3. Management of Latent TB Infection

An estimated one-third of the world's population is infected with *M. tuberculosis*. Some of these infections are latent TB infections (LTBI) i.e. when the bacteria remain inactive in the body, although they can be reactivated later. People with LTBI have no symptoms and are not infectious but they usually have a positive TST or IGRA and may develop active TB disease if not treated. Approximately 10-15% of those presumed infected may eventually develop the active disease at some point in their lives. Approximately 50% of those persons who develop clinical disease do so within five years of the initial infection, with the remaining 50% reactivating over ensuing years.[26]

If co-morbidity develops impairing the immune system e.g. HIV infection, this risk further increases. In cases where there is a long period documented between the exposure and the development of disease, dormant bacilli are thought to remain in either the lung or other sites, which can be 'reactivated' if favourable circumstances for the organism occur. However not everyone with LTBI will develop active TB disease. The majority of exposed persons will kill off the TB bacteria and will be left only with a positive skin test as a marker of exposure.

LTBI should be treated to prevent the development of active TB disease with its associated risk of the spread of TB and the development of outbreaks. Treatment of people with LTBI, including those with HIV co-infection, effectively reduces the risk of progression to active TB disease. However, there is no accurate tool to predict which individuals with LTBI are at greatest risk of developing active disease.

A person with LTBI usually has a positive TST or IGRA but no physical findings of TB disease and the chest X-ray is normal or only reveals evidence of healed infection i.e. granulomas or calcification in the lung, hilar lymph nodes or both. Persons with LTBI can develop TB disease later in life.

The following table outlines the difference between LTBI and active TB disease (table 3.1).

Table 3.1: Differences between LTBI and active TB disease

A person with latent TB infection	A person with active TB disease
No symptoms	Has symptoms which may include • Unexplained productive cough lasting 3 weeks or more • Chest pain • Productive cough/haemoptysis • Weakness or fatigue • Weight loss • Anorexia • Chills • Fever • Night sweats
Usually have a positive skin test or blood test	Usually have a positive skin test of blood test
Sputum is TB smear and culture negative	May have a positive sputum smear/culture
Normal chest X-ray or evidence of healed infection	May have an abnormal chest X-ray
Not infectious	May be infectious

3.1 Epidemiology of LTBI

In the USA, it is estimated that approximately 10 to 15 million persons have LTBI. Particularly high rates of infection are found among the urban poor such as intravenous drug users and homeless persons.[78;79] The elderly also have high rates of positive TST tests attributable to the much higher risk of TB infection during

their youth. Among the foreign-born, prevalence of infection is correlated with incidence of TB in their country of origin and the age of immigration.

The contacts of active TB cases also have a high prevalence of TB infection with the risk of infection being higher if the index case is pulmonary sputum smear positive or if the contact is close. However, absolute levels of risk have been estimated in relatively few of the studies that measured the prevalence of infection in non-contacts in the general population.[36]

In 2005, a study was undertaken in a large Dublin teaching hospital which reviewed the screening data for two groups of persons, namely new employees (n= 2,410) and a high-risk group of HIV positive patients attending the hospital (n= 331).[80] Cases with positive TSTs were offered chest X-rays and if clear of TB were categorised as LTBI. The study found that 31.7% of the HCWs had LTBI while 11% of the HIV positive group had LTBI.

There is little information in relation to the prevalence of LTBI in Ireland.

Diagnosis of LTBI

There is no gold standard test for LTBI and therefore diagnosis of active or latent TB involves a number of tests. In asymptomatic persons, exposure to and potential infection with TB can be demonstrated by a positive TST or a positive IGRA. In practice, the TST is the standard method of determining whether a person is infected with *M. tuberculosis*. Reliable administration and reading of the TST requires standardisation of procedures, training, supervision and practice. Individuals with positive skin tests are regarded as having been infected with TB. Neither TST nor IGRA can distinguish active TB disease from LTBI. Further details on the diagnosis of LTBI i.e. TSTs, IGRA and chest X-rays are outlined in chapter 2.

3.2 Risk Factors for LTBI

TB may be transmitted from a person with active TB disease and is much more likely to be transmitted from an active respiratory TB case. However, some individuals are more likely than others to develop TB infection when exposed. The most important risk factors for developing TB infection are the extent of the exposure and the infectivity of the source case.[52] Risk factors for developing TB infection are outlined as follows:

- **Closeness of contact with a source case:** close contacts at greatest risk
- **Duration of exposure to a source case:** brief exposure carries low risk
- **Sputum status of source case:** sputum smear positive case carries greatest risk
- **Extent of pulmonary disease of source case:** cavitation and cough carry greatest risk
- **Laryngeal TB:** carries the highest transmission risk
- **Age:** prevalence increases with age but incidence is highest in young children. In young children, the risk of disease after infection is up to 40%[81]
- **Cough frequency of source case:** higher cough frequency results in higher risk. However, cough frequency is a less statistically significant indicator of infectivity than extent of disease or bacteriological status
- **Delay in diagnosis or appropriate treatment of source case:** effective chemotherapy of the source case progressively reduces infectiousness (and therefore risk to contacts)
- **Open skin TB abscess:** dressing or irrigation of an open abscess can lead to infection
- **Residence in institutions.**

Risk factors for LTBI progressing to active TB disease

The risk of an individual with latent TB developing active TB varies depending on a number of factors (tables 3.2 and 3.3).[52]

