

**PROTOCOL**

**Intensified Treatment for Tuberculous Meningitis in Adult Patients  
with Enhanced Rifampicin and Levofloxacin.**

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# 1 Summary

## 1.1 Abstract

Fuelled in part by the human immunodeficiency virus (HIV) epidemic, tuberculosis (TB) remains a major global health problem (Thwaites, Nguyen et al. 2004). Of all the syndromes caused by *Mycobacterium tuberculosis* (Mtb), tuberculous meningitis (TBM) remains the most severe. Almost all patients with untreated TBM die. Since the introduction of antibiotic treatment for TB in the 1950's death rate has declined. However the morbidity and mortality overall are still high.

HIV infection is associated with a worse outcome in TBM, the death rate at 9 months being 67% compared with 25% in HIV negative patients.

The anti-tuberculous drugs have differing cerebrospinal fluid (CSF) penetration. In particular, penetration of rifampicin, a key drug, is poor. The overall high death rate in TBM patients may reflect both poor antibacterial activity of current treatment regimes and poor penetrance of those drugs into the central nervous system. Improving the antituberculous activity of current therapy may result in improved outcomes. We propose a study to assess the efficacy of an intensified anti-tubercular treatment regimen in TBM patients. This regimen will consist of standard doses of isoniazid, ethambutol/streptomycin and pyrazinamide in combination with high dose rifampicin and an added fifth drug, levofloxacin, a fluoroquinolone with excellent cerebrospinal fluid penetration and anti-tubercular activity. The study will be run on two sites in Ho Chi Minh City, Vietnam: the Hospital for Tropical Diseases (HTD) and Pham Ngoc Thach (PNT) Hospital for Tuberculosis and Lung Diseases.

*Title:* Intensified Treatment for Tuberculosis Meningitis in adult Patients with High Dose Rifampicin and Levofloxacin

*Scientific Title:* Randomized, Double Blind, Placebo-Controlled Phase III Trial of Intensified Treatment for Tuberculosis Meningitis in adult Patients with High Dose Rifampicin and Levofloxacin

*Aim:* Reduce mortality rate of tuberculous meningitis in adult patients

*Study design:* A randomized, double blind, placebo-controlled trial with 2 parallel arms.

*Sample size calculation:* 750 patients (375 per treatment group) including a minimum of 350 HIV-positive patients. The calculation assumes an overall mortality of 40% vs. 30% in the two arms, respectively (corresponding to a target hazard ratio of 0.7), a power of 80% and a two-sided significance level of 5%. Randomization ratio is 1:1.

*Inclusion criteria:* Age  $\geq$  18 years; clinical diagnosis of TBM.

*Exclusion criteria:* positive CSF Gram or India ink stain, known or suspected pregnancy; laboratory contraindications to antituberculous therapy; Multi-drug resistant TBM; lack of consent.

*Consent:* Written informed consent will be sought for all patients. Verbal consent of the patient in the presence of a signing witness will be considered acceptable when written consent is impossible. In unconscious patients, family members will be approached. If there are no relatives the consent of 2 independent physicians will be considered acceptable.

*Randomization and registration:* All patients will receive treatment with standard anti-tuberculous therapy for 9 months. Patients will be stratified according to hospital of presentation, HIV status and TBM disease severity at presentation (modified MRC grade I to III). Within each stratum, patients will be randomized to one of the two study arms: intensified treatment or identical placebos for 2 months (plus standard TB-treatment).

*Standard Anti-tuberculous Treatment:* This will be commenced according to PNT hospital and Vietnamese National TB Programme guidelines. Initial therapy will be with isoniazid 5mg/kg od po (max 300mg/day), rifampicin 10mg/kg od po, pyrazinamide 25mg/kg od po (max 2g/day) and ethambutol 20mg/kg od po (max 1.2g/day) or streptomycin 20mg/kg od im (max 1g/day) for 3 months. After 3 months, pyrazinamide



and ethambutol will be stopped and the patient will continue on rifampicin and isoniazid at the same doses for a further 6 months. (See Appendix 3.0)

*Intensified Treatment:* Intensified treatment will consist of a total dose of rifampicin of 15mg/kg/day and levofloxacin 20mg/kg/day. (See Appendix 5.0)

*Corticosteroid treatment:* A reducing dose of dexamethasone will be administered on study entry, according to the standard regimens. (See Appendix 4.0)

*Antiretroviral treatment for HIV positive patients:* Antiretroviral therapy will follow national guidelines. Antiretroviral therapy will be available through the US government's President's Emergency Plan for AIDS Relief (PEPFAR) programme. Treatment naïve HIV patients will start treatment with antiretroviral drugs after 8 weeks of TB therapy. If HIV positive patients already are on ARV treatment upon admission, ARV treatment will not be interrupted and adjusted according to individual requirements and national guidelines.

*Clinical monitoring:* Patients will be monitored closely for drug toxicity, neurological deterioration and other clinical parameters. For HIV positive patients, development of AIDS defining illnesses will be recorded. All patients will be reviewed daily as an inpatient until discharge at 2 months. Study staff will make a daily round of all inpatients to ensure uniformity of management and accurate recording of data. Once discharged, patients will be followed up as part of the Vietnamese National Tuberculosis Programme. Hospital outpatient review will occur monthly until 9 months.

*Laboratory monitoring:* Base line tests performed at admission. Routine laboratory tests will be monitored weekly as an inpatient and monthly as an outpatient. CSF samples will be taken at 0, 1, 2, 3 and 9 months. For HIV positive patients blood samples for CD4 T-lymphocyte count will be monitored at 0, 6 and 9 months.

*Radiology:* Patients will have a chest radiograph performed on admission. A CT or MRI brain scan may also be performed if clinically indicated. Further imaging will be performed in the event of a clinical deterioration.

*Data collection:* All information related to the study will be stored in individual patient case record forms. Data will be uploaded to the computerized database.

*Outcome measures:* The primary endpoint is overall survival, i.e. time to death during the study period of 9 months. Survivors will be censored at the date they were last known to be alive. The secondary endpoints are: Neurological disability at 9 months according to the "simple question" and the Rankin score (see appendix 1.3), time to new neurological event or death, time to new or recurrent AIDS defining illness or death and CD4 cell count at 9 months (in HIV positive patients only), grade 3&4 adverse events, and the rate of TB treatment interruption.

*Data analysis for the primary endpoint:* Analysis will be based on the intention to treat principle including all randomized patients. The comparison of the primary endpoint between the two treatment groups will be based on a log-rank test stratified by HIV status (positive/negative) and TBM disease severity at presentation (modified MRC grade I, II or III). The primary analysis will be supplemented by Kaplan-Meier estimates, Cox regression models, and subgroup analyses as described in the statistical section of the protocol.

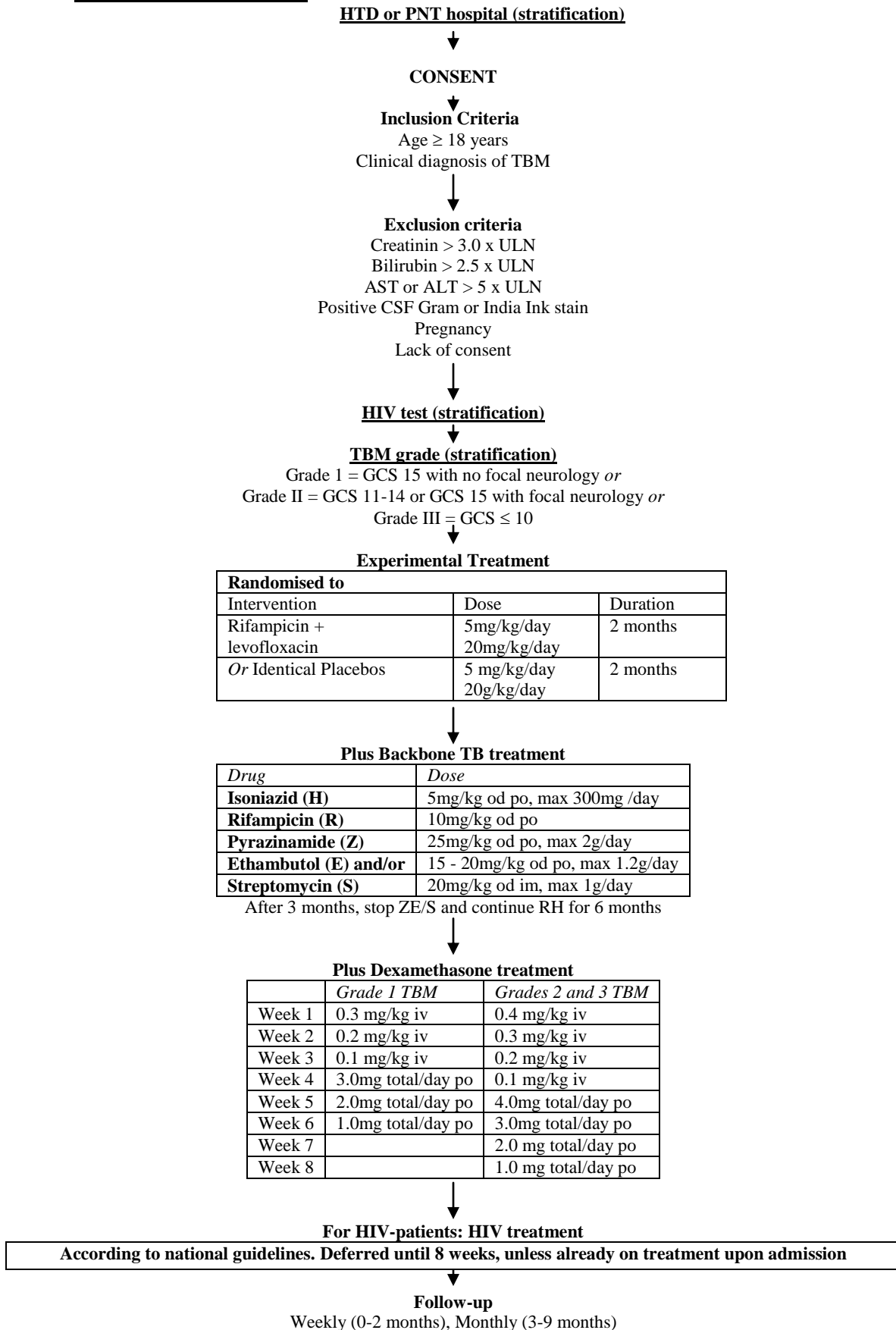
*Data safety and monitoring committee (DSMC):* An independent DSMC will oversee the safety of the trial. The DSMC will review mortality data as well as serious and grade 3&4 adverse events after 20 deaths have occurred and then after 6 and 12 months of recruitment and yearly thereafter until completion of the trial.

*Subsidiary studies.*

Pharmacokinetics

Blood and CSF dynamics of HIV/HBV/HCV viral loads

## 1.2 Trial flow diagram



### 1.3 Trial flow chart

	Base line	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC (Hb, WCC, plt)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bili, AST, ALT, Na, K, creat, glu	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Albumin/total protein	X				X				X							X
CD4 / CD8 count (HIV+)	2												2			2
HIV, HbsAg, HCV	2															
Blood cultures	3															
CSF Gram stain	X															
CSF India ink	X															
CSF cell count, protein glucose, (lactate)	10				10				10	10						10
CSF TB smear, culture, DST* and GeneXpert	X															
Sputum TB smear, culture and DST*	X															
Chest Xray ± CT brain	X															
ECG	X	X			X											
Storage EDTA	8				8				8	8			8			8
NAT2 genotype	X															
HBV/HIV/HCV viral load blood	X				X				X	X						X
HBV/HIV/HCV viral load CSF	X				X				X	X						X
Maximum blood volume	18	3	3	3	11	3	3	3	11	11	3	3	13	3	3	13
Maximum CSF volume	10				10				10	10						10

\*DST will be performed on culture positive samples for patients who have been enrolled in the study

## **2 Background and rationale**

### **2.1 Background**

Fuelled in part by the HIV epidemic, tuberculosis (TB) remains a major global health problem (Thwaites, Nguyen et al. 2004). Of all the syndromes caused by *Mycobacterium tuberculosis* (Mtb), tuberculous meningitis (TBM) remains the most severe. Almost all patients with untreated TBM die. Since the introduction of antibiotic treatment for TB in the 1950's death rate has declined. However the morbidity and mortality overall are still high.

In Vietnam with treatment the death rate in HIV negative patients is 25%, and a further 30% of patients suffer long term neurological sequelae (Thwaites, Nguyen et al. 2004). At least 50% of adult patients who are admitted with TB meningitis in Ho Chi Minh City are HIV positive. HIV significantly worsens outcome, with a mortality rate of 67% (Torok, Chau et al. 2008). In that study, 50% of the death occurred within the first 2 weeks of therapy, 75% within 1 month and all deaths occurred within 6 months (Torok, Chau et al. 2008).

### **2.2 Treatment of TBM**

Treatment schedules for TBM globally are not uniform and are mostly derived from those used for pulmonary TB. Few clinical trials have been conducted to tailor treatment for TBM patients.

Successful treatment of any form of TB requires combination therapy for several months (WHO 2003). The current treatment guidelines for TBM recommend treatment in the intensive phase with rifampicin, isoniazid, pyrazinamide and streptomycin for 3 months. This is followed by rifampicin and isoniazid for 6 months in the consolidation phase. In HIV positive patients, streptomycin is replaced with ethambutol.

The National TB-program (NTP) in Vietnam recently adjusted its guidelines and recommends to use 5 anti-tuberculous drugs in the initial month of the intensified phase for all patients presenting with TBM. This change is based on clinical experience rather than on clinical trials. For this study we have obtained approval from the NTP to use the regimen used at Pham Ngoc Thach hospital which uses 4 drugs in the intensified phase of treatment. This is in accordance with the standard regimens used in previous clinical trials on TBM-treatment and follows global guidelines. Global and hospital guidelines also recommend that all patients receive adjuvant treatment with dexamethasone, since the demonstration of their benefit in a large randomised controlled trial carried out by our group (Thwaites, Nguyen et al. 2004). Dexamethasone reduced the risk of death by 31%. While most patients in the trial were HIV-negative, a sub-analysis stratified by HIV status suggested that dexamethasone is safe and possibly beneficial in HIV positive patients. 61.4% of HIV-patients receiving dexamethasone died compared with 68.5% of patients

receiving placebo. This difference in death rates does not reach statistical significance ( $p = 0.08$ ), but importantly there was no evidence of harm. TB treatment is complicated by a significant risk of adverse drug reactions, in particular liver toxicity (Saukkonen, Cohn et al. 2006). In the dexamethason trial there was a significantly lower incidence of adverse events in patients receiving dexamethasone compared with placebo.

