British HIV Association guidelines for the treatment of TB/HIV coinfection 2010

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Contents

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The guidelines have been extensively revised since the last edition in 2005; most sections have been amended and areas where there is a need for clinical trials or data have been highlighted.

The major changes/amendments are:

- **a more detailed discussion of gamma interferon tests;**
- **new guidance on chemopreventative therapy**
- **a complete update of the drug interactions section and tables;**
- **an updated section on choice of NNRTI;**
- **a revised section on when to start HAART;**
- **a new section on isoniazid resistance and XDR;**
- **guidance on the diagnosis of IRIS;**
- **new tables for management of adverse reactions.**

1.0 Summary of guidelines

These guidelines have been drawn up to help physicians manage adults with TB/HIV coinfection. Recommendations for the treatment of TB in HIV-infected adults are similar to those in HIV-negative adults. However, there are important exceptions which are discussed in this summary. We recommend that coinfected patients are managed by a multidisciplinary team which includes physicians with expertise in the treatment of both tuberculosis and HIV.

We recommend using the optimal anti-tuberculosis regimen. In the majority of cases this will include rifampicin and isoniazid.

In the treatment of HIV, patients starting highly active antiretroviral therapy (HAART) have an ever-greater choice of drugs. We recommend that if patients on anti-tuberculosis therapy are starting HAART then antiretrovirals should be chosen to minimize interactions with TB therapy. There will be cases in which the choice of antiretrovirals is limited by intolerance, severe toxicity or genotypic resistance. TB treatment should only be modified when drug interactions with these antiretrovirals do not allow the optimal TB regimen. In some of these cases a longer duration of TB treatment may be necessary.

1.1 Diagnosis of active TB

The gold standard for diagnosing tuberculosis is microscopy followed by culture and drug sensitivity testing. Molecular diagnostics may be valuable when acid-fast bacilli are seen on smears. Rapid confirmation, by molecular diagnostics, that acid-fast bacilli are not *M. tuberculosis,* may avoid unnecessary treatment and infection-control measures.

We recommend rapid detection of rifampicin resistance using molecular techniques in patients whose initial assessment (e.g., recent immigrant from an area with a high prevalence of rifampicin-resistant disease) or clinical course suggest multi-drug resistant tuberculosis. These molecular tests should be used as an adjunct to standard laboratory techniques.

1.2 Detection of latent TB infection: Tuberculin skin test/interferon-γ assays

HIV-infected individuals with latent TB infection are much more likely to progress to active TB than HIV-uninfected people. Detection and treatment of latent TB infection is therefore important, although diagnosis can be difficult.

Tuberculin skin test (TST)/interferon-γ assays (IGRAs) are used to detect latent infection. They are not recommended as a diagnostic tool in suspected active TB as they only reflect previous mycobacterial exposure. Tuberculin skin testing is less useful in patients with HIV infection compared with HIV-uninfected patients, especially at low CD4 cell counts. IGRAs are newer blood assays from essentially MTB-specific T cells, which are generally more sensitive than tuberculin tests for detecting both active and latent disease in HIV-negative subjects. They are also more specific in BCG-vaccinated individuals. Although there are few data regarding their performance in HIV-infected patients, especially at low blood CD4 cell counts, we believe that IGRAs may have value in detecting latent TB infection and we recommend the use of IGRAs rather than TSTs as a screening tool for latent tuberculosis. However, their precise role remains unclear and draft NICE guidance suggests using IGRA testing in those patients with a CD4 count over 200 cells/μL, and both an IGRA and tuberculin test in those with CD4 counts below this threshold. Although physicians can perform both tests in severely immunosuppressed patients, we believe that there are few data to support this strategy and doing this would add complexity, cost and difficulties in interpretation. The majority of the Committee believe that an IGRA test alone would be sufficient. New data would be welcome in guiding physicians in this difficult area.

We recommend screening for latent infection in HIV-infected patients dependent on a risk assessment based on country of origin, blood CD4 cell count and length of time on antiretroviral therapy. In addition, all HIV-positive close contacts of people who have infectious TB should be followed up and offered chemo-preventative therapy according to NICE guidelines [1].

1.3 Treatment of latent TB infection

Active TB needs to be excluded before considering treatment of latent infection, which is usually with isoniazid monotherapy for 6 months or isoniazid/rifampicin for 3 months.

Starting HAART reduces the risk of reactivation of latent TB infection and is effective at reducing the incidence of new TB. We recommend that all HIV-positive patients should be offered HAART in line with the BHIVA guidelines.

1.4 Treatment of active TB

We recommend daily tuberculosis treatment whenever possible. Treatment may be given 5 days per week, but should be intensively supervised. This option may be useful in hospital or other highly supervised settings. Three-times-per-week directly observed therapy (DOT) should only be given to patients who are stable and clinically well and where local logistics enable this to be undertaken successfully

We do not recommend twice-weekly DOT for treatment of HIV/TB coinfected patients, especially in those with CD4 counts <100 cells/μL, since it has been associated with unacceptably high rates of rifamycin resistance.

In cases where multiple drug resistance is not suspected, treatment should be started with four drugs (typically rifampicin, isoniazid, pyrazinamide and ethambutol) until sensitivities are known.

We recommend a 6-month treatment regimen for drug-sensitive TB outside of the central nervous system (CNS). This is usually four drugs for 2 months, followed by

isoniazid and rifampicin for a further 4 months (at least 182 doses of isoniazid and rifampicin and 56 doses of pyrazinamide and ethambutol in total).

In drug-sensitive TB affecting the CNS we recommend 9 months of treatment. This usually consists of four drugs for 2 months, followed by 7 months of isoniazid and rifampicin [2].
Drug resistant disease should be treated by only specialists with experience in such cases, in line with NICE guidelines [1].

1.5 Drug interactions and toxicities

Careful attention should be paid to drug interactions between TB drugs, HAART and other therapy. Rifampicin is a powerful inducer of CYP450 and has effects on several metabolic pathways and PgP. Rifampicin interacts with protease inhibitors, NNRTIs, CCR5 antagonists, and antimicrobials such as fluconazole. Rifabutin is a less potent inducer of CYP450 and may be used as an alternative to overcome some of these difficulties. (For up-to-date drug interaction data go to www.hiv-druginteractions.org)

Toxicity profiles of antiretrovirals and anti-TB drugs overlap and make it difficult to determine the causative drug. For example, rashes occur with NNRTIs, rifampicin and isoniazid. Isoniazid and stavudine both cause peripheral neuropathy. All patients on isoniazid should take pyridoxine to try and prevent this complication. Patients with chronic liver disease have higher rates of toxicity and need more frequent monitoring of liver function tests. Drug absorption may be affected by advanced HIV disease.

1.6 Antiretroviral treatment

Rifamycin-based TB regimens should be used whenever possible. Coadministration guidance for first-line antiretrovirals is given below. There are few long-term clinical outcome data to support use of these TB/HIV drug combinations.

1.6.1 Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

There are no major interactions between rifampicin or rifabutin and lamivudine (3TC), emtricitabine (FTC), tenofovir, abacavir, zidovudine (AZT) or didanosine (ddI).
Stavudine (d4T) should not be given because of the increased risk of peripheral neuropathy with concomitant TB therapy.

1.6.2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

The preferred regimen for patients who have no contraindication is:

Rifampicin + Efavirenz	Use efavirenz 800mg/day in patients weighing >60kg and standard dose 600mg/day in patients weighing <60kg If side effects occur, efavirenz TDM may be useful

Other regimens include:

Rifampicin + Nevirapine*	Not recommended but if given then use standard doses and perform nevirapine TDM
Rifabutin + Efavirenz	Increase rifabutin to 450mg daily
Rifabutin + Nevirapine*	Not recommended but if given then use standard doses

1.6.3 Protease inhibitors (PI)

Rifampicin + unboosted PI	Do not use
Rifampicin + boosted PI	Not recommended because of poor pharmacokinetics and high rates of hepatotoxicity seen in healthy volunteers
Rifabutin + unboosted PI	Reduce rifabutin to 150mg daily, increase unboosted PI
Rifabutin + boosted PI	Reduce rifabutin to 150mg three times per week

1.6.4 Integrase inhibitors

Rifampicin + Elvitegravir	Do not use
Rifampicin + Raltegravir*	Studies ongoing; use with caution double dose raltegravir
Rifabutin + Elvitegravir	No data, not recommended
Rifabutin + Raltegravir	Normal doses of both drugs

1.6.5 Entry inhibitors

Rifampicin + Maraviroc*	Not recommended, but if given use double dose maraviroc
Rifabutin + Maraviroc	Use standard doses
Rifampicin + T-20	No interaction, use standard doses
Rifabutin + T-20	No interaction, use standard doses

* Where combinations are not recommended, specialist HIV treatment advice should be sought.

We recommend that TDM of NNRTI and PI should be performed when drug regimens are complex. Drug levels of anti-tuberculosis drugs should be measured when there is clinical concern regarding absorption or response to TB therapy.

1.7 Starting HAART

Starting HAART during TB treatment is complicated by overlapping toxicities, drug interactions and immune reconstitution disease, and high pill burdens may reduce adherence. Delaying HAART may lead to prolonged or worsening immune suppression. Physicians have to balance these risks when deciding when to initiate HAART. Recent data suggest early treatment reduces morbidity and mortality.

We recommend, where possible:

CD4 consistently >350 cells/μL: At physician discretion; CD4 100–350 cells/μL: As soon as practical, but can wait until after completing 2 months TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities; CD4 <100 cells/μL: start HAART as soon as practical after starting TB therapy.

See BHIVA HIV treatment guidelines for details on starting HAART [3].

1.8 Directly Observed Therapy (DOT) strategies

DOT is regarded as the gold standard for delivering TB treatment, but it may not be possible to deliver all elements of the DOT package. Witnessed supervision of treatment may be impracticable and it is important to remember that patient-centred management is the cornerstone of treatment success. We recommend that DOT be used in all cases of multi-drug resistant TB.

1.9 Relapse and treatment failure

Patients with TB, with or without HIV infection, who are failing treatment or who relapse despite therapy pose particular management problems and should be referred to clinical colleagues who have expertise in the management of relapse and treatment failure.

1.10 Control and prevention of TB

Every hospital/trust should have a policy for the control and prevention of TB. Specific consideration should be given to prevention of transmission of TB to and from immunosuppressed patients. Further guidance is contained in [4].

2.0 Introduction

Worldwide, it is estimated that 14.8% of all new TB cases in adults are attributable to HIV infection. This proportion is much greater in Africa, where 79% of all TB/HIV coinfections are found. In 2007, 456 000 people globally died of HIV-associated TB [5].

All patients with TB, regardless of their perceived risk of HIV infection, should be offered an HIV test. In the UK, an increasing number of TB cases are coinfected with HIV. In 2003, 8.3% of adults with TB were HIV infected [6]. The proportion is higher in London, with coinfection rates of 17–25% [7].

In HIV coinfection the clinical and radiographic presentation of TB may be atypical. Compared to the immune-competent population, TB/HIV patients with active pulmonary TB are more likely to have normal chest radiographs or to have sputum which is smear negative but culture positive [8–10]. The clinician caring for HIV-infected patients therefore needs to have a high index of suspicion for TB in symptomatic individuals, especially those born abroad. As the investigation and treatment of both TB and HIV require specialist knowledge, it is mandatory to involve specialists in HIV, respiratory and/or infectious diseases.

