Policy 4.4 Tuberculosis and Human Immunodeficiency Virus (HIV) Infection

Title: Tuberculosis and Human Immunodeficiency Virus (HIV) Infection
Reference Number: WA Tuberculosis Control Program Policy 4.4
Policy Statement: This policy addresses differences in the approach to the assessment and treatment of tuberculosis in patients co-infected with HIV.
Policy Sponsor: Medical Director, WA TB Control Program
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Related WA TB Control Program Policies

1.1 Diagnosis of tuberculosis – Laboratory
1.2 Diagnosis of tuberculosis – Clinical
2.1 Medical treatment of tuberculosis (adults)
2.2 Case management of tuberculosis
3.1 Diagnosis of latent tuberculosis infection
3.2 Treatment of latent tuberculosis infection
4.1 Tuberculosis (active and latent) in children
4.2 Management of tuberculosis in prisoners and immigration detainees
4.3 Tuberculosis (active and latent) in pregnant women
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5.1 BCG Vaccination
6.1 Contact tracing for tuberculosis
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6.4 Active surveillance for tuberculosis prior to anti-TNF alpha treatment
7.1 Notification of tuberculosis and enhanced surveillance data
8.1 Diagnosis and management of Hansen’s disease
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9.2 Client record management policy for the WA Tuberculosis Control Program
9.3 Fees and charges associated with tuberculosis and leprosy treatment

Document Control

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Policy 4.4    Tuberculosis and Human Immunodeficiency Virus (HIV) Infection

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Policy 4.4  Tuberculosis and HIV Infection

1.0 Introduction

The diagnosis and management of tuberculosis, both active and latent, are detailed in other WA tuberculosis (TB) control program policies listed in ‘Related Policy’ on the first page. This policy addresses differences in the approach to the assessment and treatment of tuberculosis in patients co-infected with the human immunodeficiency virus (HIV).

Untreated HIV infection leads to progressive immunodeficiency and increased susceptibility to opportunistic infections, including *M. tuberculosis*. Co-infection with HIV increases the lifetime risk of progression of latent infection of *M. tuberculosis* to tuberculosis (TB) disease from 5-10% lifetime risk in non-HIV infected individuals to 50% lifetime risk in HIV positive individuals (World Health Organisation, 2004). This risk increases with increasing immunosuppression. HIV infection increases not only the risk, but also the rate of progression of recent or latent *M. tuberculosis* infection to disease (World Health Organisation, 2004).

2.0 Diagnosis

2.1 Clinical features

The clinical presentation of tuberculosis in HIV infected persons is influenced by:

a) The degree of immune suppression in the person; and

b) The rate of disease progression.

Even in HIV-infected patients, pulmonary TB is the commonest form of TB with clinical features dependent on the degree of immunosuppression (Table 1) (World Health Organisation, 2004).

| Table 1: Features of pulmonary TB as determined by the stage of HIV infection |
|---|---|---|
| **Features of pulmonary TB** | **Early Stage of HIV infection** | **Late Stage of HIV infection** |
| Clinical picture | Often resembles post primary pulmonary TB | Often resembles primary pulmonary TB |
| Sputum smear result | Often positive | Often negative |
| Chest X-ray | Cavities common | Infiltrates with no cavities more common |

As HIV infection progresses, the CD4+ T-lymphocytes decline in number and function. This compromises the immunological suppression of *M. tuberculosis*, and disseminated and extrapulmonary TB disease become more common (World Health Organisation, 2008).
TB progresses more rapidly in immunocompromised patients, which increases the imperative for TB to be diagnosed and treatment initiated with minimal delay. Assessment for pulmonary TB should begin if cough persists for more than one week rather than three weeks in a patient known to be infected by HIV (Nachega & Maartens, 2009).

2.2 Radiographic features

Chest x-ray changes in TB and HIV co-infected patients reflect the degree of immune compromise. In HIV-infected individuals with relatively preserved immunity, pulmonary TB presents in the typical adult pattern of upper lobe predominance and cavitation. In the severe immunocompromised, the appearance is often atypical and may include non-cavitary lower or mid zone infiltrates, hilar and/or mediastinal lymphadenopathy, or may be completely normal in appearance (World Health Organisation, 2004; Nachega & Maartens, 2009). Patients with clinical features suggestive of pulmonary disease who return a normal chest x-ray should still submit sputum specimens for examination.