Another recent randomized controlled trial was conducted by our group to establish whether or not immediate antiretroviral therapy for HIV patients could be of benefit for this subgroup of TBM patients. However the timing of antiretroviral therapy in HIV patients with TBM had little effect on their mortality at nine months (Torok, unpublished work). The fact that the vast majority of deaths in HIV patients with TBM occurred during the first month of treatment suggests that tuberculosis most probably is the culprit rather than other opportunistic infections.

Sterilization of sputum in pulmonary TB can be a prolonged process. In TBM cerebrospinal fluid becomes culture negative relatively rapidly after introduction of therapy, but culture is known to have poor sensitivity and does not necessarily accurately describe sterilization within the brain parenchyma (Thwaites, Chau et al. 2004). The anti-tuberculous drugs are known to have differing CSF penetration. In particular, penetration of rifampicin, a key drug, is poor, as is that of ethambutol (Peloquin, Jaresko et al. 1997; Tappero, Bradford et al. 2005; Graham, Bell et al. 2006; McIlleron, Wash et al. 2006; Wilkins, Langdon et al. 2006). The death rate of TBM patients may reflect both poor antibacterial activity of current treatment regimes and poor penetrance of those drugs into the central nervous system. For HIV patients the excess death rate may be a reflection of even less efficient uptake of antimycobacterial drugs due to malabsorption, combined with a severely impaired immune system.

Improving the sterilising power of current therapy may result in improved outcomes of all TBM patients. We propose a randomised placebo controlled trial to test this hypothesis in patients with TB meningitis. The study will compare standard anti-tuberculous treatment with anti-tuberculous treatment intensified with high dose rifampicin and levofloxacin.

## **2.3 Rifampicin for TB meningitis**

### **2.3.1 Mechanism of action**

Rifampicin is a semisynthetic derivative of rifamycin and is a key drug in the treatment of all forms of TB, demonstrated by the fact that in tuberculous meningitis resistance to this drug is associated with high rates of relapse and death (Thwaites, Lan et al. 2005). The mechanism of action of rifampicin is the inhibition of bacterial DNA-dependant RNA polymerase. It has potent in vitro activity against Gram-

positive cocci including Staphylococcus and Streptococcus spp, Mycobacterium tuberculosis, and some Gram-negative organisms including Neisseria spp and Haemophilus influenzae. Minimum Inhibitory Concentrations (MIC) for M.tb are usually in the range of 0.1 – 1mg/L and in vitro activity is increased in the presence of streptomycin and isoniazid(Jayaram, Gaonkar et al. 2003).

### **2.3.2 Metabolism**

Rifampicin is metabolised to its desacetyl derivative via the cytochrome P450 hepatic microsomal enzymes. Desacetyl-rifampicin is also microbiologically active, although the relative activities of drug and metabolite vary from organism to organism. In general, the MIC of the metabolite is about half that of rifampicin. Metabolism is auto-induced, and thus the rate of hepatic clearance increases with time. However, final elimination is via the bile, and this step is rate limited. The elimination half –life after a 600mg dose rises to 2.5 to 3 hours, and may be as long as 5 hours with a 900mg dose. Elimination of desacetyl rifampicin is slower than that of rifampicin, and the ratio of metabolite to drug increases disproportionately as the rifampicin dose is increased(Strates 1981).

### **2.3.3 Pharmacokinetics**

Rifampicin has excellent oral bioavailability. It is lipid soluble, and this largely determines its distribution. 80 – 90% of drug is protein bound. It penetrates well into cells, and is active against intracellular bacteria, but CSF concentrations are reported to be low(Ostrow 1973; Strates 1981).

There are few data comparing Area Under the Curve (AUC) in the cerebrospinal fluid and plasma compartments, but the ratio is probably in the order of 10-20%. (Thwaites et al., unpublished data). Penetration probably is a reflection of the level of damage to the blood brain barrier and the serum protein binding of rifampicin which approaches 80% (Ostrow, 1973). The therapeutic range of Rifampicin lies between 8 – 24 ug/ml(Peloquin, Jaresko et al. 1997; McIlleron, Wash et al. 2006). HIV patients have been associated with lower plasma levels of Rifampicin (Sahai, Gallicano et al. 1997; Tappero, Bradford et al. 2005).

### **2.3.4 Higher dose Rifampicin**

Rifampicin is used throughout the whole of the 9 month treatment period in TBM. The recommended dose is 10mg/kg/day. Formulations of rifampicin usually contain a multiple of 150mg of rifampicin per tablet. Weight based dosing requires dividing tablets but in practice division of tablets is rare. In Vietnam, the NTP guidelines prescribe rifampicin dosage according to weight categories (see appendix 5.0). This

means that the median dose of rifampicin received by a patient according to weight category is 9.5mg/kg (range 7.7 to 11.3mg/kg, see appendix 5.0). Over 60% of weight categories actually receive less than the recommended 10mg/kg.

Recent data from Indonesia suggest that a dose increase from 10 to 13mg/kg/day is associated with a 65% increase in mean plasma AUC<sub>0-24h</sub> and 49% increase in plasma C<sub>max</sub> without a significant increase in the rate of adverse events (Ruslami, Nijland et al. 2006; Ruslami, Nijland et al. 2007). This is likely to be clinically important (particularly in TBM where the therapeutic index is even narrower due to poor drug penetration) because the anti-mycobacterial activity of rifampicin is exposure and concentration dependent (Gumbo, Louie et al. 2007). Of note, in the Indonesian study there was a higher rate of grade 1 or 2 transaminitis in the high dose arm, but no interruption of treatment was necessary and there was no greater risk of grade 3 or 4 transaminitis. This study was not powered to measure difference in disease outcome, but a study in pulmonary TB found a daily dosage of 1200mg of rifampicin for 3 months to result in significantly improved sputum sterilisation (Kreis, Pretet et al. 1976). A study comparing 750mg/day with 600mg/day in pulmonary TB found no difference in clinical outcome although both dosages were well-tolerated. However, the situation in pulmonary TB is not analogous to TBM, where the therapeutic index is narrower due to poor drug penetration into CSF.

Rifampicin is not only used to treat tuberculosis, but also in other chronic infections such as brucellosis and chronic staphylococcal disease. In particular in brucellosis the dosage of rifampicin is higher than that used in TB. The dose most usually trialled has been 15/mg/kg for 6 – 8 weeks, sometimes in combination with ofloxacin (Llorens-Terol and Busquets 1980; Agalar, Usubutun et al. 1999). Higher doses of rifampicin appear to be well tolerated in these patients with low rates of transaminitis and treatment interruption. Doses used in staphylococcal disease have been up to 15/mg/kg/day in adults, and 20mg/kg/day in children. Transaminitis and serious adverse events are rarely reported, consistent with the concept that hepatitis in patients on TB treatment is more likely due to isoniazid or pyrazinamide (Saukkonen, Cohn et al. 2006; Yew and Leung 2006).

### **2.3.5 Toxicities**

Rifampicin is relatively non-toxic. The most noticeable side effect is red staining of body secretions. Also known as the “red man syndrome” (Strates 1981). Other side effects include rash, flushing and gastrointestinal disturbances (usually mild). Drug-induced hepatitis (DIH) is a well recognised side-effect of TB treatment, with a frequency of between 5 and 33% (Saukkonen, Cohn et al. 2006). The drugs most usually implicated are isoniazid and pyrazinamide. However, transient elevation of transaminases (and less commonly bilirubin) is reported with rifampicin use. DIH usually responds well to treatment

interruption. A gradual sequential re-introduction of each drug is usually tolerated without recurrence of hepatitis(Saukkonen, Cohn et al. 2006). Interestingly, in the study of dexamethasone in TB meningitis by Thwaites et al. there was a marked difference in the incidence of DIH between the patients receiving dexamethasone and those receiving placebo – there were no cases of severe hepatitis in the steroid arm but 8 in the placebo arm, suggesting that the reduction in mortality in patients receiving steroids may in part be due to a hepato-protective effect of dexamethasone (Thwaites, Nguyen et al. 2004).

Based on the data presented in this section we propose an increased dose of rifampicin of 15mg/kg for patients with TB meningitis, to increase serum levels and possibly increase CSF levels of rifampicin. With this strategy we hope to improve sterilising power of the anti tubercular regimen in the brain.

## **2.4 Fluoroquinolones for TB**

Despite demonstration of *in vitro* activity of various drugs against M-tb, there has been little progress in drug development or assessment of alternative anti-mycobacterial treatment regimes in TB meningitis(Thwaites and Tran 2005). Trials in pulmonary TB have demonstrated the safety of prolonged treatment with fluoroquinolones(el-Sadr, Perlman et al. 1998; Moadebi, Harder et al. 2007). Initial results with the earlier agents (ciprofloxacin, ofloxacin), where the fluoroquinolone was substituted for one of the standard drugs, were disappointing, but the later generation drugs such as levofloxacin, moxifloxacin and gatifloxacin have improved *in vitro* activity, and there is evidence of good sterilising activity in sputum in pulmonary TB(Johnson, Hadad et al. 2006; Rustomjee, Lienhardt et al. 2008). Generally, trials of fluoroquinolones in pulmonary TB have been designed to examine the feasibility of substituting other TB drugs with a fluoroquinolone, rather than addition of a new drug to the standard regime(Moadebi, Harder et al. 2007). Improved tolerability of the treatment regime has been as much a consideration as improved efficacy. Another approach has been to try to design regimens that enable shortening of the treatment duration. Large randomised controlled trials are currently underway in Africa investigating whether short course treatment (4 months) using gatifloxacin or moxifloxacin is as efficacious as standard duration (6 months) pulmonary TB treatment.

Since the mortality rate in pulmonary TB is significantly lower than in TB meningitis, the issues facing clinicians are different(Thwaites, Duc Bang et al. 2005; Torok, Chau et al. 2008). In TB meningitis, where the mortality is high, the aim must be to reduce mortality by developing more potent anti-mycobacterial treatment combinations. Fluoroquinolones are an attractive option for the treatment of TB meningitis because of their demonstrable *in vitro* activity, tolerability, good bioavailability and ease of administration(Kennedy, Fox et al. 1993; Sirgel, Botha et al. 1997; Alvarez-Freites, Carter et al. 2002; Rodriguez, Ruiz et al. 2002; Cynamon and Sklaney 2003; Fattorini, Tan et al. 2003; Sato, Tomioka et al.



2003; Yew, Chan et al. 2003; Gosling and Gillespie 2004; Nuermberger, Yoshimatsu et al. 2004; Tortoli, Dionisio et al. 2004; Akcali, Surucuoglu et al. 2005; Paramasivan, Sulochana et al. 2005). Our centre recently completed a pharmacokinetic study comparing ciprofloxacin, levofloxacin and gatifloxacin in patients with TBM, and examining their pharmacokinetic interaction with rifampicin (Thwaites, unpublished data). We found levofloxacin to have excellent CSF penetration, with a ratio of Area Under the Curve (AUC) in CSF to AUC in plasma of 75%. This compared favourably with gatifloxacin (35%) and ciprofloxacin (14%). Levofloxacin has the additional advantages of a favourable toxicity profile, affordable cost and available safety data from clinical trials examining its prolonged use in pulmonary TB. We propose to add levofloxacin as a fifth drug in the highly active treatment arm combined with a high dose of rifampicin in this randomised placebo controlled trial.

## **2.5 Levofloxacin for TB-meningitis**

### **2.5.1 Mechanism of action**

Levofloxacin is a second generation fluoroquinolone which received approval for marketing in 1993 in Japan and 1997 in the US. It is the L-isomer of ofloxacin, the D-isomer being inactive; meaning that weight for weight it has twice the potency of ofloxacin. All fluoroquinolones inhibit replication and transcription of bacterial DNA by binding to the A-subunit of DNA gyrase, thus interfering with the resealing of broken DNA strands, frustrating bacterial protein production. This leads to rapid cell death (Lewin et al., 1991, Drlica 1999).

### **2.5.2 Microbiological activity**

The development of the fluoroquinolones has seen the extension of the spectrum of activity to cover Gram positive as well as Gram negative bacteria. Levofloxacin has moderate activity against Streptococcus and Staphylococcus species, good activity against the aetiological agents of atypical pneumonia (*L. pneumophila*, mycoplasmas) and enterobacteria, and moderate activity against mycobacterial species in vitro (Wimer, Schoonover et al. 1998). It is commonly used to treat community acquired pneumonias, sinusitis and enteric fever.

Of the 2<sup>nd</sup> generation fluoroquinolones, levofloxacin has the greatest anti-tuberculous activity. MICs for most sensitive isolates are in the order of 0.25 - 1mcg/ml (Rodriguez, Ruiz et al. 2001; Rodriguez, Ruiz et al. 2002). Plasma levels of levofloxacin in Vietnamese patients are comfortably in excess of this, with AUC<sub>0-12</sub> of 80mg/hr/L (Thwaites, unpublished data). Fluoroquinolone resistance has been identified in strains from Vietnam, but currently is rare and less frequent than rifampicin resistance (unpublished data,

M Caws). In vitro assays do not seem to clearly predict in vivo response to experimental infection and treatment(Shandil, Jayaram et al. 2007).

However, levofloxacin has performed well in human studies using surrogate markers of efficacy such as early bactericidal activity (rate of fall of colony forming units in sputum)(Johnson, Hadad et al. 2006). This is probably a reflection of its favourable pharmacokinetic profile resulting in high plasma and intracellular concentrations.

### **2.5.3 Pharmacokinetics**

Effective killing of *Mycobacterium tuberculosis* is concentration dependent. A recent study comparing the pharmacokinetics of levofloxacin (1g/day) with gatifloxacin (400mg/day) and moxifloxacin (400mg/day) in pulmonary TB patients found levofloxacin to have the most favourable indices, with ratios of free AUC:MIC 1.5 times greater than for gatifloxacin and moxifloxacin(Peloquin, Hadad et al. 2008). The ratio for levofloxacin was 180 using the MICs needed for the actual study isolates, and 93 using published MIC data. This compares with an established target ratio for AUC:MIC for fluoroquinolones of 40.