These guidelines update the BHIVA guidelines from 2005 and are designed to provide a clinical framework applicable to adults in the UK coinfected with HIV and TB. These guidelines do not cover children. They do not provide advice on HIV testing in adults with newly diagnosed TB. They are based on the evidence available, but some recommendations have to rely on expert opinion until further data are published.

These guidelines should be used in conjunction with:

- National Institute for Health and Clinical Excellence. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control, 2006 [1].
- BHIVA guidelines (www.bhiva.org/cms1222226.asp): Treatment of HIV-infected adults with antiretroviral therapy (2008).[3]
- Department of Health. The Interdepartmental Working Group on Tuberculosis. The Prevention and Control of Tuberculosis in the United Kingdom, 1998 [4].
- National Institute for Health and Clinical Excellence. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control, update 2010 [11].

3.0 Aims of TB treatment

Treatment of TB benefits the individual and also the community.

The aim of treatment is:

- to cure the patient of TB;
- to minimize the transmission of *Mycobacterium tuberculosis* to other individuals;
- to eliminate MTB infection.

4.0 Diagnostic tests
The quality of any investigation is related to the quality of the specimen and the clinical detail provided within the request. There must therefore be close liaison with the mycobacterial laboratory.

4.1 Microscopic smears
Microscopic smears of body fluids remain an essential part of TB diagnosis. Results should be available within 1 working day.

4.2 Cultures and drug susceptibility tests
Identification of mycobacteria is performed at reference centres, and is based on morphology, growth and biochemical characteristics. *M. tuberculosis* needs to be distinguished from other mycobacteria, for which treatment may be different and there are no infection control concerns.

Cultures are central to the confirmation and identification of the mycobacterium, and for drug susceptibility testing. More rapid results are obtained from liquid media, which usually grow *M. tuberculosis* in 7 to 28 days. Drug susceptibility tests are usually available within 10–21 days of the laboratory receipt of isolates and are performed by standard assays.

4.3 Molecular methods
When it is important to differentiate rapidly, gene probes are increasingly used in some laboratories, but are less sensitive than culture and are used mainly on respiratory specimens. Most nucleic acid amplification methods to detect Mycobacterium tuberculosis are complex, labour-intensive, and technically challenging. The sensitivity and specificity estimates of commercial NAATs are highly variable, compared with culture [12,13].

All specimens, even those negative for *M. tuberculosis* on PCR, still require culture because a negative PCR does not exclude TB and a positive PCR does not indicate the drug susceptibility profile [14,15]. However, recently a fully automated molecular test for tuberculosis identification and drug resistance testing has been evaluated on sputum samples from adult TB or MDRTB [16].

The Xpert MTB/ RIF, an automated molecular test for MTB identification and resistance to rifampin, uses a hemi-nested real-time PCR assay. This assay identifies more than 97% of all patients with culture-confirmed tuberculosis, including more than 90% of patients with smear-negative disease. The result can be available in hours.
The assay has been developed as a laboratory-based and point-of-care test for developing countries, but may be useful in rapid diagnosis of TB in the UK. Currently there are no data derived from children or using non-respiratory specimens in HIV-infected persons.

Molecular tests for rifampicin resistance are useful especially when MDRTB is suspected, as about 95% of isolates which are rifampicin resistant will also be isoniazid resistant. As MDR-TB is defined as TB resistant to at least rifampicin and isoniazid, patients with positive molecular based rifampicin resistance should be treated as MDR-

TB until the full resistance profile from cultures is available.
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4.4 Tuberculin skin testing

Tuberculin testing can identify patients with latent infection but there are high false-negative rates in HIV-positive patients, especially in those at low CD4 cell counts [17–23]. In patients with AIDS or CD4 <200 cells/μL, the sensitivity of the test is only 0–20%. False positives occur after bacillus Calmette–Guèrin (BCG) immunization. Some data suggest combining Interferon-γ release assays and tuberculin testing improve sensitivity [1,24]. We do not recommend the routine use of tuberculin skin tests. **[CII]**

4.5 Interferon-γ tests

HIV-infected individuals with latent TB infection are much more likely to progress to active TB than HIV-uninfected people [25]. Detection and treatment of latent TB infection is therefore important.

Blood tests are available that measure Interferon-γ release from T cells after stimulation with antigens largely specific to *M. tuberculosis* (such as ESAT-6 and CFP-10) [26]. The current commercially available tests are T-Spot.TB (which uses Elispot technology to detect the antigen specific T cells) and QuantiFERON® Gold In-Tube (an ELISA). Both tests are approved for the diagnosis of latent TB infection in HIV-negative individuals. There are some differences between the two tests, although in general they are unaffected by previous BCG and/or infection with most other mycobacteria (an important exception in the UK being *M. kansasii*). They are not licensed for the diagnosis of active TB, though the tests may be positive here too (as they detect the host immune response to mycobacterial infection).

Limited data exist regarding their performance in HIV infection, but studies suggest that Interferon-γ assays are more specific than tuberculin skin tests, especially in BCG-vaccinated subjects [27–31].This is an area of ongoing research.

They also appear to retain sensitivity more reliably at lower CD4 cell counts, although the lower threshold has not yet been defined [32,33]. Their advantages also include being a single blood test with no need for patient recall to “read” the result and no requirement for cold-chain storage. However the blood samples need processing within a limited time, and “indeterminate” (i.e. uninterpretable) IGRA results are more common in HIV-infected subjects. They are also more costly than tuberculin tests, though this may be offset by the savings in, for instance, healthcare worker time [34].The T-spot.TB test may have an advantage over the QuantiFERON® Gold In-Tube test as the number of lymphocytes used in the test is standardized.

This is a rapidly developing area but, based on current data, we suggest that IGRA rather than TSTs are used when screening HIV-positive individuals for latent TB infection. **[BIII]**

Where a patient is considered to have active tuberculosis, IGRA tests should not be used as the means by which the diagnosis is confirmed or refuted. If a test is performed, the result must be interpreted in light of the clinical picture, microbiological data and an understanding of the assay’s limitations in this population.

5.0 Type and duration of TB treatment

5.1 Treatment regimens

Most adults with previously untreated TB are given a regimen in two phases: **[AII]**

- **Initial phase**
  2 months of isoniazid, rifampicin, pyrazinamide and ethambutol.
  These 4 drugs are necessary because of the relatively high rates of isoniazid resistance in the UK, which is 7.7% overall (HPA 2007), and higher in non-white ethnic groups and those with previous treatment.
  If drug sensitivity testing shows MTB sensitive to first line agents, ethambutol can be omitted.
- **Continuation phase**
  4 months of isoniazid and rifampicin in most patients with drug-sensitive TB, prolonged to 7 months in some circumstances (see 5.2).

All patients taking isoniazid should be prescribed pyridoxine (vitamin B6) 10–25mg daily.

TB therapy can be given five times per week with standard doses. Although there are no formal clinical trial data, considerable clinical experience suggests that five-times-weekly Directly Observed Therapy (DOT) is equivalent to seven-times-weekly treatment, and can thus be considered as "daily". **[AIII]**

5.1.1 TB or other mycobacterial infection?

In many cases the treatment conundrum is whether the patient has *M. avium* complex or *M. tuberculosis* and often the physician will give the standard four-drug regimen until identification. In this situation some physicians prefer to replace rifampicin with rifabutin and add azithromycin/clarithromycin. When non-tuberculous mycobacteria are identified the regimen can be modified appropriately.

5.2 Longer continuation phase [AII]

The continuation phase should be extended to 7 months in:

- patients with drug-sensitive TB whose initial phase did not include pyrazinamide;
- patients with cavitating pulmonary disease or who remain sputum culture positive after 2 months of treatment [35].

The total treatment duration would thus be 9 months.

The continuation phase should be extended to 7–10 months in cases of CNS involvement, for instance meningitis or tuberculoma. The total treatment duration would thus be at least 9 months.

5.3 Intermittent therapy [AII]

It is recommended that patients receive daily therapy [36]. However, in some circumstances intermittent therapy can be given three times per week with dose modification [37,38] but must be by DOT, as one study showed a risk of acquired rifamycin resistance in patients given thrice weekly regimens (**[DII])**. However, DOT was used for all doses during the intensive phase but only for one dose of three per week during the continuation phase [39].

Two strategies used in HIV-negative patients have been associated with unacceptably high relapse rates and acquired rifampicin resistance in HIV-infected patients and are **not appropriate** for use in this population [40–44]. **[EII]**

These are:

- once-weekly isoniazid-rifapentine in the continuation phase;
- twice weekly isoniazid-rifampicin or isoniazid-rifabutin in patients with CD4 counts <100 cells/μL

5.4 Use of rifabutin [BII] [45]

Rifabutin has been successfully used instead of rifampicin in treating TB in HIV-negative patients [46,47]. It can be regarded as an alternative in HIV-positive patients, especially to avoid drug interactions with rifampicin, for example with protease inhibitors (see 6.0). Rifabutin showed similar efficacy to rifampicin in a single-blind randomised study of 50 HIV-positive patients in Uganda [48] and a cohort of 25 patients in the US [49].

However, there is a paucity of long-term data with rifabutin in HIV-positive adults. Rifabutin is also expensive and toxicities include bone marrow suppression, uveitis and arthralgia.

We therefore recommend that rifampicin remains the drug of choice whenever possible. In circumstances where rifampicin cannot be used (most commonly when boosted PIs are needed to treat HIV), rifabutin should be substituted.

5.5 Use of rifapentine [EII]

Rifapentine has a long serum half-life which theoretically allows once-weekly dosing. However, in the initial phase of treatment of TB in HIV-negative patients, rifapentine has unacceptable 2-year microbiological relapse rates and is not recommended Development of rifapentine resistance appears more frequent in TB/HIV coinfected patients [42] and at present rifapentine cannot be recommended and should not be used. **[EII]** There are few data regarding the interactions of rifapentine with HAART.

5.6 Duration and effectiveness of TB treatment

The optimal length of TB treatment in patients coinfected with HIV is unknown. Some trials suggest that short-course therapy need not be prolonged in HIV [37,50,51]. A review of six studies of patients with HIV infection and three studies of patients without HIV infection given treatment for 6 months (or longer) demonstrated considerable variability in published study design, eligibility criteria, site of disease, frequency and method of dosing, and outcome definitions [52]. In the reported studies, HIV-infected patients had cure rates of 59–97%, successful treatment rates of 34–100% and relapse rates of 0–10%. In patients without HIV infection, cure rates were 62–88%, successful treatment occurred in 91–99% and relapse rates were 0–3%. Although the relapse rates appeared higher in some studies of coinfected patients, other outcomes were comparable when 6-month regimens were used.

A study from Brazil showed that tuberculosis recurrence rates were high in the HIV-infected population but that if there was completion of initial tuberculosis therapy, use of antiretroviral therapy, and subsequent increases in CD4 cell counts then recurrence rates were low [53].

A recent retrospective review from the US suggested that although there were no failures in the 6 month regimen, relapse rates are four-times higher in HIV patients treated with standard rifampicin-based regimens for 6 months than in those treated for

longer [36].. However, the data were generated from a relatively small subset of patients as only 17% of the HIV-positive patients and 37% of the HIV-uninfected/unknown group were given just 6 months of rifampicin-based therapy. DOT was given to 57% of the cases. It may be the case that where adherence is suboptimal, 6 months of therapy is insufficient. The other important fact is that in this study re-infection could not be distinguished from relapse.

