Intensified antibiotic treatment of tuberculous meningitis

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ABSTRACT

Introduction

Meningitis is the most severe manifestation of tuberculosis, resulting in death or disability in over 30% of those affected, with even higher morbidity and mortality among patients with HIV or drug resistance. Antimicrobial treatment of Tuberculous meningitis (TBM) is similar to treatment of pulmonary tuberculosis, although some drugs show poor central nervous system penetration. Therefore, intensification of antibiotic treatment may improve TBM treatment outcome.

Areas covered

In this review we address three main areas: available data for old and new anti-tuberculous agents; intensified treatment in specific patient groups like HIV co-infection, drug-resistance and children; and optimal research strategies.

Expert commentary

There is good evidence from preclinical, clinical and modeling studies to support use of high-dose rifampicin in TBM, probably at least 30mg/kg. Higher dose isoniazid could be beneficial, especially in rapid acetylators. The role of other first and second line drugs is unclear, but observational data suggest that linezolid, which has good brain penetration, may be beneficial. We advocate use of molecular pharmacological approaches, physiologically-based pharmacokinetic (PBPK) modelling and pharmacokinetic-pharmacodynamic (PK-PD) studies to define optimal regimens to be tested in clinical trials. Fortunately, exciting data from recent studies hold promise for improved regimens and better outcome of TBM patients.

1. INTRODUCTION

1.1 Brief epidemiology of tuberculous meningitis

Tuberculosis (TB) is the leading infectious disease killer worldwide. Tuberculous meningitis (TBM), its most dramatic manifestation, makes up 1-2% of all TB cases in settings where the HIV prevalence is low [1, 2]. However, in settings where HIV is common, disseminated TB and TB meningitis make up a much greater proportion of TB cases [3]. A meta-analysis of post-mortem studies in low-resource settings showed evidence of active TB in 43% of deceased HIV-infected individuals, and one study noted meningeal involvement in 28% of those with disseminated TB [4, 5]. It is therefore not surprising that TB is the second leading cause of adult meningitis in many countries with high HIV prevalence [6, 7]. TBM tends to strike those at the extremes of age. It is particularly common in young children under 5 years of age [8-10], and often the leading cause of childhood bacterial meningitis in TB-endemic areas [11].

1.2 Pathogenesis and presentation of tuberculous meningitis

Much remains unclear about the pathogenesis of TBM, but old histopathological studies suggest that pulmonary infection is followed by haematogenous dissemination of bacilli, including to the meninges covering the brain, forming so-called ‘Rich foci’ [12]. Months to years later, disease may reactivate; Rich foci rupture into the subarachnoid space with dissemination of bacilli into the cerebrospinal fluid (CSF) and development of basal meningitis [13]. In children, the meningitis usually occurs as part of disseminated primary disease rather than a later re-activation, and the same may be true of HIV-infected adults where host-defence mechanisms are diminished [3]. A basal meningitis results in formation of a dense exudate on the brainstem, which can envelop cerebral arteries and cranial nerves and obstruct the flow of CSF. Entrapment of cranial nerves by the exudate can lead to ophthalmoplegia or other cranial nerve palsies, while obstruction of the CSF flow can lead to hydrocephalus. As the most severe consequence, the exudate can lead to vasculitis of blood vessels of the circle of Willis, the vertebrobasilar system, and the perforating branches of the middle cerebral artery, resulting in brain infarctions. To dampen this immunopathology, standard treatment now includes use of adjuvant corticosteroids [14],[15].

TBM presents initially as subacute meningitis, with an insidious onset of low-grade fever, malaise, weight loss and gradually worsening headache, followed by confusion, development of focal neurological symptoms like eye movement disorders or limb paralysis and progressive coma. In small children, early symptoms are non-specific including cough, fever, failure to thrive, irritability or apathy, followed by loss of consciousness and focal neurological signs [16]. Recognition and diagnosis of TBM remain a huge challenge. In the absence of a widely available, rapid and reliable

diagnostic test for extrapulmonary manifestations of TB, clinicians face a management challenge in deciding when anti-tuberculous therapy should be offered.

1.3 Prognosis of tuberculous meningitis

It is widely recognised that TBM is the most severe form of TB - death and severe neurological sequalae are common. Reported outcomes vary drastically by geographical region, prevalence of HIV co-infection, drug resistance patterns, and time period. We reviewed tuberculous meningitis studies published up to Jun 6, 2018, to examine risk of death and neurological sequalae amongst survivors. Full search strategy and search terms are shown in **Appendix 1**. After manual screening of abstracts, we included 84 studies; 12 included all ages, 35 included adults only, and 37 included children only. We present data from both retrospective and prospective studies which commenced enrolment within the past 30 years (from 1988 onwards) and which enrolled at least 100 participants (n=28; 4 all ages, 16 adults, 8 children) plus two additional smaller studies which add to limited evidence within a drug-resistant population in **Table 1**.

For adults with TBM, risk of death ranged from 7-50% [17, 18] for in-hospital mortality, up to 58% [19] at five years' follow-up. Amongst survivors, risk of neurological sequalae ranged from 14-45% [17, 20]. Amongst studies including only HIV-infected adults, mortality was 41-58% [19, 21]. The majority of studies were performed in Asia, with evidence from East and West Africa notably lacking. A study in Uganda [22] examined a TBM population with 96% HIV prevalence, and reported 44% in-hospital mortality. Seven studies recruited patients with drug-resistant TB; those with isoniazid monoresistance demonstrated a mortality of 31-56% [23, 24] whereas those with rifampicin resistance or multi-drug resistant TB had a mortality of up to 95% [[24].

With regard to paediatric TBM, eight studies recruited exclusively children; those up to Oct 2012 are more comprehensively reviewed in a meta-analysis from Chiang et al [25], who reported a risk of death of 19% (95% CI 14.0–26.1) and a risk of neurological sequelae among survivors of 54% (95% CI 42.6–64.9) amongst 1636 children studied. Within our included studies, risk of death ranged from 8-29% [26, 27] for in-hospital mortality (excluding a small case series of patients with MDR-TB[28]), and up to 34% overall [26]. Amongst survivors, risk of severe disability was up to 40%[29], and all-severity disability up to 88% [30].

1.4 Towards better treatment of tuberculous meningitis: outline of this review

Development of better treatments is a priority in light of the high mortality and neurological disability associated with TBM. Prompt diagnosis and effective antimicrobial treatment is critical to limit bacillary multiplication and associated immunopathology in the central nervous system (CNS). Host-

directed therapies targeting immunopathology are an important area of research but outside of the scope of this review [31].

In this review, we focus on intensified antibiotic treatment of TBM. First, we discuss the rationale and options for intensification of antibiotic treatment as well as available data for key anti-tuberculous agents. Secondly, we address the relevance and considerations of intensified treatment in HIV co-infection, drug-resistant TBM, and paediatric populations. Thereafter we explore ways to accelerate understanding in this field through the application of state-of-the-art and intelligent research tools. We conclude by highlighting knowledge gaps and identifying key areas for future research.