### **2.5.4 Metabolism**

Levofloxacin has excellent bioavailability with 99% absorption following oral administration, is only 25% protein-bound, and has excellent CSF penetration, with a ratio of  $AUC_{csf}/AUC_{blood}$  of 0.75, which compares favourably with other fluoroquinolones, particularly gatifloxacin (Thwaites, unpublished data). Levofloxacin is predominantly excreted via the renal route with up to 90% of a dose appearing in urine after 48 hours. The plasma half-life is 5 – 7 hours. There is minimal effect on Cytochrome p450 enzymes(Lode 2001).

### **2.5.5 Levofloxacin in tuberculosis**

Recently a review on the clinical use of fluoroquinolones for TB was published. It included all relevant clinical trials on efficacy and safety of fluoroquinolones in different TB treatment schedules. Overall conclusions were that the use of any of the fluoroquinolones for drug sensitive pulmonary TB was of no benefit to outcome, but the newer fluoroquinolones would be a reasonable option for the treatment of drug resistant TB or for patients who are intolerant to any of the first line TB drugs. An important finding was that the newer fluoroquinolones were well tolerated in all trials (Moadebi et al., 2007). Only one trial in this review used a regimen that added Levofloxacin to a highly active intermittent first-line treatment schedule;

El-Sadr and colleagues investigated in 1998 the effect of adding levofloxacin 500mg daily to the initial phase (first 2 months) of standard anti-tuberculous quadruple therapy in HIV patients with pulmonary TB.

The primary endpoint was sputum culture conversion at 2 months. The investigators found no difference in outcome between treatment arms, but then the overall success rate was high. Sputum clearance rates were 97.3% vs 95.8% (el-Sadr, Perlman et al. 1998). Importantly, there was no difference in the rate of transaminitis or other adverse events between the 2 groups.

Overall the benefit of fluoroquinolones in drug sensitive pulmonary TB may be disappointing, but no clinical trials on the use of fluoroquinolones for TBM have been published yet. Considering the variable penetration in CSF of the first-line anti-tuberculous drugs and the favourable PK data and optimal CSF penetration of levofloxacin, adding this drug to the regimen might prove of benefit to TBM patients.

### **2.5.6 Toxicity**

By 2001, there had been over 130 million prescriptions of levofloxacin worldwide (Yagawa 2001). Levofloxacin is well tolerated, the commonest side effects being mild gastrointestinal side effects including nausea, vomiting and diarrhoea. Clinical trials also reported a relatively low frequency of central nervous system (CNS) reactions such as dizziness, headache, and insomnia. There does not appear to be an increased risk of adverse events as dosage increases (Khashab, Xiang et al. 2006)

The overall adverse drug event rate is in the order of 2%, which compares well with other fluoroquinolones (Carbon 2001; Kahn 2001; Yagawa 2001). In particular, drug-induced hepatitis, cardiotoxicity and neurotoxicity seem to be less frequent than for the other fluoroquinolones. The incidence of drug-induced hepatitis is approximately 1 per 650 000 prescriptions, and levofloxacin has been used to construct relatively 'hepato-friendly' antituberculous treatment regimes in patients who have had this treatment complication (Yew and Leung 2006). The most notorious of side-effects of the fluoroquinolones in general will be described below.

The risk of toxicities must be considered in the context of the 67% death rate in HIV associated TB meningitis.

#### *2.5.6.1 Prolongation of the QTc interval and heart arrhythmias*

Prolongation of the QT interval with possible risk of cardiac arrhythmias has been a recognised side effect of fluoroquinolones for some years. Grepafloxacin was withdrawn from the market place because of prolongation of the QTc interval resulting arrhythmias and death. Levofloxacin is not generally associated with prolongation of the QT interval (Morganroth, Dimarco et al. 2005). Overall the rate of QT prolongation is estimated at less than 1 per million prescriptions.

#### *2.5.6.2 Tendonitis*

Tendonitis has been reported following fluoroquinolone therapy, including levofloxacin. However, the overall risk of this is low, estimated at 4 cases per million prescriptions (Kahn 2001). The risk of

tendonitis appears to increase with age (van der Linden, Nab et al. 2001; van der Linden, van Puijenbroek et al. 2001).

#### **2.5.6.3 Fits**

Generalised convulsions have been described with fluoroquinolone antibiotics. Interestingly, the risk of fits in mice appears to be attenuated with levofloxacin in comparison with ofloxacin (Akahane, Tsutomi et al. 1994). The overall rate of seizures from postmarketing surveillance is estimated at 2 per million prescriptions. In general, convulsions are uncommon in patients with TBM. In the event of prolonged or repeated seizures and the absence of identification of another cause levofloxacin will be with-held from the patient.

#### **2.5.6.4 Hepatotoxicity**

Life threatening hepatotoxicity has been described with some fluoroquinolones (in particular moxifloxacin) but in general is a rare side-effect of their use. There were no episodes of serious hepatic dysfunction noted in cohorts of total 36 000 patients treated with ciprofloxacin, ofloxacin, norfloxacin and enofloxacin (Clark, Layton et al. 2001). An Italian study of tolerability of levofloxacin in 40 patients with chronic liver disease did not find any episodes of decompensation with a dose of 500mg twice daily (Esposito, Noviello et al. 2006). A recently published cohort study showed that both levofloxacin and moxifloxacin caused no additional hepatotoxicity when they were used by patients with hepatitis induced by other first-line TB drugs (Ho, Chen et al. 2009). Hepatotoxicity is common in TB due to the other drugs used. The drugs most commonly implicated are isoniazid and pyrazinamide. In the event of hepatitis patients will be managed according to standard methods with withdrawal of drugs and gradual reintroduction once liver enzymes have returned to normal, according to British Thoracic Society guidelines.

### **2.5.7 Dosage**

In severe infections levofloxacin is prescribed at a dose of 20mg/kg/day. There is extensive experience with its use in this dosage in enteric fever, when it is prescribed for 1 week, and also in pulmonary TB, when it has been prescribed for 2 months (el-Sadr, Perlman et al. 1998).

Based on the presented data in this section we propose the use of levofloxacin 20mg/kg as an added fifth drug to the treatment regimen of TB meningitis. Levofloxacin is relatively safe and may be beneficial for these patients, as it has excellent CSF penetration and proven activity against *Mycobacterium Tuberculosis*.

### **3 Proposed Intensive Therapy**

We propose enhancing the antimycobacterial efficacy of current treatment for TB meningitis in Vietnam by adding levofloxacin 20 mg/kg/day to the intensive phase of treatment and increasing the dose of rifampicin to at least 15 mg/kg/day during the intensive phase of treatment for the duration of 2 months.

## **4 Study Aims**

### **4.1 Primary aim**

- To test the study hypothesis that intensifying the induction phase of treatment of TB meningitis will result in reduced mortality.

### **4.2 Secondary aims**

- To assess the effect on morbidity and disability of intensifying standard treatment.
- To assess the safety and tolerability of the intensified treatment.
- To determine the prevalence of TB drug resistance in TBM patients.
- To determine the relationship between host and pathogen genotype investigating the host-pathogen interaction in TB.
- To describe pharmacokinetics of levofloxacin, high-dose rifampicin, other antituberculous and antiretroviral drugs in plasma and cerebrospinal fluid.

## **5 Endpoints**

### **5.1 Primary endpoint**

The primary endpoint will be overall survival during a follow-up period of 9 months. For dead patients, their time to death will be analyzed. Survivors will be censored at the date they were last known to be alive (i.e. date of last follow-up visit, or loss to follow-up date, or withdrawal date).

### **5.2 Secondary endpoints**

The secondary endpoints are:

- Neurological disability at 9 months. This will be assessed using the “simple questions” and Rankin score.
- Time to new neurological event. Neurological events are defined as:
  - a. Any of the following adverse events: cerebellar symptoms, coma, hemiplegia, neurological deterioration, paraplegia, seizures, cerebral herniation or cranial nerve palsy
  - b. A fall in Glasgow coma score by  $\geq 2$  points for  $\geq 2$  days from highest previously recorded Glasgow coma score (including baseline)

- Any grade 3 or 4 adverse event (defined in Appendix 7.0)
- Rate of TB treatment interruption
- The rates of asymptomatic transaminitis and symptomatic hepatitis.
- Time to new or recurrent AIDS defining illness or death (in HIV positive patients only)
- CD4 count at 9 months (in HIV positive patients only)

## **6 Design**

### **6.1 Study design**

A randomized, double-blind, placebo-controlled trial with 2 parallel arms: intensified treatment versus placebo during the initial induction phase of treatment.

### **6.2 Randomization procedure**

Randomization will be 1:1 and stratified

according to hospital (HTD and PNT),

according to HIV status and

according to TBM disease severity at presentation (modified MRC grade I to III):

- Grade I = Glasgow coma score (GCS) 15 with no focal neurology
- Grade II = GCS 11-14 or GCS 15 with focal neurology
- Grade III = GCS  $\leq$  10

Within strata, we will use block randomization with variable block size. Stratified randomization will ensure that almost equal numbers of patients with equivalent prognosis are included in the two treatment arms.

## **7 Target Population**

All adult patients with a clinical diagnosis of TBM presenting to the Hospital for Tropical Diseases, HCMC, or Pham Ngoc Thach Hospital, HCMC, will be eligible to enter the study.

Trial Location

Pham Ngoc Thach Hospital, Ho Chi Minh City; All adult in-patient wards (A2, E1, E2, B2, B3) and OPD

The Hospital for Tropical Diseases, Ho Chi Minh City; Adult CNS ward ('malaria ward') and OPD

### **7.1 Inclusion criteria**

- Age  $\geq$  18 years

- Clinical diagnosis of TBM (Appendix 1.0)

## **7.2 Exclusion criteria**

- Positive CSF Gram or India Ink stain
- Known or suspected pregnancy
- Known hypersensitivity/intolerance to fluoroquinolones or rifampicin
- Diagnosis of Multi Drug-Resistant TBM
- Creatinine > 3 x ULN
- Laboratory contraindications to antituberculous therapy
  - a) bilirubin > 2.5 x ULN
  - b) AST or ALT > 5 x ULN
- Lack of consent

## **8 Patient management**

### **8.1 Consent**

A patient cannot enter the trial without informed consent.

Written informed consent will be sought for all patients entering the trial. When written consent is not possible verbal consent will be considered acceptable in the presence of a witness who can attest to the accurate reading of the informed consent form and the agreement of the patient. The doctor entering the patient into the trial is responsible for obtaining the patient's informed consent. In unconscious patients the consent of the relatives or family members is acceptable. If there are no relatives, the consent of two independent physicians will be considered acceptable. In this case a patient's consent will be sought as soon as the patient regains the ability to give or refuse consent.

### **8.2 Initial evaluation**

On admission all patients will have a full clinical assessment and examination to determine TBM MRC grade (see appendix 1.2), elicit any neurological symptoms and signs and to determine HIV infection stage (see appendix 2.0)

Study entry laboratory tests will be performed as per the study schedule in section 1.3.

A baseline chest radiograph will be performed. A CT or MRI brain scan will be performed if there is evidence of raised intracranial pressure or focal neurological abnormalities.

### **8.3 Enrolment, randomization and blinding**

The admitting physician will be responsible for ensuring the patient satisfies the entry criteria, obtains informed consent and starts a study drug treatment package.

Clinical details will be recorded in individual patient case record form.

Randomization will be 1:1 to the treatment arms described in section 6.2. Patients will be stratified according to hospital site (HTD and PNT), HIV status and TBM disease severity at presentation (TBM severity will be graded according to the modified MRC system, appendix 1.2). Enrolment logs specific to site, HIV positivity and severity of TBM will be used to assign patients to the next available sequential number within the appropriate stratification group. The assigned number will correspond to two coded, sealed, pre-packaged bottles which contain a 2 month supply of additional doses of rifampicin and levofloxacin or visually matched placebos of each. Bottles will be prepared centrally by an unblinded study pharmacist and distributed to the sites in batches as required. Only two central study pharmacists who will hold the master randomization list will know the contents of each bottle. This list will be accessed only in the case of emergency unblinding authorized by an investigator as per standard operating procedures. Within strata, we will use block randomization with variable block size. Stratified randomization will ensure that almost equal numbers of patients with equivalent prognosis are included in the two treatment arms. Drug appearance and administration schedules will be identical to maintain blinding amongst the attending physicians and nurses.

### **8.4 Treatments**

#### **8.4.1 TB-treatment**

All patients will receive backbone treatment with standard antituberculous therapy (section 8.1, Appendix 3.0) and adjunctive dexamethasone (section 8.2, Appendix 4.0) on study entry, according to global guidelines and approved by Pham Ngoc Thach Hospital and Vietnamese National TB Programme. (see section 2.2). All patients receiving isoniazid will also receive pyridoxine (vitamin B6).

Patients who develop TBM while on TB treatment, for example for pulmonary TB, are also eligible to enter the study. According to Vietnamese hospital guidelines, these patients will receive TBM-treatment with 5 first line TB-drugs (SRHZE) (see Appendix 3.1). For these patients this will be the “backbone” or standard TB treatment. If they consent to take part in the trial, they will be randomized to intensified TB treatment or placebo as described below.

All patients will be stratified according to hospital, modified MRC grade (Appendix 1.0) and HIV status and subsequently randomized to receive either intensified therapy with levofloxacin and additional rifampicin or identical placebos for the first 2 months of treatment.



Standard TB-treatment drugs will be provided by the National TB Programme, Vietnam. Additional Rifampicin capsules and corresponding placebos for the intensified treatment will be provided by Mekophar, Vietnam. Levofloxacin (Tavanic®) and corresponding placebos will be provided by Sanofi-Aventis, Vietnam.

#### **8.4.2 HIV treatment (for HIVpositive patients only)**

Antiretroviral therapy will be provided for patients within the current Vietnamese guidelines. Antiretroviral therapy is available for free through the US Government PEPFAR programme for in-patients with life-threatening opportunistic infections from 2 weeks after admission. HIV positive patients will be referred to the Outpatient Clinic (OPC) for HIV patients for ARV-treatment. To ensure HIV-positive patients who are treatment-naïve upon inclusion in the study will receive ARV treatment at 8 weeks and continue their treatment, they will be enrolled either at the hospital OPC or through local specialized OPC services, following local common practice and convenience for the patient.

