# GUIDELINES FOR TUBERCULOSIS PREVENTIVE THERAPY AMONG PEOPLE LIVING WITH HIV AND SILICOSIS IN SOUTH AFRICA

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

## TABLE OF CONTENT

## 1 ABBREVIATIONS

**AIDS** acquired immunodeficiency syndrome

**ART** antiretroviral therapy

**HCT** HIV counseling and testing

**HIV** human immunodeficiency virus

**INH** isoniazid

**IPT** isoniazid preventive therapy

**LTBI** latent tuberculosis infection

**MDR** multidrug-resistant (TB, resistant to at least isoniazid and rifampicin)

**M&E** monitoring and evaluation

**PMTCT** Prevention of mother-to-child transmission (of HIV)

**TB** tuberculosis

**TST** tuberculin skin test

**WHO** World Health Organization

**XDR** extensively drug-resistant TB (defined as resistance to at least rifampicin and isoniazid from among the first-line anti-TB drugs, in addition to resistance to any fluoroquinolone, and to at least one of three injectable second-line anti-TB drugs used in TB treatment [capreomycin, kanamicin and amikacin])

## 1 BACKGROUND

The dramatic spread of the HIV epidemic throughout sub-Saharan Africa in the past decades has been accompanied by up to a fourfold increase in the number of Tuberculosis (TB) cases registered by national TB programmes. It is estimated that around 70% of new adult cases of tuberculosis in South Africa are co-infected with HIV. Tuberculosis is the commonest cause of morbidity and mortality among HIV-infected persons and studies have shown that TB accelerates HIV disease progression. It is the most frequent life threatening opportunistic disease even in those receiving ART. Early cohort analyses of patients on antiretroviral therapy (ART) reveal high rates of TB in persons initiating ART, but also high rates of TB in patients on ART, particularly in the first 6 months after ART initiation.

The risk of TB in People Living with HIV (PLWH) can be significantly reduced by treatment with ART and Isoniazid Preventive Therapy (IPT). A metanalysis, showed that 6 months of IPT reduced the risk of TB in HIV-infected adults by 33% overall, with the greatest efficacy (64%) being among those who were tuberculin skin test (TST) positive ([1]). In high TB transmission settings (Botswana and South Africa), continuous IPT reduced the risk of TB while taking it, but TB rates increased soon after stopping IPT ([2,3]). Among South African gold miners, IPT for 9 months reduced the risk of TB disease at an individual level by 58% while taking it, but the protective effect was subsequently lost rapidly, and community-wide IPT did not improve TB control in the population ([3]).

Two observational studies ([4,5]) and 1 clinical trial ([6]) have shown that isoniazid with ART further reduces the risk of TB compared to ART alone. IPT is safe if given with careful clinical monitoring ([7]) and there is no evidence that it generates isoniazid resistance if active TB is excluded prior to starting IPT ([8, 9]).

The following populations are at particularly high risk of developing TB and would benefit from IPT:

- Mine workers
- Inmates
- Close contacts of people with infectious TB
- Health care workers

## 2 TB, HIV and Silicosis

A tuberculosis incidence of 16.1 per 100 person years in HIV-positive silicotics compared to 4.9 per 100 person years in HIV-positive non-silicotics have been calculated in a large South African cohort study. The incidence of TB in South African miners increased almost five-fold between 1991 and 2004 from 806 to 3 821 per 100 000 compared to a three-fold increase in incidence from 301 to 898 per 100 000 in the general population. The prevalence of HIV in South African gold miners in 2004 was 27%. Gold miners have a high prevalence of HIV and silicosis, these are both strong risk factors for tuberculosis, and worse when combined. Gold miners and foundry workers with silicosis have a threefold and tenfold higher incidences of tuberculosis respectively compared to non silicotic workers; and in some setting patients with silicosis and a positive tuberculin skin test have

an estimated 30 fold higher odds of developing TB than the general population. A combination of strategies must be implemented in the mining sector to reduce the burden of TB; among these is Isoniazid preventive therapy.