2. THE CONCEPT OF INTENSIFIED ANTIBIOTIC TREATMENT

2.1 The challenge of treating tuberculous meningitis

TBM is more challenging to treat than pulmonary TB (PTB) for a number of reasons. Most importantly, in contrast to antibiotics used to treat PTB, antimicrobials for CNS TB must cross the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB), and remain in the brain or CSF and be present at the site of infection at sufficient concentrations for a sufficient period of time to kill the TB bacilli **(Figure 1)** [32-36]. The BBB and the BCSFB separate the extracellular CNS fluid compartment, the interstitial fluid (ISF) and the CSF from the blood compartment, and transporters, like P-glycoprotein (P-gp), in endothelial cells actively pump substances out of the brain and into the blood or CSF, thereby protecting the CNS from the free entry of potentially neurotoxic substances [37, 38]. Despite the presence of these barriers designed to keep foreign materials such as xenobiotics out, resulting in some first-line TB drugs, especially rifampicin and ethambutol, penetrating the BBB and BCSFB poorly, national and international guidelines for antimicrobial treatment for TBM follow the model for PTB, with a 2 month intensive phase followed by a continuation phases of treatment, using the same first-line TB drugs and identical dosing, just prolonged for 9-12 months duration [39-41] The World Health Organisation guidelines suggest replacing ethambutol with streptomycin but this has not been widely adopted and there is little evidence to warrant this [42].

There are at least three other reasons that TBM treatment is difficult. Firstly, the anatomical distribution and quantity of bacilli and their metabolic state (and, thus, likelihood of being killed by anti-tuberculous drugs given their particular mechanisms of action) -- and the changes in these factors over time with treatment -- are poorly characterized in TBM, making it difficult to develop a new treatment model specific for TBM. Further, the integrity of the BBB and BCSFB related to infection and inflammation, as well as blood supply to the compartments where *Mycobacterium*

tuberculosis resides, are likely to change significantly over the course of treatment as antibiotics and anti-inflammatory medications are given. This may affect the penetration of antibiotics to their site of action. Lastly, it is not clear how mechanisms of bacterial killing (protein synthesis inhibition, disruption of cell wall synthesis, bacterial enzyme inhibition) influence host inflammatory responses and, in turn, vasculitis, strokes, and risk of death. Host, bacterial, and treatment effects are thus intertwined and must be taken into account when investigating optimal treatments for TBM.

2.2 Strategies to optimize TBM treatment

In the absence of basic information on the interaction of host, bacteria and treatment effects, there may be different strategies to optimize TBM treatment. One strategy might be prolonging treatment, as is often advocated. However, in one meta-analysis evaluating treatment duration, the risk of relapse was extremely low (~0.8%) and virtually identical in patients who got <6 months versus >6 months of therapy, suggesting that there is no evidence base to support longer treatment as a means to improve response to TBM treatment [43].

A more promising strategy is to increase drug exposures in the CNS. This may be achieved by increasing doses of poorly penetrating drugs, adding or replacing drugs with anti-tuberculous agents that have better BBB and BCSFB penetration characteristics [44], modification of physicochemical properties of TB drugs, intracerebral injection, olfactory route delivery, tight-junction modulation (e.g. by osmotic opening, liposome or nanoparticle-mediated permeation) and, finally, inhibition of efflux mechanisms that pump drugs out of the brain [37, 45-47]. Considering the limited availability of some of these interventions in general and particularly in settings where TB is most common, increasing doses of poorly penetrating drugs and the use of agents with improved penetration may form the most obvious way to intensify and improve TBM treatment.

To find the optimal dose of drugs for TBM, whether they penetrate poorly or relatively well across barriers, robust information on the relationship between doses and exposures achieved (pharmacokinetics, PK) and between exposures and efficacy or safety (pharmacodynamics, PD) is indispensable. Ideally, the ‘right’ dose results in maximum efficacy, with limited adverse effects **(Figure 2).** Dose-response or preferably exposure-response evaluations are part of the drug development process. However, historically, for most TB drugs currently in use **(Table 2)**, far less attention has been paid to establishing the relationship between drug concentrations and responses for optimal dose-finding. Furthermore, there has been little interest in exploring PK-PD differences among TB disease-type subsets, such as patients suffering from TBM or TBM-HIV coinfection. The paradigm that inadequate exposure results in suboptimal clinical response is nevertheless generally accepted for TB drugs and has been described in multiple studies.[48-54] Nonetheless, such a relationship could not always be identified [55-57], and for most TB drugs dose-response curves

such as presented in **Figure 2** are lacking, especially with sterilizing effect as a clinical endpoint. The search for the 'right' high-dose of rifampicin is an illustrative example of how a better understanding of TB drug pharmacokinetics and pharmacodynamics could be used to improve treatment regimens.

2.3 Rifampicin

Rifampicin is an essential component of TBM treatment. Rifampicin-resistant TBM is 69-100% fatal·[23, 58-60]. Up to now, no agents have been identified that can replace it for treatment of TBM. However, rifampicin has poor CSF penetration, and at current treatment doses, CSF concentrations of rifampicin barely exceed the minimal inhibitory concentration (MIC) against *M. tuberculosis* [61]. When interpreting rifampicin CSF concentration data, it is important to keep in mind that rifampicin in highly protein bound and that only the unbound or 'free' rifampicin is biologically active. In the absence of meningeal inflammation only the 'free' rifampicin crosses the BCSFB. Therefore, the difference of *total* rifampicin concentrations between plasma and CSF is usually much bigger than the difference between 'free' or active rifampicin concentrations, and the CSF:plasma ratio of total rifampicin will underestimate penetration of unbound (active) rifampicin.

As to the pharmacodynamics of rifampicin, it has been shown that the efficacy of this drug is exposure or concentration dependent, which means that it correlates with exposure to the drug (area under the concentration - time curve, $AUC_{0\text{-}24h}$) and/or its peak concentration (C_{max}) [62]. An increase in rifampicin dose will increase the $AUC_{0\text{-}24h}$ and C_{max} in plasma and at the sites of action in supra-proportional fashion (owing to saturable hepatic clearance), and this is hoped to enhance activity against *M. tuberculosis.*

In search of higher yet safe doses of the cornerstone TB drug rifampicin, several studies have been performed. Studies using an *in vitro pharmacodynamics system (IVPDS)* or "hollow fiber model" and studies in mouse models have suggested that higher doses of rifampicin are associated with better results and shorter treatments in pulmonary TB [62-64]. Until 2011, fourteen clinical trials had evaluated high-dose rifampicin [65]. Thirteen of these trials were published before 1985. These trials evaluated regimens with doses of rifampicin up to 1200 mg (20 mg/kg) and different dosing intervals (once, twice, thrice, six times per week, and daily). Several trials suggested an advantage in terms of likelihood of culture conversion among patients with pulmonary TB receiving at least 900 mg of rifampicin. Hepatotoxicity was rarely observed, and no trend in the occurrence of hepatotoxicity with the rifampicin dose was evident. However, attempts to use high dose rifampicin (900 mg or 15 mg/kg and more) *intermittently* rather than daily were met with a high incidence of flu-like syndrome, an allergic reaction which is ascribed to the intermittency of dosing rather than the height of the dose. Therefore, high dose rifampicin should be administered on a daily basis [65, 66].

More recently, several trials have evaluated the high dose rifampicin as a strategy for treatment shortening for pulmonary TB. Increasing doses of rifampicin up to 40 mg/kg daily were associated with a nine-fold increase in total exposure to rifampicin in plasma compared to the standard 10 mg/kg dose and were safe and tolerable over two weeks [67, 68]. From the same data, a significant exposure-response relationship could be derived between rifampicin exposure and early bactericidal activity [54]. In another recent clinical trial, a higher daily rifampicin dose of 35 mg/kg administered over a longer period of 12 weeks together with standard doses of isoniazid, pyrazinamide and ethambutol decreased the time to culture conversion compared to standard treatment [69]. PK-PD analysis revealed that higher exposures to rifampicin were the intermediary link to the decreased time to culture conversion and showed that this effect of rifampicin did not plateau at the 35 mg/kg dose [70]. Higher doses of rifampicin up to 20 mg/kg have also been studied and were safe and tolerable for other diseases such as brucellosis [71], leishmaniasis [72], and other indications [73].