Timing of initiation of antiretroviral therapy will be deferred to 8 weeks into TB treatment for ARV-treatment naïve patients. This is consistent with the results of the recent trial of immediate or deferred antiretroviral therapy in TB meningitis, carried out by our group and consistent with local practice guidelines.

There are currently 4 different treatment schedules for first line ARV treatment in Vietnam, all containing 2 NRTI's and 1 NNRTI. The majority of patients on ARV treatment will be on schedules containing nevirapine (NVP). According to Vietnamese guidelines nevirapine will be changed to efavirenz for HIV positive patients that require a TB-regimen containing rifampicin.

Reports show good clinical outcome for patients on a 600mg dose of efavirenz who are on TB-regimens containing rifampicin (Friedland, Khoo et al. 2006). Accordingly and following National treatment guidelines, the dose of efavirenz will not be increased for patients on TB-regimens containing rifampicin. Second line ARV treatment is rarely prescribed in Vietnam. Very few patients will have a PI in their treatment schedule. We will have to make decisions on dose or schedule adjustments for these patients on an individual basis, following the National guidelines (See appendix 6.1). A substudy will be conducted on the pharmacokinetic effects on the anti-retroviral drugs of the change in antibiotic and change in the dose of the rifampicin (see page 35-39). We will monitor liver function tests closely in all patients.

### **8.5 Clinical monitoring**

Patients will have daily review until discharge from hospital at 2 months. Patients will be monitored closely for

- Death (days from randomization to death)

- Neurological deterioration (onset of new focal neurological signs or fall in Glasgow coma score of  $\geq 2$  points for  $\geq 2$  days, following  $> 7$  days clinical stability or improvement after randomization)
- Drug-related adverse events (Appendix 7.0)
- New or recurrent AIDS defining illnesses (Appendix 6.2)

Uniform management of patients and recording of data will be ensured by the principal investigator who will make a daily round of all study participants. Following discharge, patients will be followed up as part of the National Tuberculosis Programme. Formal outpatient review will occur monthly until the end of treatment (9 months). Outpatient visits may occur in the patient's home when the patient can not come to the hospital.

Visits timed weekly should correspond to day 7 (+/-5), 14 (+/-5), 21 (+/-5), etc of the study beginning with enrolment day 0. Monthly visits should be timed to correspond to day 30 (+/-7), 60 (+/-7), etc.

## **8.6 Laboratory monitoring**

Inpatient laboratory monitoring (0-2 months) will be as shown in the study schedule (section 1.3).

A subgroup of patients recruited to the pharmacokinetics study will have additional blood and CSF samples taken (see section 16.1).

GeneXpert testing on CSF will be performed upon screening. The test has been approved by the WHO since 2011 for sputum specimens, but data on CSF are very limited. The aim of performing the test for research purposes on CSF, is to provide evidence that may lead to validation of this test for TBM diagnosis, which would be an important development in diagnostics for extra-pulmonary TB and CNS infections. GeneXpert MTB/RIF assay results for all patients enrolled in the study from April 2011 will be compared with conventional smear and rapid liquid culture (Bactec MGIT, Becton Dickinson, USA) using a validated clinical diagnostic algorithm as the gold standard.

Other investigations may be performed as clinically indicated. Data for the following will be recorded when analyzed for clinical care:

- CSF, if neurological deterioration (Gram stain and routine culture, ZN stain and mycobacterial culture, India ink stain and fungal culture, PCR for HSV, VZV and CMV)
- Sputum, if symptomatic (routine culture, ZN stain, PCP immunofluorescence test)
- Urine culture, if urinary symptoms (urine culture)
- Stool culture, if prolonged diarrhoea (microscopy, culture and parasites)
- Blood cultures, if persistent fever (routine and mycobacterial cultures)
- Lymph node aspiration (routine and mycobacterial cultures)

Outpatient laboratory monitoring (3-9 months) will be as shown in the study schedule (section 1.3).

### **8.7 Imaging**

Chest and brain imaging will be performed as per the study schedule and as clinically indicated – i.e. in the event of pulmonary or neurological deterioration.

### **8.8 Withdrawal from the trial**

Patients may voluntarily withdraw from the trial for any reason. If this occurs, the trial researchers are under no obligation to provide treatment. The patient's withdrawal from the trial will not affect their access to the best standard of care within the national health system. Clinical and laboratory assessment should be performed and recorded at the time of withdrawal.

If the patient has an unscheduled period off treatment or not in follow-up this should be recorded in the case report forms.

### **8.9 Recording and reporting of death, adverse events or protocol violations**

#### **8.9.1 Death**

If the patient dies, the investigator should inform the principal investigator as soon as possible and complete the specific case report form.

#### **8.9.2 Adverse events**

If the patient dies or experiences an adverse event (serious, grade 3 or 4, or one leading to modification of treatment, see Appendix 7.0 Common Toxicity Criteria) the investigator should inform the principal investigator as soon as possible and complete the specific case report form. When applicable, adverse events will be treated as per the management guidelines in Appendix 7.0.

According to the ICH Guidelines for Clinical Safety Data Management: definitions and Standards for Expedited Reporting (1994), a serious adverse event (SAE) is defined as “any untoward medical occurrence that:

- results in death
- is life threatening
- requires unplanned inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity or is a congenital anomaly/ birth defect

- any other important medical condition, which, although not included in the above, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed.”

All SAEs will be recorded on the patient CRF.

Unexpected SAEs (USAEs) and events which become of concern to study investigators during the course of the trial will be reported to the Sponsor and the responsible Hospital Ethics Committee within 24 hours of occurrence. Depending on the severity of USAEs the Ministry of Health Ethical Committee (MoH EC) will be informed as follows:

- a) *USAEs that resulting in death or are life threatening:* **Initial written report** should be sent as soon as possible and within 7 days of occurrence. The format and content of the initial report should follow the MOH report template and include all information available at the time of reporting. A **follow up report** with complete details must be sent within 15 days of the initial report.
- b) *For USAEs that do not result in death or **not** life threatening:* USAE must be reported to MoH’s EC as soon as possible and within 15 days of occurrence

All USAEs will also be reported to the Data Safety Monitoring Board and the Oxford Tropical Research Ethics Committee within 10 days of occurrence.

Unblinded summary tables of all SAEs and all grade 3 or grade 4 AEs will be reviewed by the trial’s independent Data and Safety Monitoring Committee at regular time points (see section 11).

### **8.9.3 Protocol violation**

If there is a protocol violation for any reason this will be fully recorded and reported to the principal investigator. Protocol violations which affect patient safety will be reported to the Oxford Tropical Research Ethics Board and the Ethical Committee of the Ministry of Health Vietnam.

## **9 Drug regimens**

Patients will be treated with anti-tuberculous therapy and adjunctive dexamethasone on study entry. In addition patients will be randomized to receive intensified therapy or placebo for the first 2 months. Antiretroviral therapy will be provided via referral to the Outpatient Clinic for HIV patients, sponsored by PEPFAR.

### 9.1.1 Levofloxacin/Placebo

The dose of levofloxacin will be 20 mg/kg for the first 2 months (60 days) of treatment.

### 9.2 Intensified Rifampicin/Placebo

Additional rifampicin will be prescribed to increase the dose to 15mg/kg/day for the first two months (see appendix 5.0).

### 9.3 Backbone Antituberculous therapy

This will be commenced according to Pham Ngoc Thach Hospital and Vietnamese National TB Programme guidelines and will be given for the full 9 months.

#### 9.3.1 First-line antituberculous therapy

Drug	Dose
Isoniazid (H)	5mg/kg od po, max 300mg/day
Rifampicin (R)	10mg/kg od po max dose 750mg/day
Pyrazinamide (Z)	25mg/kg od po, max 2g/day
Ethambutol (E) and/or	20mg/kg od po, max 1.2g/day
Streptomycin (S)	20mg/kg od im, max 1g/day

If the patient is comatose, the drugs can be given by nasogastric tube.

After 3 months, pyrazinamide and ethambutol/streptomycin will be stopped and the patient will continue on rifampicin and isoniazid at the same doses for a further six months.

Drugs will be administered orally or via nasogastric tube in unconscious patients.

#### 9.3.2 Second-line antituberculous therapy

Patients with a 1. definite or 2. clinical diagnosis of Multi Drug-Resistant (MDR) TBM will be excluded from the trial and referred to the MDR-TB department for second-line antituberculous treatment.

1. A definite diagnosis of MDR-TBM is the presence of MDR mycobacteria in the CSF, either detected by routine culture, MODS or Hain-test.
2. A clinical diagnosis of MDR-TBM may be suspected when the patient has recently been treated, or is still under treatment for pulmonary TB or extra-pulmonary TB (not TBM) and has been found to have MDR-TB by culture, MODS or Hain-test.

If a patient has a GeneXpert result positive for rifampicin resistance upon screening he will not be entered in the trial.

3. If a patient clinically is suspected of MDR-TBM, the caring clinician will consult the Principal Investigator.

Referral to the MDR-TB department will be done by the PI who will consult the head of the MDR-department.

If patients are not eligible for treatment at the MDR-TB department of PNT hospital, appropriate treatment will be sought where possible.

### 9.3.3 Management of antituberculous toxicity

A symptom checklist will be used to determine clinical toxicity. Routine laboratory tests will be performed weekly as an inpatient and monthly as an outpatient. Clinicians may also request additional tests if clinically indicated. (For common side effects of first-line TB-drugs; see appendix 3.0)

Therapy may need to be interrupted for severe (grade 3 or 4) adverse events. Once clinical and laboratory features resolve, drugs may be reintroduced sequentially. For detailed management (see Appendix 7.4 and 7.5)

## 9.4 Corticosteroid therapy

### 9.4.1 Dexamethasone

A reducing dose of dexamethasone will be administered on study entry, according the following regimens:

	<b>Grade I TBM</b>	<b>Grades II and III TBM</b>
Week 1	0.3 mg/kg iv	0.4 mg/kg iv
Week 2	0.2 mg/kg iv	0.3 mg/kg iv
Week 3	0.1 mg/kg iv	0.2 mg/kg iv
Week 4	3.0mg total/day po	0.1 mg/kg iv
Week 5	2.0mg total/day po	4.0mg total/day po
Week 6	1.0mg total/day po	3.0mg total/day po
Week 7		2.0 mg total/day po
Week 8		1.0 mg total/day po

### 9.4.2 Management of adverse events

For common side effects of corticosteroid therapy see Appendix 4.0

It is unlikely that dexamethasone will need to be stopped unless the patient develops severe (grade 3 or 4) adverse effects e.g. hyperglycaemia, hypertension, gastrointestinal haemorrhage,

### **9.5 Prophylaxis for opportunistic infections (for HIV positive patients)**

Patients will receive prophylaxis for opportunistic infections according to Vietnamese national guidelines. If the CD4 count is less than 200 cells/uL, then they will receive prophylaxis against *Pneumocystis jirovecii* pneumonia and cerebral toxoplasmosis with daily cotrimoxazole 960 mg/day.

### **9.6 Data on concomitant medications**

At each visit, information on other medications, including start dates and reason for taking them, will be documented in the case record forms.

## **10 Statistics**

### **10.1 Sample size and power considerations**

The trial is powered for the primary endpoint, i.e. overall survival during the 9 month follow-up period. Based on previous publications from our research group, the 9-month mortality in the control arm is expected to be around 65% in HIV-positive and 25% in HIV-negative TBM patients (Thwaites, Nguyen et al. 2004)(Torok, unpublished data). As approximately 50% of TBM patients in the participating hospitals are HIV-positive, we expect an overall 9-month mortality rate of 40% in the control arm of our trial. An absolute risk reduction of 10% in 9-month mortality from 40% to 30% due to intensified treatment was judged as both realistic and clinically relevant.

Assuming proportional hazards, these mortality estimates translate into a hazard ratio of 0.7 [ $=\log(1-0.3)/\log(1-0.4)$ ], i.e. a 30% risk reduction due to intensified treatment on the hazard ratio scale. Based on Schoenfeld's formula, a total of 247 deaths are required to detect a hazard ratio of 0.7 based on a two-sided test at the 5% significance level with 80% power; assuming an overall mortality rate of 35% in the trial, this translates into 706 required patients. In order to account for potential deviations from our assumptions and losses to follow-up, a safety margin of 6% was added to this number leading to a total sample size of **750** patients (375 per treatment group).

HIV-positive TBM patients with a very high mortality are a particularly important subgroup of our study population and we aimed to have sufficient power to also detect a benefit in this subgroup of patients alone. If intensified treatment reduces 9-month mortality by 15% in HIV-positive patients (from 65% to 50%), corresponding to a hazard ratio of 0.67, a total of 196 deaths in HIV-positive patients are required to detect this difference with 80% power; approximately **350 HIV-positive patients** are needed to observe 196 deaths during follow-up.

To guarantee both sufficient power in the subgroup of HIV-positive TBM patients and a sufficiently high event rate in the total population, the trial will continue recruitment until both a total of 750 patients and minimum of 350 HIV-positive patients have been recruited.

## **10.2 Analysis**

### **10.2.1 Analysis of the primary endpoint**

The primary endpoint of this trial is overall survival, i.e. time to death, during the entire follow-up period of 9 months. Overall survival will be analyzed with a log-rank test stratified by HIV status (positive/negative) and TBM disease severity at presentation (modified MRC grade I, II or III). Kaplan-Meier plots and explicit survival estimates at 3, 6 and 9 months of follow-up will also be calculated for the full populations and in the subgroups defined by HIV status and TBM disease severity separately.

In a second stage, overall survival will be modeled using the Cox proportional hazards regression model and the following covariates (in addition to the treatment group): TBM disease severity (grade I, II, or III), HIV status (positive/negative), participating hospital (PNT/HTD), previous TB treatment (yes/no), MDR-TB (yes/no), Isoniazid resistant TB (yes/no). A separate analysis for HIV positive patients only will be performed which will include prior antiretroviral therapy (yes/no), CD4 cell count and log<sub>10</sub>-HIV viral load at baseline as additional covariates.

