BHIVA treatment guidelines for TB/HIV infection
February 2004 (DRAFT)
Dr Anton Pozniak

Contents

1.0 Introduction
2.0 Aims of TB treatment
3.0 Treatment Regimens
4.0 Drug/drug interactions
5.0 Overlapping toxicity profiles of antiretroviral drugs with anti-tuberculous therapy
6.0 Drug Absorption
7.0 Laboratory diagnosis
8.0 When to start HAART
9.0 Directly observed therapy
10.0 Tuberculin skin testing
11.0 Chemopreventative therapy
12.0 Management of relapse treatment failure and drug resistance
13.0 Pregnancy and breastfeeding
14.0 Immune reconstitution inflammatory syndrome (IRIS) or paradoxical reactions
15.0 Prevention and control transmission of HIV related tuberculosis
16.0 Tables
17.0 References
1.0 Introduction

TB/HIV Guideline draft intro

World-wide, HIV infection is the foremost risk factor for development of tuberculosis (TB). All patients with tuberculosis, regardless of their perceived risk of HIV infection should be offered an HIV test as part of their tuberculosis treatment package. In the United Kingdom, clinicians are caring for increasing numbers of HIV-TB coinfected patients. The clinical and radiographic presentation of such individual’s disease may be atypical. Compared to the immune competent general population, HIV infected patients with active pulmonary tuberculosis are more likely to have normal chest radiographs, or be smear negative/culture positive. The clinician caring for HIV infected patients, therefore, needs to have a low index of suspicion for tuberculosis in symptomatic individuals. As the investigation and treatment of both tuberculosis and HIV require specialist knowledge and expertise, it is mandatory to involve specialist HIV, Respiratory and Infectious Diseases physicians in patient care.

These guidelines have been drawn up in response to a perceived need for a clinical knowledge base covering the treatment of both HIV and tuberculosis in co-infected patients in the United Kingdom. These guidelines do not cover HIV infected children with tuberculosis, nor do they provide advice on HIV testing in adults with newly diagnosed tuberculosis. [information on these areas may be obtained from …..xxx]

These treatment guidelines have been written to help physicians manage HIV infected patients with confirmed or suspected tuberculosis. They are based on evidence where it is available but some recommendations have to rely on expert opinion until data from trials are made available. These guidelines are not a manual for treatment of HIV/TB co infection and should be regarded as an adjunct to the BHIVA treatment of HIV guidelines and the BTS guidelines on tuberculosis.

These documents can be downloaded from:

http://www.bhiva.org

http://www.brit-thoracic.org.uk

BHIVA is aware of and involved in the creation of NICE guidelines on tuberculosis which will be available in 2005 but felt that until that time some guidance on TB in HIV should be made widely available.

Recommendations for the treatment of tuberculosis in HIV infected adults are, similar to those for HIV uninfected adults. However there are important exceptions.

1) Some intermittent treatment regimens are contra-indicated in HIV infected patients because of unacceptably high rates of relapse, frequently with organisms that have acquired rifamycin resistance. Consequently, patients with CD4 + cell counts <100/µl should receive daily or three times weekly anti-tuberculosis treatment ? good evidence for this in HIV infection (see later in text).

2) Adherence strategies including directly observed therapy (DOT) are especially important for patients with HIV related tuberculosis.

3) HIV infected patients are often taking medication, which might interact with antituberculosis medications for example rifampicin which interacts with antiretroviral agents and other anti-infectives, for example fluconazole. Drug absorption may also be affected by the stage of HIV infection.

4) There are overlapping toxicity profiles and drug/drug interactions with some antituberculosis and antiretroviral drugs which further complicates the concurrent use of HAART and tuberculosis treatment.

5) There are also concerns about the timing of commencement of HAART in relation to the start of TB treatment in the context of preventing the risk of further HIV progression and the occurrence of paradoxical reactions.
2.0 Aims of TB treatment

It should be noted that the treatment of tuberculosis has benefits not only for the individual but also to the community.

The aim of TB therapy is:

i) to cure the patient of TB and

ii) to minimize the transmission of *Mycobacterium tuberculosis* to both immune suppressed and immune competent.

3.0 Type and duration of TB treatment

3.1 Treatment Regimens

Various treatment regimens are outlined in Figure 1. Because of the relatively high proportion of adult patients in the UK with tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6 month regimen to be maximally effective. From the Mycobnet data the overall isoniazid resistance rate in the UK is 6% and higher in non-white ethnic groups and those with prior treatment. The highest rates have been found in London. Thus, in most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of two phases;

1) A 2 month initial phase of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB). If (when) drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included.

Followed by

2) a continuation phase of treatment is given for either 4 or 7 months see figure 2. The 4 month continuation phase should be used in the majority of patients.

This 6 month short course drug combination should be recommended to all HIV positive patients with pulmonary tuberculosis wherever possible.

There are important exceptions.

3.2 Seven month continuation phase

Seven month continuation phase is recommended for certain groups: e.g.

i) Patients with cavitary pulmonary tuberculosis caused by drug susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is still positive.

ii) Patients with drug susceptible organisms whose initial phase of treatment did not include PZA.

iii) a ten month continuation phase for patients with CNS involvement e.g. meningitis, tuberculomata.

3.3 Once weekly continuation phase

Once weekly continuation phase (eg with INH and RPT) is contraindicated in patients with HIV infection because of an unacceptable rate of failure/relapse, often with rifamycin resistant organisms.
For the same reason twice weekly treatment, either as part of the initial phase or continuation phase is not recommended for HIV infected patients with CD4+ cell counts <100 cells/µl. These patients should receive either daily treatment throughout or daily treatment in the initial phase or three times weekly treatment in the continuation phase as the regimens are equivalent [Am J Respir Crit Care Med. 1996 Oct;154(4 Pt 1):1034-8. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. Chaisson RE, Clermont HC, Holt EA, Cantave M, Johnson MP, Atkinson J, Davis H, Boulos R, Quinn TC, Halsey NA.]


