IPT

Version 3– April 2016

FOR ADULTS & CHILDREN


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Aurum House: 29 Queens Road, Parktown, Johannesburg, 2193, South Africa

Tel: +27 (0) 10 590 1300

Email: info@auruminstitute.org

www.auruminstitute.org

Table of Contents

BACKGROUND..... 3

IPT IN ADULTS..... 5

- ELIGIBILITY..... 6
- ASSESSMENT PRIOR TO IPT INITIATION..... 10
- ADMINISTRATION OF IPT..... 13
- MONITORING PATIENTS ON IPT..... 16
- MANAGING TREATMENT INTERRUPTION..... 18
- TB AFTER IPT..... 20
- SIDE EFFECTS OF IPT..... 21
- SCREENING ALGORITHM IN ADULTS..... 25

IPT IN CHILDREN..... 26

- ELIGIBILITY..... 27
- ADMINISTRATION OF IPT..... 30
- BABIES BORN TO MOTHERS WITH ACTIVE TB..... 32
- SCREENING ALGORITHM IN CHILDREN..... 33

TUBERCULIN SKIN TEST..... 34

- HOW TO PERFORM A TST..... 35

REFERENCES..... 41

CONTENTS

BACKGROUND

What Is Isoniazid Prevenive Therapy (IPT)?

1) IPT is the administration of isoniazid (INH) to individuals with latent infection with *Mycobacterium tuberculosis* (MTB) in order to prevent progression to active disease.

Why Should We Offer IPT In South Africa (SA)?

1) According to the World Health Organisation (WHO) Global TB Report of 2015, SA has the sixth highest incidence of tuberculosis (TB) globally, with an annual estimated incidence rate of 834 per 100 000 population.[1]
2) **HIV infection** significantly increases the risk of progression from latent to active TB disease. The risk of developing TB in people living with HIV (PLHIV) is estimated to be between 12-20 times higher than among those without HIV infection. The HIV prevalence in incident TB cases in SA in 2014 was estimated to be 61%.[1]
3) **Silicosis** is an independent risk factor for TB.[2] Gold miners with silicosis have been found to have a 3-fold higher incidence rate of TB compared to non-silicotic workers.

Foundry workers with silicosis were found to have a 10-fold higher incidence rate of TB compared to non-silicotic workers.[3] The prevalence of silicosis in ex-gold miners in SA is estimated to be between 18-25%.[2]

4) **HIV and silicosis have also been shown to have a multiplicative effect on the risk of TB.** A large South African cohort study showed the following:
   a) a TB incidence of **4.9** per hundred person years in **PLHIV without silicosis**
   b) TB incidence of **16.1** per 100 person years in **PLHIV with silicosis**[4]

Is IPT Effective?

1) Multiple studies have shown that IPT reduces the TB incidence in HIV positive adults[5]
   a) by 33% overall
   b) by 64% amongst those with a positive tuberculin skin test (TST)
2) IPT has also been shown to be effective in preventing TB disease in people with silicosis.[6]

IPT IN ADULTS

ELIGIBILITY

Which Adults Are Eligible For IPT?

1) **All adults and adolescents living with HIV**, with no signs or symptoms of TB are potentially eligible for IPT.
2) All patients with **silicosis** with no signs or symptoms of TB are eligible for IPT r**egardless of HIV status.**

IPT And Pregnancy

1) **Are pregnant women with HIV infection eligible for IPT?**
   a) **Yes.** Any pregnant woman living with HIV who is asymptomatic for TB and has no other contra-indications must be considered for IPT.
   b) The benefits of IPT use in pregnancy outweigh the risks. 10% of maternal deaths in Africa are caused by TB/HIV co-infection. Active TB during pregnancy is associated with spontaneous abortion and adverse perinatal outcomes. It has also been shown to increase all-cause neonatal mortality.

2) **When during pregnancy can IPT be taken?**

a) Once active TB disease is excluded, IPT can be started at any time during pregnancy.

b) Women who fall pregnant while on IPT should complete IPT.

c) All HIV positive pregnant women require antiretroviral therapy (ART) as lifelong therapy. In pregnant women who are not already on ART, initiation of ART is the priority. Initiate ART first and start IPT once stable.