Table 3.2: Risk factors for developing active TB disease following LTBI

Risk factor	Comment
Time since infection	Risk is highest in the first two years after infection
Age	Inverse association: Peaks in increased risk occur in the preschool years and adolescence/early childhood
Dose of infection	Risk higher if the source case is smear positive; less if smear negative/ culture positive; minimal if culture negative
Size of tuberculin reaction	The larger the reaction the greater the risk of subsequent disease. However, there is a substantial degree of variation in the extent of increased risk associated with larger tuberculin reactions (table 2.1, chapter 2)[82]
Predisposing medical conditions	HIV is the strongest risk factor. Other risk factors include: chronic renal failure or receiving haemodialysis, diabetes, haematological malignancy, jejeunoileal bypass or gastrectomy, silicosis, alcoholism and drug addiction including injecting drug users and solid organ transplantation
Immunosuppressive treatment	Current or recent oral steroids, some cancer therapy, immunosuppressive drugs, receiving Tumour Necrosis Factor-α (TNF-α) antagonist treatment
Immigrants who have recently arrived from a high incidence country	Risk is highest in the first two years[83;84]
Body weight	There is an increased risk associated with being underweight or malnourished

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Table 3.3 Risk factors for the development of active TB among persons infected with *M. tuberculosis*[30]

Risk Factor	Estimated risk of TB relative to persons with no known risk factor
High Risk	
AIDS	110-170[85]
HIV infection	50-110[6]
Transplantation (related to immunosuppressant therapy)	20-74[86]
Silicosis	30[87]
Chronic renal failure requiring haemodialysis	10-25[88]
Carcinoma of head and neck	16[89]
Recent TB infection (≤2 years)	15[90]
Abnormal chest X-ray – fibronodular disease	6-19[91]
Increased risk	
Treatment with glucocorticoids	4.9[92]
Tumour necrosis factor (TNF)- alpha inhibitors	1.5-4.0[93]
Diabetes mellitus (all types)	2.0-3.6[94]
Underweight (<90% ideal body weight; for most persons this is a body mass index ≤20)	2.0-3.0[95]
Young age when infected (0-4 years)	2.2-5.0[96]
Cigarette smoker (1 pack/day)	2.0-3.0[97]
Abnormal chest X-ray - granuloma	2.0[98]
Low risk	
Infected person, no known risk factor, normal chest X-ray ("low risk reactor")	1.0[99]

Source: Canadian Tuberculosis Standards, 6th Edition. Public Health Agency of Canada, 2007. Reproduced with the permission of the Minister of Public Works and Government Services, 2009. Available at www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf

Among persons with LTBI, dual infection with HIV is the most important risk factor for the development of TB disease.[30]

3.3 Selecting People for Treatment of LTBI

The rationale for the treatment of LTBI is to kill any residual dormant (inactive) bacilli, thus reducing or preventing the reactivation and development of TB disease. With treatment of LTBI, the number of persons who go on to have TB disease may be significantly diminished. This is an important part of TB control. If active TB has been excluded by chest X-ray and examination, then the decision to treat LTBI should be based on an assessment of the individual's situation.

High-risk individuals fall into two categories:

1. Persons presumed to have been recently infected and
2. Persons whose underlying medical conditions substantially increase their risk of developing active TB.

A multidisciplinary team approach including the patient should be adopted in the treatment and management of persons with LTBI. The assessment criteria before deciding whether to treat or not include:

- How likely is it that a person has been infected?
- How likely is it that disease will develop? (table 3.3)
- What are the risks of an adverse reaction to treatment?
- What is the likely adherence to treatment?

It is recommended that all age groups in priority groups 1 to 5 listed below should be considered for treatment of LTBI. This is similar to the US strategy for treatment of LTBI which recommends no age limits as the risk of severe fatal hepatoxicity from treatment with anti-TB drugs is considered low even in those aged over 35 years and if testing and treatment are targeted at these high risk groups then the risk: benefit ratio should be acceptable.[100] Recommendations for LTBI treatment in priority groups 6 to 9 are also listed below.

The following groups should be prioritised for the treatment of LTBI [see table 2.1 for TST (Mantoux) cut off points for treatment of LTBI in these groups]:

1. Recent converters
2. HIV positive individuals
3. Those aged less than five years
4. Persons receiving immunosuppressive therapy i.e. Tumour Necrosis Factor-α (TNF-α) antagonists
5. Persons with evidence of old healed TB lesions on chest X-ray i.e. fibronodular disease/non-calcified fibrotic lesions (if not previously treated or if treated, not adequately treated) [30;77]
6. Foreign-born persons from countries with high TB endemicity#
7. Homeless persons
8. Intravenous drug users
9. HCWs.

The risk of isoniazid toxicity has been shown to increase with age in particular in persons aged 55 years and older. [77]

Recommendation:

Groups 1-5: LTBI treatment should be offered to those in all age groups

Groups 6-8: LTBI treatment should be offered to all those aged ≤ 55 years if supervised treatment (DOT)†† is available. Otherwise it should be offered to those aged ≤35 years. These groups should be closely monitored for isoniazid toxicity[77]

Group 9: The age limit for LTBI treatment should be assessed on a case-by-case basis i.e. treat all HCWs where the risk of progression from LTBI to TB disease is high regardless of age. Where the risk of progression is low, the upper age limit is ≤35 years (chapter 9)

All others not mentioned above: The upper age limit should be ≤35 years

Care should be taken when prescribing LTBI therapy for those with co-morbidities which increase the likelihood of hepatotoxicity.