The homogeneity of the treatment effect on overall survival in the subgroups defined by TBM grade (I, II, or III), HIV status (positive/negative), prior TBM treatment (yes/no), diagnosis of MDR-TB (yes/no) or Isoniazid resistant TB (yes/no), respectively, will be examined and tested using tests of interaction between treatment and the grouping variable.

### **10.2.2 Analysis of secondary endpoints**

Neurological disability. The disability score at month 3, 6, and 9 of follow-up is defined as the higher (worse) of the “simple question” and the Rankin score assessed at that time point as previously described (Thwaites, Nguyen et al. 2004) (also see appendix 1.3). Disability score will be defined as 4 (worst outcome) if the patient died prior to the respective time point. The score of primary interest is the month 9 score which will be compared between the two arms with the generalized Cochran-Mantel-Haenzel test as described in Mantel’s generalized statistics (Agresti 2002) taking into account that the disability score is ordinal. The test will be stratified by HIV status and TBM disease severity at presentation. Patients lost to follow up will be analyzed according to their last recorded disability status. If the rate of patients lost to follow-up exceeds 10%, we will also perform an alternative analysis based on multiple imputation of missing values.



Time-to-event endpoints, i.e. time to new neurological event or death (as defined in section 5.2) and time to new or recurrent AIDS defining illness or death (in HIV positive patients only), will be analyzed with a log-rank test, Kaplan-Meier curves and Cox regression models as described for the primary endpoint above.

Adverse events and TB treatment interruptions: All reported serious and grade 3&4 adverse reactions will be listed. The proportion of patients with at least one such event (overall and for each specific event separately) and the proportion of treatment interruptions, respectively, will be compared between the two treatment groups using a generalized Cochran-Mantel-Haenzsel test stratified by HIV status and TBM disease severity at presentation.

### **10.2.3 Analysis populations**

The primary analysis population for all analysis is the full analysis patients containing all randomized patients. Patients will be analyzed according to their randomized arm (intention-to-treat). The primary endpoint, overall survival, will in addition be analyzed on the per-protocol population which excluded the following patients: patients with a final diagnosis other than TBM major protocol violations and those receiving less than 2 months of administration of the randomized study drug for reasons other than death.

## **11 Interim analysis and role of the Data and Safety Monitoring Committee (DSMC)**

An independent DSMC will oversee the trial. Interim analyses are planned after 20 deaths, additionally after 6 and 12 months of recruitment and yearly thereafter until the completion of the trial. The DSMC will be provided with unblinded survival curves and summary tables of grade 3&4 and serious adverse events. Tables will be prepared by the DSMC statistician and distributed to all DSMC members for review; the study statistician will remain blinded throughout the study..

Based on these data, the committee has to make one of the following recommendations:

- Continue the trial without modification
- Continue the trial with modification
- Stop the trial due to safety concerns

Unless the benefit of intensified treatment is shown “beyond reasonable doubt” at an interim analysis, no formal stopping for efficacy is foreseen. The Haybittle-Peto boundary, requiring  $p < 0.001$  at interim analysis to consider stopping for efficacy, should be used as a guidance. However, the DSMB recommendation should not be based purely on statistical tables but also requires clinical judgment.

As the dissemination of preliminary summary data could influence the further conduct of the trial and introduce bias, access to interim data and results will be confidential and strictly limited to the involved independent statistician and the monitoring board and results (except for the recommendation) will not be communicated to the outside and/or clinical investigators involved in the trial.

## **12 Ethical approval**

This protocol, the informed consent form and any subsequent modifications of these documents, will be reviewed by the Oxford Tropical Research Ethics Committee (OXTREC) and the Institutional Review Boards of the Hospital for Tropical Diseases, Pham Ngoc Thach hospital and the Vietnam Ministry of Health.

## **13 Confidentiality**

A unique trial number will be assigned to each patient entering the trial and will be used to identify all laboratory specimens and the case record forms. All records will be stored securely on the wards or in the OUCRU. Clinical information will not be released without written permission of the patient.

## **14 Clinical trial specimens**

All clinical trial specimens will be labeled with the patient's trial number. Samples will be transferred to the laboratories at the Hospital for Tropical Diseases and Pham Ngoc Thach Hospital for initial processing. Investigation results will be issued to the investigators in a timely manner and a hard copy of the results will be retained in the laboratory for verification. Samples will be stored securely in freezers at the Hospital for Tropical Diseases and Pham Ngoc Thach Hospital prior to transfer to the Oxford University Clinical Research Unit for further investigations and long term storage.

Samples taken for pharmacokinetic testing of HIV treatments will be sent for analysis to:

[Department](#) of Pharmacology  
Wellcome Trust Major Overseas Programme  
Mahidol-Oxford Tropical Medicine Research Unit (MORU)  
Faculty of Tropical Medicine, Mahidol University 3rd floor  
60th Anniversary Chalermprakiat Building  
420/6 Ratchawithi Road, Ratchathewi District, Bangkok 10400  
Tel: 66 2 2036368, 66 2 354 6019  
Fax: 66 2 354 6018

For samples that require transfer to institutions or laboratories outside Viet Nam, appropriate regulatory permissions will be sought.

## **15 Publication**

Any publication or presentation during the active phase of the study must have permission from the Investigators. The investigators will define the strategy for publication, resolve any problems of authorship and maintain the quality of publications. All publications will acknowledge the appropriate funding sources. The investigators are the custodian of the data and specimens generated from this trial.

## 16 Substudies

### 16.1 Pharmacokinetics of high dose rifampicin and levofloxacin in patients with TBM admitted to the Hospital for Tropical Diseases.

#### Study Aims

- i) To determine the pharmacokinetics of high dose rifampicin in plasma and CSF.
- ii) To determine the impact of high dose rifampicin on the pharmacokinetics of anti-retroviral drugs and anti-tuberculous drugs in CSF and plasma.
- iii) To relate levels of ant-retroviral drugs in CSF on HIV and HBV CSF viral dynamics.

We will compare the pharmacokinetics and steady state concentrations of rifampicin, pyrazinamide, isoniazid and the active ARV therapy (efavirenz and protease inhibitors) in cerebrospinal fluid and blood in each arm of the TBM clinical trial, to determine the impact of boosting the dose of rifampicin. Rifampicin in normal dose is an inducer of hepatic cytochrome P450 microsomal enzymes and subsequently has well-recognised drug interactions. One potentially important interaction is between rifampicin and efavirenz. Efavirenz is amongst the most frequently prescribed anti-retroviral drugs in the developed world because of its excellent tolerability and efficacy. Together with two nucleoside reverse transcriptase inhibitors, efavirenz is the anti-retroviral treatment of choice in HIV-associated TB disease. Efavirenz is also metabolized through the P450 pathway, inducing its own metabolism. Rifampicin lowers efavirenz levels by the same method, and it is usual practice to boost the dose of efavirenz in patients receiving rifampicin, although there is wide inter-individual variation in drug levels. Efavirenz resistance can be conferred by a single step mutation that also confers nevirapine resistance. A clear understanding of the pharmacokinetic interactions between efavirenz and high dose rifampicin is important to enable correct dosing decisions to be made in order to obtain maximum benefit from this drug. We will determine the effect of boosted dose rifampicin on efavirenz levels in both CSF and plasma throughout treatment, in comparison with patients receiving the standard dose. We will relate Efavirenz levels to the rate of decline in HIV load. We will measure levofloxacin levels in CSF and blood of patients and relate this to outcome, although levofloxacin, which is predominantly renally excreted, has no expected interactions with efavirenz or rifampicin.

#### 16.1.1 Pharmacokinetics of tb drugs and arvs at HTD (Plasma)

##### Study Aims:

- 1) To perform pharmacokinetics of TB and ARV drugs in the standard regimen versus intensified regimen.
- 2) To study TB drug-drug interactions (HIV negative group)

3) To monitor some ARV drugs exposure in the intensified arm (HIV positive group).

The drugs of interest are:

1. TB drugs (Isoniazid **INH**, Rifampicin **RIF**, Pyrazinamide **PZA**, Ethambutol **EMB** and Levofloxacin **LVF**).
2. ARV drugs (Efavirenz **EFV**, Lopinavir **LPV** and Ritonavir **RTV**)

Sampling schedule:

Intensive pharmacokinetics (PK) must be run at steady-state of TB drugs, therefore sampling will occur on day 14 (+14 days) of TB treatment on study.

The blood is drawn at the exact following times (in hours after dose):

0 (= pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12 hours

Total volume of blood provided = 9 x 3 mL = 27 mL. This volume is the strict minimum volume necessary to analyze from 5 (HIV-) to 8 drugs (HIV+).

Blood sample collection:

Each patient will have a heparinized intravenous cannula inserted. The scheduled time of each sample (in hours post-dose) is written in the CRF and must be exactly recorded. Blood samples are collected in lithium heparin tubes and immediately (within 5 minutes) centrifuged at 2,000 g for 15 min. The plasma must be carefully aliquoted into ascorbic acid pre-coated cryotubes and stored at -20°C in the ward. A sample collection will be organized regularly toward the OUCRU pharmacology laboratory where samples will be stored at -80°C until being analysed.

Sample size:

A: HIV negative: standard regimen vs. intensified regimen 2 groups of 15 patients

B: HIV positive treated with ARV:

Standard regimen vs. intensified regimen 2 groups of 15 patients

Important considerations in rich sampling PK:

Accuracy of sample timing is of utmost importance in this study. The exact time when treatment is given to the patient, and the time when samples are taken must be exactly recorded on CRF. For the samples, the time in hours post-dose must be respected and exactly the same for all the patients. The PK parameters are calculated using means at every time point. If a sample is not taken at the accurate time, it will be excluded from the analysis, reducing statistical power. The schedule is written in time after dose for 8 different drugs (for HIV positive group). We recommend providing both TB and ARV drugs following always the same order. This is to standardize the time interval between first and last tablet given and reduce inter-patient variability in the analysis. In order to increase bioavailability of TB drugs,

it is recommended that the patients receive the treatment in the morning following an overnight fast of at least 6 hours.

### **16.1.2 Population pharmacokinetics (Plasma and CSF) AT HTD**

#### Study aim:

To study pharmacokinetics of first line TB drugs (RIF,INH,PZA,EMB and LVF) and ARV drugs (EFV,LPV,RTV) in the plasma and the CSF.

This will allow us to determine the CSF/plasma ratio in accurate Area Under the Curve analysis between two doses. The pharmacokinetics of the drugs will be studied in the plasma and CSF and the kinetics of drug transfer between these two compartments will be considered along the treatment period.

#### Sampling schedule:

The population pharmacokinetics samples will be taken at every occasion where a lumbar puncture is clinically indicated.

HIV negative group: at month 1 (intensive phase), 2 and 9 (end of continuation phase)

HIV positive group: at month 1 (intensive phase), 2, 3 and 9 (end of continuation phase)

At every occasion, the CSF sample will be timed within one of three time-windows:

- 0-3 hours
- 3-6 hours
- 6-12 hours

A plasma sample is also required and must be taken within 15 minutes after the lumbar puncture. Patients will be randomly allocated to one of the three time-windows at the beginning of the study.

Total biological fluids volumes required are:

CSF = 5 mL x 3 or 4 occasions (1, 2, 3 and 9 months)

Blood = 3 mL x 3 or 4 occasions

#### Sample collection:

The scheduled time of each sample (in hours post-dose) will be recorded in the CRF upon receipt of the randomly assigned time-window. The exact time of sample collection must be recorded in the CRF. Blood samples are collected in lithium heparin tubes and immediately (within 5 minutes) centrifuged at 2,000 g for 15 min. The plasma must be aliquoted into ascorbic acid pre-coated cryotubes and stored at -20°C in the ward. CSF samples are collected and immediately aliquoted in ascorbic acid pre-coated cryotubes and stored -20°C in the ward. A sample collection will be regularly organized toward the OUCRU pharmacology laboratory where samples will be stored at -80°C until analysed.

#### Sample size:

We expect to recruit approximately 250 patients on the treatment study at the Hospital for Tropical Diseases. These patients will be randomized to two treatment arms (Normal vs. Intensified regimen).

Important considerations in population PK:

The exact collection time must be recorded in the CRF. The schedule is written in time after dose for 8 different drugs (for HIV positive group). It is recommended that TB and ARV drugs are always delivered in the same order. This is to standardize the time interval between first and last tablet given and reduce inter-patient variability in the analysis. In order to increase bioavailability of TB drugs, it is recommended that the patients receive the treatment following an overnight fast of at least 6 hours.

**16.1.3 Unscheduled Lumbar punctures:**

In addition to pharmacokinetic analysis of CSF and plasma samples planned for the above named studies, residual volumes from blood and CSF samples taken for clinical care can be analyzed and included in the pharmacokinetic data for patients who consent to the corresponding study. Processing must be performed as per the standard operating procedures for these studies..

**16.1.4 Sampling Schedule for PK studies**

		Base line	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9
PK study- All HTD	Population PK blood					3				3	3 (HIV)						3
	Population PK CSF					C5				C5	C5 (HIV)						C5
PK study-60 HTD	PK Study			27													

## **16.2 Viral Dynamics in cerebrospinal fluid of patients with TBM**

### **Study Aims:**

- i) To determine the characteristics and extent of replication of Hepatitis B and Hepatitis C viruses within the central nervous system in Vietnamese patients.**
- ii) To determine the dynamics of HIV, HBV and HCV replication in the central nervous system during the course of anti-retroviral and anti-tuberculous treatment.**

Hepatitis C virus is increasingly recognized as an important cerebral pathogen (Parsons, Tucker et al. 2006; Robertson, Smurzynski et al. 2007). There is evidence that infection is associated with neurological consequences (impaired neurocognitive functioning), that there is active replication within the central nervous system, and that some strains have increased neurotrophism in comparison with others (Bagaglio, Cinque et al. 2005; Seifert, Struffert et al. 2008). Similarly, Hepatitis B infection is associated with neurological complications, such as myelitis and Guillan-Barre syndrome (Pao, Wu et al. 1987; Weber, Schoeman et al. 1994; Chroni, Thomopoulos et al. 2003; Inoue, Ueno et al. 2008). While some of this may be related to circulation of HbsAg/HBsAb immune complexes, viral DNA is detectable in the cerebrospinal fluid of some patients (Pao, Wu et al. 1987). In addition to describing the dynamics of viral replication of HBV, HCV and HIV in the plasma of patients during the course of treatment in this trial, we will determine the dynamics of all 3 viruses in the cerebrospinal fluid.