IPT In Patients On ART

1) **Are patients on ART eligible for IPT?**

a) **Yes.** Although ART reduces the likelihood of developing TB disease, TB incidence in PLHIV who are on ART is still 10 times greater than in the general South African population.[7]

b) Studies have shown that IPT with ART further reduces the risk of TB compared to ART alone.[8,9,10]

2) **When can IPT be given to patients on ART?**

a) IPT should be given once patients are stable on ART.

b) In patients who qualify for both IPT and ART, ART is the priority. Initiate ART first and start

IPT after one month if stable, or as soon as practically possible.

3) **When can ART be given to a patient on IPT?**
   a) Patients who are receiving IPT and become eligible for ART should **continue with IPT** and be started on ART immediately.

4) **Are there any risks with co-administration of IPT and ART?**
   a) Receiving both IPT and ART does not appear to be associated with an increased risk of developing hepatitis.[11]
      i) Nevirapine may increase the risk of liver toxicity. If this occurs, consider switching nevirapine to efavirenz.
   b) Both isoniazid and stavudine carry a risk of peripheral neuropathy. Change stavudine to tenofovir.

5) **How should patients on IPT and ART be monitored?**
   a) Monitor clinically.
   b) Stop INH immediately if there is evidence of hepatotoxicity and refer.

IPT In Patients With Previous TB

1) **Are patients with a history of previous TB eligible for IPT?**
   a) **Yes**. IPT has been shown to provide benefit to patients who have successfully completed **drug-susceptible** TB treatment.
   b) IPT should not be offered to patients who have completed MDR- or XDR-TB treatment.

2) **When can patients with a history of TB be initiated on IPT?**
   a) Immediately after successful completion of drug-susceptible TB treatment, provided that cure has been documented.
   b) At any time after a previous episode of TB, provided that active TB disease has been excluded.

ASSESSMENT PRIOR TO IPT INITIATION

Exclude Active TB

1) Exclude active TB prior to starting IPT in order to avoid giving one anti-tuberculosis drug to patients with TB disease who require a full treatment regimen.
2) Symptom-based TB screening is sufficient to exclude TB in adults and adolescents with HIV.
3) Answering **"NO"** to the following four questions has been shown to be 98% effective in ruling out active TB disease in high prevalence settings.[12]
   a) Current cough of any duration?
   b) Persistent fever of more than 2 weeks?
   c) Unexplained/ unintentional weight loss of more than 1.5kg in a month?
   d) Drenching night sweats?
4) If a patient answers **"YES"** to any one of these four questions, do not start IPT, but investigate for TB as per National Department of Health diagnostic algorithms.
5) If a patient with TB symptoms is found not to have TB, reassess for IPT in 3 months.

Exclude Contraindications To IPT

1) Confirmed active TB or with signs and symptoms of TB
2) Active liver disease (acute or chronic)
3) Symptoms of severe peripheral neuropathy
4) History of adverse reaction to INH
5) HIV positive but TST negative in pre-ART care
6) Excessive alcohol use
   a) more than 28 units per week for men
   b) more than 21 units per week for women
7) Completion of treatment for MDR- or XDR- TB
8) Illness and/or unstable condition

Should A Tuberculin Skin Test (TST) Be Done?

1) Studies have shown that the benefit of IPT is more pronounced in individuals with a positive TST compared to those with a negative TST.[5,13,14]
2) It is recommended that all asymptomatic PLHIV have a TST in order to determine duration of IPT (see page 14 for duration of IPT based on TST result).
3) If a TST is not available at initiation of IPT, IPT should be started and all effort should be made to perform a TST as soon as possible thereafter.

Should A Screening Chest X-Ray (CXR) Be Done?

1) CXR is not a requirement to initiate IPT.
2) Where chest radiography is available and resources permit, it may be considered in addition to symptom screening, particularly in settings with a high prevalence of undiagnosed TB.

Should An Interferon Gamma Release Assay (IGRA) Be Done Prior To IPT Initiation?

1) Although IGRAs reliably identify TB infection, their role in predicting who will benefit from IPT is unknown.
2) The WHO has therefore not approved their use in resource-limited settings.
3) IGRAs are thus **not recommended prior to starting IPT.**

ADMINISTRATION OF IPT

What Should Be Checked Prior To Starting IPT?

1) Ensure that the patient:
   a) has been declared eligible
   b) has been counselled
   c) is willing to start IPT

What Dose Of INH Should Be Prescribed?

1) INH 5 mg/kg/day (maximum 300mg daily)
   Also give Pyridoxine (vitamin B6) 25mg daily

How Often Should IPT Be Dispensed?

