British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018

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These guidelines are dedicated to the memory of Professor Stephen Lawn, a scientist and clinician whose pioneering work helped transform the management of TB in people living with HIV.

Contents

1 Scope and purpose

These guidelines have been drawn up to help physicians manage adults with tuberculosis (TB)/HIV co-infection. Recommendations for the treatment of TB in HIV-positive adults are similar to those in HIV-negative adults.

1.1 Guideline development process

BHIVA fully revised and updated the association's guideline development manual in 2011. Further updates have been carried out subsequently [1]. Full details of the guideline development process, including conflict of interest policy, are outlined in the manual. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and development of recommendations (see below and Appendix 1) [2,3].

The scope, purpose and guideline topics were agreed by the writing group. Questions concerning each guideline topic were drafted and a systematic literature search was undertaken by an information scientist.

Details of the search questions and strategy (including the definition of populations, interventions and outcomes) are outlined in Appendix 2. BHIVA guidelines for the treatment of TB/HIV-1 co-infection were last published in 2011 [4]. For the 2017 guidelines, Medline, EMBASE and the Cochrane library were searched between August 2015 and January 2016. Abstracts from selected conferences (see Appendix 2) were searched between August 2015 and January 2016. For each topic and healthcare question, evidence was identified and evaluated by writing group members with expertise in the field. Using the modified GRADE system, writing group members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. An important aspect of evaluating evidence is an understanding of the design and analysis of clinical trials, including the use of surrogate marker data. Decisions regarding the clinical importance of difference in outcomes are made by the writing group.

Before final approval by the writing group, the guidelines were published online for public consultation and an external peer review was commissioned.

1.2 Involvement of PLWH

BHIVA views the involvement of PLWH and community representatives in the guideline development process as essential. The writing group included two representatives appointed through the UK Community Advisory Board (UK-CAB) and community groups are specifically invited to participate in the public consultation process.

1.3 GRADE

The GRADE Working Group [2] has developed an approach to grading evidence that moves away from initial reliance on study design to consider the overall quality of evidence across outcomes. BHIVA has adopted the modified GRADE system for its guideline development (see Appendix 1). The advantages of the modified GRADE system are: (i) the grading system provides an informative, transparent summary for clinicians, PLWH and policymakers by combining an explicit evaluation of the strength of the recommendation with a judgement of the quality of the evidence for each recommendation, and (ii) the two-level grading system of recommendations has the merit of simplicity and provides clear direction to PLWH, clinicians and policymakers.

The strength of recommendation is graded as 1 or 2 as follows:

- A GRADE 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all PLWH. Most clinicians and HIV-positive individuals should and would want to follow a strong

recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'we recommend'.

- A GRADE 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Most clinicians and PLWH would want to follow a weak or conditional recommendation but many would not. Alternative approaches or strategies may be reasonable depending on the HIV-positive individual's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'we suggest'.

The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences and, where appropriate, resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and for the purpose of these guidelines is defined as the following:

- GRADE A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials (RCTs), or overwhelming evidence of some other sort (such as well-executed observational studies with consistent strong effects and a low likelihood of uncorrected bias). GRADE A implies confidence that the true effect lies close to the estimate of the effect.
- GRADE B evidence means moderate-quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strengths such as observational studies with consistent effects and exclusion of most potential sources of bias.
- GRADE C evidence means low-quality evidence from controlled trials with several very serious limitations or observational studies with limited evidence on effects and exclusion of most potential sources of bias.
- GRADE D evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there is likely to be little confidence in the effect estimate.

1.4 Good practice points

In addition to graded recommendations, the BHIVA writing group has also included good practice points (GPP), which are recommendations based on the clinical judgement and experience of the working group.

GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence. They address an aspect of treatment and care that is regarded as such sound clinical practice that healthcare professionals are unlikely to question it and where the alternative recommendation is deemed unacceptable. It must be emphasised that GPPs are not an alternative to evidence-based recommendations.

1.5 Dissemination and implementation

The following measures have or will be undertaken to disseminate and aid implementation of the guidelines:

- E-publication on the BHIVA website and the journal *HIV Medicine*;
- Publication in *HIV Medicine*;
- Non-technical leaflets;
- Shortened version for BHIVA guidelines app;
- E-learning module accredited for CME;

- Educational slide set to support local and regional educational meetings;
- National BHIVA audit programme.

1.6 Guideline updates and date of next review

The guidelines will be next fully updated and revised in 2019. However, the writing group will continue to meet regularly to consider new information from high-quality studies and publish amendments and addenda to the current recommendations before the full revision date where this is thought to be clinically important to ensure continued best clinical practice.

1.7 References

1. British HIV Association. *BHIVA Guideline Development Manual*. 28 January 2014. Available at: www.bhiva.org/GuidelineDevelopmentManual.aspx (accessed August 2015).

2. GRADE Working Group. Grading the quality of evidence and the strength of recommendations. Available at: www.gradeworkinggroup.org/intro.htm (accessed August 2015).

3. Guyatt GH, Oxman AD, Kunz R *et al.* Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–1051.

4. Pozniak AL, Coyne KM, Miller RF *et al.* British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–524.

2 Recommendations

Diagnosis of active pulmonary TB

We recommend performing microscopy for acid-fast bacilli (AFB) in conjunction with culture and drug-sensitivity testing on respiratory samples (sputum, induced sputum or bronchoalveolar lavage [BAL]); if smear-positive this should be followed by molecular testing, e.g. Xpert MTB/RIF, for rapid identification of MTB,. (GRADE 1B)

We recommend that all pulmonary smear-negative samples be processed for culture and drug-sensitivity testing. Where there is a high index suspicion for TB, molecular tests should also be considered. (GRADE 1B)

When individuals present with symptoms suggestive of tuberculosis, we recommend asking for any known TB contact among family members, colleagues and friends. (GPP)

Diagnosis of active extra-pulmonary TB

We recommend sending CSF samples for TB molecular tests and conventional microscopy and culture for AFB for the diagnosis of TB meningitis. (GRADE 1C)

We recommend performing microscopy and obtaining cultures for mycobacteria on respiratory samples (induced sputum/BAL) in individuals with suspected pleural TB, even in the absence of obvious lung parenchymal involvement. (GRADE 1B)

We recommend obtaining material for microscopy and culture for AFB, as well as histology in combination with molecular biological techniques, for diagnosis of extra-pulmonary TB. (GPP)

Diagnosis of multidrug-resistant TB infection

We recommend the routine use of molecular techniques, in addition to phenotypic drug susceptibilities, in order to achieve rapid detection of at least rifampicin and isoniazid resistance in patients' samples. (GRADE 1C)

We recommend that individuals with positive molecular tests for rifampicin resistance should be assumed to have MDR/XDRTB and managed in conjunction with a designated MDR centre. (GPP)

Diagnosis of latent TB infection

We recommend testing HIV-positive individuals from high- and medium-TB-incidence countries for LTBI, including pregnant women, regardless of their CD4 cell count and receipt of ART, with particular attention to those with newly diagnosed HIV or who have recently been exposed to TB. (GRADE 1B)

We recommend testing HIV-positive individuals from low-incidence countries for LTBI if they have additional TB risk factors. (GRADE 1B)

Prior to testing and providing treatment for LTBI, we recommend excluding active TB, by addressing presence of TB symptoms and signs and conducting investigations as appropriate. (GRADE 1A)

We suggest that, in the UK setting, IGRA rather than TST should be used when testing HIV-positive individuals for LTBI. (GRADE 2C)

The IGRA should be repeated within 4 weeks, where practicable, if the first result is indeterminate or borderline. (GPP)

We do not recommend the use of IGRA or TST in the diagnosis, or exclusion, of active TB. (GPP)

We recommend against testing for LTBI in individuals who have been treated for active tuberculosis. Whether or not to treat for LTBI will require individual risk assessment. (GPP)

Treatment of latent TB infection

We recommend treatment for LTBI for individuals with a positive IGRA in whom active TB has been excluded by clinical assessment and chest radiography. (GRADE 1B)

If a first and repeat IGRA are either indeterminate or borderline, the clinician should use clinical judgement when deciding whether to offer treatment for LTBI. (GPP)

We recommend offering testing for, and treatment of, LTBI for all HIV-positive individuals who are close contacts of people with infectious TB as per NICE guidelines. (GRADE 1B)
We recommend treatment for LTBI with: 6 months of isoniazid plus pyridoxine; or 3 months of isoniazid plus rifampicin plus pyridoxine. (GRADE 1A)
Treatment of active drug-sensitive TB
We recommend daily administration of standard TB therapy in those with drug-sensitive TB. (GRADE 1A)
We recommend that where effective ART necessitates the use of a ritonavir-boosted PI, rifampicin is substituted with rifabutin. (GRADE 1C)
We recommend that individuals with TB meningitis receive corticosteroids. (GRADE 1A)
We recommend using fixed-dose combination tablets (rifampicin/isoniazid, rifampicin/isoniazid/pyrazinamide and rifampicin/isoniazid/pyrazinamide/ethambutol) wherever possible, in order to enhance treatment adherence. (GPP)
Management of treatment failure and relapse
We recommend a microbiological diagnosis is pursued in all individuals with treatment failure and relapse, and that advice is sought from a centre with expertise in the management of such cases. (GPP)
We recommend that individuals who are diagnosed with treatment failure/relapse are managed in conjunction with centres of expertise who may design a new regimen based on results from rapid molecular testing and whole genome sequencing. If there is a clinical need for immediate treatment then the individual should receive, as per WHO recommendations, at least two to three new drugs from different classes while awaiting the results of drug susceptibility tests. (GPP)
Management of drug-resistant TB
We recommend, in individuals who are found to be infected with isoniazid mono-resistant isolates, a regimen of daily rifampicin, ethambutol, levofloxacin and pyrazinamide for 6 months. (GRADE 1C)
We recommend that all individuals with rifamycin- (including multidrug-) resistant TB are managed in conjunction with centres of expertise in the management of drug-resistant TB. (GPP)
We recommend that all individuals with rifampicin-resistant or multidrug-resistant TB who are not already on ART initiate ART as soon as they are stable and TB treatment is tolerated. (GRADE 1B)
Directly observed therapy (DOT)
We recommend individualised, enhanced patient-centred care plans for all patients, some of which may include DOT and video observed therapy (VOT). (GPP)
We recommend against the routine use of DOT and VOT in patients with active TB (GRADE 1B), but recommend it in MDRTB cases. (GPP)
Choice of antiretroviral treatment in individuals not on ART
When to start ART
We recommend all individuals with TB be offered ART as soon as is practicable and within 8–12 weeks of the TB diagnosis. (GRADE 1A)
We recommend that individuals with a CD4 cell count <50 cells/mm^3 be offered ART as soon as is practicable and within 2 weeks. (GRADE 1A)
We recommend against the early initiation of ART in individuals with CNS TB. (GRADE 1A)
What ART to start
We recommend efavirenz (standard dose) in combination with tenofovir (TDF) and emtricitabine (FTC) as first-line ART. (GRADE 1B)
We suggest that raltegravir (RAL) or dolutegravir (DTG) can be used for individuals in whom efavirenz (EFV) is contraindicated. (GRADE 2C)

We recommend that rifabutin is used instead of rifampicin where effective ART necessitates the use of ritonavir-boosted protease inhibitors. (GRADE 1C)
We recommend against the use of nevirapine (NVP) in ART-naïve individuals with TB treated with rifampicin. (GRADE 1B)
We recommend against the use of cobicistat, with rifampicin or rifabutin. (GRADE 1D)
We recommend against the use of fixed-dose combinations containing tenofovir alafenamide (TAF) when co-administered with rifampicin/rifabutin, and bictegravir until clinical outcome data become available to support this. (GRADE 2D)
Choice of antiretroviral treatment in individuals on established ART
We recommend that individuals who develop TB on ART with undetectable HIV viral loads do not interrupt their ART. (GRADE 1A)
We recommend that rifampicin-based TB treatment is used in individuals whose established ART consists of efavirenz (GRADE 1B), raltegravir (GRADE 2C) or dolutegravir (GRADE 2C) plus two NRTIs.
We recommend that rifabutin is used instead of rifampicin where established ART necessitates use of ritonavir. (GRADE 1C)
Drug interactions and toxicities
We recommend undertaking a complete medicines reconciliation prior to starting treatment for either TB or HIV. (GPP)
We recommend using prescribing resources (e.g. www.hiv-druginteractions.org, or http://hivclinic.ca/drug-information/drug-interaction-tables/) to screen for DDIs in all individuals with TB/HIV co-infection. (GPP)
IRIS (IRIS diagnosis/management)
We recommend the use of corticosteroids tapered over 4–6 weeks in clinically significant IRIS. (GRADE 1C)
We recommend that in recurrent IRIS, and in complex cases, advice is sought from centres with experience in managing this syndrome. (GPP)
Pregnancy and breastfeeding
We recommend that pregnant and breastfeeding women with drug-sensitive TB are treated with standard first-line anti-tuberculous therapy. (GRADE 1C)
Prevention and control of transmission
We recommend that all hospitals and HIV units have a TB infection control plan, which includes adequate protection of healthcare workers and other contacts. (GRADE 1B)
Notification/tracing of contacts
We recommend that once a person has been diagnosed with active TB, the diagnosing physician should inform relevant colleagues so that the need for contact tracing can be assessed without delay. Contact tracing should not be delayed until notification. (GRADE 1B)
We recommend screening the close contacts of any person with pulmonary or laryngeal TB. (GRADE 1B)
We suggest that enhanced contact tracing for PLWH, including contacts of people with EPTB, may be appropriate because of the higher risk of the TB infection and progression, and could be implemented where feasible. (GRADE 2C)

3 Introduction

These guidelines update the previously published BHIVA guidelines on the treatment of TB/HIV co-infection from 2011 [1] and are designed to provide a clinical framework applicable to adults living HIV in the UK who have TB. They do not include management of HIV-positive children with TB. The guidance is based on the evidence available, although some recommendations necessarily rely on expert opinion until further data become available.

These guidelines should be used in conjunction with:

- National Institute for Health and Care Excellence (NICE): Tuberculosis. Available at: www.nice.org.uk/guidance/ng33 [2];
- British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 [3];
- World Health Organization 2016 guidelines for the treatment of drug-resistant tuberculosis: www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/ [4].

The World Health Organization reported the following in 2015 [5]:

- An estimated 10.4 million people developed TB and 1.4 million died of TB, with an estimated 3.5 million cases and 496,000 TB deaths among women, and an estimated 950,000 cases and 210,000 deaths among children.
- An estimated 1.2 million (11%) of the 10.4 million people who developed TB in 2015 were HIV positive.
- 1.4 million HIV-negative persons died from the disease and there were 390,000 deaths among HIV-positive people.
- An estimated 510,000 women died as a result of TB, more than one-third of whom were HIV positive.
- Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide.

The incidence of TB in England is higher than in most western European countries [6]. While it was declining during most of the 20th century, a steady increase was observed from the late 1980s to 2005.

The annual incidence rates of TB among adults living with diagnosed HIV in England and Wales declined from 17 per 1000 (420/23,990) in 2008 to 4.3 per 1000 (300/68,350) in 2011 [7]. This trend is largely due to a decline in new HIV diagnoses among men and women born in countries of sub-Saharan Africa where the prevalence of both HIV and TB is high, as well as to an increase in total number of people living with HIV [8].

TB incidence varies by demographic characteristics with rates among people born outside the UK of 7.7 per 1000 population (in 2011), women (6.7), those aged 25–39 years (10.5) and people of black African ethnicity (7.7).

The risk of developing TB is estimated to be between 26 and 31 times greater in people living with HIV than among those without HIV infection. Thus, all individuals with TB, regardless of their perceived risk of HIV infection, should be offered an HIV test.

In HIV co-infection, the clinical and radiographic presentation of TB may be atypical. Compared with the immune-competent population, TB/HIV-positive individuals with active pulmonary TB are more likely to have normal chest radiographs or to have sputum that is smear negative but culture positive [9,10] (see Section 5 and Appendix 3).

The clinician caring for HIV-positive individuals therefore needs to have a high index of suspicion for TB in symptomatic individuals, especially those who have lived in TB-endemic parts of the world. As the investigation and treatment of both TB and HIV infection is complex, it is mandatory to involve specialists in HIV, respiratory and/or infectious diseases.

3.1 References

1. Pozniak AL, Coyne KM, Miller RF *et al.* British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–524.
2. NICE. *Tuberculosis. NICE guideline [NG33]*. 2016. Available at: www.nice.org.uk/guidance/ng33 (accessed November 2017).
3. Waters L, Ahmed N, Angus A *et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. 2016 Interim update*. 2015. Available at: http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf (accessed November 2017).
4. World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis, 2016 Update. 2016.
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8. Rice B, Elford J, Yin Z *et al.* Decreasing incidence of tuberculosis among heterosexuals living with diagnosed HIV in England and Wales. *AIDS* 2013; **27**: 1151–1157.
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10. Chaisson RE SG, Theuer CP, Rutherford GW, Echenberg DF, Hopewell PC. Tuberculosis in patients with the acquired immunodeficiency syndrome. Clinical features, response to therapy, and survival. *Am Rev Respir Dis* 1987; **136**: 570–574.

4 Aims of TB treatment

Treatment of TB benefits the individual and also the community. The aims of treatment are [1]:

- To cure the patient and restore quality of life and productivity;
- To prevent death from active TB or its late effects;
- To prevent relapse of TB;
- To reduce transmission of TB to others;
- To prevent the development and transmission of drug resistance.

4.1 References

1. World Health Organization. *Guidelines for treatment of tuberculosis. 4th edn*. 2010. Available at: www.who.int/tb/publications/2010/9789241547833/en (accessed March 2017).

5 Diagnosis of active TB/HIV (diagnostic tests)

5.1 Pulmonary TB diagnosis in HIV

We recommend performing microscopy for acid-fast bacilli (AFB) in conjunction with culture and drug-sensitivity testing on respiratory samples (sputum, induced sputum or bronchoalveolar lavage [BAL]); if smear-positive this should be followed by molecular testing, e.g. Xpert MTB/RIF, for rapid identification of MTB,. (GRADE 1B)

We recommend that all pulmonary smear-negative samples be processed for culture and drug-sensitivity testing. Where there is a high index suspicion for TB, molecular tests should also be considered. (GRADE 1B)

When individuals present with symptoms suggestive of tuberculosis, we recommend asking for any known TB contacts among family members, colleagues and friends. (GPP)

5.1.1 Rationale

Microscopic smear of clinical specimens remains an essential part of TB diagnosis. The quality of any investigation is related to the quality of the specimen and the clinical detail provided with the request. There must therefore be close liaison with the mycobacterial laboratory. Results should be available within 1 working day.

Use of molecular biology allows for early identification of mycobacteria and of genotypic (rifampicin/isoniazid) drug susceptibility. The Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) is an automated molecular test for *M. tuberculosis* identification and *rpoB* mutations conferring resistance to rifampicin. It is very specific (99%) and its sensitivity for smear-positive, culture-positive TB approaches 98% compared with microscopy, which has a sensitivity of 65% [1]. The sensitivity for RIF resistance is a little lower (95%) than the sensitivity for MTB identification (see Appendix 3). In smear-positive samples, its use can allow rapid confirmation that AFB are not *M. tuberculosis*, potentially avoiding unnecessary treatment and infection-control measures [2].

The newer Gene Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA USA) has been shown to have improved sensitivity but lower specificity in HIV-positive individuals compared with Gene Xpert MTB/RIF [3] and is recommended by WHO for sputum and selected extra-pulmonary samples [4].