A recent meta analysis suggests 8 months of a rifamycin based treatment be given but the studies examined included those in which only 2 months of a rifamycin were given and in the few studies of treatment longer than 6 months the reinfection issue was not addressed [54].

Long-term randomised trials are needed to address optimal treatment duration.

We recommend that for drug-sensitive TB, not involving the CNS, regimens of 6 months should be given [41,50,51,55,56]. These should include at least 182 doses of isoniazid and rifampicin, and 56 doses of pyrazinamide (see 5.8). **[AII]** See also sections 5.3 and 5.4.

5.7 Use of corticosteroids

In HIV-infected adults with pulmonary or pleural TB, corticosteroids do not improve survival or reduce TB recurrence [57,58] and are not generally recommended [59].

In the general population, NICE guidelines recommend steroids in cases of active meningeal or spinal cord TB [1]. At present there is insufficient evidence regarding their use in HIV-infected people. A randomised controlled trial in Vietnam showed no difference in mortality or a combined outcome of death and disability in HIV-infected people with a clinical diagnosis of tuberculosis meningitis, whether they were given dexamethasone or placebo with standard TB treatment [60]. However, there were few HIV-infected people in this study and the diagnosis of TB was confirmed microbiologically in fewer than 50% of cases. This study may therefore have missed a clinically important difference.

Until more data are available we recommend that HIV-infected adults with meningeal or spinal cord TB should be given corticosteroids. **[BII]**

NICE guidelines recommend steroids for active pericardial TB. There are limited data to support this in HIV coinfection. A small randomised controlled trial of HIV-infected adults with presumed tuberculous pericarditis treated with standard TB therapy found that prednisolone resulted in better outcomes than placebo [61]. Mortality was reduced with prednisolone compared to placebo, and improvement in raised venous pressure, hepatomegaly, ascites and physical activity occurred more rapidly. Interestingly there was no faster resolution of pericardial fluid on chest radiography or echocardiogram, and since only 38% had positive *M. tuberculosis* cultures, some of the subjects may not have had pericardial TB. These results should therefore be interpreted with caution.

Until more data are available in HIV-positive patients we recommend that adults with pericardial TB should be given corticosteroids. **[AII]**

Other uses of steroids have included preventing ureteric stenosis in renal TB or enlargement of, for example, a mediastinal lymph node causing collapse of a lung lobe

and in management of TB-related immune reconstitution inflammatory syndrome (see section 10) .

The optimal dose of adjunctive corticosteroids is not known. Rifampicin induces the liver metabolism of corticosteroids, thus increasing their plasma clearance [62].

The corticosteroid and dose used in most adult trials of TB meningitis is dexamethasone 12–16 mg/day given intravenously until the patient starts taking medicines orally; then tablets can be used. Prednisolone 60 mg/day for three weeks and tapered over the next three weeks is an alternative [63].

The British Infection Society guidelines on TB meningitis [2] suggest that adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hours with a reducing course over 6 to 8 weeks. This works out to be a higher dose for most patients seen in the UK.

Studies have shown that corticosteroids increase the risk of high blood pressure, raised blood glucose and cause fluid retention [57,58]. The risk of infectious complications does not seem to be increased [57,58,61], although the data for an increase in the occurrence of Kaposi's sarcoma are contradictory.

5.8 Definition of completion of TB therapy

Treatment for a defined number of days without accounting for the number of doses taken may result in under-treatment. Determination of whether or not treatment has been completed should therefore be based on total number of doses taken as well as duration of therapy. For example:

- A 6-month daily regimen (given 7 days/week) should consist of at least 182 doses of isoniazid and rifampicin, and 56 doses of pyrazinamide.

It is recommended that all of the doses for the initial phase be taken within 3 months and those for the 4-month continuation phase be taken within 6 months. The 6-month regimen should therefore be completed by 9 months.

5.9 Interruptions of therapy [AIII]

Treatment interruptions are common in HIV-associated tuberculosis. Data to support recommendations are scant. Regardless of the timing and duration of the interruption, if the patient was on self-supervised therapy, then DOT should subsequently be used. If the patient was already being managed with DOT, additional measures may be necessary to ensure adherence, for instance provision of transport, food, social services. The CDC suggest the following [64]:

Initial phase:

- If the interruption occurs during the initial phase and is 14 days or more in duration, treatment should be restarted from the beginning.
- If the interruption is less than 14 days, the treatment regimen should be continued. The total number of doses for the initial phase should be given.

5.10 Investigations during TB treatment [AIII]

Baseline investigations:

- CD4 count and percentage;

- 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;
- prior to ethambutol: testing of visual acuity with Snellen chart and colour vision with Ishihara plates.

HIV patients have more drug reactions especially those with low CD4 counts. Further they may be starting concomitant antiretroviral and other therapies, all of which may cause hepatotoxicity. We recommend that liver function tests should be rechecked at 1–2 weeks even if asymptomatic. Patients with pre-existing liver disease need close monitoring, for instance every 2 weeks for first 2 months.

Most physicians will see the patient 2 weeks after starting antituberculosis therapy and then monthly until stable and 1–2 monthly until therapy has been completed. The role of a TB specialist nurse and multidisciplinary team is essential in the management of coinfected patients.

In patients with pulmonary TB who still have a productive cough after 2 months, therapy should have a repeat sputum smear and culture. The initial phase of treatment should be continued until results are available.

6.0 Drug–drug interactions (see Tables 4–7)

Most interactions between HIV and TB therapy are through induction or inhibition of metabolic enzymes in the liver and intestine. The most important family of enzymes is cytochrome P450 (CYP450). The CYP3A4 isoform metabolizes many drugs including protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifamycins are potent inducers of CYP3A4 65,66and have clinically important interactions with PIs and NNRTIs. Rifampicin is the most powerful inducer of CYP3A4 of all medicines. Rifapentine is a less potent inducer; and rifabutin much less so.

To a smaller extent, rifampicin also induces the activity of CYP2C19 and CYPD6.

Rifampicin also increases activity of the intestinal drug transporter P-glycoprotein (PgP) that contributes to the absorption, distribution and elimination of PIs new 67,68 ref

67. Rae JM, Johnson MD, Lippman ME, Flockhart DA. Rifampin is a selective, pleiotropic inducer of drug metabolism genes in human hepatocytes: studies with cDNA and oligonucleotide expression arrays

J Pharmacol Exp Ther. 2001;299):849- 57.

68.Li T, Chiang JY. Rifampicin induction of CYP3A4 requires pregnane X receptor cross talk with hepatocyte nuclear factor 4alpha and coactivators, and suppression of small heterodimer partner gene expression. Drug Metab Dispos. 2006;34):756-64.

The enzyme inducing effect of rifampicin takes at least 2 weeks to become maximal and persists for at least 2 weeks after rifampicin has been stopped. If antiretrovirals are started or changed at the end of TB treatment this persistent effect on enzyme induction should be taken into consideration.

Rifabutin is a less potent inducer of CYP3A4 than rifampicin [69]. Unlike rifampicin, it is also a substrate of the enzyme [65]. Any CYP3A4 inhibitors will therefore increase the concentration of rifabutin although they have no effect on rifampicin metabolism. Most PIs are inhibitors of CYP3A4 and when used with rifabutin, plasma concentrations of rifabutin and its metabolites may increase and cause toxicity [70].

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are mostly known to be free of clinically significant interactions with rifampicin. In theory they should not have significant interactions with other first line antituberculosis therapies. Few data are available for the newer antiretroviral agents. The CCR5-inhibitor maraviroc interacts with rifamycins, as do the integrase inhibitors raltegravir and elvitegravir.

Individual drug–drug interactions between rifamycins and antiretroviral agents are shown in Tables 4–7. The complexity of drug–drug interactions requires expertise in use of both antiretroviral and anti-TB drugs. One particular interaction should be noted: the 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. **[AII]**

6.1 Rifamycins and NRTIs (Table 4)

When NRTIs are given with rifampicin either the pharmacokinetics change little, or the interactions are unknown. Rifampicin reduces the AUC and increases the clearance of zidovudine via increased glucuronidation [71]. This is not clinically significant and dose alteration is not required. Rifabutin does not affect the clearance of zidovudine [72].

Triple-NRTI regimens are theoretically attractive as HAART because they are free of interactions with TB treatment, and have been used with success in Africa [73,74]. However, they are virologically inferior to HAART containing an NNRTI [75]. Quadruple-NRTI regimens (most commonly abacavir, lamivudine, zidovudine, tenofovir) have also been used in adults taking TB treatment. There are data from a small cohort to support this approach [76], but it is not recommended as standard of care in the UK.

6.2 Rifamycins and NNRTIs (Table 5)

Efavirenz, nevirapine, etravirine and the newer agent rilpivirine are substrates for, and inducers of, CYP3A4. The clinical use of these drugs together with rifamycins is complex.

6.2.1 Rifampicin and efavirenz

There is still debate regarding the appropriate dose of efavirenz with rifampicin. Several studies have found a 20–30% reduction in efavirenz levels when administered with rifampicin [77,78]. Increasing the efavirenz dose from 600mg to 800mg is effective and safe [77,79]. However, in cohort studies (in which most of the participants have an average low body weight) standard dose efavirenz has been given with rifampicin without lower drug exposure or compromised clinical efficacy [80,81]. In one study, efavirenz levels were not predicted by weight or gender and were not associated with HIV clinical outcomes – even though half the cohort had concentrations below the expected therapeutic range (1000–4000 ng/mL). This, as well as other studies, confirms the large interpatient variability in efavirenz levels [82]. No randomised clinical trial data has correlated patient weight, pharmacokinetics and clinical outcome. One observational cohort has examined PK and outcomes and weight and proposed that for patients >60kg a dose of 800mg efavirenz.should be used if the patient is on rifampicin [83].

It is therefore difficult to make recommendations for patients in the UK where body weights are usually >60kg. In fact, in one study no difference in mid-dose efavirenz levels between patients on efavirenz 800mg/d (n=31) and those on efavirenz 600mg/d (n=29) were seen in a cohort of black South Africans on rifampicin-based TB therapy [84]. This may be explained by the high rate of polymorphisms in CYP450 2B6 in black Africans, present in 20% of the black population compared with 3% of whites [85,86].

The use of 800mg may increase the risk of CNS side effects, especially in individuals with polymorphisms in CYP2B6, and this may explain high rates of clinical toxicity in some studies [87]. If side effects occur, TDM can identify those individuals with high efavirenz levels.

We recommend that when rifampicin is used with efavirenz in patients over 60kg, the efavirenz dose is increased to 800mg daily. Standard doses of efavirenz are recommended if the patient weighs less than 60kg. **[AII]** We then suggest that a TDM be performed at around week 2 of starting efavirenz and the dose adjusted accordingly. It should be made clear to patients that they need to have an extra 200mg efavirenz in addition to the Atripla. Some physicians prefer to start with 600mg efavirenz whatever the body weight and perform TDM and adjust the dose accordingly. We believe, however, that the risk of toxicity is more easily solved than the risk of potentially inducing resistance from inadequate drug levels.

6.2.2 Rifampicin and nevirapine

Rifampicin and nevirapine are both used widely in resource-poor countries because they are cheap and readily available. There are data that nevirapine levels are reduced by 20–55% by rifampicin [88–93]. WHO suggest that no ‘lead in’ period for nevirapine is needed if the patient is already on rifampicin – but they give no recommendation rating for this strategy.