1) Dispense one month's supply at a time for the first 6 months. This is to enable monthly clinical monitoring of patients during the first 6 months.
2) Thereafter, those on long-term IPT can receive 3 months' supply at a time.

How Long Should IPT Be Given For?

1) Data suggests that the initial protective effect of IPT against TB declines in the short to medium term.[14,15] The benefit of IPT has also been shown to be more pronounced in individuals with a positive TST than in those with a negative TST.[5,13,14]

2) Current guidelines base the duration of IPT on the result of the TST.

a) The following table illustrates the duration of IPT in PLHIV:

TST result	Pre-ART	On ART
TST not available	6 months	12 months
TST negative	No IPT	12 months
TST positive	36 months	36 months

b) The following table illustrates the duration of IPT in patients with silicosis:

TST result	Duration
TST not available	6 months
TST negative	No IPT
TST positive	36 months

3) There is currently no evidence for repeating IPT in those who have completed 36 months, or for extending IPT beyond 36 months.

4) If TST is not available at initiation, it must be conducted within ONE month of initiating IPT.

How Long Should IPT Be Given To Inmates In Correctional Centres?

1) IPT should be given for the duration of their incarceration.

Can IPT Be Dispensed With Cotrimoxazole?

1) Cotrimoxazole and INH can safely be co-administered.

Does IPT Have To Be Given As Directly Observed Therapy (DOT) Or Can It Be Self-Administered?

1) IPT is generally self-administered.
2) If a family member is involved in the patient's care, he or she may be enlisted to support adherence.

What Information Should Be Included When Counselling And Educating People On IPT?

1) The importance of treatment compliance.
2) Possible side effects of INH:
   a) symptoms of hepatitis including new-onset vomiting, abdominal pain, jaundice
   b) the need to stop INH and visit the clinic immediately should any of these occur
3) Symptoms of TB disease and the need to visit the clinic should these occur.
4) The fact that while IPT reduces the risk of TB disease, it may still occur.

MONITORING PATIENTS ON IPT

How Often Should Patients On IPT Be Seen?

1) Monthly for the first six months.
   a) This is to ensure close monitoring for TB symptoms and/or adverse reactions during the first six months.
2) Three monthly after the first six months for patients on long-term IPT.
3) These visits should be made to coincide with pre-ART, ART or other chronic care visits if possible, in order to avoid patients having to make multiple visits.

What Should Be Done At Follow-Up Visits?

1) TB symptom screening (for early detection of active TB)
2) On-going counselling and patient education
3) Adherence monitoring (including pill count)
4) Early identification and management of adverse events including hepatitis (nausea, vomiting, right upper quadrant pain), new or worsening peripheral neuropathy, rash
5) Social support and care

What If A Patient Has Symptoms Suggestive Of TB While On IPT?

1) Stop IPT until results of investigations are obtained.
2) Investigate for TB by following the National Department of Health TB diagnostic algorithms.
3) If TB is confirmed:
   a) start standard TB treatment
   b) patient qualifies for cotrimoxazole prophylaxis and ART
4) If TB is not confirmed:
   a) reassess and if no other contraindication, restart IPT

MANAGING TREATMENT INTERRUPTION

1) If treatment is interrupted manage as follows:

Category	Action
Less than 3 consecutive months	• Enquire about the reasons for treatment interruption • Address patient concerns • Counsel the patient on the importance of adherence • Screen for TB • Conduct investigations to exclude TB if signs and symptoms of TB are present • If asymptomatic and no signs of TB disease, continue on IPT and add missed doses of INH to total duration of IPT.
More than 3 consecutive months	• Stop IPT • If the patient returns at any point and commits to restarting IPT, the patient may be reassessed for IPT eligibility and restarted on IPT
Interruption for 2nd time, regardless of duration of interruption	• Stop IPT

When Should IPT Be Discontinued?

1) Discontinue IPT if:
   a) IPT is interrupted for the second time
   b) severe adverse reactions occur
   c) the patient develops TB disease

How Should Patients Be Followed Up Once They Have Completed IPT?

1) PLHIV should be screened for TB at each clinic visit using the 4 item TB Screening Checklist.

- Current cough of any duration?
- Persistent fever of more than 2 weeks?
- Unexplained/ unintentional weight loss of more than 1.5kg in a month?
- Drenching night sweats?

TB AFTER IPT

Is TB That Occurs After Starting IPT More Likely To Be INH Resistant?

