIP

All the authors contributed to the content of this manuscript. PJ and DR wrote the manuscript. All authors participated in the editing of the final manuscript and approved the final text.

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REFERENCES