Despite the high sensitivity and specificity, molecular biology tests have to be performed together with cultures and phenotypic drug susceptibility testing. All specimens, even those negative for *M. tuberculosis* on polymerase chain reaction (PCR), still require culture because a negative PCR does not exclude *M. tuberculosis* and a positive PCR does not currently indicate the full drug-susceptibility profile [5,6].

Whole genome sequencing (WGS) is available in the UK and is currently being used to identify clusters and to detect genotypic resistance but it requires a culture isolate; Gene Xpert can be performed on a primary sample (without the need for a positive culture), for example a sputum sample, and detects MTB and mutations associated with rifampicin resistance more quickly.

The sensitivity and specificity of IGRAs in HIV-positive people is suboptimal when used alone to ‘rule in’ or ‘rule out’ active tuberculosis disease [7-10]. IGRAs should not be used to diagnose or exclude active TB (see Appendix 3).

Identification of mycobacteria is performed at reference centres, and is based on molecular techniques, morphology, growth and biochemical characteristics.

Liquid culture media provide more rapid results than solid media and usually grow *M. tuberculosis* in 7–28 days. Drug-susceptibility tests are usually available within 10–21 days of the laboratory receipt of isolates, by WGS and phenotypic assays.

5.2 Diagnosis of extra-pulmonary TB (EPTB)

5.2.1 TB of the CNS

We recommend sending CSF samples for TB molecular tests, conventional microscopy and culture for AFB for the diagnosis of TB meningitis. (GRADE 1C)

5.2.2 Rationale

The commonest presentation of tuberculosis in the CNS is tuberculous meningitis (TBM), which is the most severe form of TB with the highest mortality (between 20% and 50%) and morbidity, as diagnosis and treatment are often delayed [11].

Less commonly it can manifest as tuberculous encephalitis, intracranial tuberculomas or tuberculous brain abscess(es) [11].

Early diagnosis is challenging due to the non-specific symptoms of TBM, such as fever, headache and vomiting, with gradual onset and duration, often lasting for weeks. Meningism, with or without focal neurological deficits, behavioural changes and alterations in consciousness are also features of TBM.

The main investigations are cranial imaging (MRI) and lumbar puncture for CSF analysis.

Significant CSF findings in TBM include a mainly mononucleate cell (lymphocytic predominant) pleocytosis in 60–85% of patients, in which the total white count ranges between 100 and 500 cells/mm^3. In advanced HIV, CSF can be acellular. Low CSF glucose levels (usually less than 2.5mmol/L) and a high protein, typically between 1 and 5 g/L, are also suggestive of TBM.

Identification of *M. tuberculosis* in CSF by culture remains the 'gold standard', but has a limited sensitivity (ranging between 10% and 60%). Microscopy with Ziehl–Neelsen staining for AFB detection has a low sensitivity in the CSF (range 10–60%), due to the small number of tubercle bacilli usually present. Large volumes (minimum 6 mL) of CSF should be examined to enhance the sensitivity [12,13].

The World Health Organization recommendation is to use Xpert MTB/RIF as the preferred initial test for diagnosis of TB meningitis over conventional tests (see Appendix 3). However, a negative Xpert MTB/RIF result on a CSF sample does not exclude TB meningitis.

Where available, use of Xpert MTB/RIF ultra is preferred as it has a higher sensitivity than Xpert MTB/RIF in diagnosing TB meningitis [14].

Adenosine deaminase (ADA) (a predominant T lymphocyte enzyme, which catalyses the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively) measurement can also be of use in the diagnosis of TB meningitis. Levels in CSF are significantly elevated in TBM with a sensitivity and specificity ranging from 60–90% and 80–90%, respectively [15]. However, the ADA assay has not been standardised and the 'cut-off' level that defines a positive result has not been determined, and consequently it is not recommended as part of routine investigation for TB meningitis [16,17].

5.3 TB pleuritis

In addition to performing pleural fluid and tissue analysis, we recommend performing microscopy and obtaining cultures for mycobacteria on respiratory samples (induced sputum/BAL) in individuals with suspected pleural TB, even in the absence of obvious lung parenchymal involvement [18]. (GRADE 1B)

5.3.1 Rationale

Where HIV is endemic, TB pleuritis is the most common cause of a lymphocytic effusion, thought to result from primary infection in 30% of patients [19].

In individuals with a suspected TB pleural effusion it is important to obtain cultures on pulmonary (generally sputum or bronchoscopic) samples, even in the absence of obvious parenchymal involvement, as even in individuals with normal underlying lung parenchyma on chest radiography, the yield of sputum culture in induced samples approaches 55% [18].

The diagnosis of TB pleuritis is also made by detection of *M. tuberculosis* in pleural fluid or pleural biopsy specimens, or by assumption if *M. tuberculosis* is identified in sputum and there is co-existent pleural effusion, either by microscopy and/or culture, or the histological demonstration in the pleura of caseating granulomas together with AFB.

Microscopy for AFB in the pleural fluid can identify *M. tuberculosis* in approximately 20% of HIV-positive individuals with pleural tuberculosis, though the yield can be up to 50% [20] if the patient's CD4 cell count is less than 100 cells/mm^3 [20,21].

TB PCR has a low sensitivity for diagnosis of pleural TB. A pooled analysis of data from 20 studies that assessed the use of pleural fluid molecular diagnostic tests showed a high specificity (97% for commercial and 91% for in-house tests), but a generally poor and variable sensitivity (62% for commercial and 76.5% for in-house tests) [6].

Where available, medical thoracoscopy may be useful in the diagnosis of pleural TB. In low TB incidence settings thoracoscopy has proved to be an effective diagnostic tool in HIV-negative patients, with a pooled sensitivity for TB on culture and histology of 93%, in combination with ADA, and a specificity of 100% [19].

Measurement and quantification of ADA in pleural fluid may also be useful. Individuals who present with a lymphocytic predominant exudative pleural effusion and raised ADA level have a high probability of having pleural TB (see Appendix 3).

5.4 Disseminated TB

We recommend obtaining material for microscopy and culture for AFB, as well as histology in combination with molecular biological techniques, for diagnosis of extra-pulmonary TB. (GPP)

5.4.1 Rationale

Data on the accuracy of molecular biological tests for diagnosis of TB in non-respiratory specimens have been reported in two systematic reviews, which both support their use in diagnosis of EPTB [22,23] (see Appendix 3).

The urine lateral flow lipoarabinomannan (LF-LAM) assay is a point-of-care (POC) test for active TB (AlereDetermine TB LAM Ag, Alere Inc., Waltham, MA, USA). The test detects lipoarabinomannan (LAM), a lipopolysaccharide present in mycobacterial cell walls, released from metabolically active or degenerating bacterial cells. This antigen appears to be present only in people with active TB disease. The advantages of the test are its simplicity and speed of use, lack of instrumentation, low cost and its implementation at the point of care. Its sensitivity is highest in those individuals with a CD4 cell count <100 cells/mm^3 [24].Therefore it represents a useful adjunctive diagnostic for those with CD4 cell counts below 100 cells/mm^3, and in those presenting seriously ill with an unknown cause.

Mycobacterial blood culture has also proven useful in diagnosis of disseminated TB in patients with low CD4 cell counts (sensitivity 20–40%) [25].

5.5 Cytopathology (lymph nodes, lung aspirate, focal lesions)

The cytopathological diagnosis of TB is based on finding acid and alcohol-fast bacilli (AFB) on Ziehl–Neelsen (ZN) staining of tissue or a cytological preparation (e.g. a lymph node aspirate). Supplementary supportive evidence is the finding of macrophage granulomas with or without necrosis.

The finding of AFB in a cytopathological specimen should be critically interpreted in the context of a patient's presentation, their imaging findings and results from other laboratory investigations. It is important to precisely identify AFB where possible, using culture and molecular diagnostic techniques.

5.6 Histopathology

The classical lesions of TB include epithelioid cell granulomas with or without Langhans giant cells and caseation necrosis, and AFB. Other diseases, infectious and non-infectious, have similar granuloma morphology as TB, and fungal stains must always be undertaken to exclude mycosis (e.g. histoplasmosis) as the relevant agent.

If TB is diagnosed histopathologically, but standard treatment appears ineffective, non-tuberculous mycobacterial infection should be considered. Other differential diagnoses that can mimic TB include: sarcoidosis, histoplasmosis, nocardiosis, leishmaniasis, granulomatous reaction to local tumour, common variable immunodeficiency syndromes, vasculitis syndromes, autoimmune diseases, and Gram-negative infections (e.g. brucellosis, melioidosis).

In difficult cases, multidisciplinary consultation is invaluable, where all the information – clinical, radiological, pathological, molecular diagnostics and results of treatment – can be critically reviewed.

Because the presence of granulomas is regarded as typical of TB, differential diagnoses should be considered, especially if response to treatment is not progressing as expected.

5.7 Diagnosis of multidrug-resistant TB

We recommend the routine use of molecular techniques, in addition to phenotypic drug sensitivities, to achieve rapid detection of at least rifampicin and isoniazid resistance in patients' samples. (GRADE 1C)

We recommend that individuals with positive molecular tests for rifampicin resistance should be assumed to have MDR/XDRTB and managed in conjunction with a designated MDR centre. (GPP)

5.7.1 Rationale

MDRTB definition: resistance to at least isoniazid and rifampicin.

Pre-XDRTB definition: resistance to isoniazid and rifampicin and either a fluoroquinolone or second-line injectable agent but not both.

XDRTB definition: resistance to isoniazid and rifampicin and quinolones and at least one of the following injectable drugs: kanamycin, capreomycin, amikacin.

The number and proportion (1.6%) of TB cases with initial MDR/RRTB in England has been relatively stable since the peak in 2011 (89, 1.8%). PHE reports that In England in 2015, 4.6% (6/130) of patients with HIV/TB co-infection had RRTB/MDRTB, and 6.2% (8/130) of TB-HIV co-infected cases had isoniazid resistance without MDR-TB [26].

The presence of the following risk factors should always raise suspicion of possible drug-resistant TB:

- Previous TB treatment;
- Contact with MDR/XDRTB index case;
- Birth, travel or work in settings with very high MDR/XDRTB prevalence (as defined by Public Health England);
- History of poor adherence to previous TB treatment regimens;
- No clinical improvement on standard TB therapy and/or sputum remains 'smear' positive after 2 months of TB therapy or remains culture positive at 3 months;
- Homelessness/hostel living and in some countries recent/current incarceration.

Molecular tests for rifampicin resistance are useful when MDRTB is suspected (e.g. a recent immigrant from an area with a high prevalence of rifampicin-resistant disease), as a large proportion of RIF-resistant strains have INH resistance as well [27] (see Appendix 3).

5.8 References

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6 Diagnosis and treatment of latent TB in HIV-positive adults

6.1 Diagnosis of latent TB

We recommend testing HIV-positive individuals from high- and medium-TB-incidence countries for LTBI, including pregnant women, regardless of their CD4 cell count and receipt of ART, with particular attention to those with newly diagnosed HIV or who have recently been exposed to TB. (GRADE 1B)

We recommend testing HIV-positive individuals from low-incidence countries for LTBI if they have additional TB risk factors. (GRADE 1C)

Prior to testing and providing treatment for LTBI, we recommend excluding active TB, by addressing presence of TB symptoms and signs and conducting investigations as appropriate. (GRADE 1A)

We suggest that, in the UK setting, IGRA rather than TST should be used when testing HIV-positive individuals for LTBI. (GRADE 2C)

The IGRA should be repeated within 4 weeks, where practicable, if the first result is indeterminate or borderline. (GPP)

We do not recommend the use of IGRA or TST in the diagnosis, or exclusion, of active TB. (GPP)

We recommend against testing for LTBI in individuals who have been treated for active tuberculosis. Whether or not to treat for LTBI will require individual risk assessment. (GPP)

6.1.1 Rationale

In the UK, the majority of cases of TB occur in those from high and medium-incidence settings [1], suggesting a substantial role for reactivation of latent infection. Individuals with latent TB infection (LTBI) are at increased risk of developing active TB, especially if they are recently infected with *M. tuberculosis* or immunocompromised [1]. HIV-positive individuals from high TB-incidence countries, especially those from sub-Saharan Africa, often present with TB as the first manifestation of immunosuppression, and mortality among HIV-positive persons with TB remains high [2]. We define high and medium TB incidence as ≥151/100,000 and 40–150/100,000 person years, respectively [3]. (See [4,5] for up-to-date TB incidence by country. LTBI testing for new entrants to the UK from high TB-incidence countries is an effective and cost-effective public health intervention [6] and is recommended by NICE [3]. WHO guidelines for low tuberculosis-burden countries [7] advise testing for LTBI in all HIV-positive individuals. However, this approach has recently been shown unlikely to be cost-effective in the UK [8].

The risk of progression to active TB in the general population is highest within the first 2–3 years following *M. tuberculosis* infection and HIV-positive individuals with LTBI are much more likely to progress to active TB than HIV-negative individuals [9]. Increased incidence of active TB is associated with low CD4+ cell counts, including while on ART, and with shorter time on ART [10-13]. Long-term successful ART substantially reduces the risk of TB among HIV-positive individuals, although it should be remembered that in populations from high TB-incidence countries, such as those of sub-Saharan Africa, the background risk of TB (irrespective of HIV co-infection) is already high [2] (see Table 6.1).

A positive IGRA in an individual with no clinical or radiological evidence of active TB indicates LTBI for clinical purposes. Before testing for or treating LTBI, active TB should be excluded with a detailed history and examination. The advantages of IGRAs include the practical benefit of a single blood test with no need for patient recall to read the result. They are more costly than TST, although the savings may offset in, for instance, healthcare worker time and possible better specificity leading to fewer individuals being treated for LTBI [6,14].

Although the proportion of individuals with a positive IGRA after treatment for active TB decreases with time [15], a positive IGRA even several years after treatment could still indicate previous

treated disease. In that population, treatment for LTBI may be considered if there has been significant new exposure only.

NICE recommends testing for LTBI with an IGRA and concurrent TST in HIV-positive individuals [3]. However, in view of operational and cost disadvantages of TST, a reduced sensitivity among those with low CD4+ cell counts, and false-positive results due to prior BCG vaccination and exposure to non-tuberculous mycobacteria, plus limited data comparing strategies of using IGRA and TST to identify LTBI among those with low CD4+ cell counts, we recommend the sole use of IGRA in a UK setting (see Appendix 4). The ongoing PREDICT study [16] may inform a more evidence-based future recommendation.

Some individuals born in low-incidence countries, including the UK, will be at greater risk of developing TB than others. We recommend considering testing for and treating LTBI in those from low-incidence countries (for example UK-born) who have additional risk factors such as exposure to a known TB case (which should be identified through routine contact tracing); travel to or periods of time (we suggest >12 months) spent consecutively in higher-incidence countries [3]. Particular additional factors of relevance to HIV-positive individuals include: a history of working in medical settings in endemic areas; injecting drug use; stage 4/5 chronic kidney disease; diabetes mellitus; receipt of chemotherapy for malignancy; immunosuppression following organ transplantation; and biological disease modifiers for inflammatory conditions.

We suggest that services make local arrangements for managing the increase in numbers requiring testing (and treating) for LTBI compared to the previous guideline, depending on numbers of patients and service capacity. We suggest that it is acceptable to discuss and offer testing to those at risk at their routine follow-up appointments.

In pregnant women newly diagnosed with HIV, we recommend testing and treating LTBI in the same way as non-pregnant individuals, including use of chest radiography, if clinically indicated. In making this recommendation, we have considered the risk of toxicity from treatment for LTBI. Hepatotoxicity in particular is associated with other co-existing risk factors (see below).

We suggest using an algorithm (Figure 6.1) similar to that proposed by the WHO for use in excluding active TB [17]. Other investigations may be necessary, for example chest radiography or lymph node biopsy (if lymphadenopathy is detected clinically or through imaging). It is important to consider the possibility of subclinical TB prior to starting ART because of the risk of IRIS, particularly among those with low CD4 cell counts [18]. (See Section 12 and Appendix 7.)

Figure 6.1. Algorithm for LTBI diagnosis and treatment

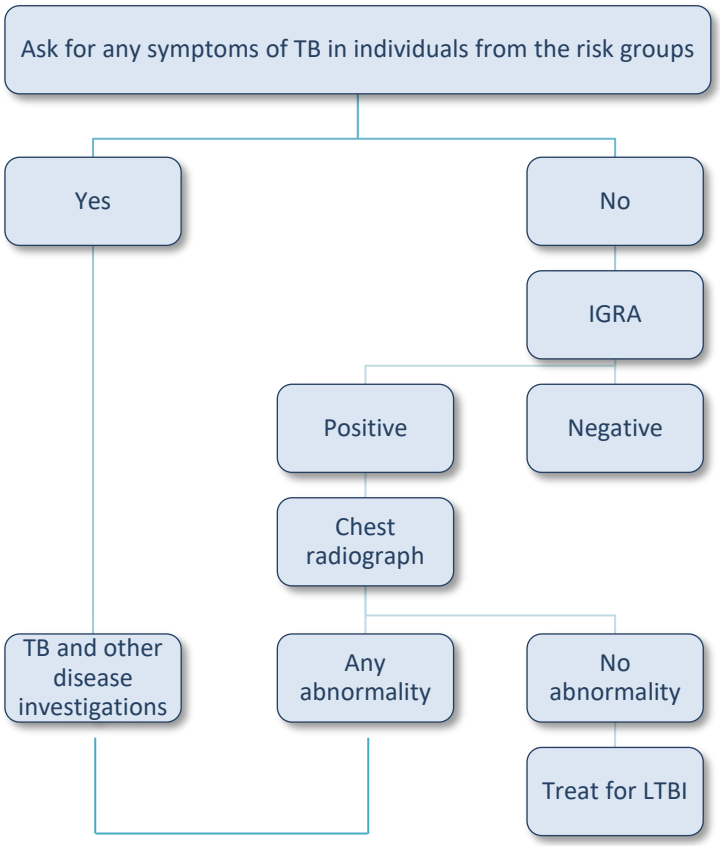

Table 6.1. Risk factors for infection with TB

Origin from high/medium TB-incidence country
HIV-positive individuals with CD4+ cell counts <200 cells/mm^3
Recent exposure to a known TB case
Diabetes mellitus
Stage 4/5 chronic kidney disease
Receipt of chemotherapy for malignancy; immunosuppression following organ transplantation; biological disease modifiers for inflammatory conditions; prolonged duration of high-dose corticosteroids (20 mg od prednisolone, or equivalent, for 2 months, or longer)
Travel to or periods of time spent consecutively in higher-incidence countries. Duration of travel to be considered if >12 months
History of working in medical settings in endemic areas
Injecting drug use

6.2 Treatment of latent TB infection

We recommend treatment for LTBI for those individuals with a positive IGRA, in whom active TB has been excluded by clinical assessment and chest radiography. (GRADE 1B)

If a first and repeat IGRA are either indeterminate or borderline, the clinician should use clinical judgement when deciding whether to offer treatment for LTBI. (GPP)

We recommend offering testing for, and treatment of, LTBI for all HIV-positive individuals who are close contacts of people with infectious TB, as per NICE guidelines. (GRADE 1B)

We recommend treatment for LTBI with: 6 months of isoniazid plus pyridoxine; or 3 months of isoniazid plus rifampicin plus pyridoxine. (GRADE 1A)

6.2.1 Rationale

There have been many short-term controlled trials in HIV-positive individuals showing a protective effect of treatment for LTBI with an efficacy ranging from 60 to 90% (see Appendix 4).