1) **No**, current data shows that it is not more likely to be INH resistant.[16,17]

How Should TB Cases That Occur After Starting IPT Be Treated?

1) Patients should be diagnosed, initiated on TB treatment and monitored as per South African TB Guidelines.
2) TB patients who fail to convert their sputum should have sputum collected for drug susceptibility testing as per routine for all patients.

SIDE EFFECTS OF IPT

What Are Common Side Effects Of IPT?

1) Patients taking IPT commonly report minor side effects, usually in the first month of treatment, which include:
   a) increased appetite
   b) headache
   c) itchy skin
   d) joint pains
   e) diarrhoea
   f) nausea and/or vomiting
   g) stomach pains
   h) decreased libido or energy

Are There Any Potentially Serious Side Effects?

1) Potentially serious side effects are uncommon:
   a) hepatitis
   b) hypersensitivity rash
   c) psychosis
   d) convulsions
   e) severe peripheral neuropathy

2) Severe hepatotoxicity and death are rare if INH is stopped as soon as patients develop symptoms suggestive of hepatitis.

How Do I Screen For and Manage Drug-Induced Hepatitis?

1) To detect **symptoms** of hepatitis ask if patient has:
   a) nausea, vomiting, abdominal pain
   b) jaundice (yellow eyes or skin)
   c) light stools or dark urine

2) Signs of hepatitis:
   a) hepatic enlargement
   b) increased liver function tests (LFTs)

3) Educating patients about signs and symptoms of hepatitis assists in early identification of this adverse event.

4) If clinical hepatitis is suspected, stop INH immediately and ensure patient is seen at hospital or by a medical officer.

5) It is not necessary to perform routine LFTs before or during IPT. Studies have shown transient increases in LFTs during IPT that revert to normal and have no clinical significance.

6) If a patient who develops hepatitis is on NVP, switch to EFV.

How Do I Screen For And Manage INH Associated Peripheral Neuropathy?

1) Patient presents with tingling, numbness, burning sensation or pain in the distal extremities, usually in a glove and stocking distribution.
2) Increase pyridoxine to 100 mg/day until symptoms resolve.
3) If the peripheral neuropathy is severe or worsens:
   a) discontinue INH immediately
   b) refer

How Do I Recognise And Manage INH-Induced Hypersensitivity?

1) This is uncommon and usually occurs 3-7 weeks after starting treatment.
2) If the patient develops a mild rash and itch:
   a) treat with antihistamines and follow up
3) If the patient develops raised, itchy rash with or without fever:
   a) discontinue INH until rash resolves
   b) re-challenge after resolution of reaction

- Begin with INH 50mg on day 1. If the original reaction was severe, begin with INH 5mg on day 1.
- If no reaction occurs after the day 1 dose, increase the INH to 300mg on day 2.
- If no reaction occurs after the day 2 dose, continue INH 300mg daily.
- If a reaction occurs during the re-challenge, stop INH.

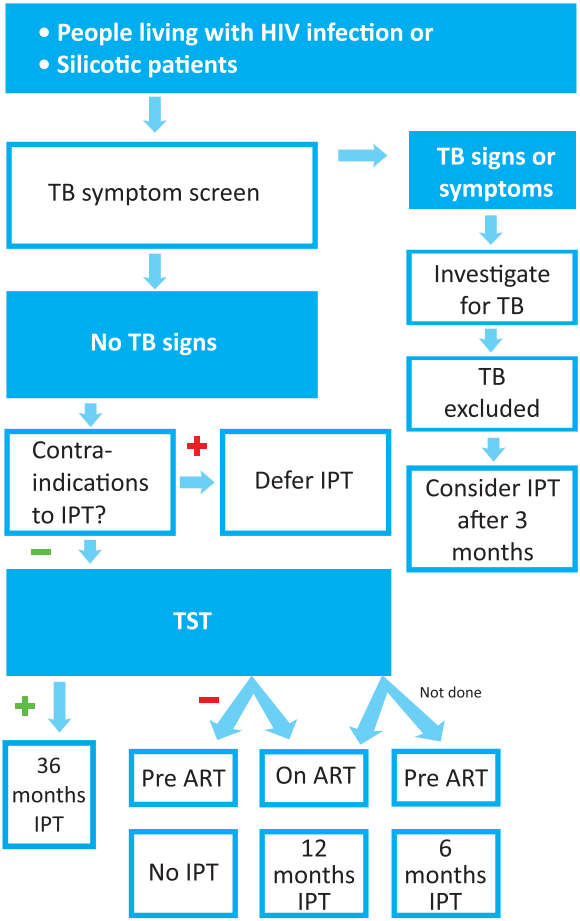
How Do I Manage Gastrointestinal (GIT) Side-Effects?