Along with the studies on pulmonary TB, high dose rifampicin has also been evaluated as a strategy to reduce mortality in TBM. Alvarez-Uria administered 900 mg (~20 mg/kg) of oral rifampicin for a median of 7 days to adults with TBM in India; no safety issues were reported in this setting [74]. In the first in a series, in an open-label, randomised phase II clinical trial in Indonesia, a 33% higher dose of rifampicin administered *intravenously* (600 mg, or 13 mg/kg iv) for two weeks resulted in a three-fold higher exposure to rifampicin in plasma and CSF during the first critical days of treatment than 450mg given orally. Six-month mortality was reduced by greater than 50% in this small study [61]. A clear concentration-effect relationship could be identified, with the ‘effect’ being survival at 8-weeks **(Figure 2)** and threshold values associated with decreased mortality could be derived through PK-PD modeling, even though data suggested that the exposures that maximized efficacy had not been reached yet [75]. Since intravenous rifampicin is not widely available and must be administered in a hospital setting, a follow-up pharmacokinetic study evaluated doses of 17 or 20 mg/kg of oral rifampicin, which resulted in total exposures in plasma approximately similar to the values after 13 mg/kg iv, but average peak plasma and CSF concentrations were lower with large interindividual variability [76]. In literature, reported rifampicin MICs for susceptible strains ranged from 0.06 to 0.4 mg/L [77, 78]. CSF concentrations after 17 or 20 mg/kg oral rifampicin ranged from 0.125-1.06 mg/L [76] and can therefore be considered to have reached MIC, but not by much.

In a third phase II trial, this time double-blinded, randomised, and placebo-controlled, 60 adult TBM patients were assigned to 10, 20 or 30 mg/kg oral rifampicin combined with standard companion TB drugs for 30 days. The double and triple dose of oral rifampicin led to three and five-fold higher total exposures in plasma in the critical early days of treatment with proportional increases in highest

recorded CSF concentrations and without an increase in the incidence of grade 3/4 adverse events. Six-month mortality was 7/20 (35%), 9/20 (45%) and 3/20 (15%) in the 10, 20 and 30 mg/kg groups, respectively (p=0·12) [79]. In contrast to the Indonesian studies, a large trial involving 817 TBM patients in Vietnam evaluating to an intensified regimen with 15 (rather than 10) mg/kg of rifampicin plus levofloxacin versus standard of care for 8 weeks did not demonstrate a survival benefit for higher doses of rifampicin [80], except for patients with isoniazid monoresistant TBM [23]. It was postulated that the lack of effect in this study can be explained by the relatively modest dose increase of rifampicin [81].

Thus, the preponderance of the evidence points to a treatment benefit with higher doses of rifampicin, but this benefit is likely only to be seen with significant dose increases. Additionally, rifampicin has been shown in vitro to have a variety of anti-inflammatory effects – inhibiting the production of lipopolysaccharide induced pro-inflammatory mediators including nitric oxide, cyclooxygenase-2, tumor necrosis factor-α, and interleukin-1β and prostaglandin E_2 [82], as well as reducing microglial activation. Whether such anti-inflammatory benefits are dose-related requires further research.

With regards to other rifamycin antibiotics, rifabutin has been effective in rabbit pneumococcal meningitis, but neither it nor the other licensed rifamycin—rifapentine-- have been tested in clinical TBM [83].

2.4 Other first-line drugs (isoniazid, pyrazinamide, ethambutol)

Isoniazid has high early bactericidal activity that kills actively growing bacteria within the first 24 hours and causes substantial decreases in culturable sputum bacilli in pulmonary TB over the first 2 weeks of treatment [84]. Isoniazid has excellent CSF penetration [74, 75, 85-87]. It is a valuable component of TBM treatment, as evidenced by a two-fold higher risk of death in isoniazid-monoresistant compared to drug-susceptible TBM [24, 58]. Adding a second bactericidal agent (like levofloxacin) does not appear to confer a survival benefit unless the patient is infected with an isoniazid-resistant strain [80]. Isoniazid is metabolized by the genetically polymorphic N-acetyltransferase 2 (NAT2). This enzyme exhibits two main phenotypes of activity: fast and slow. This acetylator status has been linked to both treatment outcome and hepatotoxicity in pulmonary TB. In TBM, exposures to isoniazid in plasma and CSF were found to be higher among slow acetylators [88]. Increasing the dose of isoniazid, e.g. to 10-15 mg/kg daily as in treatment for multi-drug resistant TB, may be an option for intensified treatment of TBM, though this remains to be proven.

Pyrazinamide also penetrates well into CSF [89] according to unpublished data from the Ruslami [61] and Yunivita [75, 76] Indonesian studies. The drug only displays limited early bactericidal activity in drug-sensitive PTB (first 2-4 days of therapy), which is considered the most critical period in TBM treatment [90,91]. Activity thereafter (days 4-14) seems comparable with rifampicin and isoniazid [90,91]. In observational studies, pyrazinamide appeared to reduce risk of death and neurologic sequelae in children with TBM allowing shortening of TBM treatment to 6 months [92]. However, while some pyrazinamide appears to be good, more is not necessarily better, at least in selected patient populations. In one study involving patients with HIV infection (median CD4 count of 41 cells/mm^3), high pyrazinamide exposures in CSF were independently associated with increased risk of death and neurotoxicity, even after adjusting for blood-brain barrier integrity [19,93]

The main function of ethambutol is to protect companion drugs against emergence of resistance, but ethambutol has poor CSF penetration, even early in treatment [86,89,94,95]. Considering this probably limited contribution, debate has arisen regarding the choice of a fourth drug in treatment of drug-sensitive TBM. But efforts to replace ethambutol, or add-on a drug to the first-line regimen have been ineffective so far [61,96] Thus, isoniazid and rifampicin are essential drugs for drug-sensitive TBM, pyrazinamide is helpful, there is not a clear role for ethambutol.

2.5 Second-line drugs: fluoroquinolones

Fluoroquinolones have excellent CSF penetration [97,98], and high activity against drug-susceptible bacteria as well as many drug-resistant bacteria. Analysis of fluoroquinolone exposure versus response revealed worse outcomes among TBM patients with lower and higher plasma and CSF exposures than for patients with intermediate exposures (U-shaped exposure-response) [99].
In a phase II trial with factorial design, TBM patients were randomized to a higher intravenous dose of rifampicin and subsequently to a standard dose of moxifloxacin, a double dose of moxifloxacin or no moxifloxacin [61]. Use of moxifloxacin was not associated with a survival benefit in this trial. The higher dose of moxifloxacin was used considering that higher exposures to moxifloxacin may be more effective in TB treatment based on studies *in vitro* and in mice, and rifampicin decreases the exposure to moxifloxacin by approximately 30% [100]. Similarly, in a large trial of intensified anti-tuberculous therapy in Vietnam, levofloxacin failed to improve survival unless the disease was caused by bacteria resistant to isoniazid [80,23]. A meta-analysis of use of fluoroquinolones in the management of TBM used data from 1115 patients and concluded that fluoroquinolones cannot be recommended at present, though the evidence was of moderate to low quality [101]. In light of two RCTs that have failed to show a benefit of quinolones in combination with current first line anti-tuberculous agents [80,102], further trials of quinolones are only likely to be warranted in combination with novel agents.

2.6 Second-line and repurposed drugs: aminoglycosides, cycloserine, ethionamide, clofazimine, and linezolid

Streptomycin distribution into brain and CSF is limited, [89] and while its use in the 1940s decreased mortality from 90% to 40-80%, this was only with long, complicated, painful treatment with repeated intrathecal injections over months [103], and its contribution to improving outcomes once multidrug regimens were available was small and only seen with intrathecal administration [97,104]. The same constraints apply to amikacin and kanamycin, with limited entry to CSF described in adult and paediatric studies [85,89].