CXR = chest radiograph; E = ethambutol; H = isoniazid; Z = pyrazinamide; R = rifampicin; R = rifapentine

3.4 Use of rifabutin

For those on complex antiretroviral regimens where there is a risk of drug/drug interactions with rifampicin, rifabutin may sometimes be substituted although there are limited data for its use HIV positive patients. A single-blind, randomised study of 50 HIV positive cases in Uganda and a cohort study of 25 patients in the USA given rifabutin as part of short course TB treatment showed similar efficacy to rifampicin in the first study and to historical data on rifampicin in the second [Schwander].

Although rifabutin seemed to perform as well as rifampicin, there are no long term follow up data to make more detailed comparisons as not all patients in the trial had reached 24 months of evaluation after completion of TB treatment.

In spite of the paucity of data regarding the use of rifabutin in HIV positive patient it is one of the drugs used in the treatment of TB in HIV. This is because rifabutin can be administered with antiretroviral treatment regimens that include protease inhibitors. However non–protease regimens are possible especially in HAART naïve patients.

We recommend that rifampicin should remain the drug of choice whenever practicable.

Rifapentine in the initial phase in TB in HIV negative patients has led to unacceptable 2 year microbiological relapse rates and can not be recommended. Data on its use in the continuation phase is encouraging but this is limited to HIV negative patients.

3.5 Duration of TB treatment

In the absence of a definitive comparative trial, it is not known if a longer duration of therapy should be used to treat tuberculosis in HIV infected patients. However there are few data to suggest that the duration of treatment for tuberculosis sensitive to first line therapy should be any different in HIV positive patients to HIV negative ones.

A review of six studies of patients with HIV infection and three studies of patients without HIV infection given six months of treatment or longer demonstrated that there exists considerable variability in terms of published study design, eligibility criteria, site of disease, frequency and method of dosing, and outcome definitions. In the reported studies, HIV-infected patients had cure rates of 59-97%; treatment success 34-100%; and relapse 0%-10%. In those without HIV infection, cure was 62%-88%; treatment success, 91%-99%; and relapse, 0%-3%. Although the rate of relapse appeared to be higher in some studies of coinfected patients other outcomes were comparable using only 6 month regimens.

Some or all of these factors have a role in explaining the differences in the present data. A multicentre study from the US found no difference between TB relapses with 6 and 9 month
**3.6 Intermittent therapy**

The indications for the use of intermittent therapy in HIV positive patients infection are almost the same as for patients without HIV infection. However two dosing strategies should be avoided as acquired rifamycin resistance has been associated with their use in HIV patients:

i) Once weekly INH–rifapentine in the continuation phase should not be used in any HIV-infected patient; and

ii) Twice weekly INH–RIF or rifabutin should not be used for patients with CD4 + lymphocyte counts less than 100 cells/µl.

In two studies, patients with acquired rifamycin resistance had very low CD4 cell counts at the time of TB diagnosis (<60 cells/µl).

These data have led the CDC in the USA to recommend that persons co-infected with HIV and TB who have CD4 cell counts <100/µl should not be treated with highly intermittent (i.e. once or twice weekly) regimens. Patients already on highly intermittent regimens should switch over to daily or three times a week. ? Clarify when?

**3.7 Baseline and Follow up**

* Evaluations after starting TB treatment

Patients in whom tuberculosis is proved or strongly suspected should have treatment initiated with isoniazid, rifampicin, pyrazinamide, and ethambutol for the initial 2 months. Monitoring of therapy is as follows:

1) A CD4 + lymphocyte count should be obtained. For all adult patients

2) Baseline measurements of serum amino transferases (aspartate aminotransferase [AST] and or alanine aminotransferase [ALT]), bilirubin, alkaline phosphatase, and serum creatinine, and a platelet count should be obtained. LFTs should be rechecked at 1-2 weeks if asymptomatic.

3) All Patients should have serologic tests for hepatitis B or C viruses

4) Testing of visual acuity should be obtained when EMB is to be used (see BTS guidelines)

5) In patients with pulmonary TB and clinical non-improvement a repeat sputum smear and culture should be performed if the patient is still productive when 2 months of treatment has been completed.

6) Chest X-ray should be performed if subsequent progress after 2 months is unsatisfactory. In pulmonary TB, a baseline and completion of treatment chest radiograph are necessary.

7) Other evaluation, e.g. Additional Chest radiograph, ultrasounds, CT scans etc. depending on the clinical need.
3.9 Definition of Completion of TB Therapy

Treatment for a defined number of days without accounting for the number of doses taken can result in under treatment. Therefore, the determination of whether or not treatment has been completed should be based on the total number of doses taken—not solely on the duration of therapy eg. 1) A 6 month daily (given 7 days/week) regimen should consist of at least 182 doses of INH and RIF, and 56 doses of PZA. 2) If the drugs are administered by DOT at 5 days/week, the minimum number of doses is 130.

A similar reduction in the target number of doses for 5 days a week administration applies to any of the regimens with a daily component. If because of drug toxicity or non-adherence to the regimen, the specified number of doses cannot be administered within the specified time period. 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 a 6 month period. The 6-month regimen should therefore be completed by 9 months. If it is not, the patient is considered to have interrupted therapy and be managed as follows. EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance. PZA may be discontinued after it has been taken for 2 months (56 doses).

[Note from Peter to discuss 5 times a week]

3.9 Interruptions in therapy

These are common in the treatment of HIV associated tuberculosis. There is no evidence on which to base detailed recommendations for managing interruptions in treatment, and no recommendations can cover all of the situations that may arise. However,

1) If the interruption occurs during the initial phase of treatment and the interruption is 14 days or more in duration, treatment should be restarted from the beginning.

2) If the interruption is less than 14 days, the treatment regimen should be continued.

NB In both 1) and 2) the total number of doses prescribed for the initial phase should be given.