2.3 Investigations

The investigation of TB disease in HIV infected persons should not differ from HIV unaffected persons. All patients, regardless of HIV status, with clinical features suggestive of pulmonary TB should submit sputum specimens for diagnostic sputum smear microscopy and culture.

Patients who are highly immunocompromised may return a negative result on sputum microscopy despite clinical and/or radiological appearances suggestive of active TB, because paucibacilliary TB is more common (World Health Organisation, 2008). Disseminated and extrapulmonary TB may be present and specimens from extrapulmonary sites should be examined for M. tuberculosis by microscopy and culture +/- PCR. For a list of suitable clinical specimens please see Appendix A Clinical specimens.

Patients with a relatively intact immune system will have a more typical granulomatous histological picture on tissue specimens. In advanced immunodeficiency, granulomas are poorly formed, due to a decrease in CD4+ T cell function (Australasian Society for HIV medicine, 2009). Nucleic acid amplification tests (NAAT) have enabled more rapid diagnosis of M. tuberculosis infection in sputum specimens. However, the positive predictive value of these tests is reduced in smear-negative sputum samples. The specificity of NAAT is high for other body fluids, for example for TB meningitis and pleural TB, but sensitivity is poor.
3.0 Treatment of active TB in HIV infected patients

The principles of anti-TB treatment are the same irrespective of HIV status, that is:

1. Internationally accepted standardised regimens are used;
2. Multi-drug regimens are used; and
3. Medication should be provided free of charge.

Issues related to the treatment of TB in HIV infected patients include:

1. The timing of anti-retroviral treatment;
2. Drug interactions between anti-tuberculosis medication and anti-retroviral treatment;
3. Immune reconstitution inflammatory syndrome (IRIS) after anti-retroviral treatment initiation; and

With regards to the management of tuberculosis in HIV co-infected patients, collaboration between the specialist TB physician and HIV physicians is essential.

3.1 Tuberculosis medication

The standard treatment of TB in HIV infected individuals does not require different drugs or duration of treatment than HIV unaffected persons (World Health Organisation, 2008; Australasian Society for HIV Medicine, 2009). The standard short-course therapy for TB is two months intensive phase of isoniazid, rifampicin, ethambutol and pyrazinamide followed by a four-month continuation phase of isoniazid and rifampicin (2HREZ 4HR). If there is evidence of slow response to treatment then prolongation of the continuous phase to 7 months should be considered. For further information on drug regimens and drug doses please see the WA TB Control Program policy 2.1 Medical treatment of tuberculosis (adults).

Daily TB treatment should be used, rather than intermittent therapy, as intermittent regimens are associated with a higher rate of relapse. The use of thioacetazone is contraindicated in HIV-infected individuals because of the risk of fatal hypersensitivity reactions and severe toxicity (World Health Organisation, 2008).

Particular care in the management of HIV co-infected patients include:

- Patients with extensive pulmonary disease e.g. cavitations or TB involving more than 2 chest x-ray zones, should have their continuation phase extended for an additional 3 months for a total of nine months treatment (Centers for Disease Control and Prevention, 2009).

- Patients with miliary, meningeal or skeletal disease should be treated for 12 months.
• All HIV infected patients receiving isoniazid should also be given **pyridoxine** 25mg daily concurrently to minimise the risk of peripheral neuropathy.

• **Adjuvant steroid treatment** can be used in HIV-positive patients (World Health Organisation, 2004). Steroids are immunosuppressants and may further depress immunity and increase the risk of opportunistic infections in HIV positive patients. However, on balance, TB/HIV patients are still likely to benefit from the use of steroids for the following indications:

  a) TB meningitis (decreased consciousness, neurological defects, or spinal block).
  b) TB pericarditis (with effusion or constriction).
  c) TB laryngitis (with life-threatening airway obstruction).
  d) Severe hypersensitivity reactions to anti-TB drugs.
  e) Severe tuberculosis associated immune reconstitution inflammatory syndrome (Department of Health and Human Services, 2012).