Management of Persons Exposed to Infectious TB after Previous LTBI Treatment

Very high risk severely immunocompromised persons (e.g. those with HIV infection) who are re-exposed to TB infection, having already completed a satisfactory course of LTBI therapy should be considered for a repeat course of treatment for LTBI. If questions arise regarding risk of TB following repeat LTBI, referral to a respiratory physician or an infectious disease consultant is recommended. [30]

Countries where the annual rate of TB disease is ≥40 cases/100,000 population

†† A way of helping patients to take their medicine for TB. A person receiving DOT will meet with a healthcare worker everyday or several times a week at an agreed place e.g. the patient's home, the TB clinic or other convenient location. The healthcare worker will observe the patient taking their medication at this place helping to ensure that higher treatment completion rates are achieved. Sometimes someone in their family or a close friend will be able to help in a similar way to the healthcare worker. Further definitions are available in the glossary of terms.

3.4 Treatment of LTBI

The choice of treatment regimen for LTBI will depend on:

- The presence or absence of risk factors for progression to TB disease
- An assessment of the likely adherence level of the patient and the amount of time available for completion of the patient's treatment
- The antibiotic susceptibility of the presumed source case
- Drug tolerance of the patient.

Poor adherence is the most important reason for the failure of LTBI treatment. Many people with LTBI do not complete treatment as most are not sick and may not feel the urgency to complete the prolonged therapy. Directly observed therapy (DOT) for LTBI is an excellent method for promoting adherence to treatment.[77] Because of limited resources, DOT (supervised therapy) for LTBI cannot be offered to all persons on LTBI treatment, however, it should be provided to those in the priority groups 6, 7 and 8 mentioned above.

However, for all others receiving LTBI treatment, a great deal can be accomplished to improve adherence by developing a relationship based on trust and support between the healthcare worker and patient.[30] Barriers to adherence should be addressed and overcome (appendix 4)[77]

Recommendation:

Directly observed therapy (DOT) should be provided for those being treated for LTBI in groups 6, 7 and 8 above i.e. immigrants from areas of high TB endemnicity, homeless persons and intravenous drug users.

Recommendation:

It is recommended that audits of compliance with LTBI therapy are undertaken.

Treatment of LTBI in adults

The effectiveness of isoniazid in preventing progression from LTBI to active TB disease was first reported in 1957 and has been confirmed by many studies since. Isoniazid is the most widely used anti-TB agent as it is relatively non-toxic, easily administered and inexpensive.

Similar treatment regimens for LTBI in adults are recommended by the UK[26] and New Zealand.[52]

The NICE guidelines[26] recommend that non HIV-infected adults are treated with either (i) six months of isoniazid or (ii) three months of rifampicin and isoniazid **or** six months of rifampicin for contacts of isoniazid resistant TB cases. This recommendation applies to persons aged 16-35 years and to persons older than 35 years for whom treatment of LTBI is recommended. These recommendations are based on a Cochrane review of randomised trials of isoniazid of at least six months duration which were placebo controlled with at least two years follow up.[101] This review states that the efficacy of treatment increased with the duration of treatment but that the efficacy of six months or 12 months did not vary significantly. In fact, the small advantage of 12 months over six months may not be worthwhile except in those individuals at high risk of developing TB.

The American Thoracic Society (ATS) 2000[34], Canadian (2007)[30] and New York guidance (2008)[77] recommend similar treatment regimes of daily isoniazid for nine months. Alternatively, a regime of rifampicin for four months may be used if isoniazid is contraindicated due to a history of an isoniazid-

induced reaction or for a contact of an isoniazid resistant-TB case or if the patient may not be able to adhere to therapy for a six to nine month period.

ATS guidelines state that although nine months of isoniazid was the preferred regimen for the treatment of LTBI, a six month regimen also provides substantial protection and has been shown to be superior to placebo in both HIV negative and HIV positive persons. However, treatment for six months rather than nine months may provide more favourable outcomes from a cost effectiveness standpoint.[34]

The rationale for the ATS recommendations was based on evidence from randomised controlled clinical trials that assessed the benefits of isoniazid. These studies showed that isoniazid was effective in preventing TB disease. Most of the studies compared isoniazid for 12 months with placebo. However, one trial, conducted by the International Union Against Tuberculosis and Lung Disease (IUATLD), was designed to evaluate various durations of isoniazid and this indicated that a 12 month regimen provided a substantial reduction in risk compared with a six month regimen among compliant persons with small lesions.[102] A further reanalysis of data from community studies in Alaska indicated that the protection conferred by taking at least nine months of isoniazid was considered greater than taking six months but it was not likely that further protection was conferred by extending the duration of treatment from nine to 12 months.[103]

Based on a review of the evidence and guidance in the international literature and by consensus of the National TB Advisory Committee, the following are the recommended treatment regimens for LTBI in adults:

Recommendation:

The recommended treatment regimens for LTBI in adults are:

(i) Isoniazid for a minimum of six months with an optimum duration of nine months

or

(ii) Rifampicin for four months

or

(iii) A combination of rifampicin and isoniazid for a duration of at least three months with an optimum of four months.

Treatment of LTBI in children

The US Centers for Disease Prevention and Control (CDC) defines paediatric TB as occurring in persons aged less than 15 years.[104] LTBI in a child can be defined as a child or adolescent with a positive TST who has no evidence of TB disease.

Infants and young children under the age of five years with LTBI have been only recently infected and therefore are at a higher risk of progressing to active TB disease. The literature suggests that 40% of untreated infants will develop active TB disease although the risk of progression decreases throughout childhood.[105] These children are also more likely than older children and adults to develop life-threatening forms of TB disease in particular meningeal and disseminated disease. Among children the efficacy of treatment of LTBI with isoniazid approaches 100% with appropriate adherence to therapy. Hepatotoxicity from isoniazid in infants and children is rare and in general children tolerate the drug better than adults.[106]

International recommendations for treatment of LTBI in children

The American Academy of Pediatrics and CDC convened the Pediatric Tuberculosis Collaborative Group. This group produced a consensus document which stated that treatment is recommended for all children and adolescents diagnosed with LTBI because:[105]

- The drugs used are safe in the paediatric population
- Infection with *M. tuberculosis* is more likely to have been recent

- Young children are at a higher risk of progression to TB disease and
- The paediatric population has more years to potentially develop TB disease.