### *2.1 TB preventive therapy and health services*

TB preventive therapy is an intervention that should be part of the package of care for people living with HIV/AIDS. TB preventive therapy should only be offered if the following prerequisites have been met:

- High quality HIV counselling and rapid testing is available.
- Patients are screened for active TB disease before initiation of TB preventive therapy.
- The HIV/AIDS programme takes responsibility for implementing TB preventive therapy.
- Health care workers are trained on administering and reading the Tuberculin skin test.
- Good follow up systems for patients on pre-ART and ART care
- There is strong collaboration between HIV/AIDS and TB programmes.

In order to provide comprehensive care to HIV/AIDS patients, TB preventive therapy must be rolled out to all public health services. Sites that already provide TB preventive therapy should be consulted to gain from local experience. Given that people living with HIV and have a positive TST benefit more from IPT than those who are TST-negative, it is recommended that TST should be used to identify such individuals. If TST was not done at initiation of IPT, it should be done at the next visit or within a month.

## 3 ISONIAZID PREVENTIVE THERAPY

### *3.1 Exclusion of active Tuberculosis in adolescents and adults*

It is essential to exclude active tuberculosis in every patient prior to starting preventive therapy. This is critical in order to avoid giving one antituberculosis drug to patients with TB disease who require a full treatment regimen. All People living with HIV should be screened for TB at every visit to a health facility or contact with a health worker. Symptom based TB screening is sufficient to exclude TB among adults and adolescents living with HIV.

TB screening is defined as a method to intensify TB case finding among HIV positive patients. It involves asking questions about TB symptoms to identify TB suspects and to find out if the patient may have active TB. This must be done routinely by trained lay counselors or health care workers. The counsellor or the health worker must systematically inquire about the presence of signs and symptoms of active TB disease, as stipulated in the table below and refer or investigate as appropriate.

**Table 1 TB symptoms and signs in adults and adolescents**

| |
|---|
| Current cough of any duration |
| Persistent fever of more than two weeks |
| Unexplained weight loss of more than 1.5kg in a month |
| Drenching night sweats |

All patients with one or more of these symptoms and signs must be further investigated for active TB disease as per national TB guidelines.

### *3.2 Exclusion of active TB in children*

Screening for TB should be part of all routine child health visits, and especially first and follow-up visits for HIV-infected children. TB screening must include questions regarding whether or not there is a household or other TB contact (or a possible TB contact), as well as screening for symptoms and signs of TB. Where a TB or possible TB contact is identified, evidence of TB disease must be actively sought as per Table 2 below.

**Table 2 TB symptoms and signs in children**

| |
|---|
| Current cough |
| Persistent fever of more than two weeks |
| Poor weight gain<br>*(where poor weight gain is defined as reported weight loss, or very low weight (weight-for-age less than –3 z-score), or underweight (weight-for-age less than –2 z-score), or confirmed weight loss (>5%) since the last visit, or growth curve flattening* |
| Fatigue |
| History of close contact with an adult or adolescent with infectious PTB (smear/ culture positive) |

All children one or more of these symptoms and signs must be further investigated for active TB disease as per national TB guidelines. If there is any suspicion that the patient has active TB disease the patient should not be started on IPT.

### *3.3 Eligibility for TB Preventive Therapy*

Clinical trials have shown that the benefit of TB preventive therapy is greatest in HIV-infected persons with a positive tuberculin skin test. Considering the high prevalence of TB infection in the country, all HIV infected adults and adolescents with no signs or symptoms suggestive of active TB are eligible for TB preventive therapy. Including:

- **Pregnant women –** In Africa 10% of maternal deaths are due to TB in HIV positive women Active TB during pregnancy is associated with adverse perinatal outcomes. Expert opinion is that the benefits of TB preventive therapy for eligible pregnant women, after exclusion of active tuberculosis disease, outweigh the risks. TB preventive therapy can be started at any time during pregnancy.