Cycloserine and ethionamide achieve high concentrations in CSF, and the latter has been used successfully as a replacement for ethambutol to enhance TBM regimens in children [74,105,106]. Both can cause CNS adverse effects including psychiatric disturbances and there are dose-limiting gastrointestinal toxicities for ethionamide. Ethionamide can be changed for the chemically similar prothionamide, and cycloserine for terizidone (containing two molecules of cycloserine) can be used interchangeably in pulmonary TB, although there is limited evidence in TBM. Clofazimine does not penetrate CSF well but in a single mouse study showed widespread brain tissue distribution [107,108]. Studies in rats suggest that para-aminosalicylic acid can cross the BBB and BCSF barriers [109], in humans the CSF concentrations of PAS are low, even in the presence of meningitis [89].

Linezolid is an approved predominantly bacteriostatic drug, which has shown efficacy against multidrug resistant (MDR) and extensively drug resistant (XDR) TB [110-112], Two recent reviews support linezolid's efficacy for treating pulmonary MDR or XDR TB, though the optimal dosing that maximizes efficacy while minimizing risk of toxicities (bone marrow suppression and peripheral neuropathy) is not firmly established [110-112]. Janssen and the TB Alliance's Nix-TB trial investigated a shorter, all-oral three-drug regimen for XDR-TB, consisting of bedaquiline, pretomanid and linezolid (600 mg BID, later changed to 1200 mg QD) for six months [113,114]. Dose reduction or interruption due to myelosuppression or neuropathy occurred only after a treatment period of 2-3 months and 4-6 months respectively, supporting a short-term linezolid intervention in TBM.

Linezolid seems successful in reaching the CSF, with CSF/serum concentration ratios varying from 0.7 to 1.0 in studies among patients with CNS infections without TB [115-117].' The impressive efficacy of linezolid in the management of critically ill patients with non-TB CNS infections (e.g. penicillin-nonsusceptible *Streptococcus pneumoniae*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*) was reviewed by Ntziora *et al*. [118].

Only two studies have evaluated the effect of linezolid in patients with TBM, both in China [119]. In a non-randomized study among adults with severe TBM, sixteen patients received adjunctive linezolid (600 mg BID, median duration 32 days) [120]. Compared to the control group, patients showed better improvement in Glasgow Coma Scale, temperature recovery, and normalisation of CSF parameters, and safety was acceptable. No pharmacokinetic data were collected. Secondly, in a small retrospective cohort children without clinical improvement after two weeks of standard treatment were given linezolid while other children continued on standard treatment only, the addition of linezolid was associated with improved clinical outcome, shortened fever clearance time, and reduced hospital stay. These results suggest that linezolid may be an effective additional drug for treatment of TBM, which is safe when given for a short duration (<4 weeks) [120].

2.7 New drugs—bedaquiline, delamanid, pretomanid

Bedaquiline appears to have poor penetration into CSF, though data are limited, and binding to tubing make drug measurement following lumbar puncture challenging [121]. Delamanid achieves CNS concentrations that are several-fold higher in brain than in plasma in rats [122], but there are no clinical data. Mass spectrometry imaging of rats following intraperitoneal administration of pretomanid demonstrated distribution of pretomanid to certain areas of the brain in uninfected animals [123]; brain or CSF distribution in infected animals or humans has not been assessed.

Thus, the second-line or new drugs with the highest likelihood of providing meaningful benefit include the following: cycloserine or ethionamide (though these drugs carry high risk of toxicity), linezolid (optimal dosing to be determined), and possibly the nitroimidazoles (e.g. delamanid or pretomanid). It is hoped that new compounds in the TB drug development pipeline (https://www.newtbdrugs.org) will have characteristics associated with high probability of achieving effective concentrations in the brain and CSF, for example high CNS multiparameter optimization desirability scores [44,124].

3. INTENSIFIED TREATMENT FOR SPECIFIC POPULATIONS

3.1 HIV co-infection

Mortality from TBM is 2 to 3-fold higher in HIV co-infected individuals. Mortality depends on stage of disease at presentation and is modified by HIV infection, with estimates of death in HIV-uninfected adults of 15%, 30%, and 50% and HIV-infected adults of 25%, 50%, and 80%, for Medical Research Council stage I, II, or III disease, respectively [125,126]. Antiretroviral therapy (ART) naïve patients who present with TBM are at high risk of severe adverse events, most likely due to immune reconstitution inflammatory syndrome (IRIS), if they initiate ART immediately [19], yet delayed ART initiation puts them at risk of opportunistic infections and other complications of AIDS. There are two

reasons why intensified antibiotic therapy might be especially relevant for HIV-infected TBM patients.

Firstly, a number of studies have reported that HIV-positive patients achieve lower plasma concentrations of the orally administered first-line anti-tuberculous drugs than their HIV-negative counterparts, particularly those with more advanced HIV [127,128,129]. Possible explanations relate to HIV enteropathy, diarrhoea, and wasting (latter leading to under-dosing using current weight-based algorithms) [127,128,130,131].' A recent meta-analysis of rifampicin pharmacokinetic data for 931 individuals concluded that HIV status affects the total exposure to rifampicin in the early days of treatment (AUC 37.2mg.h/L in HIV-positive versus 56.7mg.h/L in HIV-negative, p=0.003) but not later in therapy [132]. The lower plasma rifampicin exposure in HIV-positive individuals in the initial days of therapy may be particularly relevant in TB meningitis, which carries a high early mortality.

Secondly, compared to those without HIV co-infection, HIV-infected TBM patients generally have less meningeal inflammation, as shown lower CSF white blood cell count or protein [133-136]. When meninges are inflamed the tight junctions between cells of the choroid plexus are disrupted allowing plasma proteins and protein-bound drugs (like rifampicin) to penetrate the CSF more readily [137]. One may therefore hypothesise that reduced meningeal inflammation in HIV-associated TBM may result in lower levels of anti-tuberculous drug penetrating the BCSFB, although this has not been studied. However, if this hypothesis is valid, then intensified therapies that penetrate effectively into the CNS, regardless of degree of meningeal inflammation, will be important in HIV-associated TBM.

Theoretically, intensified antibiotic treatment might lower the risk of IRIS in TBM. IRIS is a condition that results from rapid restoration of pathogen-specific immune responses to *M. tuberculosis* resulting in exuberant inflammation [138]. Although such paradoxical reactions have also been described in HIV-uninfected patients, the incidence is much greater (up to 47%) in HIV-infected patients on initiating ART [138,139]. TBM-associated IRIS presents as a recurrence or deterioration of neurological symptoms and typically occurs within the first three weeks and up to 3 months after ART is initiated, recommenced or switched [140,138]. The risk of IRIS in TBM is much higher (RR 9.3, 95% confidence interval 1.4 to 62.2) in patients with positive baseline CSF culture compared to those with negative CSF cultures [138]. Culture positivity reflects a higher *M. tuberculosis* antigen burden, more rapid eradication of *M. tuberculosis* antigen by intensified treatment may theoretically reduce the risk of subsequent IRIS on ART initiation. It should be emphasised, however, that corticosteroids are currently the only proven therapy for paradoxical reactions, including IRIS, and that the onset of paradoxical reactions does not warrant intensification of antimicrobial therapy [140].