Several studies have compared different regimens for treating LTBI [19-21] and no difference in efficacy was found. We concur with NICE recommendations [3] and recommend either:

1. Daily isoniazid with pyridoxine for 6 months
2. Daily isoniazid (with pyridoxine) and rifampicin for 3 months

Other regimens that might be considered, depending on individual circumstances and concomitant medications, and which have evidence for equivalent efficacy include:

3. Isoniazid and rifampicin (with pyridoxine) twice weekly for 3 months [19].

Regimens 2 and 3 have been shown to be equivalent to regimen 1 in terms of TB-free survival [19] and in the prevention of incident TB after treatment and hepatotoxicity of grade 3 or above [20,21].

A regimen of rifampicin plus pyrazinamide has been shown to be effective in preventing active TB, but there is evidence that pyrazinamide-containing regimens cause more hepatotoxicity than isoniazid alone and they are therefore not recommended [21-23]. Care must be taken to avoid drug–drug interactions with ART.

Rifapentine-based regimens for LTBI treatment are not discussed in this guideline, given the lack of availability of rifapentine in the UK.

Mild, non-specific hepatotoxicity occurs in up to 20% of individuals taking isoniazid, but most of this is subclinical and evidenced only by mildly elevated serum aminotransferases (usually <100 IU/L) [24]. During isoniazid therapy for LTBI, clinical symptomatic hepatotoxicity is rare (<1%) but can be fatal, particularly if associated with other factors, for example alcohol, increased age, slow acetylator status or concurrent liver disease [25,26].

Most hepatotoxicity is self-limiting and isoniazid can be continued with clinical and laboratory monitoring. The risk of severe (ACTG grade 3 or above) hepatotoxicity associated with isoniazid therapy for LTBI is 0.1–0.3% according to different studies [27,28]. Rifampicin-containing regimens should also be prescribed with caution due to potential drug–drug interactions.

When considering treatment for LTBI, the potential benefit needs to be carefully balanced against the risk of drug-related adverse events. Individuals treated for LTBI should be informed of symptoms of hepatotoxicity, such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. Those experiencing these symptoms, particularly patients aged >65 years, should be advised to contact their healthcare providers, and to stop treatment immediately if there is a delay in doing so.

6.3 Drug-resistant TB after treatment of LTBI

Studies of isoniazid treatment for LTBI have included the risk of isoniazid-resistant active TB as a secondary outcome. Although there are theoretical concerns that widespread isoniazid monotherapy might speed the emergence of drug-resistant TB [29], evidence from trials has shown

no significant association between anti-tuberculous drug resistance and prior use of isoniazid and/or rifamycins for LTBI [19,30,31].

6.4 Secondary prophylaxis after treatment for active TB and longer-term isoniazid preventive therapy

Studies in areas of high TB incidence have shown that isoniazid prophylaxis post-treatment achieves short-term reductions in rates of TB [32,33] and that long-term isoniazid therapy (36 months in trials) reduces TB incidence [34,35] among HIV-positive individuals. Such a strategy may in fact prevent reinfection, which is more common than true reactivation in such settings [36]. For maximum benefit the isoniazid would need to be continued long-term, or at least until CD4+ cell count had substantially risen on ART, and there are no data to support such an approach, particularly from lower TB-incidence settings.

It is clear that ART protects against TB. It should be initiated if not already in place, and continued, for those with active and latent TB (see Section 9 and Appendix 8).

Continuation of TB prophylaxis after treatment of active TB is therefore not recommended in the UK setting, but ART should be continued.

6.5 Treatment of LTBI in individuals exposed to drug-resistant TB

For HIV-positive individuals with a history of exposure to drug-resistant TB (resistant to one or more first-line drugs), there are limited data to support any particular course of action. To help management of such cases an individualised management plan might be formulated from collaboration between the individual, their HIV physician, a specialist in the management of drug-resistant TB, and public health services. Options include: inform and advise the patient regarding early presentation with any symptoms of possible TB; use a treatment regimen for LTBI to which the source patient's isolate is considered to be susceptible; use of standard LTBI regimens if there is thought to have been pre-existing LTBI before the contact with drug-resistant disease occurred.

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7 Treatment of active drug-sensitive TB

We recommend daily administration of standard TB therapy in those with drug-sensitive TB. (GRADE 1A)

We recommend that where effective ART necessitates the use of ritonavir-boosted PI, rifampicin is substituted with rifabutin. (GRADE 1C)

We recommend that individuals with TB meningitis receive corticosteroids. (GRADE 1A)

We recommend using fixed-dose combination tablets (rifampicin/isoniazid, rifampicin/isoniazid/pyrazinamide and rifampicin/isoniazid/pyrazinamide/ethambutol) wherever possible, in order to enhance treatment adherence. (GPP)

7.1 Rationale

The treatment of drug-susceptible tuberculosis evolved through an international clinical trial programme to the current standard of care: short-course chemotherapy, consisting of 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol (intensive phase), followed by 4 months of rifampicin and isoniazid (continuation phase) (2RHZE/4RH) [1,2] (see Table 7.1).

We recommend the use of daily fixed-dose combinations, where available.

Table 7.1. First-line anti-tuberculosis agents and guidance on standard dosing

Drugs	Usual daily dose
Isoniazid (H)	5 mg/kg Max 375 mg
Rifampicin (R)	10 mg/kg Max 750 mg
Pyrazinamide (Z)	25–35 mg/kg Max 2 g
Ethambutol (E)	15–20 mg/kg Max 1.5 g

Several recent attempts to shorten TB therapy to 4 months (for instance, by using fluoroquinolones) have proved unsuccessful, with high relapse rates [3-6]. Intermittent administration of TB therapy should be avoided during the induction phase in HIV-positive individuals, as this strategy has been associated with acquired rifamycin resistance [7].

There is no evidence that individuals with disseminated TB should receive more prolonged therapy unless there is CNS involvement. Many clinicians use extended treatment regimens (up to 12 months, as per NICE guidance [8]) for central nervous system tuberculosis (i.e. tuberculous meningitis) even though 6–9 months may be sufficient.

Rifabutin is a rifamycin with similar activity as rifampicin against *M. tuberculosis* [9-11] although no trials have been conducted in individuals receiving ART. The main advantage of rifabutin is that it allows the co-administration of (ritonavir-boosted) protease inhibitors. (See Section 10 and Appendix 6).

Corticosteroids should be used as an adjunct to TB therapy to reduce the immune/inflammatory response to *M. tuberculosis* in those with meningitis. A randomised controlled clinical trial of individuals with tuberculous meningitis showed a 31% reduction in mortality among individuals who received adjunctive dexamethasone during the induction phase [12][13]. Participants with Grade II/III disease (Glasgow coma scale score <15 or focal neurological signs) received dexamethasone 0.4 mg/kg/day for week 1, 0.3 mg/kg/day for week 2, 0.2 mg/kg/day for week 3, and 0.1 mg/kg/day for week 4, followed by a further 4 weeks of oral therapy, starting at a dose of 4 mg/kg/day and decreasing by 1 mg/kg/day each week. Patients with mild disease received shorter (6 weeks) therapy: 2 weeks of intravenous therapy (dexamethasone 0.3 mg/kg/day for week 1 and

0.2 mg/kg/day for week 2) followed by 4 weeks of oral therapy (0.1 mg/kg/day for week 3, then a total of 3 mg/day, decreasing by 1 mg each week).

Steroids can also be used in severe immune reconstitution inflammatory syndrome (see Section 12). The use of corticosteroids in HIV-positive individuals with pericarditis and pleurisy was associated with a significantly increased risk of HIV-associated diseases (Kaposi sarcoma and CMV disease [13,14]). Additionally, in individuals with pericarditis, 6 weeks of prednisolone did not reduce the risk of death, cardiac tamponade and constrictive pericarditis [15] and although corticosteroid use in individuals with pleurisy has been associated with more rapid resolution of pleural effusions and reduced pleural thickening, there was no effect on mortality, respiratory function or pleural adhesions [14]. We therefore recommend against the routine use of corticosteroids in individuals with TB/HIV co-infection who do not have meningitis or severe IRIS; if clinically indicated, corticosteroids should be used at the lowest effective dose and for the shortest duration.

Mycobacterial disease may be due to non-tuberculous mycobacteria such as *M. avium* complex (MAC). Individuals with disseminated MAC tend to be profoundly immunosuppressed (CD4+ cell count <100 cells/mm^3 and/or concomitant opportunistic disease). Not infrequently, MAC disease is unmasked following the initiation of antiretroviral therapy. Smear AFB-positive specimens from individuals with MAC, rather than *M. tuberculosis*, would have negative molecular tests for *M. tuberculosis* DNA (see Appendix 3).

In patients with CD4+ cell counts <100 cells/mm^3, improved survival was observed with higher doses of rifampicin (15 mg/kg) during the induction phase (when starting ART at 8 weeks). There was no evidence of an increased risk of hepatotoxicity with higher-dose rifampicin [16].

Individuals with severe immunodeficiency and clinical presentation fitting with disseminated *M. avium* complex infection may benefit from the inclusion of rifabutin (instead of rifampicin) as well as clarithromycin or azithromycin in the empirical regimen to provide cover against MAC until culture results become available.

7.2 Interruptions of therapy

Anti-tuberculosis treatment interruptions can occur as a result of drug reactions and severe adverse events in HIV-associated TB. If the reason was poor adherence and the patient was on self-administered therapy, then supervised treatment should be considered. If the patient was already being managed with DOT/VOT, additional measures may be necessary to ensure adherence, for instance provision of transport, food and social services. See Table 7.2 for details on management of treatment interruptions.

Table 7.2. Management of treatment interruptions[a]**.** From [17]

Time point of interruption	Details of interruption	Approach
During intensive phase	Lapse is <14 days in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)
	Lapse is ≥14 days in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear negative on initial testing in pulmonary disease	Further therapy may not be necessary
	Received ≥80% of doses and sputum was AFB smear-positive on initial testing, or disease extrapulmonary	Continue all doses until therapy is complete
	Received <80% of doses and cumulative lapse is <3 months in duration	Continue all doses until therapy is completed (full course), unless consecutive lapse is >2 months If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (i.e. restart intensive phase, to be followed by continuation phase)[b]
	Received <80% of doses and lapse is ≥3 months in duration	Restart therapy from the beginning, new intensive and continuation phases (i.e. restart intensive phase, to be followed by continuation phase)

AFB: alcohol-acid fast bacilli

[a] According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum re-sent for AFB smear culture, and drug-susceptibility testing.

[b] The recommended time frame for regimen, in tuberculosis control programmes in the US and in several European countries, is to administer all of the specified number of doses for the intensive phase within 3 months and those for the 4-month continuation phase within 6 months, so that the 6-month regimen is completed within 9 months.

7.3 Investigations and monitoring

Prior to commencing TB therapy:
HIV plasma load and CD4+ cell count
Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), bilirubin and alkaline phosphatase
Serum creatinine and estimated glomerular filtration rate
Platelet count
Hepatitis B and C serology
We suggest visual acuity is assessed with Snellen chart and colour vision with Ishihara plates before starting ethambutol.
HIV-positive individuals are at higher risk of drug reactions, especially those with low CD4+ cell counts, and are more likely to be co-infected with hepatitis B and/or C than HIV-negative individuals. Furthermore, they may be starting concomitant antiretroviral and other therapies, all of which may cause liver enzyme elevation and/or hepatotoxicity. We suggest that liver function tests should be rechecked at 1–2 weeks. Individuals with pre-existing liver disease need close monitoring, for instance every 2 weeks for the first 2 months. Most physicians will see the patient 2 weeks after starting anti-tuberculosis therapy and then monthly until stable and 1–2 monthly until therapy has been completed.

7.4 References

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8 Management of relapse, treatment failure and drug-resistant TB including directly observed therapy (DOT)

8.1 Management of treatment failure and relapse

We recommend a microbiological diagnosis is pursued in all individuals with treatment failure and relapse, and that advice is sought from a centre with expertise in the management of such cases. (GPP)

We recommend that individuals who are diagnosed with treatment failure/relapse are managed in conjunction with centres of expertise that may design a new regimen based on results from rapid molecular testing and whole genome sequencing. If there is a clinical need for immediate treatment then the patient should receive, as per WHO recommendations [1] at least two to three new drugs from different classes while awaiting the results of drug susceptibility tests. (GPP)

8.2 Rationale

8.2.1 Definitions

- Treatment failure: smear or culture positivity at month 5 or later [1].
- Relapse: individuals previously treated for TB, declared cured or treatment completed/at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
- Treatment after failure: individuals previously treated for TB and whose treatment failed at the end of their most recent course of treatment.

After 3 months of multidrug therapy for pulmonary TB caused by drug-susceptible organisms, up to 98% of individuals will have negative cultures and show clinical improvement. All individuals with positive cultures after 3 months of appropriate treatment must be evaluated carefully to identify the cause of the delayed conversion.

The main reason for treatment failure and relapse is suboptimal prescription of, or adherence to, appropriate TB treatment. Other factors that may increase the risk of treatment failure and relapse include presence or development of drug resistance or drug intolerance, use of intermittent TB therapy, malabsorption of TB drugs, extreme biological variation in the response to TB therapy and hetero-resistance or reinfection with drug-resistant strains. Antiretroviral therapy reduces the risk of treatment failure with acquired rifamycin resistance in HIV-positive individuals, perhaps related to prompt diagnosis of HIV, and earlier ART initiation preserving immune function [2].

If treatment failure is diagnosed, barriers to adherence should be carefully explored. Every effort should be made to establish a microbiological diagnosis. *M. tuberculosis* isolates should be sent for drug susceptibility testing and a rapid molecular rifampicin resistance test should be performed to exclude acquired rifamycin resistance.

One of the fundamental principles in managing individuals with treatment failure is never to add a single drug to a failing regimen, as this may lead to acquired resistance to the new drug. We recommend seeking expert help.

If relapse is diagnosed, a similar approach as described for treatment failure should be adopted. Appropriate sampling should ensure the isolate is available for full drug susceptibility testing. If patients are too unwell to delay TB treatment until this information has become available, individuals should be re-treated with an empirical regimen based on: prior drug susceptibility test results; prior TB treatment regimen; results of the rapid molecular rifampicin resistance test; and severity of disease. Empirical regimens usually comprise standard rifamycin-based TB therapy with the addition of other agents such as fluoroquinolone and an injectable agent such as amikacin. Once drug susceptibility test results are available, the regimen should be adjusted accordingly.

8.3 Management of drug-resistant TB

We recommend, in individuals who are found to be infected with isoniazid mono-resistant isolates, a regimen of rifampicin, ethambutol, levofloxacin and pyrazinamide for 6 months. (GRADE 1C)
We recommend that all individuals with rifamycin- (including multidrug-) resistant TB are managed in conjunction with centres of expertise in the management of drug-resistant TB. (GPP)
We recommend that all individuals with rifampicin-resistant or multidrug-resistant TB who are not already on ART, initiate ART as soon as they are stable and TB treatment is tolerated. (GRADE 1B)

8.3.1 Rationale

Isolated isoniazid (INH) resistance is present in approximately 7.1% of individuals with HIV/TB in the UK [3]. Although these individuals tend to respond generally well to standard TB therapy, such therapy may incur a risk of treatment failure or relapse if administered intermittently [2]. The WHO guidance advises 6 months of therapy with rifampicin, ethambutol, levofloxacin and pyrazinamide (GRADE 1C) [4]. Levofloxacin is advised in part because of drug–drug interactions between moxifloxacin and rifampicin [4]. One meta-analysis suggests that longer regimens were associated with improved outcomes [5]. If levofloxacin is not suitable, other fluoroquinolones, like moxifloxacin, may be considered.

If there is intolerance to pyrazinamide, then levofloxacin, rifampicin and ethambutol can be given for 9–12 months. (GRADE 1D)

NICE currently recommends more prolonged administration (9–12 months) of rifamycins in combination with ethambutol for individuals with isoniazid mono-resistance [5-7], pending guideline review

Rifamycin mono-resistance is uncommon (approximately 0.3% in the UK) [3]. Although individuals infected with isolates that are mono-resistant to rifampicin have a better prognosis than those with multidrug-resistant (MDR) TB, they are at risk of treatment failure and acquisition of further drug resistance, and should be managed as MDRTB cases [6].

Multidrug-resistant TB is defined by the presence of resistance to at least isoniazid and rifampicin. When additional resistance to fluoroquinolones and second-line injectables (i.e. amikacin or capreomycin or kanamycin) is present, isolates are referred to as extensively drug-resistant (XDRTB) (see Section 5).

Approximately 1.6% of individuals with TB in the UK are infected with MDR isolates [3]. Risk factors for MDRTB include originating from/residence/travel in areas where MDRTB is endemic (especially Russia and Eastern Europe), previous TB treatment, and homelessness or hostel accommodation.

The optimal management of MDRTB is currently being investigated in randomised controlled trials.

Individuals with rifamycin- (including multidrug-) resistant TB should be managed in conjunction with centres of expertise in the management of drug-resistant TB.

MDR/XDRTB should be treated by enhanced case management, which may involve DOT/VOT throughout the whole treatment.

Treatment regimens should be based on:

Susceptibility testing for isoniazid, rifamycins, fluoroquinolones, injectable agents and other drugs if available;

Treatment history;

Tolerability of drugs for MDRTB;

Local surveillance data.

8.3.2 Treatment regimens (adapted from [8])

These regimens should be prescribed by centres with expertise in MDRTB. They are here as information only for those centres that may have shared care of individuals with HIV/DRTB.

In individuals with rifampicin mono-resistance or multidrug-resistant TB (RR or MDRTB), we recommend a regimen with at least five effective TB medicines during the intensive phase,

including pyrazinamide and four core second-line TB medicines – one chosen from group A, one from group B, and at least two from group C (see Table 8.1). (GRADE 2C)

If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five. In the UK, where phenotypic drug sensitivity testing and whole genome sequencing is used, specific choice of drugs may be used to tailor the regimen based on drug resistance mutations found.

In individuals with rifampicin-resistant or multidrug-resistant TB, we recommend that the regimen be further strengthened with high-dose isoniazid if *inhA* but not *katG* mutations are present, and/or ethambutol. (GRADE 2C)

8.3.3 Duration of MDR/XDR treatment

Duration of MDR/XDR treatment is as follows: 8 months of intensive phase, using five or more drugs, followed by 12 months of three drugs depending on response (see Table 8.1). For example, 8 months of Z, Km, Lfx, Pto and Cs, followed by 12 months of Lfx, Pto and Cs

In individuals with rifampicin-resistant or multidrug-resistant TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones, PZA and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDRTB regimen of 9–12 months may be used instead of a conventional regimen.

Surgery with minimal resection has been used successfully in the management of selected cases of pulmonary MDRTB [9].

Antiretroviral therapy reduces mortality among HIV-positive individuals with MDRTB [10-13] and should be offered to all individuals as soon as they are clinically stable and tolerating their TB treatment (see Section 9 and Appendix 7).