In the study patients receive anti-retroviral drugs in accordance with Vietnamese national guidelines. This regime will include only one HBV active drug – lamivudine. Multi-drug therapy is not currently available for patients with HBV infection in Vietnam, even if HIV co-infected. Lamivudine monotherapy has limited effectiveness, with resistance rates approaching 25% per year in other populations, although some patients have good responses for prolonged periods (Wright 2004). Low populations of quasi-species that are presumably important in the development of resistance are recognized (Ding, Wong et al. 2006). There are no data from Vietnamese patients. We will describe the viral dynamics of HBV in blood and CSF during the course of treatment with lamivudine (as part of antiretroviral therapy), determine HBV genotypes, prevalences of HBV quasi-species and the rate of development of lamivudine resistance. We will describe the changes in HCV viral load in blood and CSF throughout the course of treatment. We will relate changes in blood and CSF HBV and HCV viral dynamics to HIV viral load and response to anti-retro-viral treatment.



## 17 Appendices

### Appendix 1.0 - Diagnosis and grading of tuberculous meningitis, including outcome and disability

#### Appendix 1.1 - Diagnostic criteria for tuberculous meningitis

Classification	Diagnostic criteria
Definite TBM	Clinical meningitis plus acid-fast bacilli seen in the CSF or <i>M. tuberculosis</i> cultured from the CSF
Probable TBM	Clinical meningitis plus one of the following criteria: <ul style="list-style-type: none"> <li>• Radiographic evidence of pulmonary tuberculosis</li> <li>• Acid-fast bacilli seen in sputum or gastric fluid</li> <li>• Evidence of extra-pulmonary tuberculosis</li> <li>• CT or MRI brain scan features consistent with TBM</li> </ul>
Possible TBM	Clinical meningitis plus $\geq 2$ of the following criteria: <ul style="list-style-type: none"> <li>• History of previous tuberculosis</li> <li>• Illness duration &gt; 5 days</li> <li>• Glasgow coma score &lt; 15</li> <li>• Focal neurological signs</li> </ul> <u>and</u> $\geq 2$ of the following criteria: <ul style="list-style-type: none"> <li>• Yellow CSF</li> <li>• &gt; 50% lymphocytes in the CSF</li> <li>• CSF glucose &lt; 50% blood glucose</li> </ul>

#### Appendix 1.2 Modified MRC grading for tuberculous meningitis

TBM grade	Diagnostic criteria
Grade I	Glasgow coma score 15, no focal neurology
Grade II	Glasgow coma score 11-14 OR Glasgow coma score 15 with focal neurology
Grade III	Glasgow coma score $\leq 10$

#### Appendix 1.3 Outcome and disability grading: “Two simple questions” and Rankin score

##### The ‘Two simple questions’

Does the patient require help from anybody for everyday activities? ( <i>For example eating, drinking, washing, brushing teeth, going to the toilet.</i> )	Yes/no	Yes= Poor outcome
Has the illness left you with any other problems?	Yes/no	Yes= Indifferent outcome No= Good outcome

##### The Modified Rankin Scale

grade	Description
0	No symptoms

1	Minor symptoms not interfering with lifestyle
2	Symptoms that lead to some restriction in lifestyle, but do not interfere with the patients ability to look after themselves
3	Symptoms that restrict lifestyle and prevent totally independent living
4	Symptoms that clearly prevent independent living, although the patient does not need constant care and attention.
5	Totally dependent, requiring constant help day and night.

## **Appendix 2.0 WHO clinical staging for HIV/AIDS**

<b>Clinical Stage 1</b>
Asymptomatic Persistent generalised lymphadenopathy (PGL) Performance scale 1: asymptomatic, normal activity
<b>Clinical Stage 2</b>
Weight loss, <10% of body weight Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) Herpes zoster, within the last 5 years Recurrent upper respiratory tract infections (e.g. bacterial sinusitis) And/or performance scale 2: symptomatic, normal activity.
<b>Clinical stage 3</b>
Weight loss, >10% of body weight Unexplained chronic diarrhoea, > 1 month Unexplained prolonged fever (intermittent or constant), > 1 month Oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis, within the past year. Severe bacterial infections (e.g. pneumonia, pyomyositis) And/or Performance scale 3: bed-ridden, < 50% of the day during the last month
<b>Clinical stage 4</b>
HIV wasting syndrome, as defined by CDC <sup>1</sup> Pneumocystis carinii pneumonia Toxoplasmosis of the brain Cryptosporidiosis with diarrhoea, >1 month Cryptococcosis, extra pulmonary Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes Herpes Simplex Virus (HSV) infection, mucocutaneous >1 month, or visceral any duration Progressive multifocal leukoencephalopathy (PML) Any disseminated endemic mycosis (e.g. histoplasmosis, coccidioidomycosis) Candidiasis of the oesophagus, trachea, bronchi or lungs Atypical mycobacteriosis, disseminated Non-typhoid Salmonella septicaemia Extra-pulmonary tuberculosis Lymphoma Kaposi's sarcoma (KS) HIV encephalopathy, as defined by CDC <sup>2</sup> And/or Performance scale 4: bed-ridden, > 50% of the day during the last month

(Note: Both definitive and presumptive diagnoses are acceptable)

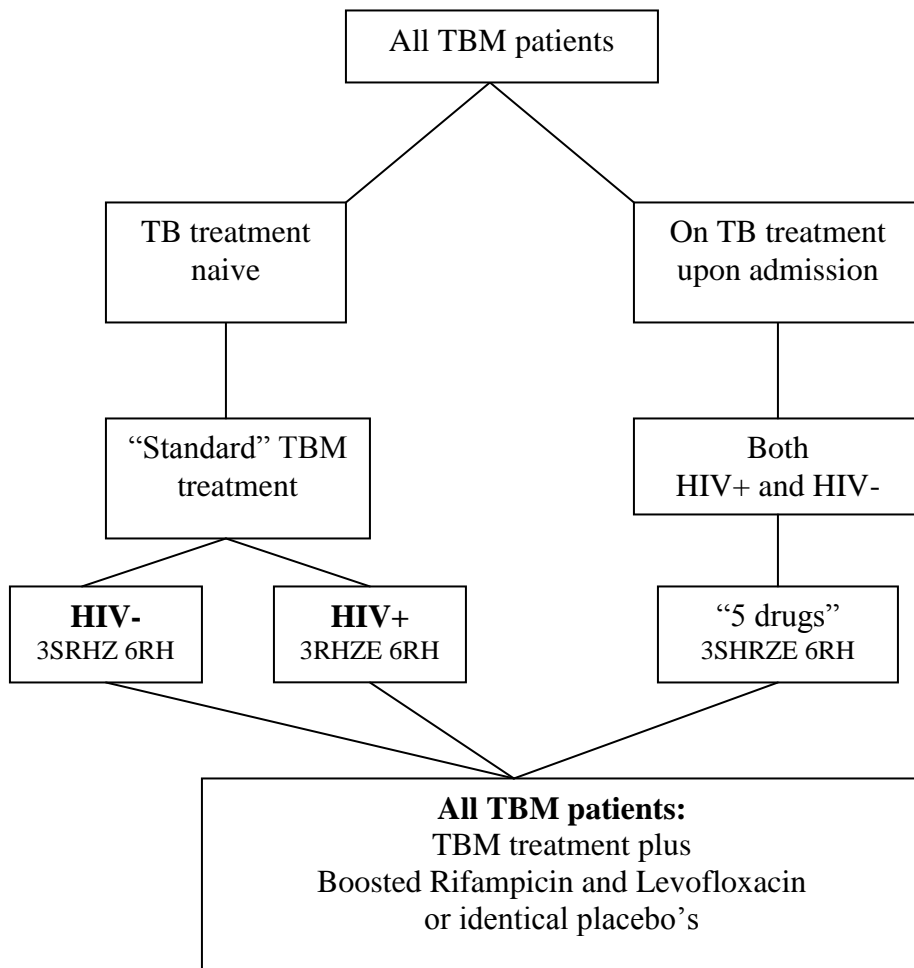
<sup>1</sup> HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month), or chronic weakness and unexplained prolonged fever (>1 month).

<sup>2</sup> HIV encephalopathy: clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.

### **Appendix 3.0 Details of backbone antituberculous therapy**

<b>Drug and dose</b>	<b>Side effects</b>	<b>Contraindications</b>	<b>Drug interactions</b>
Rifampicin 10 mg/kg 600mg od po	Orange discolouration of body fluids (urine, tears, saliva), skin rash, gastrointestinal symptoms, headache, drowsiness, abnormal liver function tests, jaundice, associated with intermittent rifampicin ‘flu-like syndrome’, haemolytic anaemia, leucopenia, thrombocytopenic purpura acute renal failure	Jaundice	Reduces efavirenz level by 25% (increase dose to 800mg). Reduces plasma concentrations of protease inhibitors and nevirapine (avoid concomitant use). Accelerates metabolism of corticosteroids, oral contraceptives, coumarins, oral hypoglycaemics, azole antifungals, phenytoin, diazepam, theophyllines, vitamin D, digitoxin, methadone, cyclosporin
Isoniazid 5mg/kg 300mg od po	Gastrointestinal symptoms, skin rash, peripheral neuritis, optic neuritis, convulsions, psychosis, vertigo, hypersensitivity reactions, hepatitis, haemolytic anaemia, aplastic anaemia, agranulocytosis, systemic lupus erythematosus-like syndrome.	Drug induced liver disease	Isoniazid plasma levels increased by: prednisolone, ethionamide. Increases plasma levels of phenytoin, carbamazepine, warfarin, diazepam. Decreases plasma levels of azoles, enflurane
Pyrazinamide 25mg/kg od po, max 2g/day	Gastrointestinal symptoms, hepatotoxicity, skin rash, arthralgia, hyperuricaemia, gout, photosensitisation	Liver damage, porphyria	Increases plasma levels of probenecid
Ethambutol 20mg/kg od po, max 1.2g/day	Optic neuritis, red/green colour blindness, arthralgia, peripheral neuritis, rarely rash, pruritus, urticaria, thrombocytopenia	Optic neuritis, poor vision	

**Appendix 3.1 Diagram of management of TBM patients on TB treatment upon admission**



## **Appendix 4.0 Details of corticosteroid therapy**

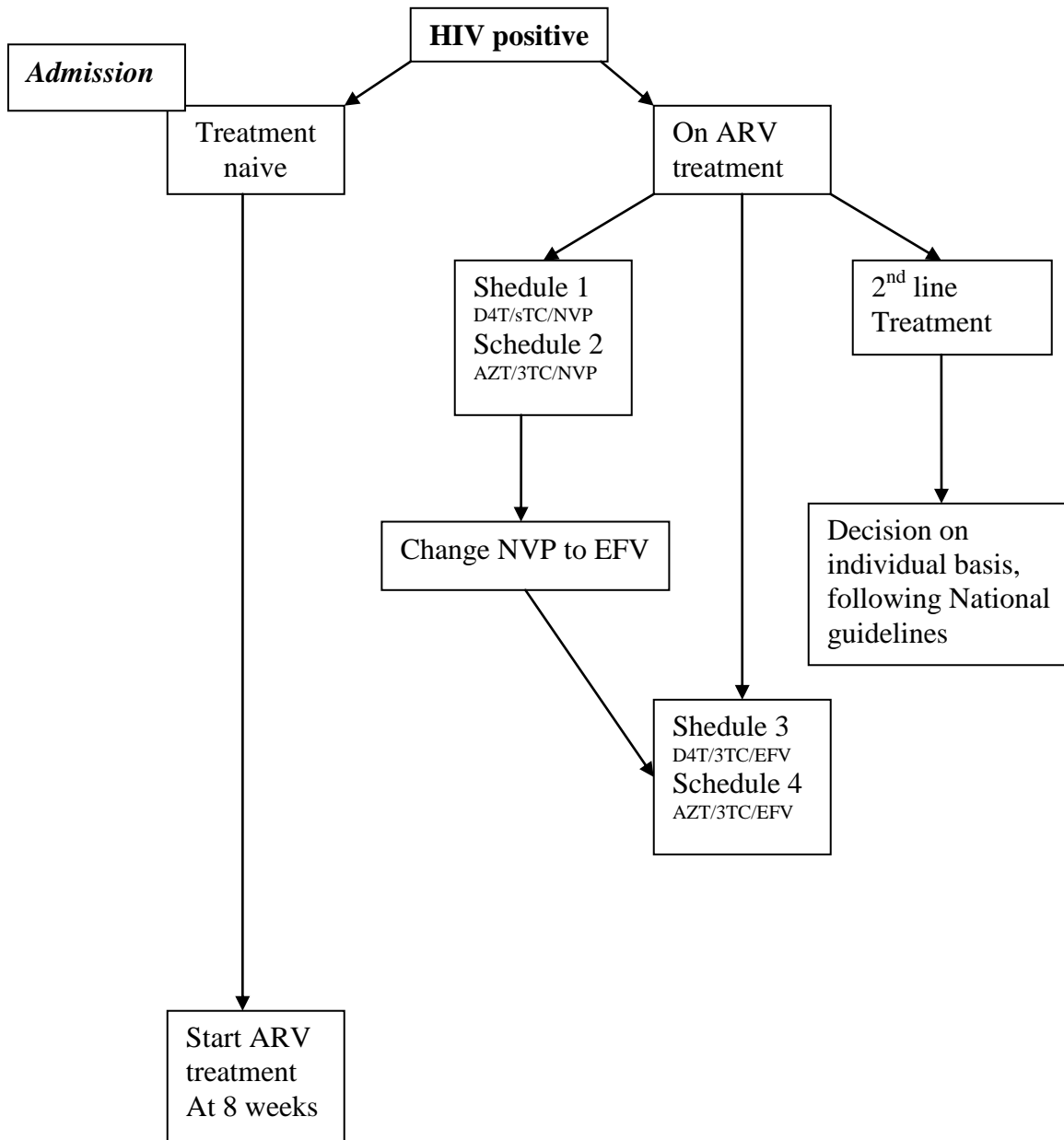
<b><i>Drug</i></b>	<b><i>Side effects</i></b>	<b><i>Contraindications</i></b>	<b><i>Drug Interactions</i></b>
Dexamethasone (See section 9.4.1 for dosing schedule)	Dyspepsia, peptic ulceration, proximal myopathy, osteoporosis, avascular osteonecrosis, adrenal suppression, Cushing's syndrome, increased susceptibility to and severity of infection; neuro-psychiatric effects	Systemic infection (unless specific antimicrobial therapy given). Avoid live virus vaccines in those receiving immuno-suppressive doses (serum antibody response diminished)	Increased risk of hypokalaemia with amphotericin (avoid concomitant use). Metabolism accelerated by rifamycins, barbiturates, carbamazepine, phenytoin, primidone (reduced effect). May enhance or reduce anticoagulant effect of coumarins.