There are two other important considerations in HIV-TB co-infection with regards to intensified treatments. Firstly, there are significant drug-drug interactions between rifamycins and many ART drugs. Rifampicin causes induction of cytochrome P-450 (CYP) enzymes, phase II metabolizing enzymes, and drug transporters, reducing concentrations of many companion drugs [141,142]. Little is known about the maximal inductive capacity of rifampicin and whether high dose rifampicin would cause more significant drug-drug interactions, though a few small studies suggest maximal induction already occurs at standard doses of rifampicin [143-145]. The second consideration is the overlapping toxicity profile of many ART and anti-tuberculous agents. For example, linezolid and zidovudine can both cause significant myelosuppression, aminoglycosides and tenofovir can cause renal toxicity, fluoroquinolones and efavirenz can cause hepatoxicity. Whilst such toxicity is relatively easy to monitor and manage in higher income settings, in lower income settings with scarcity of laboratory tests and personalised drug regimens, drug toxicity can pose a major management dilemma. Current understanding and knowledge gaps regarding TBM-HIV are summarised in **Box 1**.

3.2 Drug-resistant TBM

The treatment of TBM can be complicated by various forms of drug resistance of *M. tuberculosis*. This can be resistance to just one TB drug (monoresistance), multi-drug resistance which refers to resistance to both isoniazid and rifampicin, and extensively-drug resistant TB in which there is also resistance against any fluoroquinolone and at least one injectable TB drug [146].

Isoniazid monoresistance appears to be the most frequent form of drug-resistant TBM. Heemskerk *et al*. reported isoniazid monoresistance, rifampicin monoresistance and multidrug resistance in 27%, 0.3% and 5% of 322 TBM patients in Vietnam [23]; and the study by Vinnard *et al.* showing 10%, 2%, and 19% of 324 TBM patients with the same resistance patterns in New York, USA [24]. HIV-infected patients with TBM are at a higher risk of rifampicin-resistant TBM [24,125].

The consequences of resistance to rifampicin and/or isoniazid are enormous, with mortality rates of up to 100% [24,58-60]. An important reason for this high mortality is the slow detection of drug resistance. The availability of Xpert MTB/RIF and, more recently, Xpert MTB/Rif Ultra tests is relevant in this respect, as these tests enable the detection of *M. tuberculosis* complex and rifampicin resistance within a few hours. Still the suboptimal sensitivity of these assays in CSF and the lack of susceptibility information on other TB drugs remain a challenge.

If rapid detection of drug-resistant TBM is possible, a drug regimen can be designed based on the resistance pattern. In TBM with *monoresistance to isoniazid*, available data suggest that use of

levofloxacin with a higher dose of rifampicin can improve survival [23]. The best regimen for the treatment of MDR TBM is unknown. Of the first-line agents, pyrazinamide is often added in MDR-TB treatment in general, and this drug shows a high penetration into CSF. It should be realized, however, that MDR-TB isolates are often resistant to pyrazinamide as well and further work is needed to characterize genotypes in varying geographic regions [147]. Furthermore, in line with MDR-TB treatment for pulmonary TB, high dose isoniazid (10-15 mg/kg daily) can be considered in case of low-level resistance to isoniazid with mutations in the Inh A promoter region, outside of the katG gene.

The second-line drugs with good penetration into the CSF, are the fluoroquinolones, ethionamide/prothionamide, cycloserine/terizidone and linezolid, as discussed above. Again, it should be noted that ethionamide/prothionamide and cycloserine/terizidone are associated with CNS disturbances and these may be additive when combined. Use of pyridoxine is recommended to prevent CNS effects. Ethionamide/prothionamide also cause gastro-intestinal intolerance. There is some cross-resistance between ethionamide/prothionamide with isoniazid if the inhA mutation is present.

Based on the above, a combination of TB drugs for MDR-TBM could consist of pyrazinamide, a fluoroquinolone (moxifloxacin or levofloxacin), ethionamide/prothionamide, and cycloserine. This does not add up to the recommended five effective agents yet and a combination of ethionamide/prothionamide and cycloserine may only be tolerated for a short term. Linezolid and high dose isoniazid (in case of low level resistance) are alternatives, and some clinicians may consider aminoglycosides as a fifth drug despite their poor penetration across the BBCSF barrier. There is no clear option for further intensification. Clearly there is an urgent need for comparative trials on combinations of the available and promising drugs in drug-resistant TBM, though RCTs in drug-resistant TBM would face significant logistical challenges due to low patient numbers at any given centre.

3.3 Paediatric TBM

As noted above, compared to adults, children often have nonspecific presentations. Prodromal symptoms in older children include fever, headache, anorexia, and vomiting. In younger children, presentation is often one of nonspecific symptoms including failure to thrive, poor appetite, and vomiting. Despite the importance of early initiation of anti-TBM therapy, treatment is often delayed, as diagnosis in the paediatric population is challenging. In additional to risk of death (which appears to be lower in children than adults) and neurologic sequelae [25], TBM in children occurs in the context of a developing brain. Intellectual impairment is common, and there is a risk of developmental sequelae related to TBM that is unique to children, as the condition affects children

during important neurodevelopmental stages [148,149]. Given the high risk of functional and neurodevelopmental impairment following pediatric TBM, any improvement in treatment has the potential not only for reducing risk of death and functional disability but also for improving quality of life in young children by improving long-term neurocognitive outcomes.

Clinical trials of anti-inflammatory therapy with steroids or thalidomide have been conducted [150-152], but up to now there have been no clinical trials of antimicrobial treatments in pediatric TBM. Likewise, almost all data describing CSF concentrations of TB drugs in TBM are from adults. Best treatment practices, therefore, must be extrapolated largely from adult trials, with doses adjusted for differences in drug disposition in children. Recognizing that standard-recommended pediatric dosing of first-line drugs achieves subtherapeutic concentrations (for targets established for pulmonary TB) in a high proportion of children [153-155], it is clear that optimal treatment of TBM or CNS TB will require higher doses of the most life-saving drugs, most notably rifampicin. Based on adult PK targets for rifampicin associated with improvements in mortality and knowledge of the developmental pharmacology of this drug, rifampicin should almost certainly should be dosed at 30mg/kg or higher in children [156]. Second-line drugs have not been examined for efficacy expressly in paediatric TBM, though linezolid which was associated with improved clinical outcomes in adults, may have a role in paediatric TBM [119].

While WHO recommends treating paediatric TBM with 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 10 months of isoniazid and rifampicin, there is variability in guidelines given the paucity of clinical trials data to inform practice, and in some settings treatment duration is shorter. In South Africa, for example, children are mostly treated for six months using high-dose isoniazid, high-dose rifampicin, standard-dose pyrazinamide, and ethionamide (the latter in place of ethambutol) [106], based on cohort data showing the efficacy of this regimen. While adult trials can lend clues about the best antimicrobial treatment for pediatric TBM, independent trials in children may be especially valuable to look at paediatric-specific outcomes such as neurocognitive and functional outcomes. Phase II and III clinical trials of enhanced antimicrobial treatments for paediatric TBM are enrolling or soon to start [157].

4. SUMMARY AND CONCLUSIONS

Meningitis is the most dramatic and devastating manifestation of TB, leaving up to 50% of those affected dead or disabled. While in this review we addressed the possible role of intensified antibiotic treatment, we acknowledge that a number of other factors are also highly relevant. Timely diagnosis and treatment is the most important factor related to patient outcome, and there is a need

for earlier presentation to hospital, more sensitive rapid diagnostics, and optimal supportive care [158]. Secondly, more effective or tailored host-directed therapy could help control the immunopathology associated with TBM. Importantly, we must kill the bug to cure the patient, and intensified antibiotic treatment with drugs and doses that reach the site of disease well and slow or arrest infection-related pathology is an intervention that could be applied broadly once compelling evidence of reduced death or disability has been provided by a randomised clinical trial, of which there are number in the pipeline **(Table 3).** In fact, in some settings this is already done. As an example, Table 4 contains a treatment regimen for critically-ill patients with suspected TBM who are admitted to the intensive care unit in the Netherlands **(Table 4)**. More research is needed to examine the role of higher doses of current drugs or use of alternative drug regimens, but some candidate drugs for use and/or optimization are emerging, as discussed in this review.