Although the evidence is weak, adjuvant steroids could also be considered in:

  a) Pleural effusion (when large with severe symptoms).
  b) Hypoadrenalism (TB of adrenal glands).
  c) Renal tract TB (to prevent ureteric scarring).
  d) Massive lymph node enlargement with pressure effects.

The use of adjuvant steroid therapy in TB and HIV co-infected patients is at the discretion of the treating physician.

### 3.2 Combination anti-retroviral therapy (cART)

The timing of initiation of TB treatment with combination antiretroviral treatment should always be made in consultation with the patient’s HIV physician. If indicated, anti-retroviral therapy should be initiated during tuberculosis therapy as delay in anti-retroviral therapy until the completion of TB treatment can adversely affect survival rates (Karim & al, 2010).

The timing of initiation of cART should consider the patient’s clinical features, extent of disease and CD4+ count. The exception to this involves TB meningitis when delaying cART until completion of TB treatment may result in less adverse events than immediate initiation of cART (Török & al, 2011).

Specific recommendations regarding timing of treatments are available from the Department of Health and Human Services (2012) *Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents*. Involvement of a HIV physician is essential.

Physicians managing patients being treated for both TB and HIV infection should be aware of, and monitor the:
• Risk of the development of tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS);
• Drug interactions; and
• Compliance with a large pill burden.

When active tuberculosis is diagnosed in patients already receiving antiretroviral therapy, patients should be referred urgently to a physician experienced in TB management and the medical management of the patient should be planned in conjunction with the HIV treating physician.

### 3.3 Drug interactions

Significant drug interactions can occur between medications used to treat tuberculosis and HIV disease. A key interaction is that between the rifamycin antibiotics used in TB treatment (rifampicin, rifapentine and rifabutin) and the antiretroviral drugs. The rifamycin class of antibiotics induces the synthesis of several drug transporting and drug metabolising enzymes, the most common being the cytochrome P450 enzyme system. The rifamycin antibiotics vary in the potential as enzyme inducer with rifampicin being the most potent, rifapentine intermediate and rifabutin less active (Centers for Disease Control, 2007).

The rifamycin antibiotics play an important role in the success of tuberculosis treatment and should therefore not be eliminated from therapy except in cases of drug resistance or intolerance. Patients with HIV and tuberculosis infections should receive a rifamycin antibiotic for the full course of treatment. Medications should preferably be administered daily (Centers for Disease Control, 2007).

The rifamycin antibiotics are associated with significant interactions with most antiretroviral drugs including all protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), maraviroc and raltegravir.

Efavirenz-containing regimens are the recommended first-line ART regimens for TB patients, since interactions with rifampicin may not be clinically significant (Centers for Disease Control, 2007). No dose changes are required for either efavirenz or rifampicin, although an increase from 600mg daily efavirenz to 800mg may be recommended in patients over 60kg body weight.

Nevirapine is an alternative to efavirenz, but serum concentrations of nevirapine can be decreased by up to 50% by rifampicin. The drug combination could be used with caution with no change in dosage recommended.

Protease inhibitors are not recommended in combination with rifampicin as the decreased concentrations of these drugs would make them ineffective as antiretroviral therapy. Rifabutin has little effect on serum concentrations of protease inhibitors and could be used as a substitute. Rifabutin is as effective as rifampicin for tuberculosis treatment and has
less of an effect as an enzyme inducer than rifampicin. However, protease inhibitors may increase rifabutin levels necessitating a reduction in rifabutin dose while the patient is also taking the protease inhibitor (Centers for Disease Control, 2007).

Rifapentine is a long acting rifamycin that can be given once a week for the treatment of active or latent TB. The extent of enzyme induction and its effect on the antiretroviral drugs is unknown and at this time rifapentine is not recommended for the treatment of active or latent TB infection in patients receiving antiretroviral treatment (Department of Health and Human Services, 2012).

For further information on interactions between the drugs used to treat tuberculosis and HIV please see the Department of Health and Human Services (2012) Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents, and the Centers for Disease Control and Prevention (2007) Managing Drug Interactions in the Treatment of HIV-related Tuberculosis.