- **Patients on ART -** All people living with HIV, in whom active TB has been reasonably excluded, should be started on IPT (as soon as practically possible after initiation of ART). Patients on Pre ART care, who are receiving IPT and become eligible for ART should continue with IPT and initiated on ART. Patients on IPT and ART should be monitored clinically, and INH stopped immediately if there is evidence of severe peripheral neuropathy or hepatotoxicity.

- **Former TB patients -** IPT does provide benefit to patients who successfully complete TB treatment.IPT can be started immediately after successful completion of TB treatment provided that cure has been documented or at any time after a previous episode of TB, provided that active TB disease is excluded. There is no evidence of the role of IPT in those who have completed MDR or XDR TB treatment.

- **Patients with Silicosis –** IPT has been shown to be effective in preventing TB disease in People Living with HIV as well as people with silicosis. The risk of developing Isoniazid resistance due to mono therapy has been shown to be very low and the rates of adverse events among this group of patients low. According to the ILO system of classifying radiographs of the pneumoconioses, Silicosis for the purposes of this document is defined as – “Radiologic silicosis with profusion of opacities 1/1 or greater, or massive fibrosis”

- **Children –** If TB disease has been excluded, all HIV infected children who are close contacts of a person with confirmed infectious TB disease must receive IPT for six months.
  - Children who are re-exposed to TB infection following completion of IPT must be restarted on IPT after excluding TB disease irrespective of the interval between completion of treatment and re-exposure.
  - Pre-exposure IPT is not recommended irrespective of the HIV status of the child.
  - Children who have successfully completed TB treatment should not routinely receive IPT.

Patients with signs and symptoms suggestive of TB must be investigated for TB as per National TB Management Guidelines. If they are found not to have TB they should be reassessed in three months for eligibility, and offered IPT.

### *3.4 Who is not eligible for TB Preventive Therapy?*

The following patients should not be offered IPT:

- People with confirmed or unconfirmed active TB
- Patients with active liver disease (acute or chronic)
- Patients with symptoms of peripheral neuropathy
- Patients with history of adverse reaction to Isoniazid
- People who are HIV positive but TST negative in pre-ART care
- People with silicosis but TST negative
- Patients with excessive alcohol use - (more than 28 units per week for men and 21 units per week for women).

### *3.5 Tuberculin Skin Test*

It is recommended that all asymptomatic HIV positive patients should have a TST done so as to determine the duration of IPT. However, it should be noted that TST relies on a competent immune response and patients who are severely immune-compromised may not have a reactive TST even though they have been exposed to Mycobacterium Tuberculosis.

The tuberculin skin test measures the body's immune response to an injection of tuberculin purified protein derivative (PPD). The Mantoux test is the recommended technique that consists in injecting a known amount of PPD between the layers of the skin (intradermally). It is to be ensured that the injection goes into the skin and not under the skin. The reaction is measured at the site of injection 48-72 hours later.

| PROVISION OF IPT FOR HIV POSITIVE PATIENTS | | |
|---|---|---|
| **TST result** | Pre-ART | On ART |
| **TST not available*** | IPT for 6 months | IPT for 6 months |
| **TST negative** | No IPT | IPT for 12 months |
| **TST positive** | IPT for 36 months | IPT for 36 months |
| * Where TST is not available at initiation, it must be conducted within ONE month of initiating IPT | | |

| PROVISION OF IPT FOR PATIENTS WITH SILICOSIS | |
|---|---|
| **TST result** | **Duration** |
| **TST negative** | No IPT |
| **TST positive** | IPT for at least 36 months |
| **TST not available*** | IPT for 6 months |
| *Where TST is not available at initiation, it must be conducted within ONE month of initiating IPT | |

Where TST is not available, IPT should be initiated as per 2010 Guidelines for Tuberculosis preventive therapy among HIV infected individuals in South Africa, and all effort should be made to perform TST within a month of starting IPT.