To overcome the problem of low nevirapine levels with rifampicin, one trial administered 400mg nevirapine as lead-in dose, increasing to 600mg [94]. The pharmacokinetics were satisfactory but there was a high incidence of nevirapine hypersensitivity during the dose escalation period.

Two cohort studies have shown high rates of HIV viral suppression with standard dose nevirapine and rifampicin [89,95]. However, in a recent study of 1283 patients starting HAART while on rifampicin, 209 people on nevirapine and 1074 on efavirenz, virological failure rates were higher, with an OR (CI) of 2.9 (1.8–4.7) in the nevirapine arm *vs*. the efavirenz or not-on-TB-treatment arms [96].

We recommend that, where alternatives exist, rifampicin should not be used with nevirapine. **[DII]** If there are no alternatives to using nevirapine with rifampicin, then normal doses should be used and therapeutic drug monitoring performed.

6.2.3 Rifampicin and etravirine

No data are available and no studies are planned. It is thought that they should not be co-administered.

6.2.4 Rifampicin and rilpivirine (TMC-278)

Rifampicin reduces plasma concentrations of TMC-278 by up to 90% so these drugs should not be used together [97].

6.2.5 Rifabutin and NNRTIs

If rifabutin is used with efavirenz the rifabutin dose should be increased to 450mg daily because of the induction effect of efavirenz, which reduced the AUC of rifabutin by 38% in one small study.

Concomitant administration of nevirapine results in increased rifabutin AUC (17%) and C_{max} (28%) with no change in C_{min}. The effect on nevirapine pharmacokinetics was not significant (Viramune SPC 2007). Due to high intersubject variability, some patients may be at risk of rifabutin toxicity. Rifabutin and nevirapine can probably be given together with no adjustment in either of their dosages but more data are needed before this strategy can be recommended.

Rifabutin can be given with etravirine with no dose adjustments.

Rifabutin decreases plasma levels of **rilpivirine** by 50%, so if used together the dose of **rilpivirine** should be doubled [97].

6.3 Rifamycins and Protease Inhibitors (PIs)

In general Protese inhibitors whether boosted or unboosted should not be given with rifampicin and rifabutin should be considered instead.

6.3.1 Rifampicin and PIs (Table 6)

6.3.1.1 Unboosted PIs

Rifampicin causes a 75–95% reduction in plasma concentrations of PIs other than ritonavir [98]. Such reductions lead to loss of antiretroviral activity of PI-containing regimens and can result in the emergence of antiretroviral resistance.

Since ritonavir is itself an inhibitor of CYP3A4 it can be used in combination with rifampicin when given at full dose of 600mg twice daily [99]. However such high dose ritonavir is very poorly tolerated and seldom used [100].

6.3.1.2 Boosted PIs

Most patients are given PIs with low dose ritonavir (100mg or 200mg daily) to take advantage of its enzyme-inhibiting properties. Ritonavir boosts the concentration of the other PI allowing more tolerable dosing.

6.3.1.3 Saquinavir/ritonavir

A dose of twice-daily 400mg ritonavir with 400mg saquinavir has been used with rifampicin with acceptable PI pharmacokinetics [101]. Saquinavir 1600mg with ritonavir 200mg once daily was tested in HIV-positive patients on rifampicin-based TB therapy, and saquinavir levels were inadequate [102,103].

A pharmacokinetic study performed in healthy volunteers given saquinavir/ritonavir and rifampicin then demonstrated severe hepatotoxicity [104]. Transaminases were elevated to more than 20-times upper limit of normal.

Saquinavir/ritonavir is therefore not recommended in combination with rifampicin.

6.3.1.4 Lopinavir/ritonavir

Data regarding the interaction of rifampicin with standard-dose lopinavir/ritonavir suggest that ritonavir at low dose does not compensate for the inducing effect of rifampicin on lopinavir metabolism [105]. A popular strategy in the developing world for patients with NNRTI failure who develop TB, is to give lopinavir/ritonavir with increased-dose ritonavir. If the ritonavir dose was increased to 400mg twice daily then lopinavir trough concentrations were adequate in 9/10 subjects but there were high rates of elevated transaminases and lipids, and gastrointestinal toxicity [106]. A pharmacokinetic study in healthy volunteers was reminiscent of the saquinavir study, and was terminated early because of high rates of severe transaminitis [107].

6.3.1.5 Atazanavir/ritonavir

Recent data suggest that atazanavir with or without ritonavir boosting had unfavourable pharmacokinetics when administered with rifampicin [108–110]. Trough atazanavir concentrations were reduced by >80% [109].

6.3.1.6 Tipranavir/ritonavir

Tipranavir concentrations were reduced by 80% by rifampicin [111].

6.3.1.7 Darunavir/ritonavir

The interaction between darunavir and rifampicin has not yet been investigated. In line with other PIs, it is currently recommended that darunavir should not be coadministered with rifampicin.

6.3.2 Rifabutin and PIs (Table 6)

6.3.2.1 Unboosted PIs

The use of rifabutin in treating TB in HIV-positive patients is discussed above (see 5.5). Rifabutin can be administered with unboosted PIs except saquinavir [112], although they will rarely be used in practice. The balance between rifabutin induction and PI inhibition of CYP3A4 means that the dose of rifabutin should be decreased from 300mg to 150mg daily to avoid toxicity [48,70].

6.3.2.2 Boosted PIs

If PIs are used with low-dose ritonavir boosting then the dose of rifabutin should be reduced to 150mg three times per week [49,111]. This data has been extrapolated from PK studies in healthy volunteers and modelling. There are no clinical outcome data for either HIV or tuberculosis using this strategy. Adherence should be monitored closely as the dose of rifabutin would become inadequate if the boosted PI is not taken concomitantly. Where available, drug levels of the protease inhibitor should be measured. There have been reports of acquired rifabutin resistance occurring even using rifabutin 150mg three times a week with boosted PIs. No rifabutin drug levels were available in those patients and although other reasons may have been responsible for these failures physicians may consider measuring rifabutin and its active metabolite 25-0-desacetyl rifabutin levels if results are available in a timely manner [113].

Complex interactions may occur when a rifamycin is given with salvage regimens such as two PIs plus boosted ritonavir, or with a boosted or non-boosted PI and an NNRTI. Rifabutin is safer than rifampicin, but there are few data to guide the clinician regarding dose modification. TDM is recommended.

6.3.3 Recommendation for rifamycins and boosted protease inhibitors

We recommend that PI/ritonavir combinations should not be given with rifampicin**. [EII]** If possible the HAART regimen should be changed to avoid PIs. If effective HAART necessitates the use of PIs then rifabutin should be used instead of rifampicin. **[AII]**

6.4 Rifamycins and Integrase Inhibitors (Table 7)

Raltegravir is metabolized by UGT1A1 glucuronidation. Rifampicin is an inducer of UGT1A1, and reduces trough levels of raltegravir by approximately 60% [114]. Because the antiviral activity of raltegravir 200mg twice daily was very similar to that of the licensed dose (400mg twice daily) an earlier recommendation was that standard doses of raltegravir should be used with rifampicin. There is at least one report of raltegravir failure when given like this with rifampicin (S Taylor, personal communication).

Further PK studies show that even with double-dose raltegravir at 800mg bd the C_{trough} of raltegravir is at the lower level of what has been observed in clinical studies of raltegravir without rifampicin [115]. It appears for raltegravir that the important PK parameter is the AUC_{24} rather than the C_{trough} in PK/PD studies and thus 800mg bd may be adequate.

As there is little clinical experience with this dose in combination coadministration should probably be avoided if alternatives exist.

Elvitegravir is metabolized by CYP3A4 and should not be given with rifampicin.

The data regarding interactions with rifabutin.suggest normal doses of raltegravir and rifabutin can be used [116].

6.5 Rifamycins and CCR5-antagonists (Table 7)

Maraviroc is metabolized by CYP3A4 and its levels are reduced by rifampicin. Use of maraviroc with rifampicin is not recommended especially if a second enzyme inducer such as efavirenz is used. If they are used together then they should be used with caution and the dose of MVC be doubled to 600mg bd [117]. There are no data about interactions with rifabutin but maraviroc concentrations are predicted to be adequate, and maraviroc can therefore be given at standard doses with rifabutin.

6.6 Rifamycins and enfuvirtide (Table 7)

There are no significant interactions between rifamycins and enfuvirtide [118].

6.7 Isoniazid

Pharmacokinetic or clinical interactions between isoniazid and antiretroviral agents have not been extensively investigated. *In vitro* studies have shown that isoniazid is a weak inhibitor of CYP3A4 [119,120]. When given together with rifampicin (inducer), the inhibition effect of isoniazid is masked.

6.8 Non-rifamycin regimens

HIV-related tuberculosis may be treated with non-rifamycin-containing regimens but these are inferior in efficacy, with high relapse rates [121,122]. They should only be contemplated in patients with serious toxicity to rifamycins, where desensitization or reintroduction has failed, or in those with rifamycin-resistant isolates.There has been a review published of drug–drug interactions between drugs used in non-rifamycin regimens and antiretrovirals [123].

7.0 Overlapping toxicity profiles of antiretrovirals and TB therapy

Adverse reactions to drugs are common among patients with HIV-related tuberculosis especially if taking HAART concomitantly.

Rash, fever and hepatitis are common side effects of anti-tuberculosis drugs especially rifampicin, isoniazid and pyrazinamide. NNRTIs and cotrimoxazole cause similar adverse reactions. The coadministration of these drugs can lead to difficult clinical management decisions if these side effects occur, especially if HAART and TB drugs are started concurrently. A total of 167 adverse events were recorded in 99 (54%) of the 183 patients for whom data on therapy were available in a study from the South East of England [124]. Adverse events led to cessation or interruption of either TB or HIV therapy in 63 (34%) of the 183 patients. Side effects usually occurred in the first 2 months of treatment and were peripheral neuropathy 38 patients (21%), rash 31 patients (17%), gastrointestinal intolerance 18 patients (10%), hepatitis 11 patients (6%) and neurological events in 12 patients (7%). Rifampicin was frequently implicated by the treating physicians, and was considered responsible for almost two-thirds of adverse events.

When compared to HIV-negative TB patients, a higher rate of serious (grade III/IV) toxicities has been found in TB/HIV coinfection, but there was no difference in discontinuation rate of TB medication between the groups [125].

7.1 Hepatotoxicity [126]

Hepatotoxicity is a common and potentially serious adverse event. It is defined as:

- 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.

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

Hepatotoxicity due to isoniazid in the general population increases with age, occurring in less than 0.3% of those under 35 years and 2.3% of those over 50 years. It is also more likely with heavy alcohol intake, hepatitis C coinfection and in those also on rifampicin. High rates of adverse reactions requiring changes in therapy have been reported in HIV-infected patients who are likely to have some or all of the other risk factors above. The rates of adverse reaction were 26% in one HIV cohort compared with 3% in the HIV-uninfected group, and other studies have shown similar results [127,128].

Another study showed little increase in hepatotoxicity in HIV-positive patients with TB although only 16.3% were receiving antiretrovirals and the study included children [129].