3.4 Tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS)

The immune reconstitution inflammatory syndrome (IRIS) is a complication associated with anti-retroviral therapy resulting from the rapid restoration of a persons immune response to opportunistic infections, causing either a deterioration of a treated infection or the new presentation of a previously subclinical infection (Meintjes & al, 2008). It typically occurs within a few months after initiating anti-retroviral therapy and is most commonly associated with mycobacterial infections and other pathogens e.g. herpes virus and cryptococcal meningitis.

Tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS) is a temporary exacerbation of symptoms and/or radiographic signs of TB occurring after the start of treatment with anti-retroviral therapy. It can present as one of two main syndromes (Meintjes & al, 2008):

1. A paradoxical reaction after the start of anti-retroviral therapy in patients receiving tuberculosis treatment; and
2. A new presentation of tuberculosis that was previously subclinical.

Paradoxical tuberculosis-associated IRIS

In paradoxical tuberculosis-associated IRIS patients have been diagnosed with active tuberculosis before the initiation of anti-retroviral therapy and have shown improvement in their clinical condition. The syndrome commonly presents as a worsening in clinical symptoms or the development of new symptoms or signs after anti-retroviral therapy has been commenced. Clinical manifestations may include fever, return of a cough, worsening lymphadenopathy or worsening pulmonary infiltrates on chest x-ray (World Health Organisation, 2008; Meintjes et al, 2008).
Paradoxical tuberculosis-associated IRIS typically occurs within the first few months and up to 3 months after anti-retroviral therapy is started, restarted or changed because of treatment failure. Patients most at risk of this reaction are those with advanced HIV disease and low CD4+ counts, disseminated and extrapulmonary forms of TB, a shorter delay between the start of TB treatment and anti-retroviral therapy and a more virological response to anti-retroviral therapy (Meintjes & al, 2008). Most cases are self-limiting.

Alternative reasons for clinical deterioration should be excluded, that is a) failure of TB treatment due to drug resistance, b) non-compliance with TB medication, or c) alternative diagnosis e.g. other infection, neoplasm, or drug toxicity or reaction. Tuberculosis paradoxical reactions can also occur in HIV negative individuals and in HIV positive patients not receiving anti-retroviral therapy but this occurs less frequently compared to those on anti-retroviral therapy.

**Anti-retroviral therapy associated tuberculosis**

Anti-retroviral associated tuberculosis is active TB that is diagnosed after the initiation of anti-retroviral therapy in patients who were not receiving treatment for TB at the time anti-retroviral therapy is initiated. Active tuberculosis may occur as a result of missed diagnosis prior to anti-retroviral therapy, due to low sensitivity of TB testing prior to immune system restoration e.g. sputum smear microscopy, or the presence of active subclinical TB disease becoming symptomatic after anti-retroviral therapy is started.

**Unmasking tuberculosis-associated IRIS**

Unmasking tuberculosis-associated IRIS applies to those patients with anti-retroviral associated tuberculosis occurring within 3 months of starting anti-retroviral therapy who present with heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation (Meintjes & al, 2008). Examples would include TB lymphadenitis or abscesses with acute inflammatory features and pulmonary TB presenting with acute respiratory distress after commencing anti-retroviral therapy.

### 3.5 Mycobacterium avium complex

*Mycobacterium avium* complex (MAC) infection is important in the differential diagnosis when acid-fast bacilli are seen in patients with very low CD4+ counts. There is a strong relationship between CD4+ cell count and the presence of disseminated MAC infection, with nearly all cases occurring at a CD4+ cell count of <50 cells/µL (Australasian Society for HIV medicine, 2009 and Centers for Disease Control and Prevention, 2009).

Clinical manifestations of MAC infection are similar to *M.tuberculosis* infection, although disseminated disease is more common than pulmonary forms. Diagnosis is confirmed through the isolation of MAC from culture or identification by molecular techniques.
In cases where MAC is in the differential diagnosis, and a histological diagnosis of mycobacterial infection is made in the absence of diagnostic cultures, empirical therapy should cover both MAC and \textit{M. tuberculosis} infections. Clarithromycin should be added to the standard four-drug TB regimen until the identification of the mycobacterial species is available, either by NAAT or culture (Australasian Society for HIV medicine, 2009).