3) For patients who were smear positive initially, continued treatment to complete the planned total number of doses is needed. So,

   i) if the patient has received less than 80% of the planned total doses and the lapse is 3 months or more in duration, treatment should be restarted from the beginning.

   ii) If the interruption is less than 3 months in duration, treatment should be continued to complete a full course. Studies have not been performed in HIV patients to confirm this observation and physicians should be cautious when treating patients who have had interruptions of therapy.

Regardless of the timing and duration of the interruption, DOT should be used.

If the patient was already being managed with DOT, additional measures will be necessary to ensure completion of therapy. ? Specify?

4.0 Drug/drug interactions (see Table)

Drug/drug interactions between HIV and TB therapy arise through shared routes of metabolism and are often due to enzyme induction or inhibition.

One important family of enzymes is the hepatic cytochrome P450 (CYP) system. The isoform CYP3A4 is involved in the metabolism of many drugs including the protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs), which makes up the core of most HAART regimens.
The non-nucleoside reverse transcriptase inhibitors and protease inhibitors have clinically important drug interactions with the rifamycins.

The rifamycins are potent inducers of the CYP3A4. However, the inducing effect of rifampicin not only takes at least 2 weeks to become maximal but will also persist for at least 2 weeks after rifampicin has been stopped. If antiretroviral have been 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 but unlike rifampicin, is also a substrate of it. Therefore any CYP3A4 inhibitors will increase the concentration of rifabutin but will have no effect on rifampicin metabolism. Thus when rifabutin is given with the protease inhibitors, which are inhibitors of CYP3A4, its concentration and that of its metabolites can increase and cause toxicity.

The individual drug/drug interactions between rifamycins and antiretroviral agents are shown in table 1 and 2. The complexity of the drug/drug interaction requires expertise in the use of both antiretroviral and anti-TB drugs. One particular drug interaction should be noted. The metabolism of corticosteroids is accelerated by rifampicin and therefore doses of such drugs e.g. prednisolone, which are commonly used in TB should be increased proportionately.

4.1 Interaction between rifamycins and nucleoside / nucleotide analogues

Most nucleosides have either unknown or little change in pharmacokinetics when given together with rifampicin based regimens. Rifampicin reduces the AUC and increases the clearance of zidovudine via the mechanism of rifampicin induced, increased glucuronidation of zidovudine. This is not clinically significant and dose alteration is not required. In contrast, rifabutin does not appear to affect the clearance of zidovudine.

The previous formulation of ddl contained buffer, which affected the solubility and absorption of rifampicin and the drug doses needed to be separated in time. There is no longer a need to take these drugs separately as buffer free enteric coated ddl is used in the UK.

4.2 Rifamycins and protease inhibitors

4.2.1 Rifampicin

Rifampicin causes a 75 to 95% reduction in serum concentrations of the protease inhibitors other than ritonavir. Such reductions would lead to loss of antiretroviral activity of the protease containing regimen and consequently result in the emergence of resistance to one or more of the other drugs in the HAART regimen.

Currently most patients are given combinations of protease inhibitors, which includes a much lower dose ritonavir at 100mg twice daily in order to take advantage of its enzyme inhibiting properties. In effect ritonavir boosts the concentrations of the other protease inhibitors allowing easier and more tolerable dosing. The data from the drug/drug interaction of rifampicin with lopinavir and ritonavir would suggest that ritonavir at this low dose is not able to compensate for the induction effect of rifampicin on lopinavir metabolism.

There are preliminary data that twice daily saquinavir 1000mg with 100mg ritonavir may be used successfully with daily rifampicin and once daily saquinavir/ritonavir has also been used. However, the recommendation at present would be that low dose ritonavir/protease combinations should not be given with rifampicin based regimens if alternatives exist until more data are available.

As far as TB is concerned rifabutin appears to be as effective as rifampicin based on a small study in HIV infected patients.

4.2.2 Rifabutin

Rifabutin can be used with single (unboosted) protease inhibitors except saquinavir. However, because of the balance between rifabutin induction and protease inhibition of CYP3A4, when this combination is used a modification in the dose of the protease inhibitor may be required (see table) and the dose of rifabutin should be decreased by half to 150mg. If protease inhibitors are used with 100mg ritonavir boosting then the dose of rifabutin should be reduced to 150mg and should only be given three times a week.
Complex interactions may occur when a rifamycin is given with salvage regimens such as two protease inhibitors plus boosted ritonavir or with a protease inhibitor (boosted or not) and a non-nucleoside reverse transcriptase inhibitor. These combinations are used in patients who have had virological failure or intolerance to simpler regimens. These multiple interactions have yet to be fully studied and there are no clear guidelines regarding dosing of rifabutin when used in this circumstance.

4.3   **NNRTIs and rifamycins**

The NNRTI nevirapine is both partially metabolised by CYP 3A4 and also induces this enzyme system. The other commonly used NNRTI eavirenz behaves in a similar way. Because of this inducing effect the clinical use of these drugs together with the rifamycins is complex.

4.3.1   **Rifampicin**

When Rifampicin is used with efavirenz based regimens an increase in the dose of efavirenz to 800mg a day for patients over 50kg is required. Standard doses of efavirenz are used if the patient’s weight is less than 50Kg. Daily rifampicin should not be used with nevirapine. There are some data based on a few patients that two times a week rifampicin can be given with nevirapine based regimens. However we do not recommend twice weekly regimens in HIV patients with CD4 counts of less than 100 cells/mm$^3$.

4.3.2   **Rifabutin**

If rifabutin is used with efavirenz the rifabutin dose should be increased to 450mg a day because of the induction effect of efavirenz. Rifabutin and nevirapine have been given together with no adjustment in either of their dosages. More data is needed before this strategy can be recommended.