The Pediatric Tuberculosis Collaborative Group also recommended:

- TB disease should be excluded by chest X-ray and examination before initiating treatment for LTBI
- That the regimen for treatment of LTBI in children and adolescents should be isoniazid either daily or twice weekly for nine months and
- That if the source case is isoniazid resistant, rifampicin should be used daily for six months.

The collaborative group recommendations were based on clinical trials, which showed that treatment of LTBI in children with isoniazid therapy reduces the risk of progression to active disease.[34] The only published efficacy trials of treatment of LTBI in children are for isoniazid alone with a recommended regimen for treatment of LTBI in HIV non-infected children of a nine month course of isoniazid daily or twice weekly by DOT.

Based on a review of the evidence and guidance in the international literature and by consensus of the National TB Advisory Committee, the following are recommended treatment regimens for LTBI in children:

Recommendation:

The recommended treatment regimens for LTBI in children are:

(i) Isoniazid for a minimum of six months with an optimum duration of nine months

or

(ii) Rifampicin for six months

or

(iii) A combination of rifampicin and isoniazid for a duration of four months.

Physicians experienced in the management of children with LTBI should supervise treatment.

3.5 Treatment of Multidrug-Resistant or XDR LTBI

A source case can be sputum smear positive for MDR-TB or XDR-TB and therefore contacts have to be managed in the appropriate manner. The WHO recommends that close contacts of MDR-TB or XDR-TB patients should receive careful clinical follow-up for a period of at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB or XDR-TB is recommended. On the basis of currently available evidence, WHO does not recommend the universal use of second-line drugs for chemoprophylaxis in MDR-TB or XDR-TB contacts.[107] It is also recommended that the management and follow-up of contacts aged <5 years is undertaken in consultation with a physician who has expertise in this area.

Recommendation:

Consultation with a respiratory physician or infectious disease consultant should be sought for the management of all persons with active TB or LTBI who have been exposed to patients with MDR-TB or XDR-TB.

For treatment of LTBI in HIV infected persons, see chapter 10.

3.6 Pre-treatment Evaluation

The pre-treatment evaluation (figure 3.1) of persons who are targeted for treatment of LTBI provides an opportunity for healthcare providers to:

- Establish a rapport with the patient
- Discuss details of the patient's risk of TB
- Emphasise the benefits of treatment and the importance of adherence to the drug regimen
- Review possible adverse effects of the regimen, including interactions with other drugs, and
- Establish an optimal follow up plan.

The evaluation should include an interview conducted in the patient's primary language with the assistance of qualified medical interpreters, if necessary.

The patient history should document:

- Risk factors for TB
- Prior treatment for TB or LTBI
- Pre-existing medical conditions that may be contraindications to treatment or are associated with an increased risk for adverse effects from treatment and
- Current and previous drug therapy, with particular attention to previous adverse reactions to drugs and to current drugs which may interact with LTBI treatment e.g.
    - Isoniazid: interacts with antacids (decrease absorption of isoniazid)
    - Phenytoin and carbamezapine (isoniazid decreases metabolism of these drugs hence leading to increased blood levels); and corticosteroids (concentration of isoniazid possibly reduced by corticosteroids)
    - Rifampicin: causes reduced levels of many drugs including warfarin, methadone, oral contraceptive pill, oral hypoglycaemic agents, theophylline, ketoconazole, dapsone, PIs and NNRTIs) (figure 3.1).[77]

Recommendation:

Clinicians may choose to undertake baseline liver function tests (LFTs) for all patients aged over 14 years at the start of treatment for LTBI. However, this is not universally obligatory.

However, baseline LFTs **should be done** on the following persons prior to commencing therapy for LTBI:

1. Everyone over the age of 35 years
2. All HIV-infected persons
3. Pregnant or post-partum women (up to 2-3 months postpartum)
4. Those with a history of hepatitis, liver disease or heavy alcohol ingestion
5. Injecting drug users
6. Those on treatment with other potential hepatotoxic agents.

All patients prescribed a rifampicin-containing regime should have a baseline full blood count and platelets.[52;77]