3.6 Monitoring during treatment

Patients should be monitored closely for response to TB treatment and for the development of drug adverse effects and drug interactions. Patients with pulmonary TB should be followed up with sputum sampling at 2 months for examination for acid-fast bacilli and culture. Sputum sampling should continue until at least two consecutive specimens are negative (Australasian Society for HIV medicine, 2009). The minimum requirements for biochemical, haematological and radiological monitoring is detailed in Appendix B \textit{Recommended routine tests during treatment for active TB}. More frequent testing for HIV infected patients is at the discretion of the treating physician.

4.0 Investigation of latent TB infection (LTBI)

The tests available for screening for LTBI in Western Australia are the:

1). Tuberculin skin test (TST), also called Mantoux test, and the
2). QuantiFERON-TB Gold In-Tube test (QIFN)

These tests are indirect tests that indicate a cellular immune response to previous sensitisation with mycobacterial antigens and cannot distinguish between individuals with latent TB infection, active TB infection or past TB infection. The TST relies on a competent immune response to identify people with latent \textit{M. tuberculosis} infection and therefore a lower cut-off of 5mm diameter reaction is deemed a positive result (versus 10mm in the general population). HIV related immunosuppression can be associated with false negative results. False negative and indeterminate QIFN results increases with advancing immunodeficiency and low CD4+ counts (World Health Organisation, 2011)

On balance QIFN is the preferred test for LTBI in HIV co-infected patients, because of the risk of unrecognised false negative tuberculin skin tests.

Patients infected with HIV should be tested for tuberculosis infection if there are prior risk factors for TB i.e. a contact of infectious TB, persons born, or who have lived for a prolonged period, in countries that have a high incidence of active TB defined as >50/100 000 per year or Indigenous Australians. Patients with advanced HIV infection (CD4+ count <200 cells/\(\mu\)L) may initially return a negative screening test for latent TB and should be retested once they start anti-retroviral therapy and the CD4+ count increases above 200 cells/\(\mu\)L (Centers for Disease Control and Prevention, 2009). If there is a history of TB
exposure e.g. contact of infectious TB, then treatment for latent TB should be offered regardless of the result of latent TB tests.

Fibrotic lesions on the chest x-ray of an HIV infected persons should be assessed for active TB, and if negative, assessed for latent TB infection. HIV infected persons with a CD4+ count <200 cells/µL who have fibrotic lesions on chest x-ray should be considered as having *M. tuberculosis* infection irrespective of the results of the TST or QIFN and treated accordingly (Centers for Disease Control and Prevention, 2009).

5.0 Treatment of latent TB

The risk of active TB developing in individuals infected with both *M. tuberculosis* and HIV is much higher than for those without HIV infection, at 5–10% risk per year and 5–10% lifetime risk respectively (World Health Organisation, 2008). Preventive treatment with isoniazid in individuals, who are both TST and HIV positive, living in settings with high prevalence of TB, reduces the risk of developing active TB by around 60% (i.e. to around 40% of what it would have been without the treatment) (World Health Organisation, 2008).

Preventive therapy should be offered to all HIV infected individuals, in whom active TB has been excluded, who fulfil one of the following criteria (Centers for Disease Control and Prevention, 2009):

1. Have a TST reaction of ≥5mm in diameter or positive QIFN test and no prior history of treatment for active or latent TB;
2. Negative TST or QIFN test but is a close contact of infectious TB;
3. A history of untreated or inadequately treated healed TB (e.g. old fibrotic lesions on chest x-ray) regardless of TST or QIFN result.

There is no benefit to providing prophylaxis to anergic persons unless they have had contact with a person with infectious TB (Australasian Society for HIV medicine, 2009).

A nine-month course of isoniazid monotherapy in HIV infected patients is the treatment of choice for adults in the WA TB Control Program, at a dose of 5-10mg/kg to a maximum of 300mg daily. Pyridoxine at a dose of 25mg daily should be given concurrently to minimise the risk of peripheral neuropathy.

5.1 Primary preventive therapy

Individuals with HIV infection are at high risk of developing primary TB infection following exposure to an infectious case. Commencement of preventative treatment immediately following the exposure aims to prevent the development of primary TB infection. These patients should be offered preventive therapy regardless of TST or QIFN result. For individuals who are a contact of infectious drug resistant TB, the choice of medication should be made in conjunction with a physician experienced in the management of TB.
6.0 Pregnancy

The investigations and management of active and latent TB in HIV infected pregnant women should be no different from that in HIV negative women.