Table 8.1. Drugs with activity against MDRTB (adapted from [14] and from www.tbdrugmonographs.co.uk)

		Daily dose for adults	Comment
Group A: Fluoroquinolones			
Levofloxacin (Lfx)		10-15 mg/kg once daily	Care with QT prolongation Ciprofloxacin and ofloxacin not recommended due to likely ineffectiveness
Moxifloxacin (Mfx)		Weight **<30 kg: 400 mg once daily** **Weight 30–50 kg: 600 mg once daily** **Weight >50 kg: 800 mg once daily**	
Group B: Second-line injectable agents			
Kanamycin (Km)		15 mg/kg	Duration of use limited by ototoxicity and nephrotoxicity; monitor amikacin levels
Amikacin (Am)		15 mg/kg once daily (max 1 g/day) for 2 months then x3/week If age >59 years 10 mg/kg once daily for 3 months then x3/week	
Capreomycin (Cm)		15 mg/kg once daily	
Group C: Other core second-line agents			
Prothionamide (Pto)		15–20 mg/kg once daily	Limited by GI toxicity; add pyridoxine, up to 50 mg/250 mg prothionamide
Cycloserine/terizidone (Cs/Trd)		15 mg/kg	Limited by neurotoxicity; monitor levels; add pyridoxine, up to 50 mg/250 mg cycloserine
Linezolid (Lzd)		600 mg once daily	Use limited by haematological side effects and neurotoxicity High rates of sputum culture conversion reported in small cohort with XDRTB
Clofazimine (Cfz)		200 mg for 2 months then 100 mg daily	Caution: skin toxicity and QT prolongation
Group D: Add-on agents			
D1	Pyrazinamide (Z)	35 mg/kg	DST less reliable than for other drugs; include for entire duration of treatment for MDRTB
	Ethambutol (E)	25 mg/kg	DST less reliable; include for entire duration of treatment for MDRTB if

			DST suggests activity
	High-dose isoniazid (H^h)	900 mg once daily	Add pyridoxine
D2	Bedaquiline (Bdq)	400 mg daily for 2 weeks then 200 mg 3x weekly for 22 weeks	Both drugs cause QT prolongation Bdq has very long half-life (5.5 months); consider if no effective regimen can be composed due to resistance or tolerability Licensed for maximum 6 months
	Delamanid (Dlm)	200 mg	
D3	p-Aminosalicylic acid (PAS)	150 mg/kg (8–12g daily) in 2–4 divided doses	Limited by GI toxicity
	Imipenem-cilastatin (Ipm)	1 g twice daily if >50 kg and 15 mg/kg twice daily if <50 kg	Doses based on imipenem component
	Meropenem (Mpm)	3 g	Carbopenems and clavulanate to be used together
	Amoxicillin-clavulanate (Amx-Clv)	875/125 mg every 12 hours	

8.3.4 Newer Drugs

8.3.4.1 Bedaquiline (Bdq)

Bdq is used in the treatment of rifamycin-resistant TB. It has a novel mechanism of action. The drug inhibits mycobacterial adenosine triphosphate (ATP) synthase. It is an effective agent but may result in QTc prolongation and should not be given to individuals with a QTc interval greater than 500 ms, history of torsade de pointes or cardiac ventricular arrhythmias, or severe coronary artery disease. It can cause hepatotoxicity and liver function should be monitored monthly. It has a very long half-life (months) and interacts with drugs that are inducers or inhibitors of cytochrome P450 3A4, and thus may result in potentially significant drug interactions (see Appendix 6).

WHO recommends that Bdq may be added to a drug regimen in adult individuals with pulmonary rifamycin-resistant TB. It should be used with caution with other drugs that cause QTc prolongation such as quinolones, and Cfz, both during and in the 6 months after stopping Bdq.

Bdq is given for 24 weeks, although case reports support more prolonged use [15].

8.3.4.2 Delamanid (Dlm)

Dlm is a nitro-dihydro-imidazo-oxazole derivative, inhibiting a novel target in *Mycobacterium tuberculosis* cell wall mycolic acid synthesis. It is generally well tolerated. Other than QTc prolongation, adverse events observed in clinical studies with Dlm were generally mild to moderate. Individuals with a QTc interval greater than 500 ms should not receive the drug. There is a paucity of evidence for using Bdq and Dlm together.

8.3.4.3 Pretomanid

Pretomanid is a nitroimidazole, a class of novel anti-bacterial agents. Its mechanism of action is complex, but activity against both actively replicating and slowly dividing populations of mycobacteria make this a potential component of future TB and drug-resistant TB treatment regimens. *In vitro* activity against all tested drug-resistant clinical isolates, coupled with a lack of propensity for cytochrome P450-mediated interactions makes this drug attractive. Pretomanid has been used in combination with bedaquiline and linezolid given orally for 6 months in the NIX-TB trial [16] in patients with XDRTB and has shown promising results so far

8.4 Directly observed therapy (DOT)

We recommend individualised, enhanced patient-centred care plans for all patients, some of which may include DOT and video-observed therapy (VOT). (GPP)

We recommend against the routine use of DOT and VOT in patients with active TB (GRADE 1B), but recommend it in MDRTB cases (GPP)

8.4.1 Rationale

Directly observed therapy (DOT) is a supervision intervention, which requires that individuals be observed to swallow each dose of medication. The idea behind DOT is that it helps individuals to take their drugs as prescribed and to complete treatment, thus achieving cure and preventing the development of drug resistance. Evidence from randomised controlled trials and observational studies (of predominantly HIV-negative persons with drug-susceptible TB) suggests that DOT is not significantly better than self-administered therapy in preventing microbiological failure, relapse, or acquired drug resistance (ADR) [17,18]. Nonetheless, there are selected patient groups who may benefit from intensive support including DOT, such as migrants, prisoners, drug users (including alcohol), street- or sheltered-dwelling homeless, and those with mental health disorders [6,19]. A risk assessment should be made for each patient, as per NICE guidelines [6].

DRTB requires prolonged use of complex regimens with high pill burden and substantial toxicity. Consequently, individualised patient-centred care should be at the core of DRTB treatment/care plans and should always include measures to facilitate adherence. This includes DOT/VOT/supervised therapy, use of dosing devices, or treatment incentives; DOT may be undertaken at a health facility, in the workplace, in the community or at home.

Multidisciplinary (MDT) HIV and TB services should identify and address any factors that may make individuals interrupt or stop treatment [6]. Use of appropriate, suitably trained family or friends, social support and healthcare may promote adherence. Electronic DOT (eDOT or VOT) involves the use of electronic devices to document ingestion of medication at the appropriate date and time and can be an alternative to face-to-face contacts. Voice over internet protocol (VOIP, e.g. Skype) is becoming a more common method of performing eDOT or VOT, which may be particularly beneficial in instances where geographical distance is a factor.

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9 Antiretroviral treatment

9.1 Choice of antiretroviral treatment in individuals not on ART: when and what to start

We recommend all individuals with TB be offered ART as soon as is practicable and within 8–12 weeks of the TB diagnosis. (GRADE 1A)

We recommend individuals with CD4 cell count <50 cells/mm^3 be offered ART as soon as is practicable and within 2 weeks. (GRADE 1A)

We recommend against the early initiation of ART in individuals with CNS TB. (GRADE 1A)

9.1.2 Rationale

ART is recommended for all individuals with HIV infection [1,2]. There is accumulating evidence from multiple randomised controlled trials in varied healthcare settings that early institution of ART in individuals with tuberculosis has mortality and morbidity benefits [3-9]. The timing of ART in individuals with TB depends on the level of immunodeficiency even though there may be a greater risk of IRIS [4-6,10] (see Section 12), high pill burden and the limited time for individuals to accept life-long ART.

It is only in individuals with CD4+ cell count <50 cells/mm^3 that trials have consistently shown clinical benefit of starting ART within 2 weeks of commencing TB therapy as opposed to deferring ART for up to 2 months. Hence, we recommend that TB individuals with CD4+ cell counts <50 cells/mm^3 start ART within 2 weeks as soon as they are stable and TB treatment is tolerated.

For individuals with CD4+ cell counts 50–200 cells/mm^3, the clinical benefit of early ART (2–4 weeks *vs*. 8–12 weeks) is less clear. Trial data suggest it would appear safe to defer ART in TB individuals with CD4+ cell counts >50 cells/mm^3 until the end of the induction phase (2 months), although ART may be discussed during this time and offered to those who are ready to start (see Appendix 8).

A randomised controlled trial that compared clinical outcomes in HIV-associated tuberculous meningitis found no survival benefit and an excess of serious adverse events with early ART initiation (within 7 days) as compared with ART initiation at 2 months [11].

9.2 What ART to start in TB/HIV co-infection

We recommend efavirenz (EFV) (standard dose) in combination with tenofovir (TDF) and emtricitabine (FTC) as first-line ART. (GRADE 1B)

We suggest that raltegravir (RAL) or dolutegravir (DTG) can be used for individuals in whom EFV is contraindicated. (GRADE 2C)

We recommend that rifabutin is used instead of rifampicin where effective ART necessitates the use of ritonavir-boosted protease inhibitors. (GRADE 1C)

We recommend against the use of nevirapine (NVP) in ART-naïve individuals with TB treated with rifampicin. (GRADE1B)

We recommend against the use of cobicistat (COBI) with rifampicin or rifabutin. (GRADE 1D)

We recommend against the use of fixed-dose combinations containing tenofovir alafenamide (TAF), when co-administered with rifampicin/rifabutin, and bictegravir until clinical outcome data are available to support this. (GRADE 2D)

9.2.1 Rationale

EFV is the most widely studied 'third agent' in individuals with HIV/TB [4-7]. In clinical trials, EFV was co-administered with rifampicin at standard dose (600 mg once daily), together with zidovudine (ZDV) plus lamivudine (3TC) [7], didanosine (DDI) plus 3TC [4], stavudine (D4T) plus 3TC [5], or tenofovir plus emtricitabine (TDF/FTC) [6]. In cohort studies, EFV-based ART performed as well in HIV/TB co-infected individuals (all of whom received rifampicin) as in HIV-positive individuals without TB [12]. Hence, EFV plus TDF/FTC is considered the preferred regimen. Abacavir (ABC) may be best avoided even in those who are HLA negative unless renal insufficiency is present. IRIS and

drug hypersensitivity are relatively common in HIV/TB co-infected individuals and potentially difficult to differentiate from ABC hypersensitivity (see Section 12).
Randomised controlled clinical trials have directly compared EFV versus the integrase inhibitors raltegravir (400 mg bd/800 mg bd, non-comparative) and dolutegravir (50 mg bd, non-comparative). These studies were underpowered but support the potential use of these drugs in HIV/TB patients being treated with rifampicin, who should be carefully monitored [13,14].
In Reflate TB, a Phase 2 trial, 155 subjects on rifampicin-containing TB therapy were randomly allocated to EFV 600 mg, RAL 400 mg bid, or RAL 800mg bid, each co-administered with TDF plus 3TC [14]. At 48 weeks, proportions of virologically suppressed patients were numerically higher in the RAL arm (76–78% versus 63% in the EFV arm). Standard-dose RAL appeared to perform as well as double-dose RAL. Rates of virological failure (24–27%) and emergence of resistance (8–12%) were similar across the three study arms [14].
There are no data on the use of RAL 1200 mg od in HIV/TB patients treated with rifampicin.
Outcomes have also been reported for EFV and DTG (50 mg twice daily) in the INSPIRING study, with viral suppression in 89% of participants in the EFV arm and 81% in the DTG arm at 24 weeks [13].
Due to significant drug–drug interactions, rilpivirine (RPV) should not be co-administered with rifampicin or rifabutin, and ritonavir (/r, RTV) and cobicistat (/c, COBI)-boosted protease inhibitors should not be used with rifampicin (see Section 10).
Cohort data have reported acceptable outcomes in individuals with TB who received ritonavir-boosted protease inhibitors with rifabutin [15] but there are few data with COBI. Hence, we recommend the use of ritonavir if boosted PIs are required for HIV control.
Pharmacokinetic studies [16] confirm significant reductions in plasma tenofovir concentrations when TAF is dosed with rifampicin, although concentrations of intracellular tenofovir diphosphate remain in excess of those observed with conventional TDF dosing. However, in the absence of clinical outcome data, and with the ready availability of TDF as an alternative (where outcome data exist) the use of TAF is not recommended in individuals who receive rifamycin-based TB therapy at present.

9.3 Choice of antiretroviral treatment in individuals on established ART

We recommend that individuals who develop TB on ART with undetectable HIV viral loads do not interrupt their ART. (GRADE 1A)
We recommend that rifampicin-based TB treatment is used in individuals whose established ART consists of EFV (GRADE 1B), RAL (GRADE 2C) or DTG (GRADE 2C) plus two NRTIs.
We recommend that rifabutin is used instead of rifampicin where established ART necessitates use of ritonavir. (GRADE 1C)

9.3.1 Rationale

HIV-positive individuals should not interrupt fully suppressive ART [17]. Rifampicin-based TB therapy can be co-administered with EFV, RAL and DTG and individuals on these agents may continue their current ART [12,14].
If effective ART necessitates the use of RTV-boosted protease inhibitors, rifabutin-based TB therapy should be used [15].
The co-administration of rifampicin and COBI is contraindicated as the reduction of COBI exposure is likely to be major (drug–drug interactions between rifampicin and COBI have not been formally studied).The co-administration of rifabutin and COBI is possible, dosing rifabutin at 150 mg three times per week (as per COBI product label). However, it should be noted that no clinical data are available on the efficacy of this dose. Therefore, in the absence of COBI/rifabutin interaction data, we suggest individuals are switched to ritonavir.

Individuals who develop TB on failing ART regimens typically have adherence problems and these will be severely compounded by the addition of multidrug TB therapy. We suggest that, in rare circumstances, ART may need to be interrupted in such individuals to allow the administration of rifampicin-based TB treatment until this is established, and depending on CD4 cell count. This may be best done under directly observed conditions. (See Section 8).

9.4 References

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10 Drug–drug interactions

10.1 ART/TB drug interactions and TDM use and interpretation (including MDR and XDR)

We recommend undertaking a complete medicines reconciliation prior to starting treatment for either TB or HIV. (GPP)

We recommend using prescribing resources (e.g. the Liverpool University HIV drug interactions website: www.hiv-druginteractions.org; or the Toronto General Hospital website: www.hivclinic.ca/drug-information/drug-interaction-tables/) to screen for DDIs in all individuals with TB/HIV co-infection. (GPP)

The management and avoidance, where possible, of drug–drug interactions (DDI) between antiretrovirals and anti-TB drugs are central to good care, although this can be therapeutically challenging. Rifampicin is a potent inducer of cytochrome P450 enzymes and the drug transporter P-gp, and induction of these proteins in the gut and liver reduces bioavailability, and increases systemic clearance of a broad range of co-medications. Rifampicin also increases clearance of drugs through induction of glucuronidation. HIV NNRTIs (efavirenz, nevirapine, etravirine) are also P450 inducers whereas protease inhibitors and cobicistat are potent inhibitors of P450 CYP3A; ritonavir also being an inducer of glucuronidation.

10.2 DDIs between TB and HIV drugs

DDIs between ART and anti-tuberculosis drugs pose a particular challenge, especially if resistance to first-line regimens is likely for either infection (see Table 10.1). Discussion of DDIs between antiretrovirals and treatment for drug-resistant (MDR and XDR) TB is beyond the scope of these guidelines, and such individuals are best managed within specialised regional units: DDIs involving second-line TB agents and antiretrovirals can be seen in Table 10.2 or searched online at www.hiv-druginteractions.org or www.hivclinic.ca/drug-information/drug-interaction-tables/.

Table 10.1 summarises key DDIs involving HIV and first-line TB agents, with a summary of how these DDIs should be managed. Particular note should be taken of the following:

Efavirenz (EFV): standard doses are now recommended regardless of ethnicity or body weight. Previously, concerns about the potential reduction of EFV exposure by rifampicin led to weight-based dosing recommendations for EFV. However, standard doses of EFV in individuals also receiving rifampicin did not appear to be associated with high rates of virological failure (no direct dose comparison has been undertaken in this setting) [1]. Moreover, EFV exposures in HIV-positive individuals, although variable, are not substantially lower on rifampicin therapy compared to concentrations off therapy when studied in populations, who have generally exhibited a high carriage of cytochrome CYP2B6 poor metaboliser genotype (516 G>T allele) [2-7]. In view of these data, we now recommend that standard doses of EFV should be prescribed with rifampicin. Therapeutic drug monitoring (TDM) of plasma EFV concentrations is not routinely recommended; however, in individuals with a high body mass index, or where virological responses appear blunted, TDM should be considered. In the absence of efficacy data, individuals maintained on EFV 400 mg once daily (following the results of the ENCORE clinical trial [8]) should increase to EFV 600 mg once daily while treated with rifampicin.

The DDI between rifampicin and cobicistat (COBI) has not been studied, although the reduction of COBI exposure is likely to be major, and the combination is therefore contraindicated. By comparison, the impact on ritonavir (RTV) is modest (exposure reduced by 35%), and alternative strategies based on increasing doses of RTV and/or the boosted PI are being assessed. Nonetheless, switching to an alternative antiviral (e.g. raltegravir or dolutegravir) or rifabutin is preferred, where possible.

Co-administration of COBI with rifabutin decreased COBI C_{trough} by 66%, did not change rifabutin exposure significantly, but increased 25 OH desacetyl rifabutin more than five-fold. As a result, 150

mg three times per week dosing of rifabutin is recommended in the COBI product label. However, it should be noted that no clinical data are available on the efficacy of this dose, and 150 mg three times per week of rifabutin given with lopinavir/ritonavir (LPV/r) did not yield adequate rifabutin exposure [9]. Consequently, we advise caution when using rifabutin with COBI, and monitoring for rifabutin toxicity and HIV treatment response.

Rifampicin reduces raltegravir (RAL) exposure by 40%. The REFLATE Study [10] reported that dose increase of RAL to 800 mg bd was well tolerated but over-compensated for this interaction, whereas standard dosing (400 mg bd) only resulted in small decreases in RAL exposure. However, given the wide variability in C_{trough} at standard doses (with some individuals falling below target), and in the absence of adequately powered studies confirming the efficacy of standard dosing, we suggest using 800 mg bd of RAL with rifampicin. Moreover, given the lack of clinical and PK data we advise against the use of RAL 1200 mg od with rifampicin.

- Rifampicin is likely to exert different effects on tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF). Both TDF and TAF are substrates for P-gp; however, TDF is present in the systemic circulation as tenofovir (which is not a P-gp substrate) whereas TAF is converted to tenofovir largely within cells. Rifampicin as a potent inducer of P-gp is anticipated to have a significant effect on the bioavailability of TAF. By contrast, the impact of rifampicin on tenofovir is not likely to be clinically significant [11]. Fixed-dose combinations containing either TDF or TAF that also contain COBI are contraindicated with rifampicin (see above).

We do not recommend use of nevirapine (NVP) in HIV-naïve individuals with either rifampicin or rifabutin. However, if the patient is stable on NVP it can be continued. Caution is advised when rifabutin is used with NVP since rifabutin exposures are increased by 17%, and toxicity may be increased (Table 10.3).

It should be noted that recommendations for managing DDIs may sometimes differ between the FDA and EMEA: for example, rilpivirine (RPV) is contraindicated with rifabutin in the US, whereas increased doses of RPV are recommended by the EMEA. We have sought to highlight any significant differences and provide guidance on how these interactions can be managed in clinical practice.