### *3.6 Recommended Regimen*

IPT can be started as soon as the patient has been declared eligible, has been counselled and is willing to start IPT. The duration of IPT is guided by the TST results, since patients who are TST positive have the greatest benefit from IPT

The standard regimen for TB preventive therapy is:

| |
|---|
| **Adults:** Isoniazid (INH) 5 mg/kg/day (maximum 300 mg per day). |
| **Children:** Isoniazid (INH) 10 mg/kg/day (maximum 300 mg per day). |

Vitamin B6 (pyridoxine) 25 mg per day should be given concomitantly with Isoniazid to prevent the occurrence of peripheral neuropathy.

| Dosage recommendations for INH preventive therapy in children | |
|---|---|
| **Weight band (kg)** | **Daily Isoniazid (INH) 100mg tablet** |
| 2 – 3.4 | ¼ tab |
| 3.5 – 4.9 | ½ tab |
| 5 – 7.4 | ¾ tab |
| 7.5 – 9.9 | 1 tab |
| 10 – 14.9 | 1 ½ tabs |
| 15 – 19.9 | 2 tabs |
| 20 – 29.9 | 3 tabs |
| 30 – 40 | 4 tabs |

Patients starting TB preventive therapy should be given a one-month supply at a time for the initial 6 months after which those on long term IPT can then receive 3 months' supply. This is to monitor patients clinically for any signs of TB during first 6 months of treatment. Patients should be screened for TB symptoms and adverse events at every follow up visit.

### *3.7 Clinical Monitoring*

Patients should be monitored monthly for the first 6 months. During these visits the following should be routinely conducted;

- On-going counselling and patient education
- Adherence monitoring i.e pill count
- Early identification and management of adverse events
- TB symptom screening (for early detection of active TB)
- Social support and care

As much as possible these visits must coincide with pre-ART/ ART or other chronic visits to avoid patients making multiple visits for care.

### *3.8 Management of side effects*

| SIDE EFFECTS | SIGNS/SYMPTOMS | MANAGEMENT |
|---|---|---|
| **Peripheral Neuropathy** | Tingling or burning sensation of the fingers and/or toes that usually occurs in a stocking glove distribution | – Vitamin B6 (pyridoxine) must be increased from 25 mg to 100 mg daily until the symptoms disappear.<br>– If the peripheral neuropathy is severe or worsens, then Isoniazid should be discontinued immediately. |
| **Hepatotoxicity**<br>*Very uncommon in children.* | Symptoms:<br>Nausea, vomiting, abdominal tenderness, discomfort near the ribs on the right upper abdomen, jaundice (yellowing of skin and whites of the eyes)<br>Signs:<br>Hepatic enlargement<br>increased LFTs | – Stop Isoniazid immediately,<br>– Refer the patient immediately to the hospital/ medical officer. |
| **Gastro intestinal**<br><br>*Uncommon at recommended daily doses* | Symptoms:<br><br>nausea, vomiting, diarrhea | – Rule out other causes of nausea and vomiting,<br>– Consider measuring liver function tests to rule out drug induced hepatic dysfunction<br>– Treat symptomatically (if no other cause is found) |

| | | |
|---|---|---|
| **Flushing reaction** *Some patients experience this reaction immediately after ingesting certain foods containing tyramine (cheese, red wine) or histamine (tuna). In these cases the reaction usually resolves within 2 hours* | Symptoms:<br><br>Flushing and/or itching of the skin with or without a rash<br><br>hot flushes, palpitations, headache<br><br>Signs:<br><br>increased blood pressure | – Reassure patients and inform about avoiding tyramine and histamine containing foods while receiving isoniazid<br>– flushing is usually mild and resolves without therapy<br>– if flushing is bothersome to the patient, an antihistamine may be administered to treat the reaction |
| **Hypersensitivity** *uncommon usually occurs 3-7 weeks after initiation of therapy.* | Symptoms:<br><br>hives (raised, itchy rash)<br><br>fever (may occur) | – Discontinue until the reaction resolves<br>– Re challenge after resolution of reaction<br>▪ begin with INH 50mg on day 1<br>▪ if the original reaction was severe, begin with INH 5mg on day 1<br>▪ if a reaction does not occur after the day 1 dose, increase the INH to 300mg on day 2<br>▪ if a reaction does not occur after the day 2 dose, continue INH 300mg daily<br>▪ If a reaction occurs during drug re challenge, stop INH |
| | Mild rash and itching | – Treat with anti-histamines and follow up |