**Appendix 5.0 NTP Daily Rifampicin Dosage versus Study Intervention Daily Dosage**

<b>Patient Weight Kg</b>	<b>NTP Rifampicin dose mg</b>	<b>NTP Dose/kilo</b>	<b>Rifampicin Study dose mg</b>	<b>Dose Rifampicin mg/kilo</b>	<b>Rifampicin % dose increase by weight</b>	<b>Additional Rifampicin Dose</b>	<b>Additional Tablets</b>
30	300	10.0	450	15	150.0	150	1.0
31	300	9.7	525	16.9	174.6	225	1.5
32	300	9.4	525	16.4	174.9	225	1.5
33	300	9.1	525	15.9	174.9	225	1.5
34	300	8.8	525	15.4	174.5	225	1.5
35	300	8.6	525	15	175.0	225	1.5
36	300	8.3	600	16.7	200.4	300	2.0
37	300	8.1	600	16.2	199.8	300	2.0
38	300	7.9	600	15.8	200.1	300	2.0
39	300	7.7	600	15.4	200.2	300	2.0
40	450	11.3	600	15	133.3	150	1.0
41	450	11.0	675	16.5	150.3	225	1.5
42	450	10.7	675	16.1	150.3	225	1.5
43	450	10.5	675	15.7	150.0	225	1.5
44	450	10.2	675	15.3	149.6	225	1.5
45	450	10.0	675	15	150.0	225	1.5
46	450	9.8	750	16.3	166.6	300	2.0
47	450	9.6	750	16	167.1	300	2.0
48	450	9.4	750	15.6	166.4	300	2.0
49	450	9.2	750	15.3	166.6	300	2.0
50	450	9.0	750	15	166.7	300	2.0
51	450	8.8	825	16.2	183.6	375	2.5
52	450	8.7	825	15.9	183.7	375	2.5
53	450	8.5	825	15.6	183.7	375	2.5
54	450	8.3	825	15.3	183.6	375	2.5
55	600	10.9	825	15	137.5	225	1.5
56	600	10.7	900	16.1	150.3	300	2.0
57	600	10.5	900	15.8	150.1	300	2.0
58	600	10.3	900	15.5	149.8	300	2.0
59	600	10.2	900	15.3	150.5	300	2.0
60	600	10.0	900	15	150.0	300	2.0
61	600	9.8	975	16	162.7	375	2.5
62	600	9.7	975	15.7	162.2	375	2.5
63	600	9.5	975	15.5	162.8	375	2.5
64	600	9.4	975	15.2	162.1	375	2.5
65	600	9.2	975	15	162.5	375	2.5
66	600	9.1	1050	15.9	175.0	450	3.0
67	600	9.0	1050	15.7	175.0	450	3.0
68	600	8.8	1050	15.4	175.0	450	3.0
69	600	8.7	1050	15.2	175.0	450	3.0
70	600	8.6	1050	15.0	175.0	450	3.0
71	750	10.6	1125	15.8	150.0	375	2.5
72	750	10.4	1125	15.6	150.0	375	2.5
73	750	10.3	1125	15.4	150.0	375	2.5
74	750	10.1	1125	15.2	150.0	375	2.5
75	750	10.0	1125	15.0	150.0	375	2.5

**Appendix 6.0 HIV Management**

**Appendix 6.1 Flow diagram on management of HIV-positive patients**





## Appendix 6.2 Presumptive and definitive criteria for AIDS defining events

Based on 1993 Revised CDC classification system (MMWR 1992; 41(RR-17): 1-19) and modified for this trial

	Presumptive criteria	Definitive criteria
<b>Constitutional disease</b>		
HIV wasting syndrome	Unexplained involuntary weight loss >10% from baseline PLUS persistent diarrhoea with $\geq 2$ liquid stools/day for > 1 month OR chronic weakness OR persistent fever > 1 month. Should exclude other causes such as cancer, TB, MAC, cryptosporidiosis or other specific enteritis	
<b>Infections</b>		
Aspergillosis, other invasive	CXR abnormality compatible with aspergillosis PLUS invasive mycelia consistent with <i>Aspergillus</i> on lung biopsy or positive culture of lung tissue or positive culture of sputum	CXR abnormality compatible with aspergillosis PLUS invasive mycelia consistent with <i>Aspergillus</i> on lung biopsy PLUS positive culture of lung tissue or positive culture of sputum
Bartonellosis	Clinical evidence of bacillary angiomatosis or bacillary peliosis PLUS positive silver stain for bacilli from skin lesion or affected organ	Clinical evidence of bacillary angiomatosis or bacillary peliosis PLUS positive culture or PCR for <i>Bartonella quintana</i> or <i>Bartonella henselae</i>
Candidiasis of bronchi, trachea or lungs	None	Macroscopic appearance at bronchoscopy or histology or cytology (not culture)
Candidiasis, oesophageal	Recent onset retrosternal pain on swallowing PLUS clinical diagnosis or oral candidiasis by cytology (not culture) PLUS clinical response to treatment	Macroscopic appearance at endoscopy or histology or cytology (not culture)
Coccidioidomycosis, disseminated or extrapulmonary	None	Histology or cytology, culture or antigen detection from affected tissue
Cryptococcosis, meningitis or pulmonary	None	Histology or cytology/microscopy, culture or antigen detection from affected tissue
Cryptosporidiosis	None	Persistent diarrhoea > 1 month, histology or microscopy
CMV retinitis	Typical appearance on fundoscopy of discrete patches of retinal whitening, associated with vasculitis, haemorrhage and necrosis, confirmed by ophthalmologist	None
CMV end-organ disease	None	Compatible symptoms plus histology or detection of antigen from affected tissue

Appendix 6.2 Presumptive and definitive criteria for AIDS defining events (cont'd)

<b>Infections</b>	<b>Presumptive criteria</b>	<b>Definitive criteria</b>
CMV radiculomyelitis	Leg weakness and decreased reflexes or syndrome consistent with cord lesion presenting subacutely over days to weeks. CT/MRI shows no mass lesion. CSF shows >5 WBC with >50% polymorphs and positive CMV PCR, antigen or culture	None
CMV meningoencephalitis	Rapid (days to < 4 weeks) syndrome with progressive delirium, cognitive impairment, ± seizures and fever (often with CMV disease elsewhere) CT/MRI may show periventricular abnormalities.	Rapid (days to < 4 weeks) syndrome with progressive delirium, cognitive impairment, ± seizures and fever (often with CMV disease elsewhere) CT/MRI may show periventricular abnormalities and CSF PCR positive for CMV
HSV mucocutaneous ulceration	None	Persistent ulceration for > 1 month, plus histology or culture or detection of antigen or HSV PCR positive from affected tissue
HSV visceral disease e.g oesophagitis, pneumonitis	None	Symptoms, plus histology or culture or detection of antigen or HSV PCR positive from affected tissue
VZV multidermatomal	≥ 10 typical ulcerated lesions affecting at least 2 non-contiguous dermatomes plus response to an antiviral active against VZV unless resistance is demonstrated	≥ 10 typical ulcerated lesions affecting at least 2 non-contiguous dermatomes plus culture or detection of antigen or VZV PCR positive from affected tissue
Histoplasmosis, disseminated or extrapulmonary	None	Symptoms plus histology or culture or detection of antigen from affected tissues
Isosporiasis	None	Persistent diarrhoea for >1 month, histology or microscopy
Leishmaniasis, visceral	None	Symptoms plus histology
Microsporidiosis	None	Persistent diarrhoea for >1 month, histology or microscopy
MAC, and other atypical mycobacteriosis	Symptoms of fever, fatigue, anaemia or diarrhoea plus acid-fast bacilli seen in stool, blood, body fluid or tissue but not grown on culture and no concurrent diagnosis of TB except pulmonary	Symptoms of fever, fatigue, anaemia or diarrhoea plus culture from stool, blood, body fluid or tissue

Appendix 6.2 Presumptive and definitive criteria for AIDS defining events (cont'd)

<b>Infections</b>	<b>Presumptive criteria</b>	<b>Definitive criteria</b>
Tuberculosis, pulmonary	Symptoms of fever, dyspnoea, cough, weight loss, fatigue plus acid-fast bacilli seen in sputum, lavage, or lung tissue, not grown in culture, plus responds to standard TB treatment	Symptoms of fever, dyspnoea, cough, weight loss, fatigue plus positive TB culture or PCR from sputum, bronchial lavage, or lung tissue
Tuberculosis, extrapulmonary	Symptoms, plus acid-fast bacilli seen from affected tissue or blood but not grown in culture, concurrent diagnosis of pulmonary TB or responds to standard TB treatment	Symptoms, plus positive TB culture or PCR from affected tissue
Nocardiosis	Clinical evidence of invasive infection plus microscopic evidence of branching, Gram-positive, weakly acid-fast bacilli from affected tissue	Clinical evidence of invasive infection plus positive culture from blood or affected tissue
<i>Penicillium marneffei</i> disseminated	Characteristic skin lesions plus response to antifungal therapy for penicilliosis (in an endemic area)	Culture from a non-pulmonary site
<i>Pneumocystis pneumonia</i> (PCP)	Symptoms, any CXR appearance and CD4 count < 200, negative bronchoscopy if treated for PCP for > 7 days, no bacterial pathogens in sputum, and responds to PCP treatment	Microscopy or histology
Extra-pulmonary pneumocystis	None	Symptoms plus microscopy or histology
Recurrent bacterial pneumonia	Second pneumonic episode within 1 year, new CXR appearance, symptoms and signs, diagnosed by a doctor	Second pneumonic episode within 1 year, new CXR appearance, detection of a pathogen
Progressive multifocal leucoencephalopathy (PML)	Symptoms and brain scan consistent with PML and no response to treatment for toxoplasmosis	Symptoms and brain scan consistent with PML and positive JC virus PCR in CSF or histology
<i>Rhodococcus equi</i> disease	None	Clinical evidence of invasive infection plus culture of organism from blood or affected tissue
Recurrent salmonella septicaemia	None	Second distinct episode, culture confirmed

Appendix 6.2 Presumptive and definitive criteria for AIDS defining events (cont'd)

<b>Infections</b>	<b>Presumptive criteria</b>	<b>Definitive criteria</b>
Cerebral toxoplasmosis	Symptoms of focal intracranial abnormality or decreased consciousness, and brain scan consistent with lesion(s) having mass effect or enhancing with contrast, and either positive toxoplasma serology or response to treatment clinically and by scan	Histology or microscopy
Extra-cerebral toxoplasmosis	None	Symptoms plus histology or microscopy
<b>Neoplasms</b>		
Kaposi's sarcoma (KS)	Typical appearance without resolution. Diagnosis should be made by an experienced HIV clinician	Histology
Cervical carcinoma, invasive	None	Histology
Lymphoma, primary cerebral	Symptoms consistent with lymphoma, at least one lesion with mass effect on brain scan, no response to toxoplasma treatment clinically and by scan	Histology
Lymphoma, non-Hodgkin's B cell	None	Histology
Lymphoma, Hodgkin's	None	Histology
<b>Neurological</b>		
HIV encephalopathy	Cognitive or motor function interfering with usual activity, progressive over weeks or months in the absence of another condition to explain the findings. Should have a brain scan $\pm$ CSF examination to exclude other causes.	None
<b>Other</b>		
Indeterminate cerebral lesion (s)	Neurological illness, with evidence for an intracerebral lesion by brain scan, where the differential diagnosis is either cerebral toxoplasmosis, PML, cerebral lymphoma or HIV encephalopathy	

## **Appendix 7.0 Toxicity grading and management**

### **Appendix 7.1 Table of common toxicity criteria**

Note: ULN = upper limit of normal local reference range

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Haematological</b>				
Haemoglobin	8.0 - 9.4 g/dl	7.0 - 7.9 g/dl	6.5 - 6.9 g/dl	<6.5 g/dl
White cell count	3.0 - 3.9 x 10 <sup>3</sup> cells/ $\mu$ l	2.0 - 2.9 x 10 <sup>3</sup> cells/ $\mu$ l	1.0 - 1.9 x 10 <sup>3</sup> cells/ $\mu$ l	<1.0 x 10 <sup>3</sup> cells/ $\mu$ l
Neutrophils	1.0 - 1.5 x 10 <sup>3</sup> cells/ $\mu$ l	0.75 - 0.99 x 10 <sup>3</sup> cells/ $\mu$ l	0.5 - 0.74 x 10 <sup>3</sup> cells/ $\mu$ l	<0.5 x 10 <sup>3</sup> cells/ $\mu$ l
Platelets	75 - 99 x 10 <sup>3</sup> cells/ $\mu$ l	50 - 74 x 10 <sup>3</sup> cells/ $\mu$ l	20 - 49 x 10 <sup>3</sup> cells/ $\mu$ l	<20 x 10 <sup>3</sup> cells/ $\mu$ l
Prothrombin time	>1.0 - 1.25 x ULN	>1.25 - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
<b>Biochemical</b>				
Hyponatraemia	130 - 135 mmol/l	123-129 mmol/l	116-122 mmol/l	<116 mmol/l
Hypernatraemia	146 - 150 mmol/l	151 - 157 mmol/l	158 - 165 mmol/l	>165 mmol/l
Hypokalaemia	3.0 - 3.4 mmol/l	2.5 - 2.9 mmol/l	2.0 - 2.4 mmol/l	<2.0 mmol/l
Hyperkalaemia	5.6 - 6.0 mmol/l	6.1 - 6.5 mmol/l	6.6 - 7.0 mmol/l	>7.0 mmol/l
Hypoglycaemia	3.1 - 3.6 mmol/l 55 - 64 mg/dl	2.2 - 3.0 mmol/l 40-54 mg/dl	1.7 - 2.1 mmol/l 30 - 39 mg/dl	<1.7 mmol/l <30 mg/dl
Hyperglycaemia (fasting)	6.5 - 9.0 mmol/l 118 - 164 mg/dl	9.1 - 14.0 mmol/l 165 - 255 mg/dl	14.1 - 28.0 mmol/l 256 - 509 mg/dl	>28.0 mmol/l, >509 mg/dl or ketoacidosis
Urea	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
Creatinine	>1.0 - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Bilirubin	>1.0 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
AST or ALT or GGT	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
Alkaline phosphatase	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
Amylase	>1.0 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
<b>Urinalysis</b>				
Haematuria	Microscopic	Gross, no clots	Gross and clots	Obstruction or requiring transfusion
Proteinuria	1+ or <0.3% or <3g/l or 200mg-1g loss/day	2-3+ or 0.3 -1.0% or 3-10g/l or 1-2g loss/day	4+ or >1.0% or >10g/l or 2-3.5g loss/day	Nephrotic syndrome or >3.5g loss/day