4.4   **Non-rifamycin regimens**

HIV related tuberculosis can be treated with non-rifamycin containing regimens. The use of non-rifamycin containing regimens should be only contemplated in patients with serious toxicity to rifamycins where desensitisation/reintroduction has failed or in those with rifamycin resistant isolates. Drug/drug interactions might be fewer but a non-rifamycin regimen is inferior to a rifampicin based regimen for the treatment of HIV-related tuberculosis. If non-rifamycin treatment regimens of one years duration are used then streptomycin should be given. It should be noted that high TB relapse rates of greater than 15% have been seen even when after the initial 2 months with a rifampicin-containing regimen is then switched in the continuation phase to isoniazid and ethambutol.

5.0   **Overlapping toxicity profiles of antiretroviral drugs with anti-tuberculous 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 antituberculosis drugs especially rifampicin, isoniazid and pyrazinamide. The NNRTIs and co-trimoxazole may also cause similar features. The co-administration of these drugs can lead to difficult clinical management decisions if these side effects occur especially when 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.

Adverse events led to cessation or interruption of either their TB or HIV therapy in 63 (34%) of the 183 patients. The most common 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%).

The majority of adverse reactions occurred within the first 2 months of starting concurrent therapies and rifampicin was frequently implicated by the treating physicians accounting for almost 2/3 of adverse events.

5.1 Hepatotoxicity

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

1) A serum AST or ALT level of more than three times the upper limit of normal in the presence of symptoms, or

2) A serum AST or ALT greater than five times the upper limit of normal in the absence of symptoms.

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

If hepatitis develops then all potentially hepatotoxic drugs including INH, RIF, PZA and others eg antivirals and co-trimoxazole, should be stopped immediately.

Serologic testing for hepatitis viruses A, B, and C, if not already done, should be performed and the patient asked about any exposure to other possible hepatotoxins, especially alcohol.

As resolution of the hepatitis may be prolonged and until the cause of the hepatitis is identified then, if necessary, it would be reasonable to treat with two or more antituberculosis medications without significant risk of hepatotoxicity, such as EMB, SM, Amikacin /Kanamycin, Capreomycin, or a Fluoroquinolone.

Monitoring of serum AST (or ALT) and bilirubin and any symptoms should be performed frequently and once the AST level drops to less than two times the upper limit of normal and symptoms have significantly improved, then first line medications can be restarted using a reintroduction [see Table 4].

If the drugs cannot be restarted or the initial reaction was life threatening then an alternative regimen can be used. See below

5.2 Pre existing Liver disease

The risk of hepatotoxicity in these patients is greatest with pyrazinamide then rifampicin then isoniazid. INH and RIF are essential drugs in the short course TB treatment regimens and should be used whenever possible even in the presence of preexisting liver disease.

However if the serum AST is more than three times normal even before starting treatment due to chronic liver disease then other treatment regimens can be used e.g.

1) Avoid PZA and treat with INH and RIF for 9 months, adding EMB until INH and RIF susceptibility are demonstrated

2) Avoid INH and treat with RIF, EMB, and PZA for 2 months, followed by 7 months RE.

3) Use only one potentially hepatotoxic agent in patients with severe liver disease and treat with RIF plus EMB, for 12 months preferably with another agent, such as a fluoroquinolone, for the first 2 months; however, there are no data to support this recommendation.
In all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug induced hepatic injury. Monitoring should be performed more frequently at least 2 weekly initially in those with underlying liver problems including the usual biochemical and haematological assessments and the INR. Patients should be told to report to their physician if they develop symptoms such as nausea, vomiting, abdominal pain or jaundice.

5.3 Gastrointestinal side effects
These are common especially in the first 2-3 weeks after starting anti-tuberculosis therapy. If patients develop epigastric pain, vomiting or nausea with the first line drugs, have no evidence of hepatic disease and are unresponsive to symptomatic treatment e.g. with antiemetics then they can:

1) take their treatment with meals. Food delays or decreases the absorption of anti-tuberculosis drugs but these effects are moderate and of little clinical significance or
2) change the time of dosing.

Avoid dividing doses or changing to alternative drugs if at all possible however sometimes dividing the dose of e.g. pyrazinamide can improve tolerability.

5.4 Peripheral neuropathy
The nucleoside analogues ddI, ddc and d4T may all cause peripheral neuropathy and an additive toxicity of Isoniazid when used with d4T has been demonstrated. These antiretroviral drugs can be avoided in the HAART naïve population and alternatives should be found if possible in those already on these drugs. Pyridoxine 10-25mg daily should be used in all patients receiving isoniazid.

6.0 Drug Absorption
Malabsorption of antimycobacterial drugs with all first line therapies as well as ethionamide and cycloserine has been reported in co-infected persons. Absorption of drugs may be less in those patients with a low CD4 count, whether it be due to HIV enteropathy or other specific HIV related gut diseases resulting in sub therapeutic serum and drug levels and consequently associated with treatment failure and drug resistance. Although some studies show lower peak concentrations of rifampicin and ethambutol as well as lower AUCs compared with controls, there are other data suggesting that rifampicin is well absorbed in HIV patients even those with AIDS or with diarrhoea.

Therapeutic drug monitoring (TDM)
TB drugs:
Based on the limited amount of available data TB drug therapeutic monitoring might be useful (but is often not very helpful) in:

• patients who are at high risk of malabsorption of their TB drugs,
• in those who are responding inadequately to directly observed therapy with first line drugs
• in patients being treated for multi-drug resistant tuberculosis.
• In those who are on non-standard TB regimens or taking non-standard doses
One of the problems with monitoring anti-mycobacterial drugs in HIV positive patient is that the kinetics of absorption are not predictable. It is therefore difficult to know at what time point to measure a peak serum dose and it is probably best to measure levels at more than one timepoint post dose. Decision re dosing may be difficult as there may be long delays in results returning to the physician.

_HIV drugs:_

TDM may be relevant for PIs and NNRTIs especially when regimens are complex, when no formal PK data are available to guide the physician and when virological failure occurs.