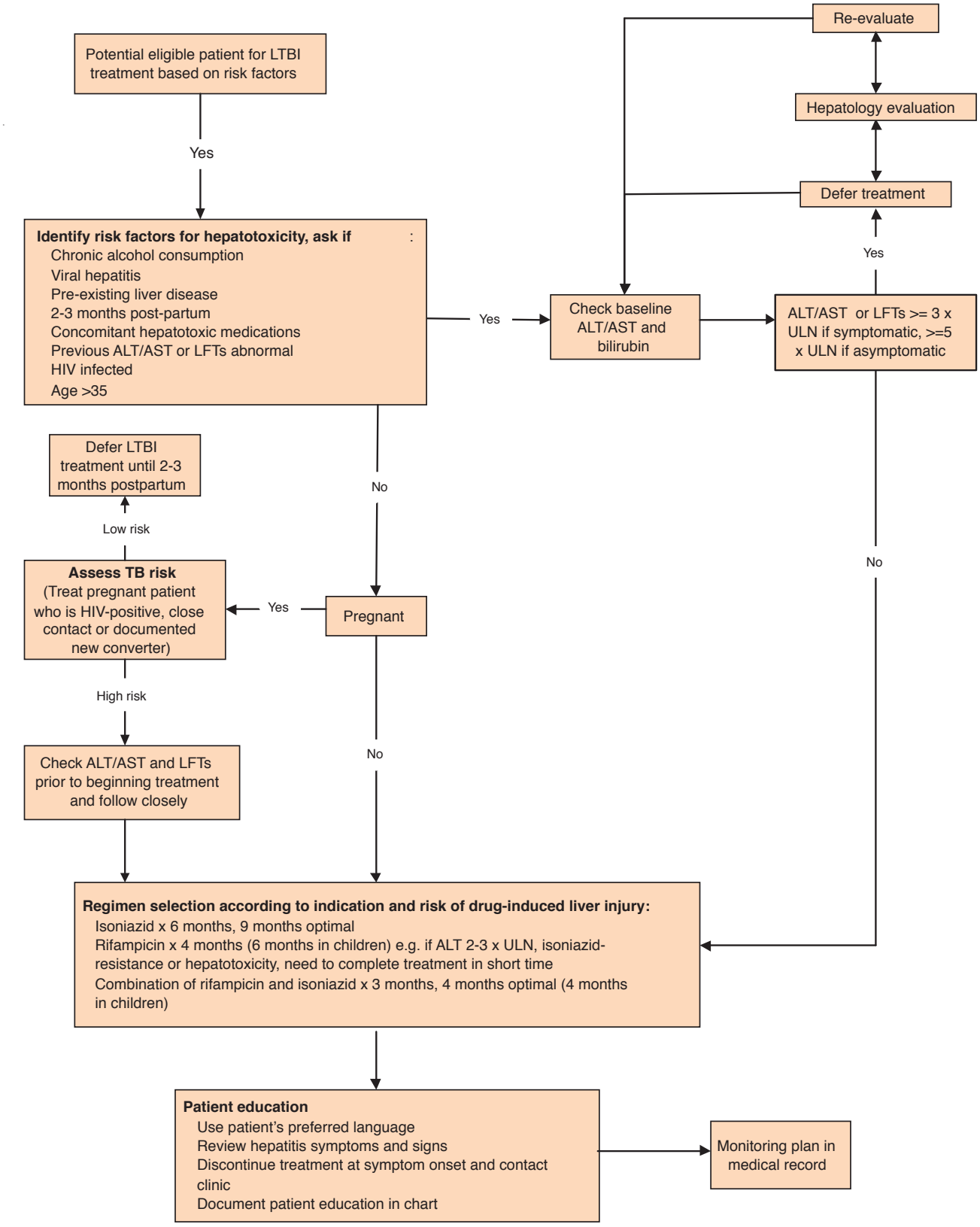
Patients with baseline transaminases of more than three times the upper limit of normal (ULN)[‡‡] should have the ALT and bilirubin retested. Screening for viral or other causes of hepatitis including alcohol and hepatotoxic drugs should also be undertaken. In this situation, the decision to treat LTBI or more likely to defer treatment should be carefully made on a case-by-case basis weighing the risk of progression to TB disease against the risk of isoniazid or rifampicin drug induced liver injury (DILI). Factors influencing the risk

[‡‡] The upper limit of normal (ULN) used should be that of the laboratory performing the assay.

of DILI include the degree of baseline ALT elevation, alcohol consumption, increasing age and evidence of active replication of the hepatitis virus.

If LTBI treatment is started, some experts recommend measuring the serum transaminases and bilirubin concentrations every 2 to 4 weeks for the first 2 to 3 months of treatment. The international normalised standard (INR) may be followed periodically as well in patients with severe hepatic impairment.[108]

Figure 3.1: Latent tuberculosis infection (LTBI) pretreatment clinical evaluation and counselling*



ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFTs = liver function tests; ULN = upper limit of normal

* Adapted from the New York City Department of Health and Mental Hygiene TB guidelines

3.7 Drug Regimens for LTBI

Isoniazid is used alone for preventive therapy for a minimum of six months with an optimum duration of nine months. The drug is given in a single daily dose of 5mg/kg (max dose: 300mg) per day for adults and 5-10mg/kg (max dose: 300mg daily) for children.[77] Ideally, anti-TB therapy for the treatment of LTBI should be dispensed in monthly allocations. However in some situations, if the clinician or public health doctor deems it appropriate it may be dispensed at less frequent intervals e.g. every two months. If isoniazid cannot be given daily, it can be given twice weekly in a dose of 15mg/kg (up to 900mg) for adults and 20-30mg/kg (up to 900mg) for children (see table 3.4).[77;109]

For persons intolerant to isoniazid or who are likely to be infected with isoniazid resistant organisms, rifampicin for four months may be used (see table 3.4).

Dosages for drugs commonly used for treatment of LTBI are outlined in table 3.4. For treatment with other drugs, referral to a clinician experienced in TB is advised, particularly for contacts of MDR-TB cases (section 3.5).

Table 3.4: Drug Regimens for LTBI

Drug and duration	Dosage		Major adverse reactions	Comments
	Daily	Twice weekly	Recommended monthly monitoring[1]	
Isoniazid Children: 6 months optimum Adults: 9 months optimum	**Children:** 5-10mg/kg (max 300mg) **Adults:** 5mg/kg (max 300mg) **Completion Criteria:** 270 doses within 12 months	**Children:** 20-30mg/kg (max 900mg) **Adults:** 15mg/kg (max 900mg) **Completion Criteria:** 76 doses within 12 months	**Symptoms:** Unexplained anorexia, nausea, vomiting, dark urine, jaundice, persistent fatigue, weakness, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, rash, persistent paresthesias of the hands and feet, arthalgia **Signs:** Elevated LFTs, hepatitis, icterus, rash, peripheral neuropathy, increased phenytoin levels and possible interaction with disulfiram **Clinical evaluation:** LFTs (if baseline is abnormal or patient has risk factors for toxicity)[2]	**Preferred regimen for all individuals** Vitamin B6 (25mg/day) or pyridoxine may decrease peripheral and CNS effects, and should be used in patients who are: - Abusing alcohol - Pregnant - Breastfeeding infants on isoniazid - Malnourished Or who have - HIV - Cancer - Chronic renal or liver disease - Diabetes - Pre-existing peripheral neuropathy *Note: aluminium-containing antacids reduce absorption*

Table 3.4 contd.