A number of priorities for future studies stand out. First, data support the use of a much higher-dose of rifampicin for TB in general and for TBM in particular. Toxicity does not seem to be higher compared to standard treatment, noting that the anticipated survival benefit would outweigh a higher potential risk of drug-toxicity. Besides high-dose rifampicin, a second approach that needs further study is the use of new drugs, especially linezolid, giving its good penetration and promising clinical effects, although this is based on two observational studies. Delamanid and pretomanid also merit further evaluation. A third priority is research in HIV-infected patients, children and drug-resistant TBM. HIV-infected patients are at much higher risk of dying, with lower average drug exposure and a higher risk of treatment complications like IRIS, drug interactions, and toxicity. Clinical trials in children are a high priority, as there are no published clinical trials in this population to date, and extrapolation of findings in adult patients is difficult in light of different PK-PD and disease characteristics. The considerable incidence of resistant TBM warrant further research in improved identification of drug resistant pathogens and comparative trials on combinations of available and promising drugs. A fourth priority is the use of innovative research strategies, including molecular pharmacology, PBPK models, adaptive trial designs, and smart quantitative pharmacology, including PK-PD assessments.

Finally, barriers to implementation of high quality care for TBM should be examined, prioritised and addressed. Delays in presentation to hospital, lumbar puncture and treatment initiation all contribute to poor outcomes. Intensified therapies for TBM holds potential to make the greatest impact on mortality only if such barriers are addressed as well. The global TBM research consortium which convenes every 1-2 years and that has issued standard case definitions for research,[159] standardized methods for enhanced quality and comparability of TBM studies,[160] and produced a recent general overview of TBM [31]. We hope this will catalyse high quality research in the field and translation of research findings to clinical practice.

Expert Commentary (500 – 1000 words)

TBM is a highly variable disease, with multiple competing causes of neurologic damage or death. Much remains unknown about immunopathogenesis in different populations and different disease stages, and how best to minimise the immunopathology. Additionally, the optimal antimicrobial chemotherapy regimen remains to be defined, and we have discussed a number of promising options and the immediate clinical trial landscape in this review. However, cases are rare in any one institution, and significant resources are required to care for any adult or child with TBM. Thus, there is much to gain from optimizing design and analysis of clinical trials in TBM. In addition, standardising of pharmacokinetic approaches across studies will allow for pooling of data or easier comparisons between studies. We believe there are a variety of innovative strategies that may add to the quality and scientific output of TBM research (**Box 2)**.

Firstly, we can take advantage of preclinical tools to aid us in designing regimens. Molecular pharmacological research using for example human liver microsomes, hepatic cell lines, brain capillary endothelial cell lines, and transporter overexpression models can help identify whether TB drugs are substrates, inhibitors and/or inducers of specific metabolic enzymes or drug transporters, including those transporters that control access of molecules to the brain or CSF [161]. It can predict drug-drug interactions mediated by metabolic enzymes or drug transporters, reveal possible synergy between drugs in combinations, and assess tissue penetration/accumulation characteristics [161]. Physiologically-based pharmacokinetic (PBPK) modelling is another valuable *in silico* tool; it combines mechanistically scaled *in vitro* experimental data about pharmacokinetics and drug distribution to relevant compartments to simulate *in vivo* behaviour, and can take into account the distribution of demographic and disease characteristics in the target population. In this way, PBPK modelling allows for prediction of drug concentrations in specific tissue compartments, such as the brain or CSF, and helps translate exposure predictions to other doses and populations. Thus, PBPK modelling can improve the efficiency and accuracy of drug, dose, and regimen selection up front.

A second important aspect is the trial design itself. Modern trial designs that are adaptive in nature and allow for testing of multiple regimens, with mid-trial selection of those arms that show enough promise to continue will help avoid late-phase trial failures which are costly in so many ways.[69] In trials for TBM, however, the optimal way to assess regimens mid-study is not clear and is made challenging by relatively low patient numbers and variability in presentation and disease severity.

Thirdly, irrespective of the trial design, integration of PK and PK-PD assessments into study design can enrich the information upon which decisions are made. For example, measurements of drug concentrations in the CSF can be useful in models linking site-of-action PK with outcomes, provided

samples are collected properly. Optimal sampling strategies should be employed to choose the best times to collect plasma samples and (generally) the single CSF sample per study participant. Timing of CSF sampling can differ among study participants so that CSF concentrations over a dosing interval can be characterized more fully using population PK modelling. Advanced pharmacometrics (pharmacokinetic-pharmacodynamic (PK/PD) modelling) is also crucial to maximize both study design and learning from rich and complex data that emerges from interventional trials. Examples include the assessment of paediatric doses of high dose rifampicin in TBM based on adult data,[156] and the evaluation of PK-PD relationships with high dose rifampicin in pulmonary TB.

When interpreting CSF concentration data, it is also important to keep in mind that unbound drug is the active drug, and highly-bound drugs may have vastly different concentrations in plasma and CSF but similar free concentrations in the two compartments. Of note, CSF concentrations do not always correlate with concentrations in the brain. While we commonly only have access to CSF to learn about CNS drug distribution, post-mortem measurement of drug in brain can provide critical information about distribution of specific drugs into granulomas and those areas affected by vasculitis and other TB-related brain pathologies. Although, animal models may be helpful in this regard, most animal models introduce TB meningitis by intracranial injections, possibly compromising the comparison with human BBB and BCSFB integrity and CNS drug entry.

To simplify TBM trials, having validated alternative endpoints could aid efficiency substantially — including CSF markers, neurocognitive or functional outcomes, microbiologic endpoints. A difference in normalisation of routine CSF parameters like glucose or more advanced (e.g. metabolomic [162] or proteomic [163]) markers could be used as surrogate markers of clinical response. Obviously, it is also important to correct the effect of intensified treatment for other factors associated with outcome (age, HIV-status, disease severity, inflammatory phenotype etc) to more accurately represent the relationship between the antimicrobial treatment and clinical outcomes [164].

Five-year review

In the era of ‘omics’ it is encouraging to see that we are beginning to understand more about the immunopathogenesis of TBM [139,162,165]. This may lead to discovery of novel targets for host immunomodulation or antimicrobial effect, as well as identification of repurposed drugs with potential activity in TBM. In five years a number of the enrolling trials of intensified antimicrobial therapy for TBM, listed in **Table 3**, will have yielded important information on the pharmacokinetics and clinical impact of higher dose rifampicin and linezolid in TBM. We will also have new insights into previously under-studied populations with TBM including children in India and Malawi and HIV co-infected adults in sub-Saharan Africa.

Key issues

- Timely diagnosis and treatment is the most important factor related to patient outcome, and there is a need for earlier presentation to hospital and more sensitive rapid diagnostics. More effective or tailored host-directed therapy will help control the immunopathology associated with TBM.

- Intensified antibiotic treatment with drugs and doses that reach the site of disease sufficiently and slow or arrest infection-related pathology is an intervention that can be applied quickly and broadly.

- More research is needed to examine the role of higher doses of current drugs or use of alternative drug regimens. Data support the use of a much higher-dose of rifampicin for TB in general and for TBM in particular. Linezolid, given its good brain penetration and promising clinical effects in two observational studies also warrant further investigation.

- Research in HIV-positive patients, children and drug-resistant TBM is a priority.