Management of hepatitis:

I. Stop all potentially hepatotoxic drugs immediately, including isoniazid, rifampicin, pyrazinamide, antiretrovirals and co-trimoxazole.
II. Check serology for hepatitis A, B and C.
III. Enquire about exposure to other hepatotoxins including alcohol.
IV. As resolution of the hepatitis may be prolonged and until the cause of the hepatitis is identified then 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 a fluoroquinolone. (N.B. moxifloxacin can cause a severe hepatitis.)
V. Monitor serum AST (or ALT), bilirubin and symptoms frequently. Once AST drops to less than twice the upper limit of normal and symptoms have significantly improved, first line medications can be restarted using a reintroduction regimen (Table 8). These are based on common practice and have not been formally validated in clinical trials. Recent data in HIV-negative/unknown patients suggest that once the AST/ALT is <100iu/L then full dose treatment may be reintroduced [130] – whether this also applies to HIV co-infected subjects remains unclear.

VI. If the drugs cannot be restarted or the initial reaction was life-threatening then an alternative regimen should be used (see 7.2).

7.2 Pre-existing liver disease

All patients 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 patients with baseline abnormal hepatic transaminases, a rise of two-to-three times this abnormal baseline should be used as threshold for hepatoxicity [126].

If hepatotoxicity occurs then other regimens can be used, for instance:

I. Avoid pyrazinamide and treat with isoniazid and rifampicin for 9 months, adding ethambutol for the first 8 weeks or until isoniazid and rifampicin susceptibility are demonstrated. **[AIII]**
II. Avoid isoniazid and treat with rifampicin, ethambutol, and pyrazinamide for 2 months, followed by 10 months of rifampicin and ethambutol. **[BIII]**
III. Use only one potentially hepatotoxic agent in patients with severe liver disease and treat with rifampicin plus ethambutol for 12–18 months, preferably with another agent such as a fluoroquinolone for the first 2 months. There are no data to support this recommendation. **[CIII]**

In patients 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. Patients should be told to report symptoms such as anorexia, nausea, vomiting, abdominal pain or jaundice immediately [131,132].

7.3 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 600mg rifampicin daily); food delays or decreases the absorption of isoniazid and rifampicin but the effect is moderate and of little clinical significance;
- change the time of dosing;
- switch to a regimen that does not have food restrictions such as rifabutin, ethambutol, pyrazinamide and a fluoroquinolone.

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

7.4 Peripheral neuropathy

The nucleoside analogues ddI and d4T cause peripheral neuropathy and there is an additive toxicity of isoniazid when used with d4T [124, 133]. In individuals already taking these antiretrovirals alternatives should be found if possible.

Pyridoxine 10mg daily should be used in all patients receiving isoniazid. If peripheral neuropathy occurs the dose of pyridoxine can be increased up to 50mg tds.

7.4.1 Recommendation [DII]

D4T should not be used as part of a HAART regimen if concomitant isoniazid is being administered. In patients on HAART coming from resource poor countries where D4T is used widely in initial therapy, switching to an alternate nucleoside should be performed.

7.5 Rash

Rashes are often mild/moderate and usually occur in the first 2 months of treatment. They should be managed in a similar way to the management of nevirapine hypersensitivity rashes. Mild rashes without mucosal involvement can be treated symptomatically. More widespread worsening rashes or those with systemic symptoms require all drug cessation, and on recovery careful drug reintroduction as per protocol (see Table 8).

One compounding issue is that patients may have also recently started cotrimoxazole or antivirals and so the offending drug can be difficult to track down.

8.0 Drug absorption

8.1 Malabsorption of drugs

In HIV infection, malabsorption has been reported with all first-line anti-TB drugs, as well as ethionamide and cycloserine. Absorption may be decreased in patients 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 [134,135]. Although some studies show lower peak concentrations of rifampicin and ethambutol as well as lower AUC compared with controls [136–140], there are other data suggesting that rifampicin is well absorbed in HIV patients including those with

AIDS or diarrhoea [141]. There are few data showing correlation of treatment failure with poor absorption [112].

8.2 Therapeutic drug monitoring (TDM)

8.2.1 TDM of TB drugs: [CII]

There are few data showing that TDM results in improved outcomes and the use of TDM in TB has been reviewed [142]. However it may be considered in the patient populations who are:

- at high risk of malabsorption of TB drugs;
- responding inadequately to DOT with first-line drugs;
- being treated for multi-drug resistant TB;
- on non-standard TB regimens or taking non-standard doses;
- on boosted PIs with rifabutin 3 times a week.

One of the problems with monitoring anti-TB drugs is that the kinetics of absorption are not predictable. It is therefore difficult to know when to measure a peak plasma level, and it is probably best to check levels at more than one time point post dose if possible. If rifabutin levels are being measured ensure that the level of 25-0-desacetyl rifabutin, the active metabolite, is also measured.
Decisions about dosing may be difficult as there can be long delays in results being returned to the physician.

8.2.2 TDM of HIV drugs: [BII]

TDM may be relevant for PIs and NNRTIs especially when regimens are complex, when no formal pharmacokinetic data are available, and when virological failure occurs.

9.0 When to start HAART

The optimal time to start HAART in TB/HIV patients is not known. Prospective trials are underway in developing countries to answer this question [143]. Much data are currently in abstract form, from presentation at meetings, and have not yet been subjected to formal peer-review. However, given the importance of this area, we have sought to provide some pragmatic guidance.

Physicians have to balance the risk of HIV progression against the hazards of starting HAART, which include toxicities, side effects, immune reconstitution inflammatory syndrome (IRIS) and drug interactions. Antiretroviral and anti-tuberculosis drugs share similar routes of metabolism and elimination, and extensive drug interactions may result in sub-therapeutic plasma levels of either or both (see 6.0). Overlapping toxicity profiles may result in the interruption of TB or HIV regimens with subsequent microbiological or virological failure (see 7.0). Deaths in the first month of TB treatment may be due to TB, while late deaths in coinfected persons are attributable to HIV disease progression [144–146].

Patients with HIV and a CD4 cell count >350 cells/μL have a low risk of HIV disease progression or death during the subsequent 6 months of tuberculosis treatment, depending on age and viral load [3]. They should have their CD4 cell count monitored regularly and antiretroviral therapy can be withheld during the short-course tuberculosis treatment.

Most patients with tuberculosis in the UK present with a low CD4 count, often <100 cells/μL. In such patients HAART improves survival, but can be complicated by IRIS and drug toxicity. Cohort data showed that at CD4 counts <100 cells/μL the short-term risk of developing further AIDS-defining events and death is high, and HAART should be started as soon as practicable [124, 147–150 Some physicians prefer to wait for up to 2 weeks before starting HAART after commencing patients on TB treatment to allow diagnosis and management of any early toxicity and adherence problems

- A randomized trial (the SAPIT study) [151] compared 2 groups starting HAART during TB therapy (one group started within 4 wks of starting TB treatment, the other started within 4 wks of completing TB treatment intensive phase) to a control group who did not start HAART until after completing their TB treatment. The data showed that deferring HAART until after TB treatment was completed was associated with a significant increase in mortality, even in patients with CD4 counts of >200 cells/μL, although there were few clinical events. We do not know if the six patients in this SAPIT study who died, out of the 86 who had TB, still had CD4 counts >200 cells/μL at the time of death.

- Further unpublished analyses of this important data set [152]showed that patients with CD4 counts <50 cells/μL at enrolment who started within 4 weeks of commencing TB treatment was associated with a 68% lower risk of developing further AIDS clinical events and death compared to those with CD4 counts <50 cells/μLwho did not start HAART.

A recent unpublished study from Cambodia suggested that treatment with HAART in the first two weeks of TB treatment resulted in a lower mortality rate than in the group delaying HAART to 8 weeks The majority of these patients had a CD4 count of <100 cells/μL at enrolment.[153]

The unpublished STRIDE (ACTG 5221) Study [154] also showed that starting HAART within 2 weeks resulted in a lower mortality rate than in the group delaying HAART until 8-12 weeks in patients who had a blood CD4 count of <50 cells/μL at enrolment.[153]

In these trials the disadvantage of starting early was an increased risk of IRIS.

Until we have further analyses of all data, we believe it is safer and more practicable to set a blood CD4 count of <100 cells/μL as the point below which HAART should be started within 2 weeks of commencing TB treatment.

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Other data sets suggest starting HAART early independent of CD4 cell counts improves long term outcome [155,156]. Some physicians believe that starting HAART irrespective of CD4 cell count, including >350 cells/μL, is beneficial in patients with active tuberculosis. Although theSAPIT study suggested HAART started during the course of TB therapy even in those with CD4 counts >350 cells/μL was beneficial, almost all the patients within this arm had a CD4 count below that threshold.

A currently unpublished study of starting HAART early versus late performed in HIV-associated TB meningitis in the developing world, where 90% were male, the majority drug users, many with advanced disease and the diagnosis being made clinically in 40%, showed no difference in mortality if HAART were started early though there was a greater incidence of severe adverse events in the early arm [157]. How this translates to UK clinical practice remains unclear. .

9.1 Suggested timing of HAART in TB/ HIV coinfection [All]

Taking into account all limited data available we recommend:

CD4 count, cells/μL	When to start HAART
<100	As soon as practical
100–350	As soon as practical, but can wait until after completing 2 months TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities
>350	At physician's discretion

10.0 Immune reconstitution inflammatory syndrome (IRIS)

After starting anti-tuberculosis treatment some patients develop an exacerbation of symptoms, signs or radiological manifestations of TB. This has been well described in patients without HIV infection, but appears to occur more commonly in HIV-positive patients [158–177]. The phenomenon is known as immune reconstitution inflammatory syndrome (IRIS), immune reconstitution disease (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 HAART-related reconstitution of immunity, which leads to an abnormal immune response to tubercle antigens released by dead or dying bacilli [178–183].

10.1 Definition

IRIS does not have a widely accepted definition although an international attempt has been made. A definition for resource-poor countries has been developed and cases need to meet three criteria (see Table 10) [184].

It is characterised by worsening or appearance of new signs, symptoms, or radiographic abnormalities, occurring after initiation of HAART, and not the result of TB treatment failure or another disease process. It is therefore a diagnosis of exclusion. It is often defined as transient 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.

The features of IRIS are:

- apparent worsening/progression of tuberculosis;
- 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 HAART;
• no evidence of TB relapse or recurrence (positive AAFB smear does not exclude diagnosis of IRIS);
• appropriate investigations have excluded disease due to other pathogens;
• drug hypersensitivity is excluded;
• a response to corticosteroids does not confirm diagnosis of IRIS.

10.2 Epidemiology of IRIS

In the era of HAART, IRIS has been reported widely and occurred in 36% (12/33) and 32% (6/19) of patients in two studies [168,174]. In another study IRIS was not significantly more common in patients receiving HAART (3 of 28 cases or 11%) compared with patients not on antiretroviral treatment (3 of 44 cases or 7%) [175]. The majority of reactions occur within 60 days of initiating HAART, with a median of 15 days [176]. IRIS does not appear to be associated with any particular antiretroviral regimen or drug class [185]. Most patients with IRIS have advanced HIV infection (in one study the median baseline CD4 count was 35 cells/μL, and median HIV viral load >500,000 copies/mL). In the recent CAMELIA Trial the risk of IRIS was increased around four-fold if HAART were started in the first 2 weeks compared to delaying HAART until beyond week eight of TB treatment [153].

With limited data it is difficult to predict risk of IRIS, but the following appear to be relevant [152,185–188].

- low baseline CD4 cell count;
- rapid recovery in CD4 numbers;
- rapid decline in HIV viral load;
- dissemination of TB outside the lung (may be due to high burden of bacilli);
- HAART started within first 2 months of TB treatment.