Drug and duration	Dosage		Major adverse reactions	Comments
	Daily	Twice weekly	Recommended monthly monitoring[1]	
Rifampicin Children: 6 months Adults: 4 months	**Children:** 10-20mg/kg (max 600mg) **Completion criteria:** 182 doses within 9 months **Adults:** 600 mg (range: 8-12 mg/kg) (max: 600mg) **Completion criteria:** 120 doses within 6 months	**Children:** not recommended **Adults:**[3] 600mg (range 8-12 mg/kg) (max 600mg) **Completion criteria:** 34 doses within 6 months	**Symptoms:** Nausea, vomiting, rash, fever or flu-like symptoms, easy bruising. **Signs:** Elevated LFTs, hepatitis, rash, thrombocytopenia Reduced levels of many drugs including methadone, warfarin, hormonal contraception, oral hypoglycaemic agents, theophylline, dapsone, ketoconazole, PIs and NNRTIs **Clinical evaluation:** - LFTs (if baseline is abnormal or patient has risk factors for toxicity)[2] - Complete blood count, including platelets as needed	May be used to treat persons who have been exposed to isoniazid-resistant, rifampicin-susceptible TB, or who have severe toxicity to isoniazid, or who are unlikely to be available for more than 4-6 months. Be aware that - There will be orange discoloration of secretions, urine, tears and contact lenses - Patients receiving methadone will need their methadone dosage increased by an average 50% to avoid opioid withdrawal - Interactions with many drugs can lead to decreased levels of either or both - Rifampicin may make glucose control more difficult in diabetics - Rifampicin is contraindicated for patients taking most PIs and NNRTIs - Patients should be advised to use barrier contraceptives while on rifampicin

[1]Baseline LFTs should be done for everyone over the age of 35, all HIV-infected persons, pregnant and post-partum women (up to 2-3 months post-partum), those with history of hepatitis, liver disease or alcohol abuse, injection drugs users and those on treatment with other potential hepatotoxic agents. A baseline CBC with platelets should be done on anyone prescribed a rifampicin-containing regimen

[2]Monthly LFTs should be conducted for all HIV infected persons, pregnant and post-partum women (up to 2-3 months post-partum), those with history of hepatitis, liver disease or alcohol abuse, injection drugs users and those on treatment with other potential hepatotoxic agents. Those whose baseline LFTs were abnormal should be monitored monthly regardless of other conditions.

[3] There is very little data or clinical experience on the use of intermittent treatment of LTBI with rifampicin. This regimen should be used with caution.

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Pyridoxine

It is believed that isoniazid competes with pyridoxyl phosphate for the enzyme apotryptophanase, which may lead to symptoms of pyridoxine (vitamin B6) deficiency. Pyridoxine administration may decrease the peripheral and CNS effects complicating isoniazid use. If on isoniazid, pyridoxine 10mg daily (20mg daily may be used if 10mg tablets are not available) should be prescribed for:

- all adults, including pregnant women
- children who have poor nutrition and therefore are at risk of pyridoxine deficiency
- children who develop paraesthesia
- breastfeeding infants on isoniazid
- a fully breastfed infant if the mother is on isoniazid, regardless of whether the infant is on anti-TB treatment
- In particular, those with, pre-existing peripheral neuropathy, diabetes, chronic renal or liver disease, cancer, alcoholism, malnutrition, other immunosuppressive conditions or HIV.[52 77]

As there are no side effects to low dose pyridoxine, many centres routinely prescribe it to prevent the development of neuropathy.[30] However, it is not routinely prescribed in children except in the situations mentioned above.

LTBI treatment: contraindications

Isoniazid

- Previous history of an isoniazid-induced reaction including hepatic, skin or allergic reaction
- Close contact with a person who has isoniazid-resistant TB
- Pregnancy: unless the woman is HIV infected or has been recently infected i.e. is a close contact of an infectious TB case. In these cases, a risk assessment should be undertaken on a case-by-case basis and treatment deferred if possible until after the first trimester. Apart from the above situations, the small benefits of LTBI treatment in pregnancy are not thought to outweigh the small risks associated with taking the medications
    - For all other pregnant women, treatment if indicated for LTBI (provided active TB disease is excluded) should be deferred until two to three months post-partum (figure 3.1)
    - The need to treat active TB disease during pregnancy is unquestioned. Treatment of LTBI is more controversial since the possible risk of hepatotoxicity must be weighed against the risk of developing TB disease
    - In pregnant women known or suspected to be infected with a TB strain resistant to at least isoniazid and rifampicin treatment for LTBI should be deferred until after delivery. This will avoid possible adverse effects of the medications on the developing foetus. [30;34;77]

An alternative regimen to isoniazid is to give patients (with or without HIV infection) four months of rifampicin for treatment of LTBI. This course is especially recommended if there are contraindications or resistance to isoniazid but not to rifampicin and if there may be adherence problems and the individual is unlikely to complete a six or nine month course of therapy.