### 7.0 Laboratory diagnosis

The quality of any investigation is related to the quality of the specimen and the request. There must therefore be close liaison with the mycobacterial laboratory.

#### 7.1 Microscopic smears

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

#### 7.2 Cultures

These are central for the confirmation and identification of the mycobacterium and for drug susceptibility testing. More rapid results are obtained from liquid media, which usually grows MTB in 7 to 28 days.

Identification of mycobacterium based on morphology, growth and biochemical characteristics are performed at mycobacterium reference centres. Rapid gene probes can be used but this should be fully discussed with the laboratory. These are less sensitive than culture and are used mainly on respiratory specimens. These are often requested when it is important to differentiate the diagnosis of MTB from other atypical Mycobacterium where the treatment may be different or there are infection control concerns. However, it should be noted that all specimens even those that are negative on PCR still require culture and that a negative PCR does not exclude TB and a positive PCR does not indicate the drug susceptibility profile. In many cases the treatment conundrum is whether the patient has mycobacterium avium or mycobacterium tuberculosis and often the physician will wait for the routine identification and in the meantime add clarithromycin to the standard 4-drug regimen. Some physicians prefer to replace rifabutin for rifampicin in this situation. When the organism has been identified then the regimen is modified appropriately.

#### 7.3 Drug susceptibility tests

These are usually available within 10-21 days of the laboratory receipt of the isolates and are performed by standard assays. Molecular detection of rifampicin resistance (and pyrazinamid) is available although it is not 100 percent specific. Isn’t the sensitivity more important here?

These molecular tests are useful when drug resistance is suspected as the majority about 95% of patients who are rifampicin resistant will also be isoniazid resistant.

Patients with PCR positive rifampicin resistance should be treated as MDR-TB until the full resistance profile from cultures are available.

### 8.0 When to start HAART
The optimal time to start HAART in TB/HIV patients is not known. Physicians have to balance the risk of HIV progression if HAART is delayed against the risk of having to discontinue therapies because of toxicities, side effects, paradoxical reactions or unforeseen drug/drug interactions if HAART is started. Similar routes of metabolism and elimination and extensive drug interactions may result in sub-therapeutic plasma levels of antiretroviral agents and furthermore, overlapping toxicity profiles may result in the interruption or alteration of TB and HIV regimens with potential subsequent microbiological or virological failure. In coinfected patients delaying the start of HAART can simplify patient management, limit the development of side effects and drug interactions and the risk of immune restoration reactions.

Patients with HIV disease and a CD4 cell count of greater than 200/microL cells have a low risk of HIV disease progression or death during the subsequent 6 months of tuberculosis treatment. They should have their CD4 cell count, monitored regularly and antiretroviral therapy withheld if possible during the short course tuberculosis treatment.

Most patients with tuberculosis in the UK present with a low CD4 count often below 100 cells/mm3. Some recommend that antiretroviral therapy be delayed until the first 2 months of tuberculosis therapy has been completed. Others would only recommend this strategy for those with a CD4 greater than 100 cells/ml because of the short term risk of developing further AIDS defining events and death. One retrospective study has shown that starting HAART early in severely immunosuppressed HIV positive patients presenting with TB is associated with decreased mortality and a lowering of the rates of progression. Prospective data on these patients are needed.

### 8.1 Suggested timing of HAART in HIV/TB coinfection

<table>
<thead>
<tr>
<th>CD4 count cells/mm³</th>
<th>When to treat with HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>As soon as possible-dependent on physician assessment, some delay up to 2 months</td>
</tr>
<tr>
<td>100-200</td>
<td>After 2 months of TB treatment</td>
</tr>
<tr>
<td>&gt;200</td>
<td>After completing 6 months TB treatment</td>
</tr>
</tbody>
</table>

NB: regular 6-8 weekly CD4 monitoring should be performed and if the cd4 count falls patient may need to start HAART.

### 9.0 Directly observed therapy (DOT)

The use of directly observed therapy should be the gold standard for treatment of HIV related tuberculosis especially with the use of intermittent dosing. It is recommended that all patients with MDR TB have DOT.

It is not always practicable to observe all doses strategy or fulfil all the requirements of the DOTs and in these cases close supervision of treatment is important.

Patient centered care should be at the core of multidisciplinary management and should always include an adherence strategy that emphasizes directly observed therapy (DOT). This may include DOT/supervised therapy for the antivirals.

DOT usually requires that patients are observed to ingest each dose of antituberculosis medications, to try and ensure the completion of therapy. Programs utilizing DOT as the central element in a comprehensive, patient centered approach (enhanced DOT) have higher rates of treatment completion than less intensive strategies. Any DOT plan should be individualized to incorporate measures that facilitate adherence to the drug regimen. Such measures may include,
for example, social service support, treatment incentives, housing assistance, referral for treatment of substance misuse, and coordination of tuberculosis services with those of other providers.

10.0 Tuberculin skin testing

In the pre HIV era patients newly diagnosed with pulmonary tuberculosis had a positive response to 5 units intermediate strength PPD testing in about 75% - 85%.

In HIV and TB coinfection there is a reduction in the proportion of those reacting to PPD as the CD4 count falls, from 50%-90% in those who have a CD4 count of ≥500 cells down to 0% - 20%, in those patients who have AIDS or advanced HIV infection and a CD4 count of ≤200 cells/microL. This limits the tuberculin test as a diagnostic tool.

Specific non-reactivity to PPD is difficult to distinguish from the general poor immune responsiveness seen in HIV patients and anergy testing using a panel of antigens gives inconsistent and ambiguous results and is not a recommended strategy.

HAART can improve immunological responses to tuberculosis but patients most likely to revert from a negative to a positive PPD are those whose with a CD4 count of greater than 200 cell/mm3 rise from baseline.