Special situations include (Centers for Disease Control and Prevention, 2009):

i. If a woman is taking anti-retroviral therapy for prophylaxis of perinatal HIV transmission and will stop this treatment after delivery, then treatment of latent TB infection can be deferred until after delivery; and

ii. For women on long-term anti-retroviral therapy, treatment of latent TB infection with isoniazid is recommended during pregnancy.

The management of pregnant women with HIV and TB co-infection should be discussed with a specialist in HIV medicine.

7.0 Children

In children several HIV-related diseases may present in a similar way to TB e.g. viral or bacterial pneumonia, lymphocytic interstitial pneumonitis, bronchiectasis, pneumocystis carinii pneumonia and Kaposi’s sarcoma. Many of the clinical features that are used to suggest a diagnosis of childhood TB could apply to any of the above diseases in the presence of HIV infection. There may be multiple and concurrent opportunistic infections so the presence of one of the above infections does not exclude TB being present as well (World Health Organisation, 2006). Lymphoid interstitial pneumonitis is the most difficult condition to distinguish from TB, due to radiological similarities.

If active TB is suspected in a HIV infected child, these cases should be referred to and managed by clinicians familiar with both paediatric TB and HIV. The clinical assessment and investigation of TB should be the same as in an HIV uninfected child. The interpretation of tuberculin skin testing in the presence of HIV infection is less reliable. An immunocompromised child may have a negative tuberculin skin test despite having TB.

Most current international guidelines recommend that TB in HIV-infected children should be treated with a 6-month regimen as in HIV-uninfected children. However, some national guidelines recommend that HIV-infected children with pulmonary TB be treated for 9 months, and those with extrapulmonary TB be treated for 12 months (Centers for Disease Control and Prevention, 2004).
8.0 BCG disease

Bacille Calmette-Guérin (BCG) vaccination should not be given to HIV-infected children due to the increased risk of disseminated BCG disease. BCG disease can be categorized as (Hesseling & al, 2005):

I. Local disease – This involves a local process at the site of vaccination e.g. BCG injection site abscess or severe BCG scar ulceration.

II. Regional disease – Involvement of any regional lymph nodes or other regional lesions beyond the vaccination site e.g. ipsilateral axillary gland enlargement, suppuration or fistula.

III. Distant disease - Involvement of any site beyond a local or regional ipsilateral process e.g. BCG isolated from pulmonary secretions, cerebrospinal fluid, urine etc.

IV. Disseminated disease – BCG confirmed from >1 remote site and/or at least blood or bone marrow culture.

BCG immune reconstitution syndrome, BCG-IRS, is defined as BCG disease that presents in an HIV infected child within 3 months after the initiation of anti-retroviral therapy (Hesseling & al, 2005). It can occur with local, regional, distant or disseminated disease as described above.

The management of BCG disease is specialized, and HIV-infected children suspected of having BCG disease should be referred to a paediatrician experienced in TB treatment for management. *Mycobacterium bovis* is generally resistant to pyrazinamide and treatment may require higher doses of other first-line TB medications (World Health Organisation, 2006).
9.0 Works Cited


**Endorsing Authority**

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**Feedback or comments related to this policy should be addressed to the Medical Director, WA TB Control Program** Justin.Waring@health.wa.gov.au
## Appendix A: Clinical Specimens

The sample types appropriate for the culture of mycobacteria are:

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<th>Specimen type</th>
<th>Specimen requirements</th>
<th>Special instructions</th>
<th>Unacceptable specimens</th>
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<tr>
<td>Abscess contents, aspirated fluid</td>
<td>As much sample as possible</td>
<td></td>
<td>Dry swab</td>
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<tr>
<td>Blood</td>
<td>5-10 ml in MycoF-Lytic bottle</td>
<td>Do not refrigerate MycoF-Lytic bottles</td>
<td>EDTA inhibits mycobacterial growth; coagulated blood</td>
</tr>
<tr>
<td>Body fluids (pleural, pericardial, peritoneal, etc.)</td>
<td>As much sample as possible (10-15 ml minimum)</td>
<td>AFB’s may be present in very low numbers in pleural &amp; peritoneal fluids (~1 cfu/500 ml)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Bone in sterile container without preservatives or fixative</td>
<td></td>
<td>Specimen in formalin</td>
</tr>
<tr>
<td>Bone marrow (BM)</td>
<td>As much sample as possible in MycoF-Lytic bottles. Do not refrigerate MycoF-Lytic bottles</td>
<td>Because BM is also cultured at 32°C, subculture from MycoF-Lytic bottle to B83 media</td>
<td></td>
</tr>
<tr>
<td>Broncho-alveolar lavage or bronchial washings</td>
<td>~5 ml in a sterile container</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial brushings</td>
<td>Sterile container</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal Fluid</td>
<td>&gt;2ml in sterile container</td>
<td>Use maximum volume attainable</td>
<td></td>
</tr>
<tr>
<td>Gastric lavage fluid</td>
<td>5-10 ml collected on waking to obtain sputum swallowed during sleep</td>
<td>Requires neutralisation with 100 mg sodium carbonate if delay &gt;4h</td>
<td>Non-neutralised samples &gt;4h</td>
</tr>
<tr>
<td>Lymph node</td>
<td>Fresh tissue</td>
<td></td>
<td>Specimen in formalin</td>
</tr>
<tr>
<td>Skin lesion material</td>
<td>Sterile container</td>
<td>Swabs in transport medium are acceptable only if biopsy or aspirate material is unavailable</td>
<td>Dry swab</td>
</tr>
<tr>
<td>Smear on slides</td>
<td>Smear over 1.5 x 1.5-cm area</td>
<td>Heat fix &amp; transport as biohazard (mycobacteria can survive 2 h @ 60°C)</td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>5-10 ml in sterile container. Collect 3 consecutive early morning sputa</td>
<td>Utility of culturing stool remains controversial. Smear negative samples will not be cultured</td>
<td>Frozen samples. Direct smear negative samples</td>
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<tr>
<td>Stool</td>
<td>&gt;1 g in sterile container</td>
<td></td>
<td>Frozen samples. Direct smear negative samples</td>
</tr>
<tr>
<td>Tissue biopsy sample</td>
<td>As much as possible</td>
<td></td>
<td>Specimen in formalin</td>
</tr>
<tr>
<td>Transtracheal aspirate</td>
<td>As much as possible</td>
<td></td>
<td></td>
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<tr>
<td>Urine</td>
<td>3 consecutive (full or clean catch) first morning voids</td>
<td></td>
<td>Non-first morning voids</td>
</tr>
<tr>
<td>Wound material</td>
<td>As much as possible</td>
<td>Swabs in transport medium are acceptable only if biopsy or aspirate material is unavailable</td>
<td>Dry swab</td>
</tr>
</tbody>
</table>
Appendix B: Recommended routine tests during treatment for active TB

Pre-treatment:
- Sputum x 3 (+/- urine) for acid fast bacilli microscopy and culture
- Chest x-ray
- Liver & kidney function tests, C-reactive protein, full blood count
- HIV serology, +/- Hep B & C serology
- Colour vision & visual acuity – ethambutol treatment only

2 weeks:
- Liver function tests, full blood count
- Colour vision & visual acuity – ethambutol treatment only

2 months:
- Sputum x 2 for acid-fast bacilli microscopy and culture (pulmonary TB)
- Chest x-ray (if initial x-ray abnormality)
- Liver function & other tests – only if clinically concerned, or initially abnormal.
- Colour vision & visual acuity – if still on ethambutol treatment

2 - 6 months
- Sputum x 2 for acid-fast bacilli microscopy and culture. If a 2 month test is positive repeat sputum x2 for acid-fast bacilli microscopy and culture at 3 months
- Chest X-ray (if initial x-ray abnormality)
- Blood tests - only if concerned or initially abnormal. Consider liver function testing if hepatitis B or C positive, HIV infection, pre-existing liver disease, alcohol use or older age group.

6 months / completion:
- Chest x-ray (all cases, even in extra pulmonary tuberculosis)
- Sputum x 2 for acid fast bacilli microscopy and culture if patient is able to produce.