Rifampicin

- A history or rifampicin-induced reactions including skin and other allergic reactions, hepatitis or thrombocytopenia
- Pregnancy unless the woman is HIV infected, has been recently infected and is a close contact of an isoniazid-resistant case or is intolerant to isoniazid (see under isoniazid and figure 3.1)
- Current treatment with a protease inhibitor (PI) or certain non-nucleoside reverse transcriptase inhibitors (NNRTIs).[77]

LTBI treatment: precautions

Persons with any of the conditions outlined below should be referred to a respiratory clinician or infectious disease consultant for treatment of LTBI:

- Acute or chronic liver disease of any aetiology
- Acute liver disease: If a person with acute liver disease has a high risk of progression to TB disease for example if the person is on immunosuppressive therapy and also had prolonged contact with a highly infectious TB case, then a risk assessment should be carried out to determine whether they should be treated for LTBI
- Receiving other drugs which may interact with anti-TB drugs
- History of heavy alcohol ingestion
- History of previous discontinuation of isoniazid because of possible, but not definite, related side effects e.g. headaches, dizziness, nausea
- Major concerns about adherence to treatment
- Major concerns about adherence to arrangements for biochemical or clinical monitoring
- Peripheral neuropathy or risk factors for its development e.g. insulin dependent or type II diabetes, alcoholism, chronic renal failure or malnutrition. Pyridoxine 10mg daily (or 20mg if 10mg not available) should be offered to these patients (see section on pyridoxine).

Recommendation:

A consultant with expertise in TB should always be consulted when treating a patient with LTBI with documented hepatotoxicity.

A risk-benefit approach on a case-by-case basis should be adapted to commencing treatment for LTBI on these patients. Treatment of patients with underlying liver disease should be undertaken in consultation with a consultant hepatologist.

Recommendation:

Breastfeeding is not a contraindication to LTBI therapy. Isoniazid or rifampicin are not secreted in sufficient quantities in breast milk to harm the baby.[52;77]

Monitoring during treatment

Clinical monitoring is indicated for all patients and ideally involves monthly visits, or at the discretion of the physician, where patients are educated about the symptoms and signs that can result due to adverse effects of the drug(s) being prescribed and the need for prompt cessation of treatment and clinical evaluation should symptoms occur.

The symptoms of adverse affects include:[34;52]

- unexplained anorexia
- nausea
- vomiting
- dark urine
- jaundice
- rash
- persistent paresthesia of the hands and feet
- persistent fatigue

- weakness or fever lasting three or more days
- abdominal tenderness (especially right upper quadrant discomfort)
- easy bruising or bleeding and
- arthralgia.

The interval between commencing isoniazid and the appearance of hepatitis varies widely. Using a standardised proforma may facilitate monthly clinical monitoring (appendix 5). Appropriate educational materials (information leaflet) in the patient's language should be provided (appendix 6).

Liver function tests (LFTs)

Monthly LFTs during treatment of LTBI are indicated for patients whose baseline liver function tests are abnormal and for all HIV-infected persons, pregnant and post-partum women (up to 2-3 months post-partum), those with a history of hepatitis, liver disease or heavy alcohol ingestion, injecting drug users and those on treatment with other potential hepatotoxic agents.[77]

Some experts recommend that healthy adults aged >35 years on LTBI treatment with isoniazid or isoniazid with rifampicin have eight weekly monitoring of LFTs or at one, three and six months for those on a nine month regimen. The frequency depends on the perceived hepatotoxicity risk and effectiveness of patient education.[108]

In addition, laboratory testing (e.g. liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate patients who develop acute arthritis) should be used to evaluate possible adverse effects that occur during the course of treatment.

Interventions for hepatotoxicity during treatment for LTBI

If hepatic side-effects occur during treatment, expert advice should be sought from the treating physician. A hepatology evaluation should be undertaken and hepatology consultation is recommended for unusual or severe cases of hepatitis particularly those who become sufficiently ill to require hospitalisation.[108]

Isoniazid should be withheld if hepatic transaminases (ALT) are at least three times the ULN when the patient is symptomatic (jaundice or symptoms of hepatitis) or if at least five times the ULN when the patient is asymptomatic. An isoniazid rechallenge should be considered when the ALT is less than twice the ULN. This should be decided by the treating physician on a case-by-case basis.

A rapid increase in ALT may be an indication for more frequent monitoring i.e. every two weeks instead of monthly, particularly if one of the above treatment-limiting ALT thresholds is being approached or if the patient has previously identified risk factors for hepatotoxicity.

For the few patients who may begin isoniazid LTBI treatment with a baseline ALT >3 times the ULN, some experts recommend that in the absence of adequate clinical data that treatment should be discontinued if there is more than a two- to threefold increase above baseline or if there is a mental status change, jaundice or significant increase in bilirubin or INR.[108]

More detailed information on the hepatoxicity of anti-TB therapy is available in the Official American Thoracic Society's Statement: Hepatotoxicity of Anti-TB Therapy.[108]

Recommendation:

Ideally monthly clinical monitoring (at the discretion of the clinician) is recommended for all patients receiving treatment for LTBI.

Interruptions in therapy

Adherence to treatment regimens is recognised as a significant problem, especially in relation to the treatment of LTBI, with CDC stating that only 60% of patients who start treatment for LTBI complete at least six months of treatment.[34] The length and complexity of the regimen and the side effects of the medication influence adherence to treatment. Directly observed therapy (DOT) has been used to try to improve adherence to treatment regimens. Ideally, patients should receive medication on a regular dosing schedule until completion of the indicated course. However, in practice some doses may be missed, requiring the course to be lengthened.

If interruptions in therapy occur the person responsible for supervision must decide whether to restart a complete course of treatment or whether simply to continue as originally intended.