- Use of innovative research strategies are essential, including molecular pharmacology, physiologically-based pharmacokinetic (PBPK) models, adaptive trial designs, and smart quantitative pharmacology, including pharmacokinetic-pharmacodynamic (PK-PD) assessments.

Author	Site	Study Years	Design	N	% HIV	MRC Grade	Mortality	Sequalae
ADULTS								
AFRICA								
Cresswell [22]	Uganda	2010-2017	RC	142 (≥18y)	96	17% I; 69% II; 14% III	In-hospital: 62/142 (**44%**).	-
Marais [166]	South Africa	2009	RC	120 (≥18y)	88	33% I; 68% II/III	In-hospital: 45/120 (**38%**). 6-month: 58/120 (**48%**).	-
Patel [167]	South Africa	1999-2002	RC	30 INH-R, RIF-R (0.4-45y)	60	27% I; 37% II; 27% III	17/30 (**57%**) (follow-up unclear).	-
ASIA								
Nguyen [163]	Vietnam	2014-2016	RCT	120 (≥18y)	0	38% I; 49% II; 13% III	60-day: 11/120 (**9%**). *4/41 (10%) placebo; 6/39 (15%) aspirin 81mg; 1/40 (3%) aspirin 1000mg.*	Infarction: 15/102 (15%). *8/35 (23%) placebo; 2/30 (7%) aspirin 81mg; 5/37 (14%) aspirin 1000mg.*
Heemskerk [23]	Vietnam	2011-2014	RCT	322 with resistance profile (≥18y) (I: Rifampicin 10 mg/kg/d; II: 15 mg/kg/d & levofloxacin)	43	35% I; 44% II; 22% III	9-month: 90/322 (**28%**). *27/86 (31%) INH-R; 11/16 (69%) MDR/RIF-R; 52/220 (24%) INH/RIF-S.*	Neurological events: 64 (20**%**).
Gu [168]	China	2008-2012	RC	156 (adults; age not specified)	NR	25% I; 51% II; 24% III	12-month: 44/156 (**28%**).	'Poor' outcome: 60/156 (39%)
Alvarez-Uria [169]	India	2010-2013	RCT	203 (adults) (I: standard iATR (RHZE); II) double-dose dose RH & substitution of E for levofloxacin & ethionamide)	100	NR	12-month: 89/203 (**44%**) *I) 70/138 (51%); II) 19/65 (29%).*	-
Alvarez-Uria [170]	India	2009-2011	PC	1000 (adults)	100	NR	1-month: **16%,** 3-month: **26%,** 6-month: **31%,** 12-month: **39%,** 24-month: **46%.**	-
Torok [19]	Vietnam	2005-2007	RCT	253 (adults) (I: immediate ART; II: deferred ART)	100	32% I; 39% II; 29% III	9-month: 146/253 (**58%**) *I) 76/127 (60%); II) 70/126 (56%).*	-
Kalita [20]	India	NR	PC	122 (4-82y; 7 <12y)	4	33% I; 56% II; 12% III	3-month: 25/122 (**21%**). 6-month: 28/122 (**23%**).	Stroke: 55/122 (45%).
Hsu [171]	Taiwan	2000-2006	RC	108 (≥19y)	NR	22% I; 52% II; 26% III	9-month: 42/108 (**39%**).	-
Torok [172]	Vietnam	2001-2003	RCT	545 (≥14y) (I: dexamethasone; II: placebo)	18	32% I; 45% II; 23% III	3-month: 148/545 (**27%**) *I) 59/274 (22%); II) 89/271 (33%)* 9-month: 199/545 (**37%**) *I) 87/274 (32%); II) 112/271 (41%)* 5-year: 249/493 (**51%**) *I) 121/250 (48%); II) 128/243 (53%)*	-
SOUTH AMERICA								
Croda [21]	Brazil	1999-2007	RC	108 (6-53y)	100	37% I; 40% II; 23% III	In-hospital: 31/108 (**29%**). *MDR 3/8 (38.8%)* 9-month: 44/108 (**41%**). *MDR 5/8 (71%)*	-
Cecchini [18]	Argentina	1996-2004	RC	141 (≥15y)	72	NR	In-hospital: 71/141 (**50%**). HIV+ 64/101 (63%). HIV- 7/40 (18%).	-
NORTH AMERICA								
Vinnard [173]	United States	1993-2005	RC	1896 (269 ≥14y)	41	NR	End-of-treatment (unspecified): 541/1896 (**29%**). *INH-R 43/123 (35%) INH-S 498/1773 (28%)*	-
Vinnard [24]	United States	1992-2001	RC	324 (16 ≤19y) (I: INH-S/RIF-S; II: INH-R/RIF-S; III: INH-S/RIF-R; IV: MDR)	63	NR	End-of-treatment (unspecified): 183/324 (**57%**). *60-day: I) 102/225 (45%); II) 18/32 (56%); III) 5/6 (83%); IV) 58/61 (95%) MDR*	-
EUROPE								
Miftode [17]	Romania	2004-2013	RC	127 adults; 77 children (age divide not specified)	0	15% I; 2% II; 23% III	In-hospital: Adults 9/127 (**7%**); Children 6/77 (**8%**)	Neurological sequalae: Adult 18/77 (14%); Children 28/77 (36%).
Senbayrak [174]	9 European countries	2000-2012	RC	142 (≥14y) (I) Fully sensitive; II) INH-R/RIF-S; III) MDR)	2	NR	35/142 (**25%**) (follow-up unclear). *I) 29/122 (24%); II) 3/9 (33%); III) 2/5 (20%).*	-
Pehlivanoglu [175]	Turkey	1998-2009	RC	160 (≥14y)	1	16% I; 84% II/III	In-hospital: **10%**. 6-month: **17%**.	Neurological events: Hospitalisation 34%; 6-month 13%.
Efsen [176]	9 European countries; Argentina	2004-2006	RC	100 (≥16y)	100	NR	12-month: **51%.**	-
CHILDREN								
AFRICA								
Padayatchi [28]	South Africa	1992-2003	RC	8 MDR-TB	75	NR	In-hospital: 7/8 (**88%**).	-
Schoeman [30]	South Africa	NR	RCT	141 (range NR; mean <36mo) (I): Prednisolone; II) No steroid)	NR	0% I; 52% II; 48% III	6-month: 17/141 (**12%**). *I) 4/63 (6%); II) 13/54 (24%).*	Mildly disabled: 70/117 (60%). *I) 40/63 (64%) II) 30/54 (56%)* Severely disabled: 33/117 (28%). *I) 14/63 (22%) II) 19/54 (35%)*
ASIA								
Dhawan [27]	India	NR	PC	130	-	-	In-hospital: 38/130 (**29%**).	Severely disabled: 34/92 (37.0%).

Bang [177]	Vietnam	2009-2011	PC	100 (2-180mo)	4	48% I; 33% II; 18% III	8-month: 15/100 (**15%**).	Moderate disability: 21/81 (26%). Severely disabled: 6/81 (8%).
Nataprawira [26]	Indonesia	2007-2010	RC	128 (7-162mo)	NR	7% I; 42% II; 51% III	44/128 (**34%**) (follow-up unclear). In-hospital: 10/128 (8%).	-
Kumar [29]	India	2002-2004	PC	150 (1mo-12y)	NR	NR	In-hospital: 20/150 (**13%**).	Mild sequalae: 47/150 (31%). Severe sequalae: 60/150 (40%).
Karande [178]	India	2000-2003	PC	123 (3mo-12y)	7	4% I; 10% II; 86% III	End-of-treatment (unspecified): 28/123 (**23%**).	Disability: 70/123 (57%).
NORTH AMERICA								
Duque-Silva [179]	United States	1993-2011	RC	200 (<18 years)	1	NR	End-of-treatment (unspecified): 9/190 (**5%**).	-

Table 1. Clinical outcomes from TBM studies in adults and children. Studies published up to June 6, 2018; commenced enrolment 1988-; ≥100 participants (two smaller studies included which add to limited evidence within a drug-resistant population). RC = retrospective cohort; PC = prospective cohort; RCT = randomized controlled trial. NR = not recorded.