10.3 Clinical features of IRIS

IRIS most often presents with fever and increased or new lymphadenopathy [158-189]. The skin overlying lymph nodes is often inflamed and dusky red, and the nodes can spontaneously rupture. New or worsening pulmonary lesions, pleural and pericardial effusions, ascites, psoas abscess, cutaneous lesions and new or expanding central nervous system tuberculomata, for example, have also been described

10.4 Management of IRIS [AIII]

TB treatment failure, drug hypersensitivity and other opportunistic infections and malignancies need to be excluded.

10.4.1 Corticosteroids [AII]

The management of IRIS may require moderate to high-dose corticosteroids to control symptoms. Prednisone or methylprednisolone have been used at a dose of 1–1.5 mg/kg and gradually reduced after 1 to 2 weeks. Patients 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%. Patients may require steroids for prolonged periods of time and IRIS may relapse when the dose is reduced, necessitating higher doses. Physicians should be aware of the metabolic side effects and potential for serious infections, for instance cytomegalovirus retinitis with high dose corticosteroids.

A placebo controlled study of giving steroids or placebo in early IRIS showed a benefit but the data have to be interpreted with caution as a substantive proportion of the placebo arm were treated with open label prednisolone [190].

10.4.2 Other treatment options

Recurrent needle aspiration of nodes or abscesses 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. 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 [191]. **[DII]**

Preliminary data suggest a potential role for IL-2 and granulocyte-macrophage colony stimulating factor (GM-CSF) in improving abnormal T cell responses [192]. **[DIII]** Other therapies such as hydroxychloroquine are as yet unproven. There is one case report of the resolution of IRIS in an HIV-negative patient with the use of infliximab [193]. **[DIII]**

11.0 Directly observed therapy (DOT)

There have been no randomized controlled trials or systematic reviews into the use of DOT in TB/HIV coinfection. However, the use of directly observed therapy is seen as the gold standard by WHO and CDC for the treatment of HIV-related tuberculosis, especially when using intermittent dosing. It is recommended by NICE for those deemed likely to have poor adherence, including those who are street- or shelter-dwelling homeless [1].

To help prevent the emergence of resistance, combination tablets (e.g. Rifater, which includes rifampicin, isoniazid and pyrazinamide) should be used whenever practicable.

It is recommended that all patients with MDR-TB have DOT. **[AII]**

Patient-centred care should be at the core of multidisciplinary management and should always include an adherence strategy. This may include DOT/supervised therapy for HAART [194]. **[BIII]** However, there are no published data on the utility and efficacy of combined HAART/TB DOT in treating HIV/TB coinfection.

DOT usually requires that patients be observed to ingest each dose of anti-tuberculosis medication. Any treatment plan should be individualized to incorporate measures that facilitate adherence. These may include social service support, treatment incentives, housing assistance, referral for treatment of substance misuse, and co-ordination of tuberculosis services with those of other providers. There are many patients taking both HIV and TB therapies concomitantly. A maximum adherence model which is patient-centred, and utilizes family and friends and other social support as well as health care workers to ensure adherence, is an approach being examined more closely.

12.0 Management of relapse, treatment failure and drug resistance

12.1 Relapse

TB relapse is defined in a patient who has become (and remained) culture-negative while receiving therapy but after completion of therapy shows:

- culture-positive again;
- or clinical or radiographic deterioration consistent with active TB.

Every effort should be made to establish a diagnosis and obtain microbiological confirmation of the relapse to enable testing for drug resistance. IRIS events can mimic treatment relapse (see section 10). Strong consideration should be given to obtaining a rapid molecular rifampicin resistance test for all HIV-positive patients with relapse or treatment failure. These are available in TB reference laboratories and advice should be sought from them as soon as the diagnosis is contemplated.

Most relapses occur within 6–12 months of completing therapy. In patients with initially drug susceptible TB, who were treated with rifamycin-containing regimens using DOT, relapse is with susceptible organisms in nearly all cases. In patients who self-administered therapy or received a non-rifamycin regimen, relapse incurs a substantial risk of acquired drug resistance.

The selection of empirical treatment for patients with relapse should be based on the prior treatment regimen and severity of disease:

I. For patients with prior TB caused by drug susceptible organisms, who received DOT with a rifamycin based regimen, initiation of the standard four-drug regimen is appropriate until the results of drug susceptibility tests are available. **[AII]**

II. For patients with life-threatening TB, at least three additional agents to which the organisms are likely to be susceptible should be included, even if the criteria in (I) are fulfilled. **[AIII]**

III. For patients with relapse, who did not receive DOT, or had treatment interruptions, or who were not treated with a rifamycin based regimen, then it should be assumed that drug resistance is present. Treatment is initially with isoniazid, rifampicin and pyrazinamide plus an additional three agents. Such agents could include a fluoroquinolone, an injectable such as amikacin, with or without additional oral drugs such as para-aminosalicylic acid (PAS), cycloserine, prothionamide and clarithromycin. **[AIII]**

12.2 Treatment failure

Treatment failure is defined as continued or recurrently positive cultures during the course of anti-tuberculosis therapy. After 3 months of multi-drug therapy for pulmonary tuberculosis caused by drug susceptible organisms, up to 98% of patients will have negative cultures and show clinical improvement. All patients with positive cultures after 3 months of appropriate treatment must be evaluated carefully to identify the cause of the delayed conversion. Patients whose sputum cultures remain positive after 4 months of treatment should be classified treatment failures.

There are many reasons for treatment failure in patients receiving appropriate regimens. These include:

- non-adherence;
- drug resistance;
- malabsorption of drugs;
- laboratory error;
- extreme biological variation resulting in a prolonged time to respond.

- Re-infection with a drug resistant strain

If treatment failure occurs, the case should be referred to a regional centre [1]. *M. tuberculosis* isolates should be sent to a reference laboratory for drug susceptibility testing to both first- and second-line agents. One of the fundamental principles in managing patients with treatment failure is never to add a single drug to a failing regimen, as this leads to acquired resistance to the new drug. Instead, at least two, and preferably three, new drugs should be added, to which the patient has not been exposed and to which susceptibility is thought likely. Empirical regimens usually include a fluoroquinolone, an injectable agent such as amikacin, and an oral agent such as cycloserine, prothionamide, clarithromycin or para-aminosalicylic acid (PAS). Once drug susceptibility test results are available, the regimen should be adjusted accordingly.

12.3 Management of INH resistance without rifampicin or other significant drug resistance

The ATS and BTS have recommended several treatment regimens for the treatment of INH-resistant TB, which include: a) 12 months of rifampicin and ethambutol (12RE); b) 6 months of rifampicin, ethambutol and pyrazinamide (6REZ); c) 2 months of rifampicin, ethambutol and pyrazinamide then 10 months of rifampicin and ethambutol (2REZ/10RE); and d) 2 months of rifampicin, ethambutol and pyrazinamide or streptomycin then 7 months of rifampicin and ethambutol (2REZ or S/7RE).

The efficacies of these regimens have not been fully evaluated in prospective trials in HIV-positive subjects and we recommend 12 months of rifampicin and ethambutol with pyrazinamide also given in the first 2 months (2REZ/10RE).

If INH resistance is only discovered at 2 months of initial four drug treatment then one can either continue with RE for 10 months or continue REZ for a total of six months. In patients with extensive disease, one might continue both E and Z with R for 9–12 months or even use RE with a quinolone.

12.4 Multi-Drug resistant-TB (MDR-TB)/and extensively resistant TB XDRTB [195]

TB resistance to at least isoniazid and rifampicin is known as MDR-TB and isolates are at high risk of further acquired drug resistance. Risk factors for MDR-TB include:

- previous TB treatment;
- birth, travel or work in an area endemic for MDR-TB;
- history of poor adherence;
- sputum smear positive after 2 months; TB therapy or culture positive at 3 months;
- homelessness/hostel living.

All such patients should be referred to regional treatment centres, regardless of HIV status. There is a web based discussion forum that can be used by the physician managing such cases. Further details are available on the BTS website at www.brit-thoracic.org.uk/tuberculosis.aspx

Although patients with strains resistant to rifampicin alone have a better prognosis than those with MDR-TB, they are also at increased risk of treatment failure and further resistance and should be managed in consultation with an expert. There are no definitive randomized or controlled studies to define best regimens for MDR-TB. In principle, patients should be given four drugs to which the organism is susceptible. Recommendations are therefore based on the resistance profile and expert opinion. The optimum duration of treatment of MDR-TB in HIV patients has also not been established, but many cases are treated for at least 18 months to 2 years after cultures revert to negative.

The drugs used to treat MDR-TB include the second line and other drugs that are listed in Table 3. There are no formal data regarding interactions between these drugs and antiretrovirals but a review of the subject has been published [123]. Ethionamide has significant interactions because it is metabolized by the CYP450 system, although which isoenzyme is unknown. There is no guidance about dose adjustment but therapeutic drug monitoring may be useful. There is a potential for renal toxicity with aminoglycosides and tenofovir but there are few data on drug interactions between antiretrovirals and second-line anti-tuberculous treatment except for clarithromycin. Expert advice should be sought through the expert physicians network (www.brit-thoracic.org.uk/tuberculosis.aspx).

Novel drugs are being developed for treatment of MDR-TB, e.g. TMC 207, but are not available in the UK.

Surgical resection in the management of pulmonary MDR-TB can be used but results of randomized trials are awaited.

12.5 XDR-TB

Extensively drug-resistant TB (XDR-TB) is defined as TB that is resistant to at least isoniazid plus rifampicin, and to fluoroquinolones, and at least one of three injectable drugs (capreomycin, kanamycin or amikacin). XDR-TB has a high mortality [196] but is fortunately still rare in the UK. As for MDR-TB, all cases should be referred to consultants with expertise in management.

12.6 Chemo preventative therapy in MDR/XDR-TB

In HIV-infected individuals exposed to MDR-TB, chemo-preventative therapy may be considered. If given at all it should be based on the drug sensitivity of the index case's isolate. Despite the lack of evidence, the CDC, the American Thoracic Society, and the Infectious Diseases Society of America have suggested that for the treatment of latent infection in people exposed to MDR-TB a two-drug regimen of pyrazinamide and ethambutol *or* pyrazinamide and a quinolone (levofloxacin, moxifloxacin or ofloxacin) can be offered [197]. Further guidance is contained in [4,198].

As with MDR TB in XDR-TB any chemo-preventative therapy should be based on the drug sensitivity of the index case.

The balance of benefits versus detriments associated with treatment for latent tuberculosis infection in people exposed to MDR-TB or XDR-TB is not clear. The drugs

have potential serious adverse effects and any decision to start or not needs careful consideration and expert advice.

13.0 Pregnancy and breast-feeding

Although tuberculosis in pregnancy carries a risk of tuberculosis in the fetus, the main problem of tuberculosis in pregnancy is a poor fetal outcome [199]. Treatment should be initiated whenever the probability of maternal disease is moderate to high. The initial phase should consist of isoniazid, rifampicin and ethambutol. Pyrazinamide is probably safe in pregnancy and is recommended by the WHO and the International Union against Tuberculosis and Lung Disease (IUATLD). These first-line drugs cross the placenta but do not appear to be teratogenic.

Streptomycin can cause congenital deafness [200] and prothionamide is teratogenic, so both should be avoided. Ethionamide causes birth defects at high doses in animals [201].