### *3.9 Treatment interruption*

If a patient has an interrupts treatment for less than 3 consecutive months,

- Enquire about the reasons for treatment interruption
- Address patient concerns or
- Counsel the patient on the importance of adherence.
- Screen for TB
- Conduct investigations to exclude TB
- If asymptomatic and no signs of TB disease, restart on Isoniazid.

### *3.10 Discontinuation of IPT*

IPT should be discontinued if the patient

- Interrupts TB preventive therapy for a second time
- Develops severe adverse events
- Develops TB disease

## 4 MONITORING AND EVALUATION

### *4.1 Data collection*

At facility level the data on TB screening for HIV positive patients is recorded in the HCT, PMTCT, Pre-Art registers as well as in ART patient records and registers. There currently are no registers for patients on IPT to enable cohort analysis of the patient outcomes.

The data elements collected at facility level is:

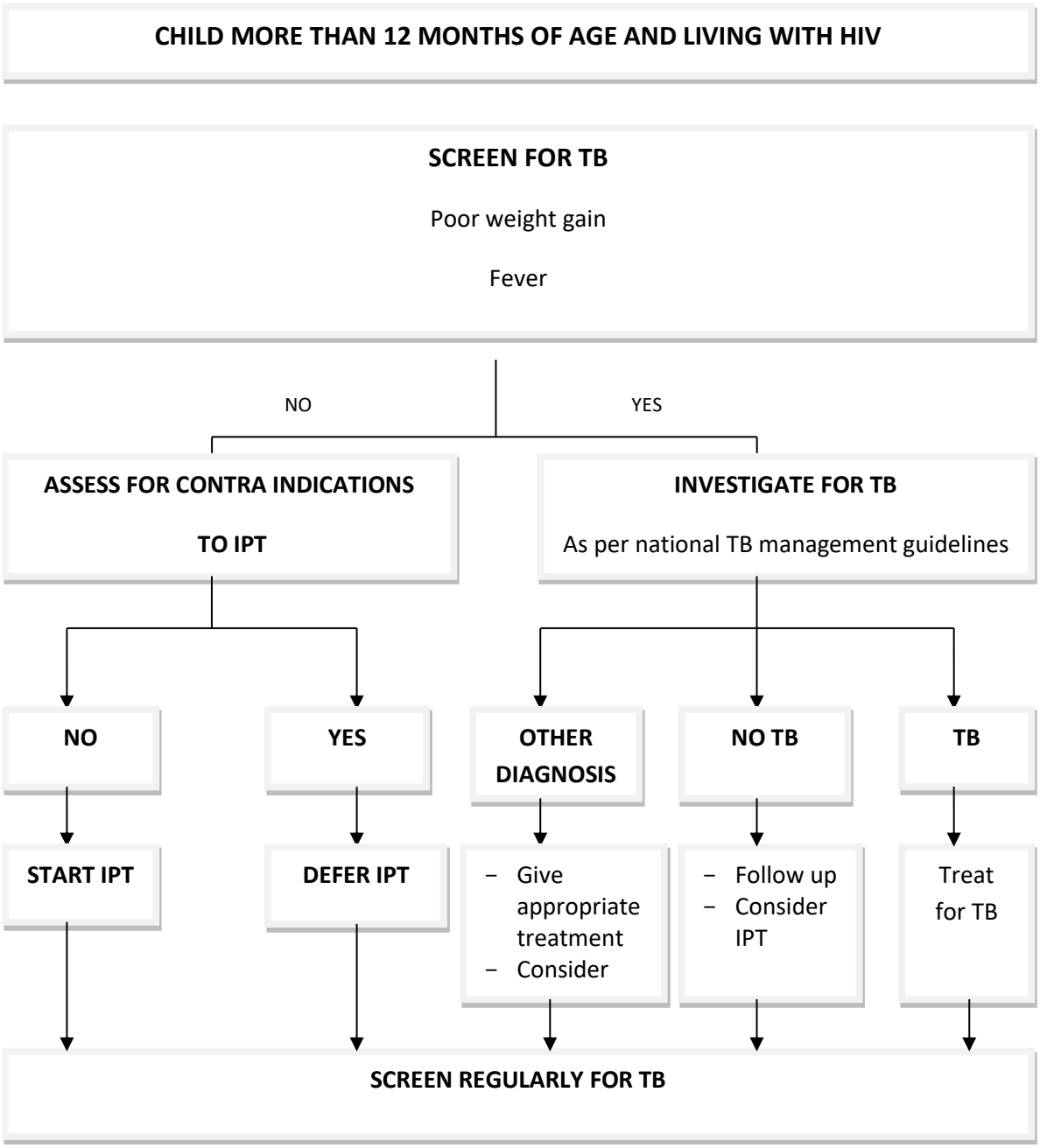
- The number of people who are HIV positive
- The number of people who are HIV positive screened for TB
- The number of HIV positive people screened for TB who were asymptomatic
- The number of asymptomatic HIV positive people who had TST done
- The number of asymptomatic HIV positive people who were TST negative
- The number of asymptomatic HIV positive people who were TST positive
- The number of asymptomatic, TST positive, HIV positive people who were started on IPT
- The number of asymptomatic, TST negative, HIV positive people who were started on IPT
- The number of people who complete IPT (6, 12 or 36 months)
- The number of people who develop active TB while taking IPT
- The number of people who stopped IPT