1) GIT side-effects are uncommon at recommended daily doses.
2) Nausea, vomiting and diarrhoea may occur.
3) Management:
   a) Exclude other causes of nausea and vomiting
   b) Consider doing LFTs to exclude hepatic dysfunction
   c) If no other cause is found, treat symptomatically

What Do I Do If Other Serious Side Effects Occur?

1) Other serious side effects include seizures, psychosis and rash.
2) Stop INH and treat the symptoms and/or refer depending on the severity of the symptoms

SCREENING ALGORITHM IN ADULTS



IPT IN CHILDREN

ELIGIBILITY

Which Children Are Eligible For IPT?

1) Where a TB contact has been identified and once active TB disease has been excluded, the following children should receive IPT:
   a) All children under 5 years of age (irrespective of HIV status)
   b) All HIV-infected children under 15 years of age
2) **NOTE:** Children under 2 years of age, regardless of HIV status, staying with their mothers in correctional centres should receive IPT

Can Children Who Have Not Been Exposed To TB Receive IPT?

1) **No**. Pre-exposure IPT is not recommended in children, regardless of HIV status.
2) Exposure is evidenced by:
   a) Close contact with an infectious PTB case, or
   b) TST positive in absence of previous TB or IPT

How Should TB Be Excluded In Children?

1) Ask about the following:
   a) Current cough or wheeze >2 weeks, not improving on treatment

b) Persistent fever for >2 weeks
c) Documented weight loss or failure to thrive (check RTHC)
d) Fatigue (less playful or always tired)
e) History of close contact with an adult or adolescent with infectious TB (smear/culture positive)

2) If any one of the above is present, investigate for active TB.
3) If there is any suspicion that the patient has active TB disease, do not start IPT.

Can IPT Be Repeated In Children?

1) Yes. Children, who complete a course of IPT and are re-exposed to TB, must have another course of IPT with each new exposure to an infectious TB case, after active TB disease is excluded.
2) IPT can be repeated irrespective of the interval between completion of TB treatment and re-exposure.
3) If re-exposed to an infectious TB source case while on IPT, continue IPT for as long as the source case remains infectious.

Should Children Who Have Completed TB Treatment Receive IPT?

1) Children who have successfully completed TB treatment should not routinely receive 6 months of IPT.

Exclude Contraindications To IPT

1) Do not give IPT in the following circumstances:
   a) Hypersensitivity to INH
   b) Prior INH-associated hepatic injury
   c) Acute hepatic disease
2) Exercise caution in the following circumstances:
   a) Hepatic impairment
   b) Severe renal impairment
   c) Peripheral neuropathy

ADMINISTRATION OF IPT

What Dose Of IPT Should Be Used In Children?

1) INH 10mg/kg/day (maximum dose 300mg/day)
   Also give:
   Pyridoxine 25mg daily (> 5 years of age)
   Pyridoxine 12.5mg daily (< 5 years of age)
2) If INH is unavailable in syrup form, tablets may be used. The 100mg tablets can be broken and dissolved in water or multi-vitamin syrup.
3) The following weight-based dosing table can be used:

Dosage recommendations for INH preventive therapy in children	
Body weight (kg)	**Daily INH 100 mg tablet**
2.0 - 3.4	¼ tablet
3.5 - 4.9	½ tablet
5.0 - 7.4	¾ tablet
7.5 - 9.9	1 tablet
10.0 - 14.9	1½ tablets
15.0 - 19.9	2 tablets
≥20.0	3 tablets