Appendix 7.1 Table of common toxicity criteria (cont'd)

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Gastrointestinal</b>				
Stomatitis/mouth ulcers	Mild discomfort, no limits on activity	Some limits on eating or talking	Eating/talking very limited	Requiring IV fluids
Nausea	Mild or transient discomfort, maintains reasonable intake	Moderate discomfort or significantly decreased intake for > 3 days	Severe discomfort or minimal intake for ≥ 3 days	Hospitalization required
Vomiting	Mild or transient, 2-3 episodes per day or mild vomiting lasting < 1 week	Moderate or persistent, 4-5 episodes/day or vomiting lasting ≥ 1 week	Severe vomiting of all foods/fluids in 24 hours or orthostatic hypotension or IV fluids required	Hypotensive shock or hospitalization required for IV fluids
Diarrhoea	Mild or transient, 3-4 loose stools/day or mild diarrhoea lasting < 1 week	Moderate or persistent, 5-7 loose stools per day or diarrhoea lasting ≥ 1 week or nocturnal loose stools	Bloody diarrhoea or orthostatic hypotension or ≥ 7 loose stools per day or requiring IV fluids	Hypotensive shock or hospitalization required for IV fluids
Clinical pancreatitis	Mild abdominal pain, amylase < 2.5 x ULN, other causes excluded	Moderate abdominal pain, amylase < 2.5 x ULN, other causes excluded	Severe abdominal pain, amylase > 2.5 x ULN, hospitalization required.	Severe abdominal pain, shock/hypovolaemia, amylase > 5 x ULN, hospitalization required
<b>Neurological</b>				
Headache	Mild, no treatment	Moderate or requires non-narcotic analgesia	Severe or responds to first narcotic	Intractable or requiring repeated narcotics
Consciousness	Difficulty in concentration or memory	Mild confusion or lethargy <50% waking hours	Disorientation or stupor >50% of waking hours	Coma or seizures
Mood	Mild anxiety or depression	Treatment required for anxiety or depression	Treatment and assistance required, severe depression, mania or anxiety	Acute psychosis or hospitalization
Psychosis	Mild agitation or confusion	Some limitation in activities of daily living and minimal treatment required	Treatment and assistance required, severe agitation or confusion	Toxic psychosis or hospitalization
Cerebellar	Slight incoordination or dysdiadichokinesia	Intention tremor or dysmetria or slurred speech or nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with activities of daily living	Unable to stand

Appendix 7.1 Table of common toxicity criteria (cont'd)

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Neurological</b>				
Motor	Mild weakness in feet but able to walk or mild increase or decrease in reflexes	Moderate weakness in feet (unable to walk on heels or toes), mild weakness in hands but still able to do most hand tasks, or loss of previously present reflex or development of hyperreflexia or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop) and moderate proximal weakness (e.g. in hands interfering with activities of daily living or requiring assistance to walk or unable to rise from chair unassisted)	Confined to bed or wheelchair because of muscle weakness
Clinical myopathy	Minimal findings	Moderate myalgia or difficulty climbing stairs or rising from sitting position, able to walk, may need NSAID	Moderate to severe myalgia needing NSAID, assistance required for walking or general activities	Severe myalgia unrelated to exercise requiring narcotics, unable to walk or necrosis or oedema
Sensory	Mild impairment (decreased sensation e.g. vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Moderate impairment (moderately decreased sensation e.g. vibratory, pinprick, hot/cold to ankles) or joint position or mild impairment that is not symmetrical	Severe impairment (decrease or loss of sensation to knees or wrists) or loss of sensation of moderate degree in multiple different body areas (e.g. upper and lower extremities)	Sensory loss involves limbs and trunk
Parasthaesia	Mild discomfort, no treatment	Moderate discomfort, requiring non-narcotic analgesia	Severe discomfort or symptoms respond to narcotic analgesia	Incapacitating or not responsive to narcotics
Peripheral neuropathy	Mild paraesthesia, numbness, pain or weakness, not treated	Moderate paraesthesia, numbness or pain, objective weakness, requires analgesic	Severe, narcotic required, interferes with normal activity	Intolerable, incapacitating, unable to walk despite narcotics, paralysis
<b>Respiratory</b>				
Bronchospasm	Transient, no treatment, 70-80% peak flow or FEV1	Requires treatment, normalizes with bronchodilator, 50-69% peak flow or FEV1	No normalization with bronchodilator, 25-49% peak flow or FEV1, retractions	Cyanosis, intubated or <25% peak flow or FEV1

Appendix 7.1 Table of common toxicity criteria (cont'd)

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Cardiovascular</b>				
Cardiac arrhythmia		Asymptomatic, transient dysrhythmia, no treatment	Recurrent or persistent dysrhythmia, symptomatic, treatment required	Unstable dysrhythmia, hospitalization and treatment required
Hypertension	Transient, increase >20mm/Hg, no treatment	Recurrent, chronic increase >20mm/Hg, requires treatment	Acute treatment required, outpatient, hospitalization possible	Hospitalization required
Hypotension	Transient, orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid required, no hospitalization required	Hospitalization required
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade or pericardiocentesis or surgery required
Haemorrhage	Microscopic or occult	Mild, no transfusion	If Hb <6.6 g/l or if Hct <20% transfuse packed red cells or whole blood based on clinical care Gross blood loss or transfused 1-2 units	Massive blood loss or transfused >2 units
<b>Other</b>				
Fever, oral, > 12 hours	37.7-38.5°C	38.6-39.5°C	39.6-40.5°C	>40.5°C
Fatigue	Normal activity reduced by <25%	25-50% decrease in normal activity	>50% decrease in activity,	Cannot work, unable to care for self
Hypersensitivity	Pruritus without rash	Localized urticaria	Generalised urticaria or angioedema	Anaphylaxis
Rash	Rash, erythema or pruritus	Diffuse maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis or mucous membrane involvement or suspected Stevens-Johnson or erythema multiforme or necrosis requiring surgery
General	General mild, transient, easily tolerated, no treatment	Moderate, discomfort, interrupts usual activity, may require minor treatment	Severe, considerable interference with usual activity, requires treatment or intervention	Incapacitating or lifethreatening, requires treatment and/or hospitalization



## **Appendix 7. 2 Guide to management of toxicities**

### 7.2.1 Grade 1 clinical or laboratory toxicities

- Continue study drugs

### 7.2.2. Grade 2 clinical or laboratory toxicities

- Continue study drugs
- If relevant, monitor more closely and consider more frequent laboratory assessments
- Investigate to exclude other causes

### 7.2.3 Grade 3 clinical or laboratory toxicities

- Monitor more closely
- Perform more frequent laboratory assessments
- Investigate to exclude other causes
- For AST or ALT > 5 x ULN stop all study drugs until toxicity resolves and consider reintroduction of antituberculous drugs sequentially (Appendix 7.5).
- For other grade 3 toxicities the clinician may immediately stop study drugs if confirmatory test cannot be performed within 72 hours or if the clinician determines that continuation of study drugs is unsafe while awaiting test results
- Fill in an adverse event form and inform the DSMC

### 7.2.4 Grade 4 clinical or laboratory toxicities

- Monitor more closely
- Perform more frequent laboratory assessments
- Investigate to exclude other causes
- For all grade 4 toxicities that are attributable to antituberculous drugs, stop all drugs until toxicity resolves and restart antituberculous drugs sequentially (Appendix 7.5)
- For all grade 4 toxicities that are clearly attributable to antiretroviral drugs, stop relevant drugs until toxicity resolves and consider switching to alternative drugs as indicated in Appendix 7.6
- For other grade 4 toxicities the clinician may immediately stop study drugs if confirmatory test cannot be performed within 72 hours or if the clinician determines that continuation of study drugs is unsafe while awaiting test results
- If any doubt about management discuss with the principal investigator
- Fill in an adverse event form and inform the DSMC

### Appendix 7.3 Management of serious adverse effects of drugs requiring drug discontinuation

Adverse effect	Possible offending drugs	Clinical signs/symptoms	Management
Severe skin rash and/or Stevens-Johnson syndrome	Rifampicin, isoniazid, pyrazinamide, ethambutol, efavirenz	Rifampicin may cause petechial rash due to thrombocytopaenia. All TB drugs may cause severe rash and/or Stevens-Johnson syndrome	Stop rifampicin for petechial rash with low platelets and do not reintroduce. For severe rash and/or Stevens-Johnson syndrome, stop all drugs. Once rash has improved restart TB drugs sequentially (Appendix 7.5) followed by ART. If rash recurs, stop suspect drug permanently.
Severe anaemia	Zidovudine most likely. Rifampin and isoniazid may cause haemolytic anaemia	Pallor, tachycardia, shortness of breath on exertion	Stop zidovudine and consider alternative drug. Exclude haemolysis.
Acute hepatitis	Rifampicin, isoniazid, pyrazinamide. Less common with zidovudine, didanosine, stavudine	Fatigue, anorexia, gastrointestinal symptoms, jaundice, hepatomegaly, AST or ALT > 5 x ULN	Monitor serum bilirubin and transaminases. Stop all drugs until symptoms resolve and AST improves to < 2.5 x ULN. Then reintroduce TB drugs sequentially (Appendix 7.5) followed by ART
Acute pancreatitis	Stavudine, didanosine	Nausea, vomiting, abdominal pain	Monitor serum amylase. Stop all ART until symptoms resolve.
Lactic acidosis	All nucleoside analogue reverse transcriptase inhibitors (NRTIs)	Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnoea) or neurologic symptoms (including motor weakness).	Stop all ART. Symptoms may continue or worsen after discontinuation of ART. Supportive therapy.
Peripheral neuropathy	Isoniazid, ethambutol, stavudine, didanosine. Lamivudine less likely	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.	Give pyridoxine. Stop suspect NRTI and consider alternative drug.

## Appendix 7.4 Management of common adverse effects of antituberculous medications

Adverse effect	Management
Gastrointestinal symptoms	Common in the first few weeks of treatment. Liver function tests should be checked and if the AST < 2 x ULN, the symptoms are assumed not to be due to hepatic toxicity. The initial management is to change the hour of drug administration and/or to administer the drugs with food.
Rash	If mild, affecting only a limited area or predominantly causing itching an antihistamine may be given for symptomatic relief and antituberculous medications may be continued. A petechial rash may be caused by rifampicin induced thrombocytopenia – check platelet count and, and if low, stop rifampicin permanently. If there is a generalized erythematous rash, especially if associated with fever and/or mucous membrane involvement, stop all drugs. Once the rash has improved restart antituberculous drugs according to Table 7.5
Drug fever	Fever may persist for 2 months after treatment has been initiated. Recurrence of fever in a patient who has been on therapy for several weeks may be due to drug fever, especially if the patient is showing clinical and microbiological improvement. Fever may also be a feature of immune reconstitution syndrome or other HIV-related infections. Potential causes should be excluded before stopping antituberculous drugs – drug fever usually resolves in 24 hours. Once the fever has resolved restart drugs according to Table 7.5
Hepatitis	Isoniazid, rifampicin or pyrazinamide can all cause drug-induced liver injury Asymptomatic increases in AST occurs in around 20% of patients treated with 4 drugs and most resolve spontaneously. The frequency of clinical and laboratory monitoring should increase but therapy should not be altered. However, if AST or ALT >5 x ULN all hepatotoxic drugs (ie Rifampicin, Rifampicin study drug/placebo, isoniazid, pyrazinamide and any other hepatotoxic drugs) should be stopped. Levofloxacin/placebo and ethambutol/streptomycin can be continued, but if hepatitis continues to worsen stopping levofloxacin must be considered. The patient should be evaluated for other causes (viral hepatitis, alcohol intake, other hepatotoxins, biliary tract disease) before diagnosing drug-induced hepatitis. Once symptoms have resolved and AST returns to < 2 x ULN antituberculous medications may be restarted according to Appendix 7.5

### Appendix 7.5 Reintroduction of antituberculous therapy

Based on British Thoracic Society Guidelines for chemotherapy and management of tuberculosis (Thorax 1998; 53: 536-548)

Drug	Day 0	Day 3	Day 6	Day 9	Day 12	Day 15	Day 18	Day 21	Day 24	Day 27
Isoniazid 50mg	X									
Isoniazid 300mg		X	X	X	X	X	X	X	X	X
Rifampicin 75mg			X							
Rifampicin 300mg				X						
Rifampicin 450mg					X					
Rifampicin 600mg						X	X	X	X	X
Rifampicin Study drug/Placebo							X	X	X	X
Pyrazinamide 250mg								X	X	X
Pyrazinamide 1g									X	X
Pyrazinamide 1.5g (if wt < 50kg)									X	X
Pyrazinamide 2g (if wt ≥ 50kg)										X

#### Notes

1. Closely monitor patient's clinical condition and liver function tests while reintroducing drugs
2. If no reaction occurs to a new drug then increase the dose to maximum or add the next drug every 3 days, according to the table
3. If a reaction occurs, stop the offending drug and await resolution of symptoms
4. If pyrazinamide found to be the offending drug, extend treatment period and continue ethambutol for initial 3 months
5. **Note: Levofloxacin (or placebo) and ethambutol/streptomycin are not interrupted for hepatotoxicity.**

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