This data can be disaggregated by age, pre ART, ART and by gender

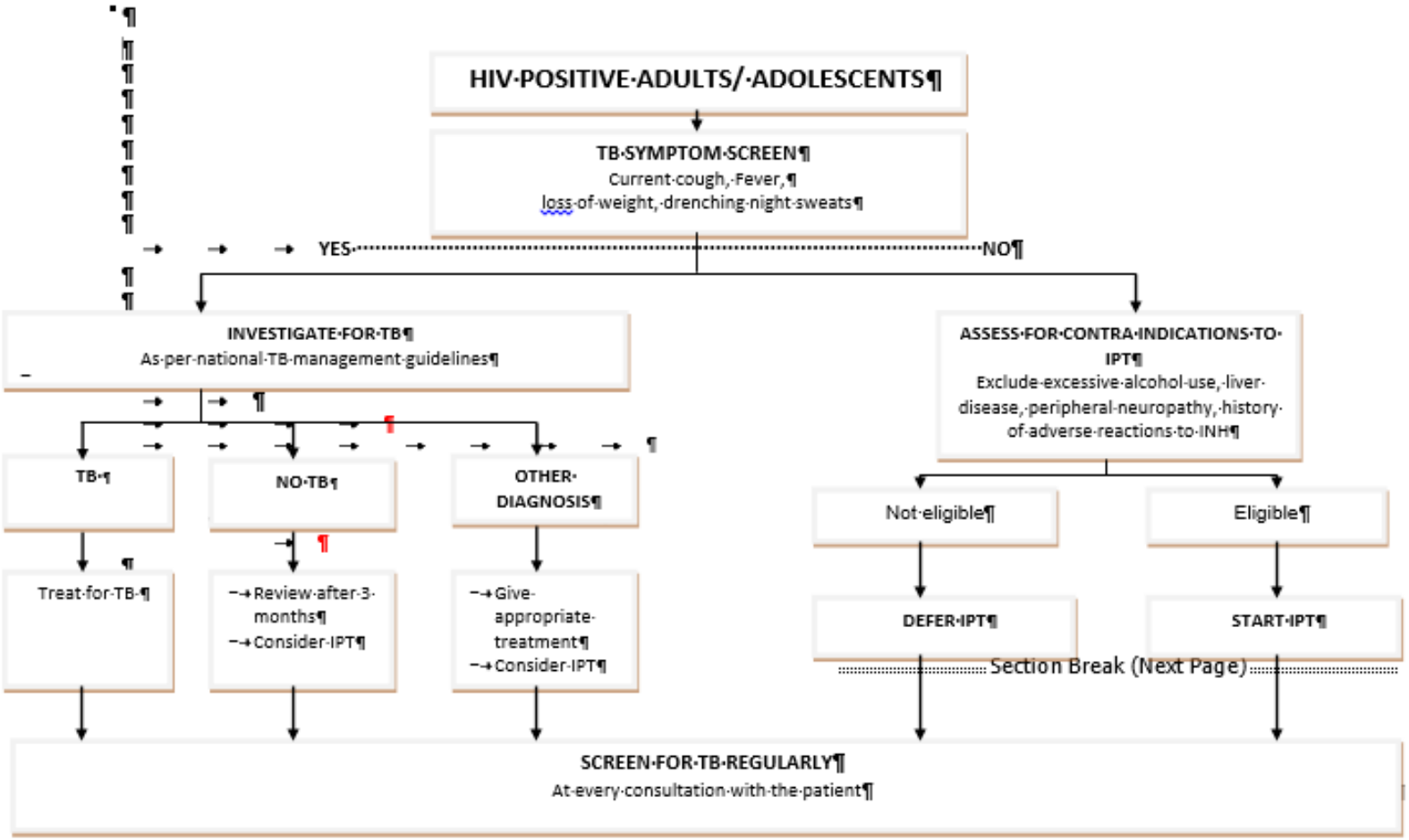
### *4.2 Information flow*

Monthly PHC tick sheets are submitted to the sub district or district for data checks and entry into the DHIS. The data is then reported to the next level. Quarterly reports can be generated at all levels on the key indicator for monitoring IPT implementation

## 5 ANNEXURE A: TB SCREENING ALGORITHM FOR IPT IN HIV POSITIVE CHILDREN



## 6 ANNEXURE B: TB SCREENING ALGORITHM FOR IPT IN ADOLESCENTS AND ADULTS



## 7 ANNEXURE C: TB SCREENING TOOL


**TB SYMPTOM SCREENING TOOL FOR ADULTS AND CHILDREN**

**PATIENT DETAILS**

Surname: _____ First Name: _____

Physical Address: _____ Age: _____

_____

Telephone Number: _____ Patient folder Number: _____

**MEDICAL HISTORY**

| | | | | |
|---|---|---|---|---|
| Close contact of a person with infectious TB: | Yes | No | Unknown | (Tick √) |
| Type of index patient: | DS-TB | Rif Resistant TB | MDR-TB or XDR-TB | |
| Diabetic: | Yes | No | Unknown | |
| HIV Status: | Positive | Negative | Unknown | |
| Other: (Specify) | | | | |

**TB SYMPTOM SCREEN**

**1. ADULTS**

| **Symptoms** (Tick √) | **Yes** | **No** |
|---|---|---|
| Cough of 2 weeks or more OR of any duration if HIV positive | | |
| Persistent fever of more than two weeks | | |
| Unexplained weight loss >1.5kg in a month | | |
| Drenching night sweats | | |

**2. CHILDREN**

| **Symptoms** (Tick √) | **Yes** | **No** |
|---|---|---|
| Cough of 2 weeks or more which is not improving on treatment | | |
| Persistent fever of more than two weeks | | |
| Documented weight loss/ failure to thrive (*check Road to Health Card*) | | |
| Fatigue (less playful/ always tired) | | |
| *If "Yes" to one or more of these questions, consider TB.* | | |
| *If the patient is coughing, collect sputum specimen and send it for Xpert testing.* | | |