Table 10.3. Drug interactions between rifabutin and ART

ART	Dose adjustment (ART)	TB therapy	Dose adjustment (RBT)
Boosted PI	No change	RBT	150 mg od
NVP	200 mg bd	RBT	300 mg od
EFV	600 mg od	RBT	450 mg od
RAL	400 mg bd	RBT	300 mg od
DTG	50 mg od	RBT	300 mg od

10.2.1 Other DDIs

Individuals with TB/HIV co-infection often have multiple comorbidities such as diabetes, chronic obstructive pulmonary disease (COPD), chronic hepatitis and cardiovascular disease. Rifampicin (and also HIV drugs such as NNRTIs, RTV and COBI) is also likely to impact on the safety or efficacy of these treatments. It is not possible to provide a complete list of DDIs, and prescribers should consult their usual prescribing resources when attempting to manage these interactions. For DDIs involving HIV drugs, the Liverpool (www.hiv-druginteractions.org) or Toronto websites (www.hivclinic.ca/drug-information/drug-interaction-tables/) are recommended.

Some common challenges are listed:

Metabolism of corticosteroids (e.g. prednisolone) is accelerated by rifamycins and higher doses are needed.

The dose of steroid should be increased by around 50% with rifampicin and 33% with rifabutin.

Reduced plasma levels and increased elimination of methadone can occur with concurrent administration of rifampicin, which has been associated with symptomatic opioid withdrawal [12,13].
Dose titration of methadone may be necessary, if opioid withdrawal is experienced. Close monitoring is warranted, particularly for withdrawal symptoms during initiation, and methadone side effects on cessation of rifampicin.
No apparent effect of rifabutin on either peak levels of methadone or systemic exposure were observed [14].
Methadone withdrawal is less likely than with rifampicin, but monitor and adjust dose if needed, on introduction and cessation of rifabutin
Rifampicin decreased exposure to sublingual (AUC decreased by 25–70% in two studies) [15] but not intravenously administered buprenorphine. Opiate withdrawal was observed in 50% of participants. Rifabutin administration to buprenorphine-maintained subjects resulted in a 35% decrease in AUC, with no opiate withdrawal observed [16].
Interactions are also likely with cardiovascular, antidepressant, antiepileptic and immunosuppressant drugs.
Where there may be opposing effects, any induction effect from rifampicin is likely to predominate.
Concomitant chronic viral hepatitis infection increases the risk of liver toxicity with HIV and TB therapy; however, this does not preclude the use of first-line agents for either infection. Use of directly acting antivirals for hepatitis C is contraindicated or not recommended with rifampicin, and DDIs involving HCV drugs and anti-tuberculosis therapy can be searched at www.hep-druginteractions.org. We suggest for the vast majority of individuals to treat TB first, then HCV.
Diabetes mellitus triples the risk of active TB [17], and HIV-infection is also associated with increased prevalence of glucose intolerance. Rifampicin will lower exposures to sulfonylureas, and most other diabetic drugs (with the exception of insulin and metformin). This could significantly impair glycaemic control. Exposure to gliptins may also be modestly reduced by rifampicin.
Isoniazid is an inhibitor of some cytochrome P450 isoforms, and inhibition of clearance of some sulfonylureas may occur. However, when co-dosed with rifampicin, the enzyme induction by rifampicin is likely to predominate.

10.2.2 Managing DDIs

Clinical surveys have consistently demonstrated poor medication recording, and incomplete concordance between hospital and community health records in HIV-positive patients.
Particular co-medications known to be poorly captured must be actively sought, e.g. oral contraceptives, long-acting hormonal contraceptive implants, herbal medications and vitamins, ‘over-the-counter drugs’ and recreational drugs. Clinically significant DDIs are likely in HIV-positive patients with TB.

10.2.3 Therapeutic drug monitoring (TDM)

The use of TDM of HIV or TB drugs in managing individuals with TB/HIV co-infection should only be considered in specific scenarios, such as:
Concerns over treatment adherence (HIV or TB drugs)
Blunted virological response, or development of low-level viraemia (HIV drugs)
Individuals receiving rifabutin 150 mg three times per week with COBI (TB drug)
This list is not exhaustive, and TDM may sometimes help to distinguish the contribution of specific components (e.g. adherence, excluding a significant DDI, body weight) within complex clinical scenarios.

10.3 References

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Table 10.1. Drug interactions between anti-tuberculosis and antiretroviral drugs

	Eth	INH	PZA	Rbt	Rif	Notes
ATV	◆4	◆4	◆4	■	●1	Unboosted ATV is contraindicated with Rif (ATV exposure ↓80%) If using Rbt, reduce Rbt dose to 150 mg daily; monitor for Rbt toxicity
ATV/r	◆4	◆4	◆4	■1	●1	Boosted ATV is contraindicated with Rif If using Rbt, reduce Rbt dose to 150 mg daily, or 300 mg 3×/w; monitor for Rbt toxicity
ATV/c or DRV/c	◆4	◆4	◆4	■4	●4	COBI is contraindicated with Rif; monitor for Rbt toxicity
DRV/r	◆4	◆4	◆4	■3	●2	Has not been studied with Rif – modelling and simulations suggest higher DRV/r doses could potentially overcome Rif induction but safety data are lacking and the combination is not recommended If using Rbt, reduce RBT dose to 150 mg daily, or 300 mg 3×/w; monitor for Rbt toxicity
LPV/r	◆4	◆4	◆4	■1	●1	Use of Rif not recommended. However, doubling the dose of LPV/r (e.g. 800/200 mg bd) or 'super-boosting' with RTV (e.g. 400/400 mg bd) has been used in adults, and additional RTV boosting in children. Monitor for liver and GI toxicity. Once-daily LPV/r is contraindicated with Rif If using Rbt, reduce Rbt dose to 150 mg daily. Dosage of Rbt 300 mg 3×/w with LPV/r has been associated with sub-therapeutic Rbt exposure, and development of rifamycin mono-resistance; monitor for Rbt toxicity
EFV	◆4	◆3	◆4	■3	■1	EFV can be prescribed at standard doses with Rif, regardless of ethnicity or weight. Weight-based dose increment of EFV is no longer recommended with Rif. However, reduced doses of EFV 400 mg daily is not recommended If using Rbt, increase Rbt dose to 450 mg daily to compensate for reduced exposure due to EFV; monitor for Rbt toxicity
ETR	◆4	◆4	◆4	■2	●2	Use of Rif should be avoided. A case report observed reduced ETR exposures but successful virological suppression with ETR 200 mg bd and Rif ETR can be administered at standard doses (in the absence of a second enzyme inducer) with Rbt. ETR exposure ↓ 37% – monitor virological response
NVP	◆4	◆4	◆4	■3	●1	Use of Rif is not recommended (label states contraindicated). NVP levels ↓ 20–55%, and the CARINEMO Study failed to demonstrate non-inferiority against EFV. If starting NVP on

						a patient established on Rif, do not use lead-in dosing Rbt should be used with caution in individuals on NVP. In contrast to EFV, NVP increased Rbt exposure by 17%; standard doses of both drugs should be administered
RPV	◆4	◆4	◆4	●3	●1	RPV is contraindicated with Rif Rbt decreased RPV exposure by 46%, and the combination is not recommended (contraindicated in US PI). Increased doses of RPV 50mg od should be used (European SPC)
ABC	◆4	◆4	◆4	◆4	■4	Potential mild decrease in ABC exposure due to increased glucuronidation with Rif, use standard doses of both drugs
FTC	◆4	◆4	◆4	◆4	◆4	No significant drug interactions anticipated
3TC	◆4	◆4	◆4	◆4	◆2	No significant drug interactions anticipated
TDF	◆4	◆4	◆4	◆4	◆3	No clinically significant interaction with Rif (tenofovir exposure reduced 12%) No clinically significant interaction with Rbt (not studied)
TAF	◆4	◆4	◆4	■4	■4	Rif may reduce TAF bioavailability through transporter (P-gp) induction and is not recommended. (Note: TAF or TDF administered with COBI is contraindicated because of Rif induction of COBI metabolism) Rbt expected to reduce TAF exposure through P-gp induction, the combination is not recommended
ZDV	◆4	◆4	◆4	◆2	■2	Rif increases clearance of ZDV, reducing plasma exposure by 47%. Use with caution ('Avoid' European SPC; 'dose modification not warranted' US PI)
DTG	◆4	◆4	◆4	◆2	■1	Rif decreased DTG exposures by 54%, increasing dose to DTG 50 mg bd has been used in limited clinical studies and is recommended Rbt has no clinically significant effect on DTG. Use standard doses of both drugs
EVG/c	◆4	◆4	◆4	■3	●2	COBI is contraindicated with Rif Caution with Rbt. EVG $C_{trough}\downarrow$ 67%. If using Rbt, reduce Rbt dose to 150 mg daily; monitor for Rbt toxicity and HIV treatment response

RAL	◆4	◆4	◆4	◆2	■1	Rif reduces RAL exposure by 40%. The REFLATE Study reported that dose increase of RAL to 800 mg bd was well tolerated but over-compensated for this interaction, whereas standard dosing (400 mg bd) only resulted in small decreases in RAL exposure. However, given the wide variability in C_{trough} at standard doses (with some individuals falling below target), and in the absence of adequately powered studies confirming the efficacy of standard dosing, we prefer using 800 mg bd of RAL with Rif No clinically significant interaction was observed between RAL and Rbt; use standard doses of both drugs
MVC	◆4	◆4	◆4	■4	■1	Rif reduces MVC exposure by 60–70% (note: MVC was dosed at 100 mg bd in this study, and the magnitude of drug interaction with full dose MVC is unknown). MVC should be dosed at 600 mg bd with Rif. MVC should be avoided with Rif in individuals also taking another enzyme inducer (e.g. EFV, NVP or ETR), or in those with an eGFR <30mL/min or on haemodialysis No clinically significant interaction was observed between MVC and Rbt; use standard doses of both drugs. (Note: MVC and Rbt doses should be reduced in the presence of a protease inhibitor or COBI)
T20	◆4	◆4	◆4	◆4	◆4	No significant drug interactions anticipated

Table 10.2. Drug interactions between second-line anti-tuberculosis and antiretroviral drugs

	Group A		Group B			Group C				Group D*					
	Levo	Moxi	Amik	Capr	Kan	Pro	Cyclo/ Teri	Linez	Clof	Bedaq	Del	PAS	Imi/Cil	Mero	Co-amox
ATV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
ATV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
ATV/cor DRV/c	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
DRV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
LPV/r	4	4	4	4	4	4	4	4	4	4	2	4	4	4	4
EFV	4	4	4	4	4	4	4	4	4	2	3	4	4	4	4
ETR	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
NVP	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
RPV															

	Group A		Group B			Group C				Group D*					
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
ABC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
FTC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
3TC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
TDF	4	4	4	4	4	4	4	4	4	2	4	4	4	4	4
TAF	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
ZDV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
DTG	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
EVG/c	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

	Group A		Group B			Group C				Group D*					
RAL	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4
MVC	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	■ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4
T20	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4	◆ 4

11 Drug absorption, toxicity and management

11.1 Malabsorption of drugs

In HIV infection, malabsorption has been reported with all first-line anti-tuberculosis drugs, as well as ethionamide and cycloserine. Absorption may be decreased in individuals with a low CD4+ cell count because of HIV enteropathy or other HIV-related gut disease. Sub-therapeutic plasma drug concentrations may cause treatment failure and drug resistance [1,2]. Although some studies show lower peak concentrations of rifampicin and ethambutol, as well as a lower AUC, compared with controls [3-7], there are other data suggesting that rifampicin is well absorbed in HIV-positive patients, including those with other AIDS conditions or diarrhoea [8]. There are few data showing a correlation of treatment failure with poor absorption [9]. Intravenous preparations of rifampicin, isoniazid and ethambutol are available for individuals without a reliable enteric route of administration, e.g. on ITU or post-operatively (see Appendix 5, Table A5.1)

11.2 Overlapping toxicity profiles of antiretrovirals and TB therapy

Adverse reactions to drugs are common among individuals with HIV-related TB, especially if taking ART concomitantly. Rash, fever and hepatitis are common adverse effects of anti-tuberculosis drugs, especially rifampicin, isoniazid and pyrazinamide. NNRTIs and co-trimoxazole cause similar adverse reactions.

The co-administration of these drugs can lead to difficult clinical management decisions if these occur, especially if ART and TB drugs are started concurrently.

11.3 Drug induced liver injury (DILI)

Drug-induced liver injury has been defined as [10]:

- Serum AST or ALT >3x upper limit of normal in the presence of symptoms, or
- Serum AST or ALT >5x upper limit of normal in the absence of symptoms

Other causes of liver dysfunction, such as resulting from other administered drugs and viral hepatitis, should be investigated.

Hepatotoxicity may be caused by many drugs used in the treatment of HIV-positive patients, for instance azoles and macrolides, and not all hepatotoxic reactions are due to anti-tuberculosis therapy.

The risk of hepatotoxicity caused by isoniazid increases with age, occurring in <0.3% of those under 35 years old and in 2.3% of those >50 years old. It is also higher in those with heavy alcohol intake or hepatitis C virus co-infection and in those also on rifampicin. Slow acetylator status and glutathione S-transferase (GST) variants may also contribute. High rates of adverse reactions requiring changes in therapy have been reported in HIV-positive individuals who are likely to have some or all of the other risk factors mentioned above. In one study, adverse reactions were present in 26% of an HIV-positive cohort compared with 3% of an HIV-uninfected group and other studies have shown similar results [11,12].

Another study reported little increase in hepatotoxicity in HIV-positive individuals with TB although only 16.3% were receiving ART and the study included children [13].

11.3.1 Management of suspected DILI

We recommend the following when serum AST or ALT >3× upper limit of normal in the presence of symptoms, or serum AST or ALT>5x upper limit of normal in the absence of symptoms (GRADE 1B):

Consider stopping all potentially hepatotoxic drugs immediately, including isoniazid, rifampicin, pyrazinamide and co-trimoxazole. cART should only be stopped/modified if it is likely to be causing hepatotoxicity.

Check serology for hepatitis A, B and C, and if clinically indicated delta and hepatitis E.

Enquire about exposure to other hepatotoxins, including alcohol.

As resolution of the hepatitis may be prolonged, until the cause of the hepatitis is identified, it may be necessary to treat with two or more anti-tuberculosis medications without significant risk of hepatotoxicity, such as ethambutol, streptomycin, amikacin/kanamycin, capreomycin or levofloxacin (N.B. moxifloxacin can cause a severe although infrequent hepatitis). Monitor serum ALT/AST, bilirubin and symptoms frequently.

Once ALT/AST drops to less than twice the upper limit of normal and symptoms have significantly improved, first-line medications can be restarted using a re-introduction regimen (see Appendix 5, Table A5.2). These recommendations are based on common practice and have not been formally validated in clinical trials. Data in HIV-negative/unknown individuals suggest that once the ALT/AST is <100 IU/L then full-dose treatment may be reintroduced [14]: whether this also applies to HIV co-infected individuals remains unclear.

If the drugs cannot be restarted or the initial reaction was life-threatening then an alternative regimen should be used (see Section 11.4).

11.4 Pre-existing liver disease

All individuals should be screened for active hepatitis B and C. The risk of hepatotoxicity with pre-existing liver disease is greatest with pyrazinamide, then isoniazid, and then rifampicin. Isoniazid and rifampicin are essential drugs in short-course TB treatment regimens and should be used whenever possible, even in the presence of pre-existing liver disease.

In individuals with baseline abnormal hepatic transaminases, a rise of two-to-three times this abnormal baseline should be used as the threshold for hepatotoxicity [10].

If hepatotoxicity occurs, then other regimens can be used as follows:

Avoid pyrazinamide and treat with isoniazid and rifampicin for 9 months, adding ethambutol for the first 8 weeks or until isoniazid and rifampicin susceptibility is demonstrated.

Avoid isoniazid and treat with rifampicin, ethambutol,pyrazinamide and levofloxacin for 6 months.

In individuals with severe liver disease, we suggest that physicians seek advice from an expert centre.

In individuals with pre-existing liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury. This should include AST (or ALT), platelet count and prothrombin time at least 2-weekly initially. Individuals should be told to immediately report symptoms such as anorexia, nausea, vomiting, abdominal pain or jaundice [15,16].

11.5 Gastrointestinal side effects

Epigastric pain, nausea and vomiting are common, especially in the first 2–3 weeks after starting anti-tuberculosis therapy. If the patient has no evidence of hepatic disease and is unresponsive to symptomatic treatment, for instance with anti-emetics, then they can:

Take medications with meals (except with doses under 600 mg rifampicin daily): food delays or decreases the absorption of isoniazid and rifampicin;

Change the time of dosing;

Switch to a regimen that does not have food restrictions such as rifabutin, ethambutol, pyrazinamide and a fluoroquinolone.

Individuals should avoid dividing doses or changing to alternative drugs if at all possible, although dividing the dose, for instance of pyrazinamide, can improve tolerability.

See Appendix 5, Table A5.1 for further guidance.

11.6 Peripheral neuropathy

Pyridoxine 10 mg daily should be used in all individuals receiving isoniazid. If peripheral neuropathy occurs, the dose of pyridoxine can be increased to 50 mg od. Second-line drugs, such as cycloserine and prothionamide, need higher-dose pyridoxine.

11.7 Rash

Rash is often mild/moderate and usually occurs in the first 2 months of treatment. Of the four standard treatment drugs for TB, ethambutol most often causes rash. Mild rash without mucosal involvement can be treated symptomatically. More widespread or worsening rash or individuals who also have systemic symptoms require cessation of all drugs, and on recovery careful drug re-introduction (see Appendix 5, Table A5.2).

A confounding issue is that individuals may have also recently started co-trimoxazole or ART and so the offending drug can be difficult to identify.

There are several recommendations for drug reintroduction. Although they have been used in liver disease, they can be used for grade 1–3 rash .

11.8 Reintroduction of TB drugs after DILI or rash

For most mild/moderate reactions, once AST or ALT levels fall below twice the upper limit of normal, bilirubin levels return to the normal range and hepatotoxic symptoms have resolved then: Reintroduce all the drugs at once; or if the reaction recurs using this strategy:

Sequentially reintroduce each of the anti-TB drugs at full dose over a period of no more than 10 days, starting with ethambutol and either isoniazid (with pyridoxine) or rifampicin. See Appendix 5, Table A5.2.

If the reaction was moderate or there was a recurrence of the DILI or rash on reintroduction as above, then give ethambutol full dose and follow the protocol in Appendix 5, Table A5.2.

If the reaction is severe or occurs again after the above reintroduction, start with one-tenth of the first-day dose for each drug.

Individuals who are infectious should be treated with at least two active drugs while standard therapy is reintroduced. Suitable agents would be ethambutol and streptomycin or ethambutol and moxifloxacin.

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12 Immune reconstitution inflammatory syndrome

We recommend the use of corticosteroids tapered over 4–6 weeks in clinically significant IRIS. (GRADE 1C)

We recommend that in recurrent IRIS, and in complex cases, advice is sought from centres with experience in managing this syndrome. (GPP)

12.1 Rationale

After starting anti-tuberculosis treatment, some individuals develop an exacerbation of symptoms, signs or radiological manifestations of TB. This has been well described in individuals without HIV infection, but appears to occur more commonly in HIV-positive individuals [1-19]. The phenomenon is known as IRIS, IRD or paradoxical reaction.

The aetiology of these reactions is unknown, but they are presumed in HIV disease to occur at least in part as a consequence of ART-related reconstitution of immunity, which leads to an abnormal immune response to tubercle antigens released by dead or dying bacilli [20-23].

12.2 Definition

IRIS does not have a generally accepted definition, although one was developed for use in resource-poor countries that is often used. Here, cases need to meet three criteria (see Appendix 7) [24].