Completion of therapy is based on the total number of doses administered not on the duration of therapy alone. The nine month regimen of daily isoniazid should consist of a minimum of 270 doses administered within 12 months, which allows for minor interruptions in therapy. The six month regimen of isoniazid should consist of at least 180 doses administered within nine months.[34]

When therapy is restored after an interruption of more than two months, a medical examination to rule out active TB disease is indicated.

3.8 Risk of TB Associated with the Use of TNF-α Antagonists

TNF-α antagonists offer great promise to patients suffering a number of immune-mediated diseases and have been used safely in many patients worldwide. However, it is plausible that these agents may carry a risk of reactivation of LTBI or of new TB infection. Concern is supported by the finding of a possible increased risk of TB in peer-reviewed publications from a number of countries. While the design of these studies does not allow causality to be concluded, the consistency of the studies and the temporal association with the agents, together with the gravity of the consequence for individual patients and for the wider community suggest that a precautionary approach is appropriate. Manufacturers of TNF-α antagonists have indicated that TB is a possible side effect of treatment and a number of guidelines for management of this risk have been issued by professional organisations and individuals.

The following recommendations (summarised in figure 3.2) are taken from a briefing paper prepared by members of the National TB Advisory Committee in consultation with members of the Irish Society for Rheumatology. The full version of this document is available at: www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/Guidance/.

1. Prior to commencing TNF-α antagonists, patients should be thoroughly assessed for clinically active TB disease, including clinical history, physical examination and chest radiograph. If clinically active TB disease is diagnosed, it should be treated as per existing guidelines (chapter 5).

2. Patients without clinically active TB disease should be screened for LTBI with clinical history, assessment of risk factors (for example time spent living in a high incidence country, immunocompetence, etc.), physical examination, chest radiograph and TST.
   - IGRA testing may be a useful adjunct in screening where it is available.

3. Patients without radiographic evidence of TB but with a positive TST should be classified as a case of LTBI.
   - For the purpose of LTBI screening prior to commencing TNF-α antagonists, 2TU Mantoux testing is recommended. While reactions over 10mm should be interpreted as indicating TB infection, this cut off may not be reliable for some patients being considered for treatment with TNF-α antagonists since their disease and co-medications may lead to anergy. Therefore, the use of a 5mm cut-off may be more useful for patients who are considered to be immunocompromised. It

is recognised that on the basis of individual risk assessment, clinicians may prefer to use an even more conservative cut-off for individual patients. Although a negative TST (Mantoux test) reduces the probability of LTBI, a high clinical suspicion for LTBI should be maintained, since the reaction to tuberculin may be complicated by anergy.

- It is recommended that the interpretation of Mantoux testing in the context of testing for LTBI prior to commencement of a TNF-α antagonist should not usually take account of the patient's BCG history.

4. It is recommended that patients diagnosed with LTBI should be treated. Options for treatment include at least nine months of isoniazid, which is associated with a lower risk of hepatotoxicity, or four months of rifampicin (R) +/- isoniazid, associated with a higher risk of hepatotoxicity but offers the advantage of shorter duration which may promote successful completion of treatment for some patients. Rifampicin for four months may also be used if isoniazid is contraindicated e.g. a past history of an isoniazid induced reaction. Pyridoxine may also be used in combination with these regimens.

5. Optimal timing of initiation of TNF-α antagonists is challenging and in the absence of high-quality evidence to support specific recommendations in this regard, decisions on the treatment of individual patients need to be made collaboratively by patients and clinicians following a careful assessment of the risks of TB disease and the benefits of TNF-α antagonist treatment and discussion of individual preferences.
   - Initiation of TNF-α antagonists prior to commencement of treatment of clinically active TB disease or LTBI should be avoided
   - The risk associated with commencement or re-commencement of TNF-α antagonists in the setting of clinically active TB disease requires particularly careful assessment; where possible, it is recommended that TNF-α antagonists be postponed until curative treatment has been satisfactorily completed; in some cases, clinicians and patients may prefer to avoid TNF-α antagonists completely in this scenario
   - The risk associated with commencement or re-commencement of TNF-α antagonists in the setting of LTBI also requires careful assessment; again, where possible, it is recommended that TNF-α antagonists be postponed until LTBI treatment has been satisfactorily completed. However, clinicians and patients may, on balancing risks and benefits, prefer to initiate TNF-α antagonists during treatment for LTBI; while no specific duration of LTBI treatment prior to initiation of TNF-α antagonists can be recommended on the basis of currently available evidence, where possible, a longer duration of satisfactory LTBI treatment is suggested as good practice in managing the risk of initiation of TNF-α antagonists.

6. Clinically active TB disease may still arise in patients treated with TNF-α antagonists despite a negative initial assessment or LTBI treatment. Therefore, it is recommended that a high index of clinical suspicion for development of TB is exercised in the setting of any clinical deterioration while patients are undergoing TNF-α blockade.

7. Cooperation between clinicians initiating TNF-α antagonists and clinicians with expertise in TB is recommended in the assessment and management of patients.

8. Clinicians are encouraged to report all adverse drug events associated with the use of TNF-α antagonists to the Irish Medicines Board (IMB).

It is suggested that these national recommendations provide a framework for the drafting of guidelines for use by individual professional societies, units and clinicians on the use of TNF-α antagonists in clinical guidance; it is recognised that such guidelines may have broader concerns than the management of the risk of TB (e.g. surveillance for other side effects) and may wish to include local good practice advice, however, guidelines should be made cognisant of these recommendations.

Recommendation:

Prior to commencing TNF-α antagonists, patients should be thoroughly assessed by the treating physician for clinically active TB disease and for LTBI.

Figure 3.2: Algorithm for TB assessment prior to the use of TNF-α antagonists