10.1 Who should have tuberculin testing?

The reason to do a tuberculin test it is to identify those patients who may have latent infection and prevent reactivation. US guidelines recommend that all newly diagnosed HIV patients should have a tuberculin skin test so that those with a positive test (>5mm induration) can be given isoniazid or other chemo preventative therapy. Whether this policy has any long term public health impact on TB control in countries where tuberculosis has a relatively low prevalence is not known.

There are many factors which may affect the usefulness of such a broad strategy such as the lower PPD positive rates in HIV positive patients, the effect of BCG immunisation on PPD reactivity, the relative short term impact of chemopreventative therapy where there are high rates of exogenous infection and the effect of HAART in preventing tuberculosis reactivation and progression to infection.

11.0 Chemopreventative therapy

There have been several short term controlled trials in HIV positive persons showing the protective effect of chemopreventative therapy.

A protective effect of Isoniazid is found only in those who are tuberculin skin test positive. This protective effect appears to only last 2 _ to 4 years as compared with 19 years in non HIV populations. Such a short term effect in HIV positive patients studied especially in areas of high TB prevalence may be explained by the fact that the majority of the tuberculosis in HIV population arises from exogenous sources and thus are not from reactivation of latent TB but are new. Beyond recognised outbreaks, there is little evidence to suggest that re-infection (as opposed to reactivation) is a major factor in the UK.

11.1 The treatment of latent tuberculosis infection

The treatment of latent tuberculosis infection include:

i) INH for a total of 9 months

ii) RIF with INH for a total of 4 months.

Short courses of chemopreventative therapy using other drugs have been recommended to help overcome poor adherence. Unfortunately rifampicin and pyrazinamide given three times a week for
2 months has been associated with severe and fatal hepatic reactions in 5 non-HIV patients with a total of 21 cases of liver injury reported to CDC however this complication was not been seen in the studies of HIV positive patients taking this regimen.

It is known from RFLP studies that many tuberculosis infections in HIV positive patients in TB endemic areas appear to be new infections rather than reactivation of the original TB.

Isoniazid may prevent such exogenous infection but would then have to be given long term or at least until there was a substantial CD4 rise on HAART. There are no current data to support such a strategy.

12.0 Management of relapse, treatment failure and drug resistance

12.1 Relapse

TB relapse is defined as a patient becoming and remaining culture negative while receiving therapy but after completion of therapy becomes:

i) culture positive again or

ii) has clinical or radiographic deterioration that is consistent with active tuberculosis.

Every effort should be made to establish a diagnosis and to obtain microbiological confirmation of the relapse to enable testing for drug resistance.

Most relapses occur within the first 6–12 months after completion of therapy.

Patients whose initial tuberculosis was drug susceptible and who were treated with rifamycin containing regimens using DOT, relapse with susceptible organisms in nearly all cases. In patients who received self administered therapy or a non rifamycin regimen and who relapse the risk of acquired drug resistance is substantial.

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

1) For patients with tuberculosis that was caused by drug susceptible organisms and who were treated under DOT, initiation of the standard four drug regimen is appropriate until the results of drug susceptibility tests are available.

2) For patients who have life threatening forms of tuberculosis, at least three additional agents to which the organisms are likely to be susceptible should be included even if the criteria in 1) are fulfilled.

3) For patients with relapse who did not receive DOT, who were not treated with a rifamycin based regimen, or who are known or presumed to have had irregular treatment, or poor adherence then it should be assumed that drug resistance is present and to treat with INH, RIF, and PZA plus an additional two or three agents. Such agents would include a fluoroquinolone, an injectable agent such as SM especially if initial resistance testing had shown susceptibility to amikacin, kanamycin or capreomycin, with or without additional oral drugs such as cycloserine, prothionamide and clarithromycin.

12.2 Treatment failure

Treatment failure is the continued or recurrently positive cultures during the course of antituberculosis therapy. After 3 months of multi-drug therapy for pulmonary tuberculosis caused by drug susceptible organisms, 90–95% 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:

1) non-adherence
2) drug resistance
3) malabsorption of drugs
4) laboratory error and
5) a few patients take a long time to respond as part of extreme biological variation. If treatment failure occurs the case should be referred to a regional centre. (See Interdepartmental working group on tuberculosis document) Any *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 to which the patient has not been exposed and susceptibility thought likely should be added.

Empirical regimens usually include a fluoroquinolone and an injectable agent such as SM and an oral agent such as paraminosalicylic acid (PAS), cycloserine, or prothionamide. Once drug susceptibility test results are available, the regimen should be adjusted according to the results.

### 12.3 MDR-TB

TB resistant to at least INH and RIF (multi-drug resistant [MDR]) are at high risk of further acquired drug resistance. All Such patients whatever their HIV status should be referred to regional treatment centers.

Although patients with strains resistant to RIF alone have a better prognosis than patients with MDR strains, they are also at increased risk for treatment failure and additional resistance and should be managed in consultation with an expert.

There are no definitive randomized or controlled studies to establish the best regimens for treating patients with various patterns of drug resistant tuberculosis. Such treatment recommendations are based on expert opinion. The role of resectional surgery in the management of patients with pulmonary MDR tuberculosis has not been established in randomized studies and results have been mixed.

### 13.0 Pregnancy and breastfeeding

Because of the risk of tuberculosis to the fetus, treatment of tuberculosis in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. PZA can probably be used safely during pregnancy and is recommended by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD). (cf BTS guidelines) Although all of these drugs cross the placenta, they do not appear to have teratogenicity effects. Streptomycin has harmful effects on the human fetus (congenital deafness) and should not be used as prothionamide is teratogenic.

NB If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

Pyridoxine supplementation (10-20 mg/day) is recommended for all patients taking INH including pregnant women.
14.0 Immune reconstitution inflammatory syndrome (IRIS) or paradoxical reactions

Some patients after starting antituberculosis treatment will develop an exacerbation of symptoms, signs, or radiological manifestations of tuberculosis. This has been well described in patients without HIV infection, but appears to occur more commonly in HIV positive patients. The aetiology of these reactions is unknown, but it is presumed in HIV disease that they occur at least in part as a consequence of HAART related reconstitution of immunity leading to an abnormal immune response to tubercle antigens released by dead or dying bacilli.