IRIS may present in two different ways:

1. The 'paradoxical' worsening of symptoms of a known disease, either at a new body site or at the original body site, or
2. The 'unmasking' of an occult opportunistic infection, in which disease that was not clinically apparent prior to ART manifests during ART

IRIS is characterised by the worsening or appearance of new signs, symptoms or radiographic abnormalities, occurring after the initiation of ART, and not the result of TB treatment failure or another disease process. It is therefore a diagnosis of exclusion. It is often transient in duration but can last many months. It is usually seen when the TB is microbiologically controlled, but cases can occur with viable organisms isolated on culture. Some clinicians feel that there must be a significant inflammatory component to the presentation for this to be classified as IRIS.

The features of IRIS are:

Apparent worsening/progression of TB;

May occur at original site of disease or at remote site;

May occur at any time after initiation of TB treatment;

Associated with commencing or continuing ART;

No evidence of TB relapse or recurrence (positive AFB smear does not exclude diagnosis of IRIS);

Appropriate investigations have excluded disease attributable to other pathogens;

Drug hypersensitivity is excluded;

A response to corticosteroids does not confirm a diagnosis of IRIS;

12.3 Epidemiology of IRIS (see also Appendix 7)

With limited data it is difficult to predict the risk of IRIS, but the following appear to be relevant [25-29]:

Low baseline CD4+ cell count;

Rapid recovery in CD4+ cell count;

Rapid decline in HIV viral load;

Dissemination of TB outside the lung (may be attributable to high burden of bacilli);

Short time interval between start of anti-TB treatment and initiation of ART.

12.4 Clinical features of IRIS

IRIS most often presents with fever and increased or new lymphadenopathy. The skin overlying lymph nodes is often inflamed and dusky red, and the nodes can spontaneously rupture [24]. New

or worsening pulmonary lesions, pleural and pericardial effusions, ascites, psoas abscess, cutaneous lesions and new or expanding CNS tuberculomas, for example, have also been described.
Hepatic involvement with granulomatous hepatitis and cholestatic LFT derangement can present as IRIS and may be difficult to differentiate from DILI.
A diagnosis of IRIS should be made only if TB treatment failure, drug hypersensitivity and other opportunistic infections and malignancies are excluded.

12.5 Management of IRIS

12.5.1 Corticosteroids

The management of IRIS may require corticosteroids, sometimes for prolonged periods, in order to control symptoms. There is no consensus on what is an optimal and effective dose to use, although prednisone or methylprednisolone have been used at a dose of 1–1.5 mg/kg, with gradual reduction after 1–2 weeks. Individuals who have been on rifampicin for 2 weeks or more will have increased liver metabolism of corticosteroids, such that the corticosteroid is effectively reduced by 33–50%. Individuals may require steroids for prolonged periods of time and IRIS may recur when the dose is reduced, necessitating higher doses. Physicians should be aware of the metabolic adverse effects and potential for serious infections, for instance local and systemic viral infections such as cytomegalovirus retinitis or Kaposi sarcoma, with high-dose corticosteroids.
A placebo-controlled study comparing the effect of steroids with that of placebo in early IRIS showed a benefit of steroids, but the data have to be interpreted with caution as a substantive proportion of those receiving placebo were treated with open-label prednisolone [30].
Studies investigating prevention of IRIS have been conducted in high HIV/TB settings as a public health approach: in patients at high risk of paradoxical TB-IRIS and improving on TB treatment, prednisolone during the first 4 weeks of ART reduced the incidence of TB-IRIS by 30%, reduced requirement for corticosteroids to treat TB-IRIS by 53% and was well-tolerated with no excess risk of infection or malignancy [31]. This approach is not currently recommended in the UK setting.

12.5.2 Other treatment options

Recurrent needle aspiration of lymph nodes or abscesses to remove pus and caseous material is appropriate if they become tense and/or inflamed. This can prevent spontaneous rupture, which may lead to long-term sinus formation and scarring.
Other treatments have as yet little evidence supporting their use. Non-steroidal anti-inflammatory agents are generally not helpful. Temporary discontinuation of antiretroviral therapy has also been advocated but can cause precipitous falls in CD4+ cell counts. TB medication should be continued.
Leukotriene overactivity has been implicated in IRIS, and montelukast can be considered as an alternative to steroids, but may need to be continued for a long period [32].
Expert advice may be invaluable as the efficacy of other therapies such as thalidomide, toclizumab, interleukin-2, infliximab[33], and hydroxychloroquine have been reported as anecdotal cases [34].

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13. Pregnancy and breastfeeding

We recommend that pregnant and breastfeeding women with drug-sensitive TB are treated with standard first-line anti-tuberculosis therapy. (GRADE 1C)

13.1 Rationale

Women with active TB should be treated in pregnancy. However, there are insufficient clinical trial data on the safety, tolerability and efficacy of TB treatment in pregnancy. During pregnancy, there are many changes in pharmacokinetics and TDM of anti-tubercular drugs may be advisable. Rifampicin levels are slightly higher in pregnancy, suggesting no dose adjustments are necessary [1]. Rifampicin does not decrease efavirenz (EFV) exposure in pregnancy and standard doses of EFV should be used [2].

For the first-line drugs rifampicin, ethambutol and pyrazinamide, there are no available data to suggest teratogenic effects or need for dose adjustment. There are no data for rifabutin in women, although there were no teratogenic effects in rats or rabbits. Isoniazid is not teratogenic even when used in the first 4 months of pregnancy [3].

Pregnant women may also be at increased risk of peripheral neuropathy with isoniazid and should be offered standard treatment with pyridoxine 10–25mg daily [4].

Treatment of MDRTB should be supervised by clinicians with expertise in the field.

Streptomycin, amikacin and kanamycin can cause congenital deafness [5] and prothionamide is teratogenic, so both should be avoided. Ethionamide causes birth defects at high doses in animals [6]. Bedaquiline has a Class B pregnancy category and could be considered for use in pregnant women, but safety has not yet been established [7]. Delamanid is available on compassionate use in pregnancy.

Pregnant women should be tested for latent TB in the same way as non-pregnant women (see Section 6). In a UK setting the current guidelines suggest testing with IGRA only. Thresholds for interpretation of TST and IGRA do not change during pregnancy, although in pregnancy there is considerable discordance between TST and IGRA screening results.

It is extremely important to exclude active disease, especially for those at risk of being recently infected with TB, or who have a low CD4+ cell count, to prevent haematogenous spread of *M. tuberculosis* to the placenta and active TB peri-/postpartum.

Isoniazid given as treatment for latent TB infection does not usually cause significant hepatotoxicity [3,8] and does not seem to be associated with adverse pregnancy outcomes, but the number of women studied is small [3]. Isoniazid is therefore recommended for treatment of latent TB infection even during the first trimester for pregnant women who have likely been infected recently, and are therefore at higher risk of disease progression, to prevent the haematogenous spread of *M. tuberculosis* to the placenta (see Section 6). For pregnant women with less likelihood of progression to active disease, isoniazid can be deferred until after delivery [9].

UK guidelines recommend against HIV-positive mothers breastfeeding, but some women may choose to do so if they continue suppressive ART. Tuberculosis treatment is in itself not a contraindication to breastfeeding if the woman is deemed non-infectious, and is being treated with first-line agents [10]. Anti-tuberculosis drugs are present in breast milk but only at low concentrations and therefore appear to be safe [11].

In women of childbearing age, offer contraception as part of TB care, particularly MDR care. (GPP)

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14. Prevention and control

We recommend that all hospitals and HIV units have a TB infection control plan, which includes adequate protection of healthcare workers and other contacts. (GRADE 1B)

For good control of TB there should be:

- Recognition that TB is a potential diagnosis;
- Early diagnosis and active case finding;
- Timely commencement of treatment with an appropriate drug regimen;
- Treatment support including DOT;
- Early consideration of drug resistance in non-responding patients;
- Awareness of social and cultural barriers to accessing health services.

14.1 Hospital care of individuals with potential or known TB requires: considerations

Unless there is a clear clinical or public health need, such as homelessness, people with suspected infectious or confirmed pulmonary TB should not be admitted to hospital for diagnostic tests or for care.

Do not admit people with suspected infectious or confirmed pulmonary TB to a ward containing people who are immunocompromised, including people with HIV, unless they can be cared for in a negative pressure room on the same ward.

In people who may have TB, only carry out aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment in an appropriately engineered and ventilated area (ideally a negative pressure room).

Minimise the number and duration of visits a person with TB makes to an outpatient department while they are still infectious. To minimise the risk of infection, people with infectious TB should be seen at times or in places away from other (especially immunocompromised) people.

For people who may have infectious tuberculosis:

Provide care in a monitored negative pressure room if possible; and

Have specimens sent for rapid diagnostic tests, such as nucleic acid amplification tests (see Section 5 and Appendix 3).

Consider de-escalating isolation as per NICE guidance

NB. The infectious period for MDRTB on second-line treatment is unknown.

For guidance on adequate protection of healthcare workers and other contacts: see NICE guidance for infection control in confined settings. In essence:

Appropriate isolation of infectious patients;

Cough hygiene;

Risk assessment for drug resistance;

Adequate negative pressure rooms that are properly monitored;

Aerosol-generating procedures (bronchoscopy, sputum induction or nebuliser treatment) should only take place in negative pressure rooms;

Consider all individuals potentially infectious until proven otherwise;

No mixing of HIV-positive individuals or other immunosuppressed individuals with TB patients;

Hospital TB control plan based on risk assessment;

Adequate protection of healthcare workers and other contacts.

14.3 Recommended reading

Guidelines for the prevention and control of transmission of TB include:

NICE: Tuberculosis, clinical diagnosis and management of TB, and measures for its prevention and control, 2016. Available at: www.nice.org.uk/guidance/ng33/chapter/Recommendations#infection-control. See also: www.gov.uk/government/collections/tuberculosis-and-other-mycobacterial-diseases-diagnosis-screening-management-and-data

Public Health England: Tuberculosis (TB): collaborative strategy, 2015. Available at: www.gov.uk/government/publications/collaborative-tuberculosis-strategy-for-england
WHO policy on TB infection control in health-care facilities, congregate settings and households, 2009. Available at: www.who.int/tb/publications/tb-facilities-policy/en/
Department of Health: Tuberculosis prevention and treatment, a toolkit for planning, commissioning and delivering high-quality services in England, 2007. Available at: http://webarchive.nationalarchives.gov.uk/20130123192158/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_075621
The Interdepartmental Working Group on Tuberculosis: The prevention and control of tuberculosis in the United Kingdom, 1998. Available at: http://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006196

15. Notification/tracing of contacts

We recommend that once a person has been diagnosed with active TB, the diagnosing physician should inform relevant colleagues so that the need for contact tracing can be assessed without delay. Contact tracing should not be delayed until notification. (GRADE 1B)

We recommend screening the close contacts of any person with pulmonary or laryngeal TB. (GRADE 1B)

We suggest that enhanced contact tracing for PLWH, including contacts of people with EPTB, may be appropriate because of the higher risk of the TB infection and progression and could be implemented where feasible [1]. (GRADE 2C)

15.1 NICE guidelines [2]

In asymptomatic close contacts older than 65 years, consider a chest X-ray (if there are no contraindications), possibly leading to further investigation for active TB.

Do not routinely assess social contacts of people with TB, who will include most workplace contacts.

15.2 Assessing the need for tracing social contacts of people with pulmonary or laryngeal TB

This should be done when the index case is judged to be particularly infectious (for example, evidenced by transmission to close contacts); or

Any social contacts are known to possess features that put them at high risk of going on to develop active TB.

15.3 Offer 'inform and advise' information to all contacts of people with smear-positive TB

The management of contacts of MDRTB individuals needs to be guided by a comprehensive individual risk assessment that takes into consideration the balance between risk and benefits for the individual. Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years is an alternative to provision of preventive treatment for contacts with MDRTB cases. (See also Section 5.)

15.3 Notification

TB is a notifiable disease in the UK, as it is in many other countries.

If the patient is concerned about disclosure of HIV status following notification by an HIV physician, then the notification can be done by any physician involved in clinical care.

15.4 References

1. Wingfield T, MacPherson P, Cleary P, Ormerod LP. High prevalence of TB disease in contacts of adults with extrapulmonary TB. *Thorax* 2017.

2. NICE. *Tuberculosis. NICE guideline [NG33]*. 2016. Available at: www.nice.org.uk/guidance/ng33 (accessed November 2017).

16. Death and clinico-pathological audit

Despite diagnosis and treatment, individuals with HIV and TB infection still die. Some arrive moribund as late presenters and the diagnosis is made at autopsy. Autopsy examination in individuals with known HIV/TB co-infection is useful: it categorises the extent (often underestimated clinico-radiologically) and the pathological type of disease; it enables audit of medical practice.

The causes of death in HIV/TB include:

- Active progressive TB, causing lethal critical organ damage and/or systemic septic shock;
- Secondary effects of TB, e.g. lung haemorrhage, meningo-vascular obstruction and stroke;
- IRIS affecting one or more critical organs, e.g. lung, brain;
- Anti-TB drug toxicity, e.g. in the liver;
- Other HIV- or non-HIV-related comorbidities in a person effectively treated for TB, which influenced why the person died;
- Other fatal disease in a person diagnosed with and treated for TB, without laboratory confirmation, who shows at autopsy no evidence of having had TB.

At autopsy, culture of tuberculous tissue should be performed routinely, to evaluate drug sensitivity and bacterial viability.

Autopsies in the UK and Ireland are either requested by clinicians or commanded by a coroner or procurator fiscal (in Scotland). If the autopsy is coronial, every endeavour should be made to obtain the report for clinical audit. At the time of autopsy, discussion with the pathologist is helpful to clarify the clinico-pathological issues and so optimise the utility of the outcome of the examination.

17. Appendices

Appendix 1. Summary of the modified GRADE system

BHIVA revised and updated the Association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3].

1A Strong recommendation. High-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Consistent evidence from well-performed, randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Strong recommendations, can apply to most individuals in most circumstances without reservation. Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.	**2A** Weak recommendation. High-quality evidence. Benefits closely balanced with risks and burdens. Consistent evidence from well-performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Weak recommendation, best action may differ depending on circumstances or individuals or societal values.
1B Strong recommendation. Moderate-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Evidence from randomised, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk. Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.	**2B** Weak recommendation. Moderate-quality evidence. Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens. Evidence from randomised, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise). Further research may change the estimate of benefit and risk. Weak recommendation, alternative approaches likely to be better for some individuals under some circumstances.
1C Strong recommendation. Low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain. Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.	**2C** Weak recommendation. Low-quality evidence. Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens. Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain. Weak recommendation; other alternatives may be reasonable.
1D Strong recommendation.	**2D** Weak recommendation.

Very low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence limited to case studies. Strong recommendation based only on case studies and expert judgement.	Very low-quality evidence. Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens. Evidence limited to case studies and expert judgement. Very weak recommendation; other alternatives may be equally reasonable.

References

1. British HIV Association. *BHIVA Guideline Development Manual*. 28 January 2014. Available at: www.bhiva.org/GuidelineDevelopmentManual.aspx (accessed August 2015).

2. GRADE Working Group. Grading the quality of evidence and the strength of recommendations. Available at: www.gradeworkinggroup.org/intro.htm (accessed August 2015).

3. Guyatt GH, Oxman AD, Kunz R *et al.* Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–1051.

Appendix 2. Systematic literature search

QUESTIONS and PICO criteria

Databases searched: Medline, Embase, Cochrane Library

Conference abstracts searched:

- The Union World Conference against Lung Disease (IUATLD)
- IAS Conference on HIV Pathogenesis and Treatment
- International AIDS Conference
- Conference on Retroviruses and Opportunistic Infections
- European Conference on Clinical Aspects and Treatment of HIV Infection
- International Congress on Drug Therapy in HIV Infection
- British HIV Association Annual Conference
- International Conference on Antimicrobial Agents and Infectious Disease ICAAC

Date parameters:

- Databases: 2011–June 2015
- Conference abstracts: 2013–July 2015

Systemic literature searches were undertaken from published work and conference abstracts up until June 2015 as described in the BHIVA guidelines development manual.

The population was defined as HIV-positive adults affected by tuberculosis.

Search questions were set by the Writing Group within each search as listed below.

Search 1: Diagnosing active TB in HIV-positive adults

Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic

Population: HIV individuals with suspected tuberculosis

Intervention: diagnosing presence of active TB

Comparator: none

Outcomes: TB treatment

1. Pulmonary TB diagnosis

What clinical signs, symptoms or risk factors are suggestive of active pulmonary TB?

What is the optimal diagnostic test for active pulmonary TB?

In the presence of a negative culture, what other tests support an accurate positive diagnosis in subjects with suspected respiratory TB?

Is there a difference in diagnostic accuracy according to the level of immunosuppression?

2. Extra-pulmonary TB diagnosis (EPTB)

What clinical signs, symptoms or risk factors are suggestive of active EPTB?

What is the optimal diagnostic test for EPTB in HIV?

In the presence of a negative culture, what other tests support an accurate positive diagnosis in subjects with suspected respiratory TB?

Is there a difference in diagnostic accuracy according to the level of immunosuppression?

3. MDRTB

What are the relative risk factors associated with resistance or MDR?

What is the optimal method to diagnose MDRTB?

Search 2: Latent TB in HIV-positive adults

Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic

Population: HIV individuals exposed to tuberculosis
Intervention: prevention of TB
Comparator: none
Outcomes: death, morbidity, TB transmission, drug resistance

1. Diagnosis of latent TB

Who should be screened for latent TB?
How should latent TB be diagnosed in HIV-positive adults?

2. Treatment of latent TB

Who should be treated for latent TB?
What is the optimal treatment for latent TB in HIV?
What is the optimal duration of treatment?

Search 3: Treatment of active TB in HIV
Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic
Population: HIV individuals with active tuberculosis
Intervention: TB treatment
Comparator: none
Outcomes: death, morbidity, TB transmission, drug resistance

1. Full sensitive TB

What anti-tubercular treatment should be recommended?
Are there differences in treatment in pulmonary/EPTB?
What is the optimal duration of treatment in pulmonary TB?
What is the optimal duration of treatment in EPTB?
When should rifabutin be used?
When should rifapentine be used?
When should steroids be used?
Are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?
MDR/XDRTB
What anti-tubercular treatment should be recommended?
What is the optimal duration of treatment according to the different resistance profiles?
Treatment interruptions
What is the best approach to re-establish appropriate treatment for people receiving drug treatment for active TB who experience treatment interruptions?
TDM
What is the role of TDM?

2. DOT

What is the role for DOT?

Search 4: Drug toxicity
Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic
Population: HIV individuals with active tuberculosis
Intervention: management of toxicity

Comparator: none
Outcomes: death, morbidity

1. Hepatotoxicity

How is hepatotoxicity defined?
When does hepatotoxicity generally occur?
What is the best management of hepatotoxicity?
Pre-existing liver disease
What routine screen should be performed?
Who is at greater risk of hepatotoxicity?
How is hepatotoxicity recognised in individuals with pre-existing liver disease?
What is the optimal treatment in individuals with pre-existing liver disease?
Gastrointestinal side effects
When does gastrointestinal toxicity generally occur?
What is the best management of gastrointestinal toxicity?
Peripheral neuropathy
When does peripheral neuropathy occur?
Should ART be changed in individuals experiencing peripheral neuropathy?
What is the best management of peripheral neuropathy?
Rash
When does rash generally occur?
What is the best management in case of rash?