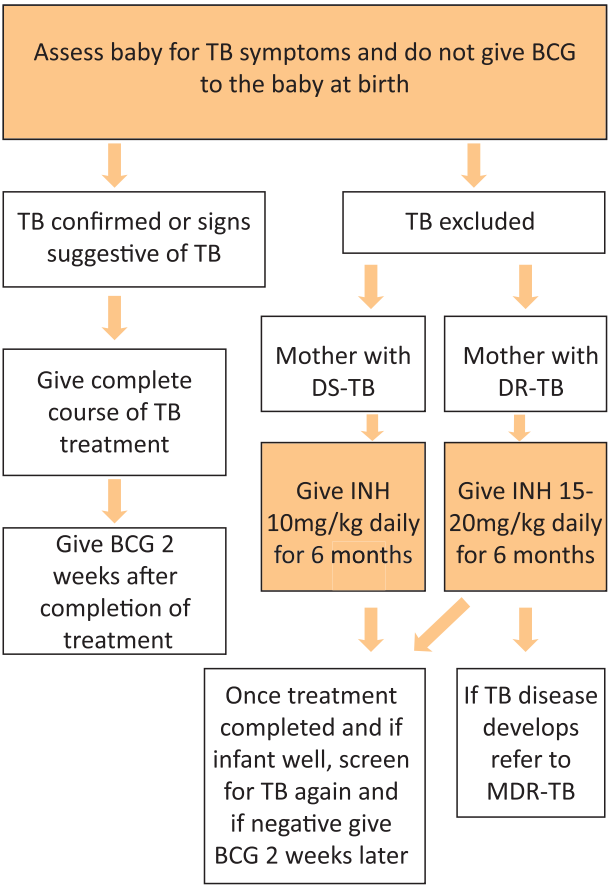
What Is The Duration Of IPT In Children?

1) IPT in children is given for 6 months.

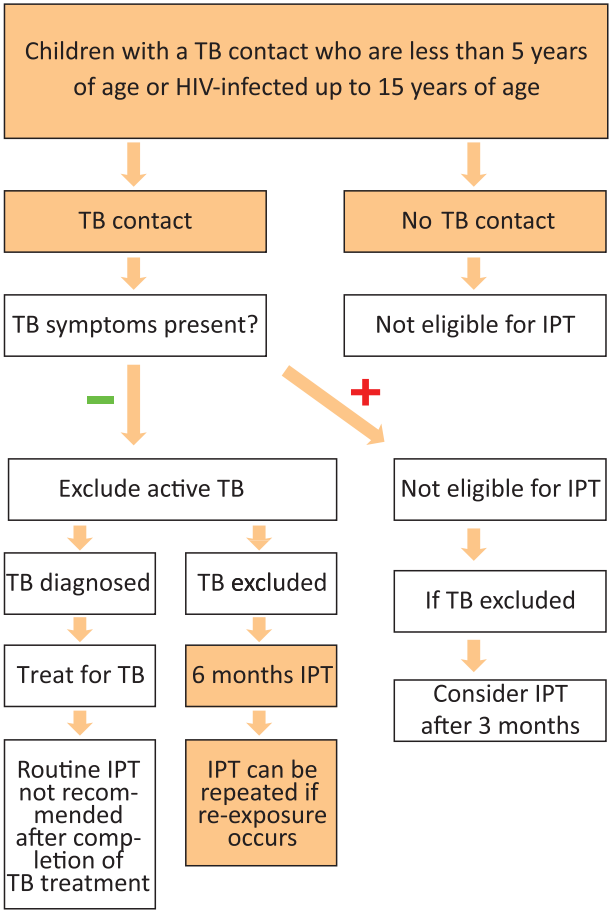
Preventive Therapy For Drug-Resistant TB In Children

1) Contacts of source cases with **MDR-TB/XDR-TB**:
   a) A trial of a 12 month fluoroquinolone-based regimen for latent MDR-TB infection was found to be safe and well tolerated, and no TB cases occurred in those treated
   b) Consult an expert regarding use of preventive therapy
   c) Follow-up closely for 2 years and ensure household infection control practices are observed
2) Contacts of source cases with **isoniazid mono-resistant TB:**
   a) Give rifampicin 10-15mg/kg daily for 4 months
3) Contacts of source cases with **rifampicin mono-resistant TB** (must be confirmed by culture-based drug susceptibility test results confirming RIF resistance and INH susceptibility and not just GeneXpert RIF resistance):
   a) Give isoniazid 10mg/kg daily for 6 months

BABIES BORN TO MOTHERS WITH ACTIVE TB



SCREENING ALGORITHM IN CHILDREN



TUBERCULIN SKIN TEST

HOW TO PERFORM A TST

Administration

1) Preparation

a) Gather the following equipment:

- Tuberculin purified protein derivative PPD-RT23 2TU or PPD-S 5TU (check expiration date)
- Tuberculin syringe with a short bevel
- Alcohol swabs
- Pen
- Sharps container

b) Discuss with patient:

- Explain the procedure
- Ensure that the patient is able to return in 48-72 hours

2) Procedure

a) Wash hands prior to the procedure

b) Choose and clean injection site:

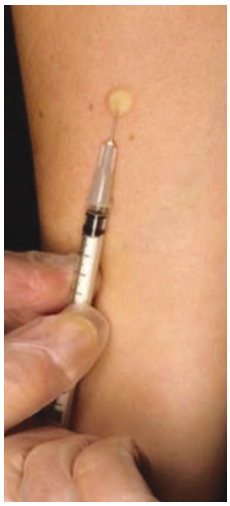
- Place the left forearm palm up on a well-lit surface
- Locate an area midway between the elbow and wrist, which is free of scars and sores
- Clean the area with an alcohol swab and allow to dry

c) Prepare the tuberculin:

- Draw up 0.1 ml of tuberculin

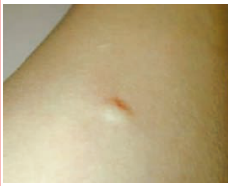
d) Inject tuberculin:

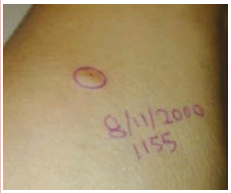
- Insert the needle slowly, keeping it almost parallel to the skin
- The needle bevel should face upwards and be visible just below the skin surface
- Ensure injection goes into the skin (intradermal) and not under the skin
- Inject the tuberculin – a tense, pale wheal should appear as you inject
- Dispose of the needle and syringe in the sharps container



e) Check injection Site:

- A flat wheal of 8-10mm in diameter should be visible
- If not, the tuberculin has been injected too deeply
- Repeat the injection at a site at least 5cm away or on right forearm
- If the wheal is visible, a pen can be used to draw a wide circle around the site to indicate the area.





f) Discuss the following with the patient:

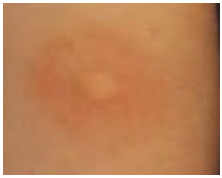
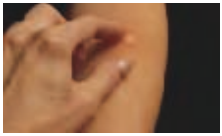
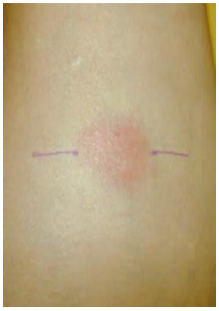
- Ensure that the patient has the return date
- Explain care of the site:
  - Keep clean and dry
  - Avoid use of creams, lotions or bandages
  - Getting the site wet with water is not harmful, but do not wipe or scrub

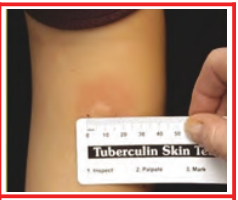
g) Record the relevant information including:

- Date
- Time
- Location of injection

Reading

The TST must be read 48-72 hours after administration. If the patient does not return within this time frame, the test must be repeated.

1) Gather the following equipment: • Pen • Clear flexible ruler	
2) Inspect the site: • Inspect the site under good light • Identify induration (hard, dense, raised formation)	
3) Palpate induration: • Palpate the edges of the induration with your fingertips • The area of induration and not redness (erythema) is measured	
4) Mark the induration: • With the pen, draw horizontal lines from the periphery towards the edge of the induration • The raised edges of the area of induration will prevent the pen from drawing onto the indurated area	

5) Measure the diameter of the induration: • Use the ruler to measure the widest transverse diameter in millimetres	
6) Record the diameter of the induration: • Record the measurement in millimetres • Do not record as positive or negative • If no induration, record as 0mm	

Interpretation

1) Decide on whether the TST result is positive or negative based on the following table:

Immune status	HIV-infected/ Severe Malnutrition	HIV-uninfected
Diameter of induration	5mm or more	10mm or more

2) Consider the following causes of false negative TST results:

a) HIV infection
b) Severe malnutrition
c) Severe viral infections (e.g. measles, chicken pox)
d) Cancer
e) Immuno-suppressive drugs (e.g. steroids)
f) Severe disseminated TB

3) Consider the following causes of false positive TST results:

a) Non-tuberculous Mycobacterium
b) Prior BCG vaccine

REFERENCES

REFERENCES

This document is based on the following guideline:

GUIDELINES FOR ISONIAZIDPREVENTIVE THERAPY IN SOUTH AFRICA, 2014

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