These reactions do not have a widely accepted definition. They are characterised by worsening or appearance of new signs, symptoms, or radiographic manifestations of tuberculosis that occur after initiation of HAART and are not the direct result of TB treatment failure or another disease process. They are often defined as transient but can last many months. They are usually seen when the TB is microbiologically controlled but cases can occur with viable organisms isolated on culture. Such paradoxical reactions have been reported in immunocompetent patients before HIV became prevalent. Worsening of nodal disease occurred in around 10% of some populations and central nervous system disease with enlarging tuberculoma was sometimes seen.

14.1 Epidemiology

In the HAART era IRIS has been reported widely and occurred in 36% (12/33) and 32% (6/19) of patients in two of these studies but in another paradoxical worsening was not significantly more common in patients receiving HAART (3 of 28 cases or 11%) compared with 3 of 44 cases (7%) in patients not receiving antiretroviral treatment.

Reactions occur within a median of 15 days after HAART. IRIS does not appear to be associated with any particular antiretroviral regimen or drug class. Most patients with IRIS have advanced HIV infection; and a median baseline CD4 cell count of 35 cells/mm$^3$ and a median HIVRNA level of 581,694 copies/ml. Its relationship to the initiation of antiretroviral therapy suggests that, as the immune system recovers from profound immunosuppression, abnormal responses toward mycobacterial antigens occur.

IRIS most often presents with fever and increased or new lymphadenopathy. The skin over the nodes is often inflamed and the nodes can spontaneously rupture. Pleural and pericardial effusions, ascites, psoas abscess, cutaneous lesions and new or expanding central nervous system tuberculomata have also been described as have worsening pulmonary lesions.

With such small data sets in the literature it is difficult to know who is at risk of IRIS but a low baseline CD4 cell count and a rapid recovery in CD4 numbers appear to be relevant. Cases with dissemination outside the lung may also be of increased risk. HAART started within the first 2 months of tuberculosis treatment was associated with an increased risk of an IRIS. This may be due to the high burden of bacilli inducing immunologic changes associated with the rapid rise in CD4 cells.

14.2 Diagnosis and management of IRIS

The diagnosis of IRIS must be one of exclusion as it can be confused with recrudescence of tuberculosis due to treatment failure and with drug hypersensitivity. Other infections common among immunocompromised patients should be excluded. The management of patients with IRIS is usually with high dose corticosteroids to control symptoms. Prednisone or methylprednisolone have been used at a dose of about 1 mg/kg and gradually reduced to a reducing regimen after 1 to 2 weeks. After 2 or more weeks of rifampicin has begun there is an inducing effect on the metabolism of corticosteroids such that the steroid is effectively reduced in efficacy by 33-50%. It is not unusual for patients to be on these for prolonged periods of time and the dose to be increased again when the IRIS relapses or recurs. Physicians should be aware of the metabolic side effects and potential to develop serious infections e.g. with CMV in patients on high doses of steroids.

Nonsteroidal anti-inflammatory agents tend not to be helpful. Temporary discontinuation of antiretroviral therapy has also been advocated but can cause precipitous falls in CD4 counts. Recurrent needle aspiration of nodes or abscesses especially if they become tense and/or inflamed
can prevent spontaneous rupture which if occurs can lead to long-term sinus formation and scarring.

15.0 Prevention and control transmission of HIV related tuberculosis

The guidelines for these are in the Interdepartmental Working Group on Tuberculosis published in 1998 by the Department of Health and is available on the Department of Health website [insert Link]. In summary, for good control of tuberculosis there should be:

1) a recognition that tuberculosis is a potential diagnosis
2) that the diagnosis should be confirmed as soon as possible
3) that drug resistance should be considered early in non-responding patients or when patients have a history compatible with drug resistant
4) there should be no delay in starting treatment
5) treatment should be started with appropriate drugs and
6) patients should have supervised therapy.

There should be appropriate accommodation for isolation of patients with potential tuberculosis and those with known tuberculosis. A risk assessment should always be made. There should be adequate isolation rooms and negative pressure facilities should be properly monitored. Aerosol generating procedures should not take place except in negative pressure rooms in patients with suspected or confirmed with tuberculosis. All patients with suspected or confirmed pulmonary tuberculosis should be considered potentially infectious until proven otherwise. There should be no intermingling of HIV infected or other immunosuppressed patients with patients who have potentially or infectious tuberculosis.

All hospitals should have a TB control plan based on risk assessment. There should be 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.

Concerns over deductive disclosure of HIV status if the HIV treating physician notifies a patient can be overcome as any physician involved in the patients care can notify the patient.

Contact tracing should follow the BTS guidelines but requires considerable sensitivity.
16.0 Tables

Table rating system for the strength of treatment recommendations based on quality of evidence*

in Table 1.

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 that either are not randomized or were conducted in other populations
III. Expert opinion


First line drugs
Isoniazid
Rifampicin*
Rifapentine
Pyrazinamide
Ethambutol
Streptomycin
Amikacin/kanamycin*
Capreomycin

Second line drugs
Cycloserine
Pro/Ethionamide
Levofloxacan*
Moxifloxacan*
Gatifloxacan*
pAminosalicylic acid

Streptomycin

*Rifabutin may be substituted for rifampicin in some situations eg drug/drug interactions
only experts skilled in the treatment of dealing with difficult TB should prescribe TB regimens.
Drug Interactions between Tables

Key for interaction tables.

| No Interaction – dose as normal | | |
| Potential Interaction – see advice | | |
| Definate interaction – do not combine | | |

Reverse Transcriptase Inhibitors (RTIs):