Search 5: Starting ART

Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic
Population: HIV individuals with tuberculosis
Intervention: starting antiretroviral therapy in individuals affected by tuberculosis
Comparator: none
Outcomes: death, TB-associated morbidity, AIDS, non-AIDs comorbidities

1. Starting ART

What is the optimal timing to start antiretroviral treatment in antiretroviral-naïve adult individuals on treatment for tuberculosis?

2. Antiretroviral-naïve patients

Is there robust evidence that one antiretroviral regimen is superior to others?
Should the regimen be changed after the end of tuberculosis treatment?

3. Pharmacokinetics: individuals on ART

Should ARV drugs and dosages be altered in case of concomitant treatment for tuberculosis?

Search 6: Diagnosing and managing immune reconstitution inflammatory syndrome (IRIS)

Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic
Population: HIV individuals with active tuberculosis
Intervention: TB treatment
Comparator: none
Outcomes: death, morbidity

1. Diagnosis

- Who is at higher risk of developing IRIS?

- Which are common manifestations of IRIS?
- What are the optimal diagnostic methods to identify IRIS?

2. Treatment
   - How is IRIS best treated?
   - Should ART ever be interrupted?

Search 7: Treatment failure and relapse
Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic
Population: HIV individuals with active tuberculosis
Intervention: TB treatment
Comparator: none
Outcomes: death, morbidity, TB transmission, drug resistance

1. Treatment failure

How is treatment failure defined?
What is the optimal management of treatment failure?

2. Relapse

How is relapse defined?
What is the optimal management of TB relapse?

Search 8: Pregnant and breastfeeding women with TB/HIV
Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic
Population: Pregnant/breastfeeding HIV individuals with active tuberculosis
Intervention: TB treatment
Comparator: none
Outcomes: fetal death, fetal death morbidity, TB transmission, morbidity, death

1. Pregnant women

When should TB treatment start?
What is the optimal treatment for pregnant women?
What are the risks for the foetus?
Breastfeeding women
What is the optimal management of women who are breastfeeding?
What are the risks for the child?

Search 9: Prevention and control of transmission
Study design: Systematic reviews (SRs), randomised control trials (RCTs), observational, risk, economic
Population: general population
Intervention: prevention of TB transmission
Comparator: none
Outcomes: latent TB infection, active TB infection

1. Isolation

- In which situations (and for how long) should patients be put in isolation room?
- How should aerosol-producing procedures be performed in order to contain
- transmission?

2. Notification
- When should a notification be made?
- Who should perform the notification?

3. Tracing contacts
- When should contacts of a patient with TB be traced?
- How should the tracing be performed?

4. Risk assessment
- How should a risk assessment be carried out?
- What kind of screening (and how often) should be performed in healthcare workers?

The following Appendices contain additional information that the writing group used to base their decisions.

Appendix 3. Diagnosis of active TB/HIV (diagnostic tests)

Use of Rapid PCR testing

Pulmonary disease

Xpert MTB/RIF has higher sensitivity for TB detection in smear-positive than smear-negative patients, and when used in combination with smear microscopy and can increase TB detection by 23%.

The WHO performed a systematic review on diagnostic accuracy in pulmonary TB [1]. A total of 9558 participants, in 27 studies, were included in the review. The reference standard for detecting pulmonary TB was culture (solid or liquid).

When used as an initial diagnostic test replacing smear microscopy, Xpert MTB/RIF achieved an overall pooled sensitivity of 88% (95% credible interval [2]: 84–92%) and a pooled specificity of 99% (95% CrI: 98– 99%) (22 studies, 9008 participants).

When used as an add-on test following a negative smear-microscopy result, Xpert MTB/RIF yielded a pooled sensitivity of 68% (95% CrI: 61–74%) and a pooled specificity of 99% (95% CrI: 98–99%) (23 studies, 7151 participants). For smear-positive culture-positive TB, the pooled sensitivity of Xpert MTB/RIF was 98% (95% CrI: 97–99%) (23 studies, 1952 participants); for smear-negative culture-positive TB, the pooled sensitivity was 68% (95% CrI: 61–74%) (23 studies, 7151 participants).

For people living with HIV, the pooled sensitivity of Xpert MTB/RIF was 79% (95% CrI: 70–86%) (seven studies, 1789 participants); for people without HIV infection, the pooled sensitivity was 86% (95% CrI: 76–92%) (seven studies, 1470 participants).

CNS TB

A systematic review conducted by the WHO on the sensitivity and specificity of molecular methods (Xpert MTB/RIF) for the detection of TBM [3] showed a pooled sensitivity across studies of 79.5% (95% CI: 62.0–90.2%), and a pooled specificity of 98.6% (95% CI: 95.8–99.6%). In this review a total 709 CSF samples (in 16 studies) were tested with Xpert MTB/RIF, and the results were compared against culture as a reference standard. Another systematic review found similar results for sensitivity of Xpert in detection on TBM, with a median sensitivity of 85% (IQR: 0.75–1.00) [4], and a pooled sensitivity of 81% (95% CI: 0.59–0.92), respectively [5]. In particular, higher sensitivity and specificity is found when concentrated CSF is analysed compared to unconcentrated samples (84.2% *vs*. 51.3%, 98% *vs*. 94.6%, respectively) [5].

Xpert Ultra has even higher sensitivity then Xpert or culture, and it is now recommended by the WHO as the initial test for suspected tuberculous meningitis. A study conducted in Uganda on 129 HIV-positive adults with suspected meningitis assessed Xpert MTB/RIF Ultra diagnostic performance against uniform clinical case definition or a composite reference standard of any positive CSF tuberculous test [6]. Xpert Ultra had 95% sensitivity (95% CI 77–99) for tuberculous meningitis, which was higher than either Xpert (45% sensitivity, CI 24–68; *P*=0·0010) or culture (45% sensitivity, CI 24–68; *P*=0·0034).

Pleural TB

Five meta-analyses have shown that pleural fluid ADA has a sensitivity of approximately 92% and a specificity of 90%, for identifying TB [7-12]

The level of ADA correlates with the probability of having pleural TB, with the most accepted cut-off value being of 40 U/L [13]: a diagnosis of pleural tuberculosis is highly probable if the fluid ADA is above 70 U/L and the pleural fluid has a lymphocyte-to-neutrophil ratio greater than 0.75.

A presumptive diagnosis of tuberculous pleuritis can be made if the pleural fluid ADA is between 40 and 70 U/L and the patient has a lymphocyte-to-neutrophil ratio of more than 0.75.

While the level of immunity seems to inversely correlate with the presence of mycobacteria in the pleural fluid, with higher positive smears and positive culture samples in immunodeficient patients, a low CD4+ cell count does not correlate with sensitivity of this test [14]. We suggest sending pleural fluid for microscopy and culture, and quantification of ADA in pleural fluid. Diseases other than TB can cause a high level of ADA, like complicated parapneumonic effusions, empyemas and lymphomas, where ADA activity in pleural fluid is generally >250 U/L [15].

Extrapulmonary TB

A systematic review [4] analysed 27 studies (with a total of 6026 non-respiratory samples), including studies enrolling HIV-positive subjects. Xpert reliably detected the vast majority of non-respiratory samples testing smear-positive, culture-positive for *M. tuberculosis*, but only approximately two-thirds of smear-negative samples. The overall specificity was found to be very high across the majority of studies, whereas sensitivity was found to be extremely heterogeneous, depending also on the type and quality of tissue/sample. Sensitivity ranged between 25% and 100% when Xpert and culture were both applied to the index non-respiratory samples. Much higher sensitivity was seen when testing lymph node samples, other tissue samples and cerebrospinal fluid compared to the results of testing pleural fluid and other serous fluids. To note, high sensitivity was also observed when testing gastric aspirate samples. Another systematic review and meta-analysis [5] analysed 18 studies (evaluating 4461 samples) and found no differences in diagnostic accuracy between studies with >10% versus <10% HIV-positive individuals. However, in some studies a very high sensitivity of Xpert detection of EPTB in lymph node tissue was found in HIV subjects, both dependently and independently of CD4+ cell count. Other studies [16,17] assessing the utility of Xpert in detecting disseminated disease from urine in HIV-positive individuals showed a strong inverse association between Xpert sensitivity and CD4+ cell count: sensitivity increased to 60% in individuals with CD4+ count <100 cells/mm^3 [17]. These results demonstrate that urine-based diagnosis may be particularly useful for routine investigation among HIV-positive individuals with advanced infection.

MDR/XDR

A systematic review [18] of 56 studies on the diagnostic accuracy of molecular genetic tests for drug resistance has shown that rapid molecular tests for rifampicin and isoniazid resistance are sensitive, specific and cost-effective when added to culture drug susceptibility testing.

Pooled sensitivity for GenoType® MTBDRplus (Hain Lifescience, Nehren, Germany) was 83.4% for isoniazid and 94.6% for rifampicin resistance, for INNO-LiPARif.TB® (Fujirebio Europe, Ghent, Belgium) was 95.4% for rifampicin resistance, and for Xpert® MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA) was 96.8% for rifampicin resistance; equivalent pooled specificity was 99.6%, 98.2%, 99.7% and 98.4%, respectively.

When used to detect rifampicin resistance, Xpert MTB/RIF achieved a pooled sensitivity of 95% (95% CrI: 90–97%; 17 studies, 555/2624 total specimens) and a pooled specificity of 98% (95% CrI: 97–99%; 24 studies, 2414 specimens, including true negatives and false positives). Early detection of isoniazid resistance is valuable as appropriate treatment may prevent the further development of MDRTB [19].

Antigen testing–urine LAM

The urine lateral flow lipoarabinomannan (LF-LAM) assay is a point-of-care (POC) test for active TB (AlereDetermine™ TB LAM Ag, AlereInc, Waltham, MA, USA), commercialised in January 2013. The test detects lipoarabinomannan (LAM), a lipopolysaccharide present in mycobacterial cell walls, released from metabolically active or degenerating bacterial cells. This antigen appears to be present only in people with active TB disease. The advantages of the test are its simplicity and speed of use, lack of instrumentation, low cost and its implementation at the point of care.

It represents a useful add-on diagnostic tool for subjects with difficulty producing any sputum, with extrapulmonary or disseminated TB, as often is the case in advanced HIV immunodeficiency.
A Cochrane review [20] of five studies, with a total of 2313 participants conducted in low- or middle-income countries with the objective of assessing the accuracy of this test for the diagnosis of active TB in adults with HIV has shown that overall LF-LAM has a low sensitivity. LF-LAM alone had median pooled sensitivity and specificity of 45% and 92% in patients with active TB/HIV. When LF-LAM was used in combination with sputum microscopy, the pooled sensitivity was 59%, while the pooled specificity was 92%. Pooled sensitivity and specificity of LF-LAM were 56% and 90% in participants with a CD4 cell count < 100/mm^3 (859 participants, 47% with TB) versus 26% and 92% in participants with a CD4 cell count > 100/ mm^3 (1410 participants, 30% with TB).
In HIV-positive individuals with low CD4 cell counts who are seriously ill, LF-LAM may help with the diagnosis of TB: although characterised by limited sensitivity (and therefore required to be used in conjunction with microscopy and molecular tests), it provides the most rapid means of conducting an initial diagnostic screen at the point of care.
However, it has lower specificity than the molecular diagnostic tests, and false positive tests can result from cross-reaction with a number of other bacteria, including those present in oral flora such as various species of *Actinobacteria* (*Nocardia* and *Streptomyces*), *Candida* and non-tuberculous mycobacteria [21].
Few systematic reviews have evaluated the role of IGRAs in diagnosing active tuberculosis in HIV-positive patients [22-25]: results are consistent in showing a sensitivity of QFT-GIT of approximately 65% and a sensitivity of about 70% for T-SPOT.TB. However, there is no consistent evidence that the IGRAs are more sensitive for detecting tuberculosis in individuals with active disease. Data from the five studies reporting comparisons between QFT-GIT and TST yielded a pooled sensitivity of 67% and 60%, respectively.

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Appendix 4. Treatment of latent TB infection

Excluding active TB

Before testing for, or treating LTBI, active TB should be excluded with a detailed history and examination.

Results from a meta-analysis of 12 observational studies, nine of which were based in Africa and three in South-east Asia, including over 8000 HIV-positive participants, showed that individuals reporting none of current cough, night sweats, fever or weight loss have a very low probability of having active TB (negative predictive value of 97.7% at 5.0% TB prevalence among people living with HIV) [1].

Interferon-gamma release assays (IGRAs)

Interferon-gamma release assays (IGRAs) are blood tests that measure interferon-gamma release from T cells after stimulation with antigens largely specific to *M. tuberculosis* (such as early secreted antigen target [ESAT-6] and culture filtrate protein [CFP-10]) [2]. The current commercially available tests are the T-Spot.TB (Oxford Immunotec, Abingdon, Oxfordshire, UK), which uses enzyme-linked immunosorbent spot (ELISPOT) technology to detect the antigen-specific T cells, and the QuantiFERON-TB Gold (QFT-GIT) and QuantiFERON-TB Gold Plus (Qiagen, Manchester, UK) which are enzyme-linked immunosorbent assays.

All tests are approved for the diagnosis of LTBI in HIV-negative individuals. There are some differences between the two test platforms although in general they are unaffected by previous BCG immunisation and infection with most non-tuberculous mycobacteria (an important exception in the UK being *Mycobacterium kansasii*).

The risk of tuberculosis in the short- to medium-term in HIV-positive adults with a negative QFT-GIT seems to be low [3]. However, indeterminate or borderline IGRA results are more common in HIV-positive individuals as HIV-associated immunosuppression, measured by circulating CD4+ T cell count, reduces the ability of IGRAs (both QFT-GIT, and to a lesser extent, T-SPOT.TB) to detect LTBI and reversions/conversions occur close to cut-off values [4,5].

TST can also identify individuals with LTBI and those who benefit from treatment in high tuberculosis-incidence settings [6] but false-negative TST results were shown to be more common among HIV-positive individuals in the pre-ART era, especially in those with low CD4+ cell counts [7-11]. False positives occur after BCG immunisation or following exposure to non-tuberculous mycobacteria.

A Cochrane review including 12 trials with a total of 8578 randomised participants located across a spectrum of low to high TB-incidence countries found that treating LTBI in HIV-positive individuals with a positive TST is effective in reducing the incidence of active TB (relative risk 0.38, 95% CI: 0.25-0.57) [12]. Efficacy was similar for all regimens, regardless of drug or duration of therapy, although shorter, multidrug regimens were associated with more discontinuation due to adverse effects than longer isoniazid-only regimens. However, the great majority of participants were not using effective ART when the studies of LTBI therapy were performed.

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Appendix 5. Treatment of drug-sensitive TB: drug regimens

The treatment of drug-susceptible tuberculosis evolved through an international clinical trial programme to the current standard of care: short-course chemotherapy, consisting of 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol (intensive phase), followed by 4 months of rifampicin and isoniazid (continuation phase) (2RHZE/4RH). These studies were conducted in the era before HIV co-infection in TB individuals became widespread.

A clinical trial in the pre-ART era, which compared 6 versus 12 months of short course chemotherapy, was limited by high mortality but showed high rates of recurrent TB with 2RHZE/4RH [1]. Subsequent studies reported that recurrent TB in HIV-positive individuals is usually due to re-infection; relapse rates after 2RHZE/4RH were no more common than those observed in HIV-negative individuals [2-4]. Short-course chemotherapy thus became the standard of care irrespective of HIV status.

Several recent attempts to shorten TB therapy to 4 months (for instance, by using fluoroquinolones) have proved unsuccessful, with high relapse rates [5-8]. Intermittent administration of TB therapy should be avoided during the induction phase, as this strategy has been associated with acquired rifamycin resistance [9].

Pyrazinamide is an essential component of short-course chemotherapy [10-12]; the duration of TB treatment should be extended to 9 months for individuals who are unable to take pyrazinamide. Individuals with positive TB cultures at the end of the intensive phase are at increased risk of relapse [13]. Poor adherence should be re-assessed, drug susceptibility testing conducted, and treatment extended to 9 months.

There is no evidence that individuals with disseminated TB should receive more prolonged therapy. Many clinicians use extended treatment regimens (up to 12 months as per NICE guidance [14]) for central nervous system tuberculosis (i.e. tuberculous meningitis) even though 6–9 months appears to be sufficient [15,16].

Rifabutin is a rifamycin with similar activity against *M. tuberculosis* as rifampicin [17-19] although no trials have been conducted in individuals receiving ART. The main advantage of rifabutin is that it allows the co-administration of (ritonavir-boosted) protease inhibitors (see Sections 9 and 10). The optimal dose of rifabutin in individuals who receive PI/r has not been established [20]. The currently recommended dose of 150 mg/day results in adequate rifabutin exposure but 15-fold increased exposure of rifabutin metabolites. Good clinical outcomes have been reported with reduced dose rifabutin (150 mg/day or 150 mg three times per week) and clinically significant toxicity (bone marrow suppression, uveitis and arthralgia) appears to be relatively uncommon [20-22] (see Section 10).

Rifapentine is a long-acting rifamycin that allows once-weekly supervised administration (together with moxifloxacin) during the continuation phase [7]; no outcome data are available for HIV-positive individuals on ART.