If pyrazinamide is not included in the initial phase, the minimum duration of therapy is 9 months. As in the general population pyridoxine 10 mg/day is recommended for all women taking isoniazid. In pregnancy antiretroviral pharmacokinetics are variable and TDM is recommended.

Women who are breast-feeding should be given standard TB treatment regimes. **[AIII]**

Pregnant women are usually on a PI-boosted HAART regimen and therefore should receive rifabutin as part of their antituberculous regimen. There are no adequate and well-controlled studies of rifabutin use in pregnant women. No teratogenic effects were observed in reproduction studies carried out in rats and rabbits.

14.0 Treatment of latent TB infection – HAART, anti-tuberculosis drugs or both?

14.1 Prophylaxis in those at risk of TB – risks and benefits

Persons from resource-poor countries, especially Sub-Saharan Africa, often present with TB as their first manifestation of immunosuppression. Others who are diagnosed with HIV have high rates of latent TB infection. Low CD4 cell counts and not being on antiretroviral therapy are also associated with an increased risk of reactivation of latent tuberculosis [202,203].

Widespread use of HAART has reduced the risk of developing clinical TB among persons infected with HIV. In several studies the risk of TB was up to 80% lower in those prescribed HAART. The protective effect was greatest in symptomatic patients and those with advanced immune suppression and was not apparent in those with CD4 counts >350 cells/μL [204–206]. The effect is almost certainly related to improvements in systemic immunity (reflected by increasing CD4 cell count) to a point where the risk of new infection or reactivation is greatly diminished.

There have been many short-term controlled trials in HIV-positive persons showing the protective effect of chemo-preventative therapy,207–213]. A significant protective effect of isoniazid is found only in those who are tuberculin skin test-positive, and appears to only last 2 to 4 years as compared with at least 19 years (suggesting protection is lifelong) in TB control programs of non-HIV populations where active cases were also treated, limiting the risk of any reinfection occurring. This is an important point as the HIV populations studied have mainly been in areas of high TB prevalence, where most TB

arises from new infection rather than reactivation [53]. Apart from recognized outbreaks, there is little evidence to suggest that reinfection (as opposed to reactivation) is a major factor in the UK. Chemo-preventative therapy might therefore have a longer duration of effect in the UK but there are no data to support this hypothesis.

There are some data from Brazil to suggest that a combination of HAART and isoniazid may be more effective than either alone in controlling TB [205]. The epidemiological situation in the UK is different however.

Chemo-preventative therapy without HAART seemed to have little effect on HIV progression and mortality in the long term [211]. There are also theoretical concerns that widespread isoniazid monotherapy might speed the emergence of drug resistant TB [214]. However, in a recent meta-analysis of 13 studies investigating the risk of developing isoniazid resistance as a result of chemopreventative therapy, the relative risk for resistance was 1.45 (95% confidence interval 0.85–2.47). Results were similar when studies of HIV-uninfected and HIV-infected persons were considered separately. Analyses were limited by small numbers and incomplete testing of isolates, and their findings did not exclude an increased risk for isoniazid-resistant TB after isoniazid preventatative therapy [215].

The other risk of isoniazid preventative therapy is hepatotoxicity. The BTS Joint Tuberculosis Committee used a rate of 278/100 000 for serious hepatotoxicity. It may be more frequent in HIV-positive patients and those with active viral hepatitis (see section 7.1) – though the data are conflicting.

14.2 Chemopreventative therapy for latent tuberculosis in HIV-positive patients in the UK

As there are no definitive data from developed countries on whether giving chemopreventative therapy to patients with a positive IGRA will reduce the risk of developing TB, the available large cohort data from Europe were examined to provide a basis for a pragmatic clinical approach to this problem and to calculate the risk of developing active tuberculosis [202,203]. The risk of developing active TB versus the risk of developing hepatitis on isoniazid prophylaxis was then used as the counterpoint to decide on whether chemopreventative therapy should be offered or not. A similar exercise has been performed to help decide whether to give chemopreventative therapy to patients starting anti-TNF therapy, where the risk of developing TB is balanced against the risk of isoniazid-induced hepatitis.

In an HIV-infected individual with a positive IGRA, the risk of developing active TB, and therefore the need for chemopreventative therapy, is based on (see Table 9 and flow chart):

- region of origin;
- current blood CD4 cell count;
- duration of time on HAART.

HIV-positive patients at increased risk fall into the following groups:

- Sub Saharan Africa – if length of current antiretroviral therapy is under 2 years, whatever the current blood CD4 cell count.
- medium TB incidence countries – if length of current antiretroviral therapy is under 2 years and current CD4 count is less than 500 cells/μL

- low incidence countries, e.g. Caucasians from the UK – if not on antiretrovirals, or length of current antiretroviral therapy is less than 6 months and current CD4 count is less than 350 cells/μL.

Patients should be offered screening with IGRA if (and only if) they are in one of these groups and would benefit from chemoprophylaxis **[BII]**.

If the IGRA result is positive then we recommend the patient is given chemoprophylaxis.

If the IGRA result is negative then no chemoprophylaxis is needed.

If a patient is tested with an IGRA outside of these guidelines (not in one of the risk groups above), then no chemoprophylaxis is needed, even if the result is positive.
These recommendations are based on extrapolation from available data and further analyses are under way to refine this approach. If an IGRA test is indeterminate then we suggest repeating it and if still indeterminate the clinician should use clinical judgment regarding whether to give chemopreventative therapy or not.

This Committee is aware that this new guidance will need local interpretation with regard to available resource, and that it should be subject to early audit (2010 NICE guidance on IGRA testing). Draft NICE guidance suggests using IGRA testing in those patients with a CD4 count over 200cells/μL and both an IGRA and tuberculin test in those with CD4 counts below this threshold. Although physicians can perform both tests in the severely immunosuppressed patients we believe that as there are few data to support this strategy doing this would add complexity, cost and difficulties in interpretation and believe that an IGRA test alone would be sufficient at every CD4 count count stratum. New data would be welcome in guiding physicians in this difficult area.

It is important to note that HIV-positive patients who are in close and prolonged contact with patients with proven or assumed active tuberculosis should be screened for TB and if no active disease is found chemopreventative therapy recommended.

Though few data are available for patients receiving cancer chemotherapy or prolonged high-dose corticosteroids (>20mg od prednisolone for more than 2 months) where the prognosis is > 1 year, it may be reasonable to give isoniazid prophylaxis to all those with a positive IGRA who do not have active tuberculosis.

14.3 Drug regimens for chemopreventative therapy
Individuals with a positive Interferon-γ assay but no clinical or radiological evidence of active TB are assumed to have latent infection. Active TB should be excluded with a detailed history and examination and at least a chest radiograph. Other investigations might be necessary, for example lymph node biopsy (if lymphadenopathy), or colonoscopy and biopsy (if diarrhoea). It is especially important to consider subclinical TB prior to starting HAART because of the risk of IRIS [216] (see also 10.0).

Alternatives for treating latent tuberculosis:

- isoniazid for 6 months [210]; **[A11]**
- rifampicin with isoniazid for 3 months; **[BI]**
- rifampicin for 4 months**. [BIII]**

Shorter courses using other drugs have been tried to help overcome poor adherence. Rifampicin and pyrazinamide given daily or twice weekly, for 2 months has been used successfully in HIV-positive patients [209,212,213] but is not recommended **[DII]** because in largely non-HIV patients it has been associated with severe or fatal hepatic reactions in at least 50 cases in the USA [217].

14.4 Post-treatment prophylaxis

Studies in areas of high TB prevalence have shown that isoniazid prophylaxis post-treatment achieves short-term reductions in rates of TB [218,219]. Such a strategy may in fact prevent reinfection, which is more common than true reactivation in such settings [220]. For maximum benefit the isoniazid would need to be continued long-term, or at least until CD4 cell count had substantially risen on HAART, and there are no data to support such an approach. It is clear that relapse rates are lower in patients on HAART, associated with both improved CD4 cell counts and achieving an undetectable viral load [221].

Post-treatment TB prophylaxis is therefore not recommended, but HAART should be continued. **[DII]**

15.0 Prevention and control of transmission

Guidelines for prevention and control of transmission of TB include:

- National Institute for Health and Clinical Excellence. *Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control*, 2006;
- Stopping Tuberculosis in England: An action plan from the Chief Medical Officer, published by Department of Health, 7 October 2004;
- Tuberculosis prevention and treatment: a toolkit for planning, commissioning and delivering high-quality services in England, published by Department of Health, 15 June 2007;
- The Prevention and Control of Tuberculosis in the United Kingdom published by The Interdepartmental Working Group on Tuberculosis, 1998 [4].

These are available at:
www.dh.gov.uk/en/Publichealth/Communicablediseases/Tuberculosis/index.htm

In summary, for good control of TB there should be:

- recognition that TB is a potential diagnosis;
- prompt confirmation of diagnosis;
- no delay in starting treatment;
- an appropriate drug regimen;
- supervised therapy;
- early consideration of drug resistance in non-responding patients.

Hospital care of patients with potential or known TB requires:

- appropriate isolation of patients;
- risk assessment for drug resistance;
- adequate negative pressure rooms which are properly monitored [4];

- aerosol generating procedures (bronchoscopy, sputum induction or nebuliser treatment) should only take place in negative pressure rooms;
- consider all patients potentially infectious until proven otherwise;
- no mixing of HIV-infected or other immunosuppressed patients with TB patients;
- hospital TB control plan based on risk assessment;
- adequate protection of health care workers and other contacts.

15.1 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.
Contact tracing should follow the NICE guidelines [1] but requires considerable sensitivity.

16.0 Death and clinico-pathological audit

Despite diagnosis and treatment, patients with HIV and tuberculosis still die. It is important that as many such patients as feasible are examined by autopsy. This categorises the pathology and enables audit of medical practice. The significant categories of causes of death include:

- active, progressive tuberculosis;
- secondary effects of tuberculosis (e.g. lung haemorrhage, meningovascular obstruction);
- IRIS affecting one or more critical organs (e.g. lung, brain);
- anti-tuberculosis drug toxicity;
- other HIV- or non-HIV-related disease in a person effectively treated for TB;
- other disease in a person diagnosed with and treated for TB, without laboratory confirmation, who shows at autopsy no evidence of having had TB.

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

Autopsies are either requested by clinicians or commanded by a Coroner (in UK) or Procurator Fiscal (in Scotland). If the autopsy is coronial, every endeavour should be made to obtain the autopsy report for clinical audit. Before any autopsy, discussion about the clinico-pathological issues with the pathologist is recommended.

17.0 Tables

Table 1: Abbreviations

AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the curve
BHIVA	British HIV Association
BTS	British Thoracic Society
CDC	Centers for Disease Control and Prevention, USA
CNS	central nervous system
CYP	cytochrome 450
d4T	stavudine
ddC	zalcitabine
ddI	didanosine
DOT	directly observed therapy
E	ethambutol
H	isoniazid
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
INH	isoniazid
IGRA	interferon gamma release assay
IRD	immune reconstitution disease
IRIS	immune reconstitution inflammatory syndrome
MDR-TB	multi drug resistant tuberculosis
NICE	National Institute for Health and Clinincal Excellence
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PAS	para-aminosalicylic acid
PCR	polymerase chain reaction
PgP	P-glycoprotein
PI	protease inhibitor
R	rifampicin
TB	tuberculosis

TDM	therapeutic drug monitoring
TST	tuberculin skin test
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB
Z	pyrazinamide

Table 2: Strength of treatment recommendations based on quality of evidence*

Strength of the recommendation:

A Preferred; should generally be offered

B Alternative; acceptable to offer

C Offer when preferred or alternative regimens cannot be given

D Should generally not be offered

E Should never be offered

Quality of evidence supporting the recommendation:

I. At least one properly randomized trial with clinical end points

II. Clinical trials either not randomized or conducted in other populations

III. Expert opinion

* *Adapted* from Gross PA, Barrett TL, Dellinger EP *et al*. *Clin Infect Dis* 1994; **18**: 421.