<table>
<thead>
<tr>
<th>Anti-retroviral</th>
<th>Rifampicin</th>
<th>Rifabutin</th>
<th>Isoniazid</th>
<th>Pyrazinamide</th>
<th>Streptomycin</th>
<th>Amikacin</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
<th>Ofloxacin</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI's</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>EC capsules</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>only (DDI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Stavudine (D4T)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine (DDC)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Non-Nucleoside Reverse Transcription Inhibitors (NNRTIs):

<table>
<thead>
<tr>
<th>NNRTI's</th>
<th>Rifampicin</th>
<th>Rifabutin</th>
<th>Isoniazid</th>
<th>Pyrazinamide</th>
<th>Strepto-myacin</th>
<th>Amikacin</th>
<th>Clarithromycin</th>
<th>Azithro-myacin</th>
<th>Ofloxacin</th>
<th>Cipro-floxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>96% □ in Delavirdine with Rifampicin no change in Rifampicin</td>
<td>80% □ in Delavirdine and highly significant change in Rifabutin levels</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>7</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>
Efavirenz

- Dose of Efavirenz should be increased to 800mg OD. No dose adjustment required for Rifampicin.
- In 1 small study Efavirenz reduced the AUC of Rifabutin by 38%. No effect on Efavirenz. May consider increasing the dose of Rifabutin by 50% (450mg).

Nevirapine

- 58% in Nevirapine AUC no change in Rifampicin.
- Dose both as normal.

Protease Inhibitors (PIs):

<table>
<thead>
<tr>
<th>PI's</th>
<th>Rifampicin</th>
<th>Rifabutin</th>
<th>Isoniazid</th>
<th>Pyrazinamide</th>
<th>Streptomycin</th>
<th>Amikacin</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
<th>Ofloxacain</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>82% in AUC for Amprenavir</td>
<td>Reduce dose of Rifabutin half (150mg od) monitor for signs of neutropenia.</td>
<td>3,4,11</td>
<td>4,11</td>
<td>4,11</td>
<td>4,11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Indinavir</td>
<td>89% in AUC for Indinavir</td>
<td>AUC 33% for Indinavir and ↑AUC 204% for rifabutin</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Kaletra</td>
<td>AUC for Kaletra</td>
<td>Reduce dose of Rifabutin to 150mg three times a week</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

In renal impairment ↓ Clarithromycin dose by 50% (clearance 30-60 mls/min), and by 75% (clearance <30 mls/minute).
<table>
<thead>
<tr>
<th>PI's</th>
<th>Rifampicin</th>
<th>Rifabutin</th>
<th>Isoniazid</th>
<th>Pyrazinamide</th>
<th>Streptomycin</th>
<th>Amikacin</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
<th>Ofloxacin</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nelfinavir</strong></td>
<td>82% ↓ AUC for Nelfinavir</td>
<td>3</td>
<td>Reduce dose by half (150mg) No dose adjustment needed for Nelfinavir</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>Ritonavir</strong></td>
<td>35% ↓ AUC for Ritonavir</td>
<td>10</td>
<td>7-fold ↑AUC for Rifabutin at 500mg bd</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><strong>Saquinavir</strong></td>
<td>70% ↓ AUC of Fortovase (SG) and a 80% ↓ AUC for Invirase (HG)</td>
<td>9</td>
<td>Co-administration results in significantly reduced plasma levels of Saquinavir</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Boosted Protease Inhibitors</strong></td>
<td>3</td>
<td>Very little information available. Consider using Rifabutin 150mg Three times a week as per Kaletra</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
GUIDELINES FOR THE REINTRODUCTION OF ANTI-TUBERCULOUS CHEMOTHERAPY FOLLOWING ELEVATION OF LIVER FUNCTION TESTS or cutaneous reaction grade 1-3 Day

Isoniazid Rifampicin Pyrazinamide

<table>
<thead>
<tr>
<th>Day</th>
<th>inh</th>
<th>rif</th>
<th>pza</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>150mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>300mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>300mg</td>
<td>75mg</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>300mg</td>
<td>150mg</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>300mg</td>
<td>300mg</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>300mg</td>
<td>450mg &gt; 50kg / 600mg &lt; 50kg</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>300mg</td>
<td>450mg/600mg</td>
<td>250mg</td>
</tr>
<tr>
<td>9</td>
<td>300mg</td>
<td>450mg/600mg</td>
<td>500mg</td>
</tr>
<tr>
<td>10</td>
<td>300mg</td>
<td>450mg/600mg</td>
<td>1g</td>
</tr>
<tr>
<td>11</td>
<td>300mg</td>
<td>450mg/600mg</td>
<td>1.5g &gt; 50kg / 2g &lt; 50kg</td>
</tr>
<tr>
<td>12</td>
<td>300mg</td>
<td>450mg/600mg</td>
<td>1.5g/2g</td>
</tr>
<tr>
<td>13</td>
<td>300mg</td>
<td>450mg/600mg</td>
<td>1.5g/2g</td>
</tr>
</tbody>
</table>

Add in Ethambutol once all other 3 drugs are at full dose.

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

Commonly used modifications include those with 3 days between each drug being restarted after the full introduction of the previous drug.

**Definition of IRIS**

- Apparent worsening/progression of the tuberculosis.
- This may occur at the original site of the disease or at a more remote site.
- Symptoms, signs, laboratory or radiological findings consistent with another diagnosis excludes IRIS.
- IRIS may occur at any time point after initiation of TB treatment.
- The occurrence of IRIS is associated with commencing or continuing HAART.
- There must be no evidence of TB bacteriological relapse or recurrence. A positive AAFB smear does not exclude a diagnosis of IRIS.
- The patient should have had appropriate other investigations to exclude concomitant disease due to other pathogens.
- Drug hypersensitivity is excluded.
- A-response to corticosteroid treatment does not confirm a diagnosis of IRIS.
17.0 References

NOTE: REFERENCES SECTION STILL TO BE COMPLETED AND EDITED