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Table A5.1. Drug dosing modifications: food effect, alternatives in swallowing difficulties and doses in renal impairment

Drug	Food effect	Alternatives for individuals with swallowing difficulties	Considerations for renal impairment
Ethambutol 400 mg tablets 100 mg tablets	Absorption is not significantly impaired by food	Only film-coated tablets available: strength 400 mg or 100 mg	Ethambutol should preferably be avoided in individuals with renal impairment, but if used the dose should be reduced as determined by blood levels of ethambutol. Toxic effects are more common if renal function is impaired. No specific recommendation for haemodialysis
Isoniazid Oral	Isoniazid tablets should be taken preferably on an empty stomach, i.e. at least 30 minutes before a meal or 2 hours after a meal See fixed dose combinations below	Isoniazid is available as 50 mg/2 mL solution for injection (see below)	No dosage reduction of Isoniazid is necessary when given to individuals with mild renal failure Use of isoniazid should be carefully monitored in individuals with severe renal impairment (glomerular filtration rate of less than 10 mL/minute) and slow acetylator status: a dose reduction of about 100 mg might be necessary to maintain trough plasma levels at less than 1 µg/mL Isoniazid is removed by both haemodialysis and peritoneal dialysis; therefore, isoniazid should be administered immediately after dialysis
Isoniazid 50 mg/2 mL solution for injection (intramuscular,	Tyramine- and histamine-containing foods should be avoided	N/A	No dosage reduction of Isoniazid is necessary when given to individuals with mild renal failure Use of isoniazid should be carefully monitored in individuals with severe renal impairment (glomerular filtration rate of less than 10 mL/minute) and slow

<table>
<tr><td>intravenous, intrapleural, or intrathecal injection)</td><td>by individuals receiving isoniazid</td><td></td><td>acetylator status: a dose reduction of about 100 mg might be necessary to maintain trough plasma levels at less than 1 µg/mL
Isoniazid is removed by both haemodialysis and peritoneal dialysis; therefore, isoniazid should be administered immediately after dialysis</td></tr>
<tr><td>Pyrazinamide Zinamide® Tablets 500 mg</td><td>No specific recommendation</td><td>Only tablet formulation available</td><td>Reduction in the size and/or frequency of dose is recommended for individuals with renal insufficiency
No specific recommendation for haemodialysis</td></tr>
<tr><td>Rifabutin Mycobutin® 150 mg capsules</td><td>Dose can be taken at any time, independently of meals</td><td>Only capsule formulation available</td><td>Severe renal impairment (creatinine clearance below 30 mL/min) requires a dosage reduction of 50%
No specific recommendation for haemodialysis</td></tr>
<tr><td>Rifampicin Rifadin® 300 mg Capsules</td><td>Dose should preferably be taken at least 30 minutes before a meal or 2 hours after a meal to ensure rapid and complete absorption</td><td>Rifadin® infusion (see below)
Rifadin® 100 mg/5 mL oral suspension (dose is equivalent to capsule formulation)</td><td>At a dose of up to 600 mg/day, half-life does not differ in individuals with renal failure and, consequently, no dosage adjustment is required
No specific recommendation for haemodialysis</td></tr>
<tr><td>Rifampicin Rifadin® for Infusion 600 mg</td><td>N/A</td><td>N/A</td><td>At a dose of up to 600 mg/day, half-life does not differ in individuals with renal failure and consequently, no dosage adjustment is required
Cautions should be taken in case of renal impairment if dose >600 mg/day
No specific recommendation for haemodialysis</td></tr>
<tr><td>Streptomycin IM or IV injection/infusion</td><td>N/A</td><td>N/A</td><td>Streptomycin is excreted unchanged in the urine by glomerular filtration; dosage should also be reduced in those with renal impairment, and plasma-drug concentration should be monitored
No specific recommendation for haemodialysis</td></tr>
<tr><td>Levofloxacin Tavanic®</td><td>Tablets may be taken during meals</td><td>Tablet can be divided into</td><td><table><tr><td></td><td colspan="3">Dose regimen</td></tr><tr><td></td><td>250 mg/24 h</td><td>500 mg/24 h</td><td>500 mg/12 h</td></tr></table></td></tr>
</table>

<table>
<tr>
<td>Evoxil®
Film-coated tablets
5 mg/mL solution for infusion</td>
<td>or between meals; should be taken at least 2 hours before or after iron salts, zinc salts, magnesium- or aluminium-containing antacids</td>
<td>equal halves at score line, but swallowed without crushing
Solution for infusion</td>
<td>
<table>
<tr><th>Creatinine clearance</th><td>first dose: 250 mg</td><td>first dose: 500 mg</td><td>first dose: 500 mg</td></tr>
<tr><td>50–20 mL/min</td><td>then: 125 mg/24 h</td><td>then: 250 mg/24 h</td><td>then: 250 mg/12 h</td></tr>
<tr><td>19–10 mL/min</td><td>then: 125 mg/48 h</td><td>then: 125 mg/24 h</td><td>then: 125 mg/12 h</td></tr>
<tr><td><10 mL/min (including haemodialysis and CAPD) [1]</td><td>then: 125 mg/48 h</td><td>then: 125 mg/24 h</td><td>then: 125 mg/24 h</td></tr>
</table>
[1]No additional doses required after haemodialysis or continuous ambulatory peritoneal dialysis
</td>
</tr>
<tr>
<td>Moxifloxacin
Avalox® film-coated tablets
400 mg/250 mL solution for infusion</td>
<td>Tablet may be taken independent of meals; approx. 6 hours should be left between administration of agents containing magnesium, aluminium, iron or zinc and administration of moxifloxacin</td>
<td>Tablet must be swallowed whole
Solution for infusion (dose equivalent to tablet formulation)</td>
<td>No adjustment of dosage is required in individuals with mild to severely impaired renal function or in individuals on chronic dialysis, i.e. haemodialysis and continuous ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>Rimstar® film-coated tablet/
Voractiv® film-coated tablet
Rifampicin 150 mg
Isoniazid 75 mg</td>
<td>Tablets should be taken in a fasting state at least 1 hour before a meal
Tyramine- and histamine-</td>
<td>Only film-coated tablets available</td>
<td>Voractiv should be used with caution in individuals with moderate renal impairment (creatinine clearance 30–60 mL/min); Voractiv is contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min)
No specific recommendation for haemodialysis</td>
</tr>
</table>

Pyrazinamide 400 mg Ethambutol 275 mg	containing foods should be avoided by individuals receiving isoniazid		
Rifinah coated tablets Rifampicin 300 mg Isoniazid 150 mg or Rifampicin 100 mg Isoniazid 150 mg	Tablets should preferably be taken on an empty stomach at least 30 minutes before a meal or 2 hours after a meal Tyramine- and histamine-containing foods should be avoided by individuals receiving isoniazid	Only film-coated tablets available	No specific recommendation. See individual drugs above No specific recommendation for haemodialysis
Rifater® Tablets Rifampicin 120 mg Isoniazid 50 mg Pyrazinamide 300 mg	Tablets should preferably be taken on an empty stomach at least 30 minutes before a meal, or 2 hours after a meal Tyramine- and histamine-containing foods should be avoided by individuals receiving isoniazid	Only tablets available	The precautions for the use of Rifater are the same as those considered when a triple individual administration of rifampicin, isoniazid and pyrazinamide is required No specific recommendation for haemodialysis

Table A5.2. Protocol for reintroducing TB drugs after DILI or grade 1–3 rash (adapted from a reintroduction protocol for cutaneous reactions [1]).

Day	Isoniazid (mg)	Rifampicin (mg)	Pyrazinamide (mg)
1	50		
2	150		
3	300		
4	300	75	
5	300	150	
6	300	300	
7	300	450 <50 kg or 600 >50 kg	
8	300	450/600	250
9	300	450/600	500
10	300	450/600	1000
11	300	450/600	1500 <50 kg or 2000 >50 kg
12	300	450/600	1500/2000
13	300	450/600	1500/2000

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Appendix 6. Drug–drug interactions of MDRTB drugs and ART

Amikacin/kanamycin/streptomycin

An interaction with FTC, 3TC or TDF is unlikely as most aminoglycosides are eliminated by renal glomerular filtration rather than active transport. However, as aminoglycosides are nephrotoxic, monitor renal function.

Since aminoglycosides are nephrotoxic, renal function should be monitored periodically as changes in the renal function may impair FTC elimination. Co-administration with nephrotoxic agents is unlikely to be of concern for TAF.

Capreomycin

Capreomycin is possibly excreted partly by tubular secretion. There is potential for exposure of capreomycin or FTC/3TC/TDF/TAF to be increased via competition for renal transporters.

Since aminoglycosides are nephrotoxic, renal function should be monitored periodically as changes in the renal function may impair FTC elimination. Co-administration with nephrotoxic agents is unlikely to be of concern for TAF.

Cobicistat is unlikely to inhibit OAT and OCT renal transporters at clinically relevant concentrations, therefore an interaction with capreomycin is unlikely.

Levofloxacin

Levofloxacin may cause QTc prolongation and the European SPC for ATV, LPV, EFV and RPV advise caution when co-prescribing with drugs known to induce QTc interval prolongation. There is no warning concerning DRV with RTV or COBI.

Levofloxacin is eliminated renally, mainly by glomerular filtration and active tubular secretion. *In vitro* data indicate that levofloxacin inhibits OCT2 and could potentially increase 3TC concentrations.

Moxifloxacin

Moxifloxacin may cause QTc prolongation and the European SPC for ATV, LPV, EFV and RPV advise caution when co-prescribing with drugs known to induce QTc interval prolongation. There is no warning concerning DRV with RTV or COBI.

Moxifloxacin is predominantly glucuronidated by UGT1A1. EFV and ETV induce UGT1A1 and therefore could potentially decrease moxifloxacin levels.

Para-aminosalicylic acid

RPV does not inhibit OCT2 in the range of clinically relevant concentrations [1].

As para-aminosalicylic acid and FTC, 3TC, TDF are predominantly renally eliminated, including active tubular secretion, there is potential for competition for elimination via renal transport proteins, which may lead to increased concentrations of either drug.

Clofazimine

- Pharmacokinetic interaction is unlikely. However, caution must be used as clofazimine with LPV/r, ATV/r, RPV, EFV may prolong the QTc interval.

Bedaquiline

Bedaquiline is metabolised by CYP3A4 and moderate or strong CYP3A4 inhibitors (such as ATV, DRV, RTV, COBI, LPV) may increase bedaquiline exposure, which could potentially increase the risk of adverse reactions.

Bedaquiline prolongs the QTc interval. When bedaquiline is co-administered with other medicinal products that prolong the QTc interval (ATV, LPV, RPV, EFV), an additive or synergistic effect on QTc prolongation cannot be excluded. The combination of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided. If co-administration is necessary, clinical monitoring, including frequent electrocardiogram assessment and monitoring of transaminases, is recommended.

Co-administration of bedaquiline (400 mg single dose) and LPV/r (400/100 mg twice daily) to 16 HIV/TB-negative subjects increased bedaquiline AUC by 22% and had no effect on C_{max}.
Co-administration of bedaquiline (400 mg single dose) and EFV (600 mg once daily) to 33 HIV/TB-negative subjects decreased bedaquiline AUC by 18% and had no effect on C_{max}. EFV pharmacokinetics were similar to historical data from HIV-positive subjects.
ETR may reduce bedaquiline exposure due to induction of CYP3A4, resulting in loss of activity.
Co-administration of bedaquiline (400 mg single dose) and NVP (200 mg twice daily for 4 weeks) in HIV-positive individuals had no clinically relevant effect on bedaquiline exposure (AUC increased by 3%, C_{max} decreased by 20%).

Delamanid

QTc prolongation has been observed in individuals treated with delamanid. This prolongation increases slowly over time in the first 6–10 weeks of treatment and remains stable thereafter. QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively. Treatment with delamanid should not be initiated in individuals taking medicinal products that are known to prolong the QTc interval (e.g. ATV, LPV, RPV, EFV) unless the possible benefit of delamanid is considered to outweigh the potential risks. Such individuals should receive very frequent monitoring of ECG throughout the full delamanid treatment period.
Co-administration of delamanid with a strong inhibitor of CYP3A4 (LPV/r) was associated with a 30% higher exposure to the metabolite DM-6705, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with any strong inhibitor of CYP3A4 is considered necessary it is recommended that there is very frequent monitoring of ECGs throughout the full delamanid treatment period.
The complete metabolic profile of delamanid has not yet been elucidated, and there is a potential for drug interactions with other co-administered medications, if significant unknown metabolites are discovered.
For latest drug interaction recommendations, and for details of the supporting evidence, and changes in drug exposure, please see www.hiv-druginteractions.org and/or http://hivclinic.ca/drug-information/drug-interaction-tables/

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Appendix 7. IRIS

Definition [1]

Proposed case definition for TB – PARADOXICAL IRIS	
<u>Clinical criteria</u> **At least one major or two minor clinical criteria must be met. The absence of alternative explanations for clinical deterioration is also required.**	
Major criteria	(1) New or enlarging lymph nodes, cold abscesses or other focal tissue involvement (2) New or worsening radiological features of TB (includes chest radiograph, abdominal ultrasound or CT scan features) (3) New or worsening central nervous system TB (meningitis or focal neurological involvement) (4) New or worsening serositis (pleural effusion, ascites, pericardial effusion or arthritis)
Minor criteria	(1) New or worsening constitutional symptoms such as fever, night sweats, or weight loss (2) New or worsening respiratory symptoms such as cough, dyspnoea, or stridor (3) New or worsening abdominal pain (4) In retrospect, the resolution of clinical or radiological findings of the IRIS episode without having made a change in TB treatment
Alternative explanations for clinical deterioration to be excluded	(1) Failure of TB treatment due to drug resistance (2) Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in individuals with smear-negative PTB and extra-pulmonary TB where the initial TB diagnosis has not been microbiologically confirmed) (3) Drug toxicity or reaction

Proposed case definition for TB – UNMASKING IRIS	
<u>Clinical criteria</u> **Major and one of two minor clinical criteria must be met.**	
Major criteria	Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART
Minor criteria	(1) Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. (2) Once established on tuberculosis treatment, a clinical course that is complicated by a paradoxical reaction

Epidemiology of IRIS

In the ART era, IRIS has been reported widely. Two studies reported respectively IRIS occurrence in 36% (12 of 33) and 32% (6 of 19) of individuals [2,3]. Another study did not find any significant difference in onset of IRIS in individuals receiving ART (3 of 28 [11%]) compared with individuals not on antiretroviral treatment (3 of 44 [7%]) [4].

According to the literature the majority of reactions occur within 60 days of initiating ART, with a median of 15 days [5]. IRIS does not appear to be associated with any particular antiretroviral regimen or drug class [6]. Most individuals with IRIS have advanced HIV infection (in one study the median baseline CD4+ cell count was 35 cells/mm^3, and median HIV viral load >500,000 HIV-1 RNA copies/mL).

In the CAMELIA trial the risk of IRIS was increased around four fold if ART was started in the first 2 weeks compared with delaying ART until beyond week 8 of TB treatment [7].

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Appendix 8. When to start ART in TB/HIV infection

It is only in individuals with CD4+ cell count <50 cells/mm^3 that trials have consistently shown clinical benefit of starting ART within 2–4 weeks of starting TB therapy as opposed to deferring ART for up to 2 months. The ACTG A5221 (STRIDE) trial compared early (<2 weeks) *vs*. delayed (8–12 weeks) introduction of ART in individuals with CD4+ cell counts <250 cells/mm^3. The risk of AIDS and death (12.9 *vs*. 16.1%, *P*=0.45) was not significantly lower with early ART in the overall study population, but in those with CD4+ cell counts <50/mm^3 (a pre-specified subgroup analysis), a lower incidence of AIDS and death was observed with early ART (15.5 *vs*. 26.6%, *P*=0.02) [1]. The SAPIT trial compared early (<4 weeks) versus delayed (8–12 weeks) ART in individuals with CD4+ cell counts <500 cells/mm^3. The risk of AIDS and death (6.9 *vs*. 7.8%, *P*=0.73) was not significantly lower with early ART in this study but a lower incidence of AIDS and death was observed with early ART in those with CD4+ cell counts <50 cells/mm^3 (8.5 *vs*. 26.3%, *P*=0.06) [2]. The CAMELIA trial compared outcomes in individuals with HIV/TB co-infection with CD4+ cell counts <200 cells/mm^3 who started ART at 2 *vs*. 8 weeks after commencing TB treatment. Early introduction of ART was associated with a 38% (*P*=0.006) reduction in mortality; older age, low Karnofsky score, disseminated and multidrug-resistant TB were other predictors of death [3].

For individuals with CD4+ cell counts 50–200 cells/mm^3, the clinical benefit of early ART (2–4 weeks *vs*. 8–12 weeks) is less clear. The CAMELIA trial showed lower mortality [3] whereas the SAPIT trial [2] and ACTG A5221 trial [1] did not. For individuals with CD4+ >200 cells/mm^3 there is no mortality benefit from starting ART sooner than 2 months after start of TB therapy. The largest of the RCTs, which included individuals with HIV/TB co-infection with CD4+ cell counts >220 cells/mm^3, showed that ART could be deferred until after 6 months of TB treatment without any increase in TB treatment failure or death [4]. By contrast, the SAPIT study found that sequential therapy (6 months of TB treatment followed by ART) was inferior to an integrated strategy (ART initiated during TB treatment), with significantly higher mortality in both the low (<200 cells/mm^3) and high (200–500 cells/mm^3) CD4+ cell count stratum [5]. A trend towards improved outcomes with integrated treatment was also reported in individuals with CD4+ cell counts >350 cells/mm^3 [6]. Similar rates of suppression of HIV replication were observed in these trials with early [1-3] vs. delayed ART [1,3,7].

A study conducted in Vietnam on 253 patients with TB meningitis (median CD4+ cell count 41 cells/mm^3) were randomised to immediate ART versus deferred ART (after 2 months of TB treatment) failed to show improvement on survival in the immediate treatment arm, with more grade 4 adverse events [8].

It is hard to establish whether the findings of this study would be generalisable to other settings. The optimal timing of ART initiation in TB meningitis remains therefore to be established.

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Appendix 9. Glossary

3TC	Lamivudine
ABC	Abacavir
ADA	Adenosine deaminase
ADR	Acquired drug resistance
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
Amx/clv	Amoxicilline/clavulanate
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate synthase
ATV	Atazanavir
ATV/c	Atazanavir/cobicistat
ATV/r	Atazanavir/ritonavir
AUC	Area Under under the curve
AZT	Zidovudine
BAL	Bronchoalveolar lavage
BCG	Bacille-Calmette-Guérin
Bdq	Bedaquiline
BHIVA	British HIV association
CBNAAT	Cartridge-based NAAT
Cfz	Clofazimine
CM	Capreomycin
CME	Continuing medical education
CMV	Cytomegalovirus
CNS	Central nervous system
COBI	Cobicistat
COPD	Chronic obstructive pulmonary disease
CRS	Creditor reporting system
Cs	Cycloserine
CSF	Cerebrospinal fluid
C_{trough}	Trough concentration
CYP	Cytochrome P
DDIs	Drug–drug interactions
DILI	Drug-induced liver injury
Dlm	Delamanid
DOT	Directly observed treatment
DRTB	Drug-resistant tuberculosis
DRV	Darunavir
DRV/c	Darunavir/cobicistat
DRV/r	Darunavir/ritonavir
DST	Drug-susceptibility testing
E	Ethambutol
eDOT	Electronic directly observed treatment
EFV	Efavirenz
EMEA	European Medicines Agency

EPTB	Extra-pulmonary tuberculosis
ETH	Ethambutol
Eto	Ethionamide
ETR	Etravirine
EVG/c	Elvitegravir/cobicistat
FTC	Emtricitabine
GFX	Gatifloxacin
GPP	Good practice points
GRADE	Grading of Recommendations Assessment Development and Evaluation
GST	Glutathione S-transferase
H	Isoniazid
H^H	High-dose isoniazid
HIV	Human immune deficiency virus
IGRA	Interferon gamma release assay
INH	Isoniazid
IPT	Isoniazid preventative therapy
IRD	Immune reconstitution disease
IRIS	Immune reconstitution inflammatory syndrome
ITU	Intensive treatment unit
KM	Kanamycin
LF-LAM	Lateral flow lipoarabinomannan
LTBI	Latent tb TB infection
Lzd	Linezolid
MAC	*Mycobacterium avium* complex
MDG	Millennium development goal
MDR	Multidrug-resistant
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MTB	*Mycobacterium tuberculosis*
MVC	Maraviroc
MXF	Moxifloxacin
NAAT	Nucleic acid amplification test
NICE	National Institute for Health and Care
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
PCR	Polymerase chain reaction
PI	Protease inhibitor
PLWH	People living with HIV
POC	Point of care
Pto	Prothionamide
PZA	Pyrazinamide
QTc	Corrected QT interval
R	Rifampicin
RAL	Raltegravir
Rbt	Rifabutin
RCT	Randomised clinical trials

Rif	Rifampicin
RR	Rifampicin-resistant
RTV	Ritonavir
SAE	Serious adverse event
SHA	System of health accounts
SNP	Single nucleotide polymorphism
STD	Sexually transmitted disease
T20	Enfuvirtide
TAF	Tenofovir alafenamide
TB	Tuberculosis
TBM	Tubercular meningitis
TDF	Tenofovir disoproxil fumarate
TDM	Therapeutic drug monitoring
TNF	Tumour necrosis factor
Trd	Terizidone
TST	Tuberculin skin test
UK-CAB	UK Community Advisory Board
VOIT	Voice over internet protocol
VOT	Video-observed treatment
WGS	Whole genome sequencing
WHO	World Health Organization
XDRTB	Extensively drug-resistant TB
Z	Pyrazinamide
ZN	Ziehl–Nielsen