*If the patient is not coughing but has the other symptoms, clinically assess the patient or refer for further investigation.*

Date of last TB test: _____

Patient referred for assessment and investigation: Yes No

Date of referral: _____ Facility name: _____

Name: _____ Date: _____/_____/_____

# 8 ANNEXURE D: TUBERCULIN SKIN TEST

## *8.1 Performing a Mantoux Tuberculin Skin Test*

a. The Mantoux TST is the most reliable test available. The test requires:
    - 2 units of tuberculin purified protein derivative PPD-RT23 2TU or
    - 5 units of PPD-S 5TU.
b. Use a single-dose tuberculin syringe and a short 27-gauge needle with a short bevel to do the test.
c. Draw up 0.1ml of PPD of the correct strength into the syringe.
d. Clean an area of skin in the mid anterior section of the forearm. The PPD is injected between layers of skin (intradermally). Keep the needle almost parallel to the skin, with the bevel pointing upwards during insertion. It is important to ensure that the injection goes into and not under the skin. A small papule should form at the injection site; if it does not, the PPD has been injected too deeply and the test should be repeated at a different site.
e. The reaction to the test at the site of the injection is measured 48-72 hours later by noting the widest **transverse** point across the edges of the raised, thickened area. This area of induration and not redness is measured.
f. To help measure accurately, mark the edges of the induration at the widest point with a pen and measure the exact distance between the two points in millimetres.

| **Reading the Tuberculin Skin Test** | | |
|---|---|---|
| **Immune Status** | **HIV positive, malnourished, severe illness** | **Others (including previous BCG)** |
| Diameter of induration in positive test | ≥5 mm | ≥10 mm |

## *8.2 Interpreting a positive TST*

A positive test indicates infection with TB, but not necessarily TB disease. In a child under 5 years or an HIV-infected child of any age, a positive skin test indicates recent infection and is a risk factor for progression to disease. In the presence of other features such as a history of a TB contact, signs and symptoms of TB and chest x-ray changes, a positive tuberculin skin test is suggestive of TB disease in children

## *8.3 Interpreting a negative TST*

A negative tuberculin skin test does not exclude TB; various conditions may cause a false negative reaction including:

- HIV infection
- Malnutrition
- Severe viral infections (e.g. measles, chicken pox)
- Cancer
- Immuno-suppressive drugs (e.g. steroids)
- Severe disseminated TB.

## 9 ANNEXURE E: REFERENCES


1) Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database st Rev 2004; (3):CD000171

2) Samandari T, Agizew TB, Nyirenda S et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: A randomised double-blind, placebo-controlled trial. Lancet 2011; 377:1588-1598

3) Churchyard GJ, Fielding KL, Lewis JJ et al. A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control. N EnglJ Med 370;4. January 2014.

4) Golub JE, Pronyk P, Mohabi L et al. Isoniazid preventive therapy, HAART and the tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS. 2009 Mar 13;23(5)

5) Charalambous S, Grant AD, Innes C, et al. Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme. . AIDS. 2010 Nov;24Suppl 5:S5-13.

6) Rangaka MX, Wilkinson RJ.Isoniazid prevention of HIV-associated tuberculosis. Lancet Infect Dis. 2013 Oct;13(10):825-7.

7) Grant AD, Fielding KL, Mngadi K, Churchyard GJ. Adverse events with isoniazid preventive therapy: experience from a large trial in South Africa. AIDS 2010, 24(suppl 5):S19-S27.

8) Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis. 2006, 12:744-751.

9) Van Halsema CL, Fielding KL, Chihota VN et al. Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting. AIDS 2010, 24:1051-55.

10) World Health Organisation. Guidelines for Intensified TB case finding and Isoniazid preventive therapy for people living with HIV in resource constrained settings. 2011

11) Barnes D, Churchyard G, Costa E et al. Guideline on isoniazid preventive therapy for patients with silicosis in southern Africa. 2007