Table 3: Drugs used in the treatment of TB

First-line drugs	**Second-line drugs**
isoniazid	sparfloxacin, ofloxacin, levofloxacin, moxifloxacin
rifampicin*	rifabutin*
pyrazinamide	streptomycin, amikacin, kanamycin
ethambutol	cycloserine
	protionamide, ethionamide
	capreomycin,
`	para-aminosalicylic acid
Other drugs used in the treatment of	MDR-TB but with few or no clinical outcome data
	clarithromycin, azithromycin
	amoxicillin with clavulanic acid
	linezolid**

* Rifabutin may be substituted for rifampicin as a first-line drug in some situations, e.g. drug interactions. It is used in second line when there is rifampicin resistance but rifabutin sensitivity remains.

Only physicians skilled in the treatment of TB should prescribe TB regimens.

** The maximum recommended duration of linezolid is usually 28 days. All patients on linezolid should have their complete blood counts monitored weekly and be advised to report any new signs and symptoms. There have been reports of optic and peripheral neuropathy, especially after 28 days of therapy.

See BNF for standard doses of individual drugs and fixed dose formulations.

Tables 4–7: Drug interactions

More information at University of Liverpool website: www.hiv-druginteractions.org

Dose adjustments are described below for antiretrovirals given with rifampicin, rifabutin and clarithromycin.

No dosage adjustments are advised with isoniazid, pyrazinamide, streptomycin, amikacin, kanamycin, ethionamide, azithromycin, ofloxacin or ciprofloxacin.

Key for interaction tables

No Interaction – use standard doses	♦
Potential Interaction – see advice	■
Definite interaction – do not combine	●

Table 4: Nucleoside reverse transcriptase inhibitors (NRTIs)

	Rifampicin	Rifabutin
Abacavir	♦	♦
Didanosine EC	♦	♦
Emtricitabine	♦	♦
Lamivudine	♦	♦
Stavudine	♦	♦
Tenofovir	♦	♦
Zidovudine	♦	♦

Table 5: Non-nucleoside reverse transcription inhibitors (NNRTIs)

	Rifampicin	Rifabutin
Efavirenz	■ Efavirenz levels ↓ by 20–30% Efavirenz increased to 800mg daily if weight >60kg Efavirenz at 600mg daily if weight <60kg Rifampicin at standard dose	■ Rifabutin levels ↓ by 38%. Rifabutin increased to 450mg daily Efavirenz at standard dose
Nevirapine	● Nevirapine levels ↓ 20–55% No change in rifampicin Not recommended	♦ Use standard doses but little data so not recommended
Etravirine	No data available	♦ Use standard doses but little data so use with caution
TMC-278	● TMC-278 levels ↓ 90% Do not use	■ TMC-278 levels ↓ 50% Double dose TMC-278

Table 6: Protease inhibitors (PIs)

PI	Rifampicin	Rifabutin
Atazanavir	● 80% ↓ level atazanavir Do not use	■ Reduce rifabutin to 150mg daily
Atazanavir/ Ritonavir	● ↓ level atazanavir Do not use	■ Reduce rifabutin to 150mg 3x per week
Darunavir/ Ritonavir	● No data Do not use	■ Reduce rifabutin to 150mg 3x per week
Fosamprenavir/ Ritonavir	● ↓ levels amprenavir Do not use	■ Reduce rifabutin to 150mg 3x per week
Lopinavir/ Ritonavir	● 75% ↓ level lopinavir Higher doses cause heptatotoxicity Do not use	■ Reduce rifabutin to 150mg 3x per week
Ritonavir as single agent	■ 35% ↓ level ritonavir Can be used at 600mg twice daily but very poorly tolerated	
Saquinavir/ Ritonavir	● ↓ level saquinavir Higher doses cause heptatotoxicity Do not use	■ Reduce rifabutin to 150mg 3x per week
Tipranavir/ Ritonavir	● 80% ↓ level tipranavir Do not use	■ Reduce rifabutin to 150mg 3x per week

Table 7: Integrase inhibitors and entry inhibitors

	Rifampicin	Rifabutin
Elvitegravir	● Elvitegravir levels ↓ Do not use	No data
Raltegravir	● Raltegravir levels ↓ 60% Even at 800mg bd use with caution as C_{min} ↓ %	Use standard doses
Maraviroc	■Use with caution Maraviroc levels ↓ Double maraviroc dose to 600mg bd	♦ Use standard doses
Enfuvirtide (T-20)	♦ No interaction Use standard doses	♦ No interaction Use standard doses

Table 8

Guidelines for the re-introduction of anti-tuberculosis chemotherapy following elevation of liver function tests or cutaneous reaction grade 1–3

Day	Isoniazid	Rifampicin	Pyrazinamide
1	50mg		
2	150mg		
3	300mg		
4	300mg	75mg	
5	300mg	150mg	
6	300mg	300mg	
7	300mg	450mg <50kg or 600mg >50kg	
8	300mg	450mg/600mg	250mg
9	300mg	450mg/600mg	500mg
10	300mg	450mg/600mg	1g
11	300mg	450mg/600mg	1.5g <50kg or 2g >50kg
12	300mg	450mg/600mg	1.5g/2g
13	300mg	450mg/600mg	1.5g/2g

If the reaction is severe, start with one-tenth of the first-day dose for each drug.

Adapted from a reintroduction protocol for cutaneous reactions (Girling DJ. Adverse effects of antituberculous drugs. *Drugs* 1982; **23**: 56–74).

Patients who are infectious should be treated with two active drugs whilst standard therapy is reintroduced. Suitable agents would be ethambutol and streptomycin or ethambutol and ofloxacin/moxifloxacin (note reports of severe hepatotxicity with moxifloxacin). In patients who are non-infectious, ethambutol should be started once the other three drugs are at full dose.

An alternative reintroduction regimen was described in 1996 for patients with hepatotoxic adverse reactions [222] and adopted by the Joint Tuberculosis Committee in 1998 [55]:

Once liver function is normal the original drugs can be reintroduced sequentially in the order isoniazid, rifampicin, pyrazinamide, with daily monitoring of the patient's condition and liver function. Isoniazid should be introduced initially at 50mg/day increasing sequentially to 300mg/day after 2–3 days if no reaction occurs and then continued. After a further 2–3 days without reaction rifampicin at a dose of 75mg/day can be added, increasing to 300mg/day after 2–3 days, and then after a further 2–3 days without reaction to 450mg(<50mg) or 600mg(>50kg) per day as appropriate for the patient's weight, and then continued. Finally pyrazinamide can be added at 250mg/day, increasing to 1gm/day after 2–3 days and then 1.5gm (<50kg) or 2.0gm (>50kg) per day.

Example of alternative schedule

Day	Isoniazid	Rifampicin	Pyrazinamide
1	50mg		
2	50mg		
3	150mg		
4	300mg		
5	300mg		
6	300mg	75mg	
7	300mg	75mg	
8	300mg	150mg	
9	300mg	300mg	
10	300mg	300mg	
11	300mg	450mg <50kg or 600mg >50kg	
12	300mg	450mg/600mg	
13	300mg	450mg/600mg	
14	300mg	450mg/600mg	250mg
15	300mg	450mg/600mg	250mg
16	300mg	450mg/600mg	500mg
17	300mg	450mg/600mg	1g
18	300mg	450mg/600mg	1.5g <50kg or 2.0g >50kg
19	300mg	450mg/600mg	1.5g/2g

Table 9

Recommendations for Chemopreventative Therapy in HIV-Infected Persons by IGRA Status and Epidemiologic Risk Factors [202,203]

IGRA positive

Sub Saharan Africans	→ whatever blood CD4 cell count and length **HAART** <2years
Medium incidence	→ blood CD4 count < 500 cells/μL and length **HAART** <2years
Low incidence	→ blood CD4 count <350 cells/μL and not on treatment or on treatment < 6/12

IGRA negative

No chemopreventative therapy

Footnote
Regions of origin (1) sub-Sahara Africa;
(2) medium-risk regions, including Eastern Europe, Central Asia, North Africa and the Middle East, South Asia, East Asia, and the Caribbean; and
(3) low-risk regions.

Table 10

Case definition of IRIS [184]

Although this was developed for a resource-poor setting it is comprehensive and is a useful checklist.

There are three components to this case definition:
(A) Antecedent requirements
Both of the two following requirements must be met:
• Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis [55].

• Initial response to tuberculosis treatment: the patient's condition should have stabilised or improved on appropriate tuberculosis treatment before ART initiation – e.g., cessation of night sweats, fevers, cough, weight loss. (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported.)

(B) Clinical criteria
The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, reinitiation, or regimen change because of treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

• New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement – e.g., tuberculous arthritis

• New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)

• New or worsening CNS tuberculosis (meningitis or focal neurological deficit – e.g. caused by tuberculoma)

• New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor criteria

• New or worsening constitutional symptoms such as fever, night sweats, or weight loss

• New or worsening respiratory symptoms such as cough, dyspnoea, or stridor

• New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded if possible*
• Failure of tuberculosis treatment because of tuberculosis drug resistance
• Poor adherence to tuberculosis treatment
• Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed).

18.0 Key Points:

18.1 Treatment of uncomplicated non-CNS tuberculosis
A four-drug regimen of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months; followed by rifampicin and isoniazid for 4 months.

18.2 Treatment of CNS or MDR-TB
A prolonged treatment duration is recommended.
TB meningitis is treated for at least 9 months.
In MDR-TB treatment for up to 2 years may be indicated.

18.3 Treatment schedule
Daily therapy is recommended.
If therapy is given 3 or 5 times per week it should be supervised, preferably as DOT.

18.4 Liver disease
Patients with pre-existing liver disease need their liver function tests monitored closely. They need to be advised to present immediately if they develop vomiting, abdominal pain or jaundice.

18.5 Molecular diagnostic techniques
Molecular diagnostic tests can give rapid identification of mycobacterial species.
PCR probes can rapidly detect resistance to rifampicin.
These results can help decisions about treatment and infection control measures.

18.6 Notification of TB
All patients with TB, regardless of HIV status, must be notified.

18.7 Infection Control
All potentially infectious patients should be managed in appropriate isolation facilities, such as negative pressure rooms, with staff and visitors wearing high-efficiency particulate filtration masks.

18.8 Drug interactions
Complex drug interactions occur between rifamycins and antiretroviral drugs and other drugs that may affect dosages and dosing frequencies.

18.8 Starting HAART

Starting HAART in patients on antituberculous medication should take into consideration primarily the CD4 cell count but other factors such as adherence, potential toxicities and drug–drug interactions are also important.

18.9 Chemopreventative therapy

IGRA tests are preferred to Tuberculin skin tests (eg Mantoux). Chemo-preventative therapy should be considered for all IGRA positive HIV-infected patients dependent on a risk assessment based on country of origin, blood CD4 count and length of time on HAART.

Appendix

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