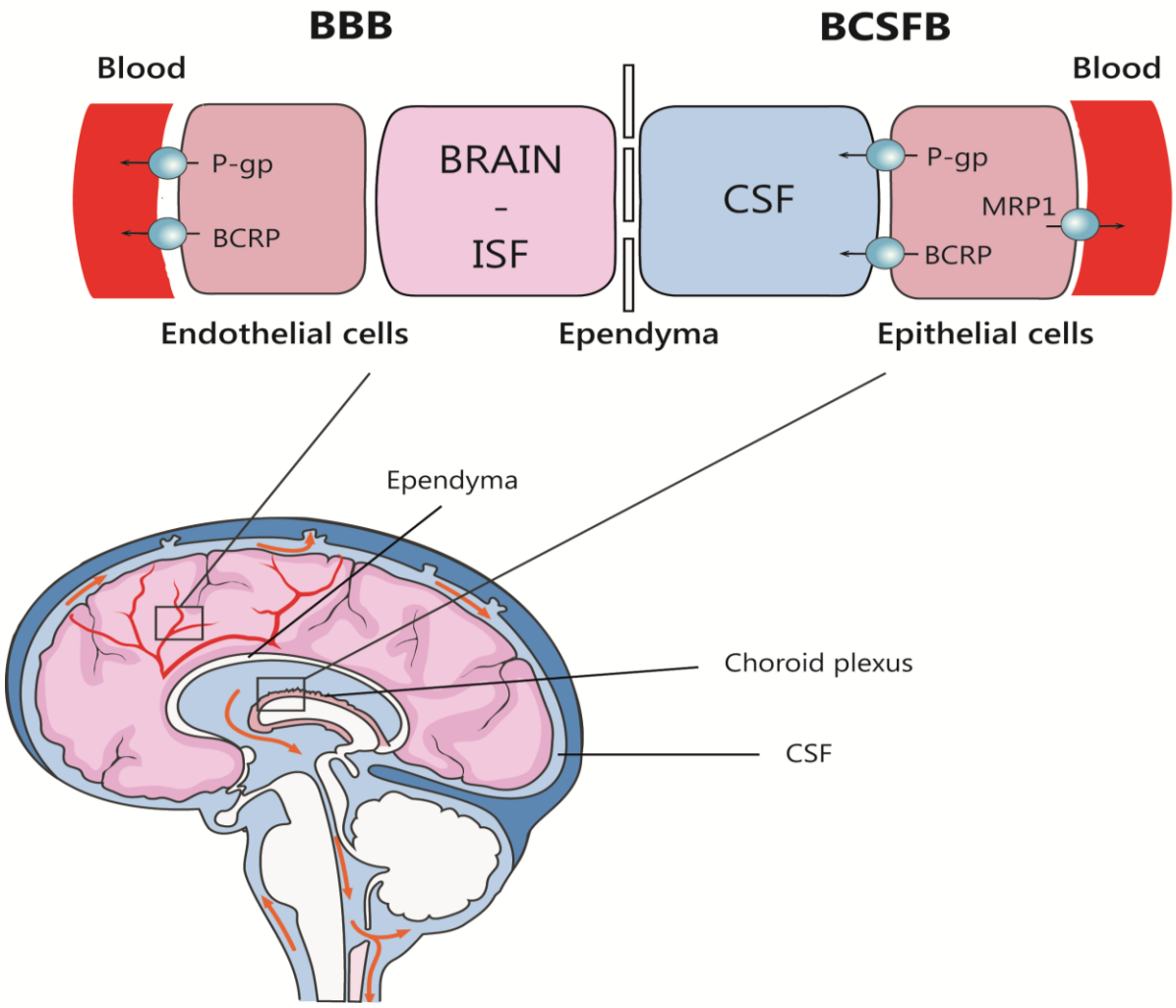

Figure 1. Schematic overview of the relation between the blood-brain barrier (BBB), made up by brain endothelial cells, and the blood-CSF barrier (BCSFB), made up by choroid plexus epithelial cells. The ependymal lining of the cerebral ventricles forms the barrier between brain (and its interstitial fluid, ISF) and CSF. According to this simplified paradigm, there is free exchange of drug between the brain ISF and CSF, and CSF drug concentrations approximate the free drug concentration in plasma that is able to penetrate the BBB, BCSFB, or both. Displayed efflux transporters may actively disturb this equilibrium, by actively transporting drugs into the blood or CSF

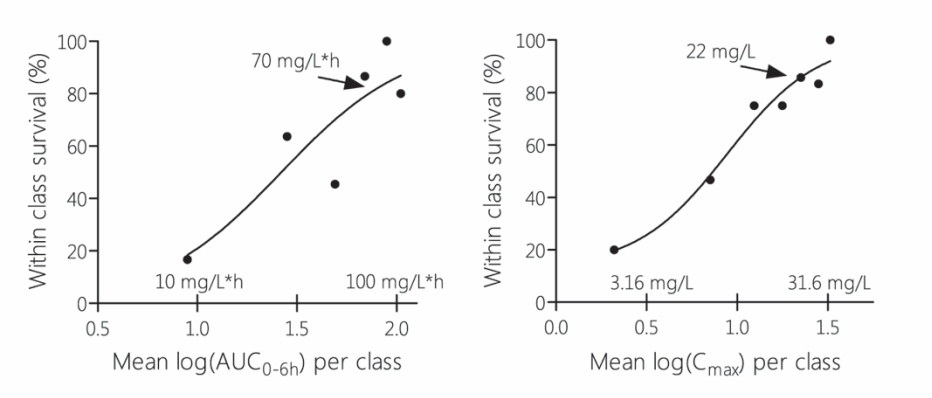

Figure 2. Concentration-response curves displaying the effect of rifampicin plasma $AUC_{0\text{-}6h}$ (left) and C_{max} (right) exposure on survival, and the corresponding exposure threshold values associated with maximal survival. Te Brake *et al.* aimed to deduce concentration thresholds predictive of good treatment response in TBM. For this classes of 20mg.h/L for $AUC_{0\text{-}6h}$ and 5mg/L for C_{max} were constructed (and included a minimum of 3 participants in each class), the percentage survival within each class was calculated. 8-week survival was used as the response parameter. Concentration-response curves were generated by non- linear regression fitting.

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)	Metabolism/ Elimination	Half-life (hr)	Relevant interactions	WHO TBM daily dose & duration	Toxicity	Renal impairment (CrCl <30ml/min)	Paediatric dose
First-line												
Rifampicin	PO; IV	70	-30%	89	10-20	Rapid hepatic deacetylation (7% excreted unchanged) Excretion: faeces (60-65%); urine (30%)	3.35± 0.66	Cytochrome P450 inducer	10mg/kg; 12 months	Orange staining of body fluids; rash/pruritus; gastrointestinal upset; flu-like syndrome; hepatotoxicity; haematological abnormalities	No dosage adjustment necessary	10-20mg/kg
Isoniazid	PO; IV; IM	~100	-50% C_{max}	0-10	80-90	Hepatic acetylation (50-90% excreted unchanged) Excretion: urine (~80%); faeces (<10%)	0.5-5	Cytochrome P450 inhibitor	4–6 mg/kg; 12 months	Hepatotoxicity; peripheral neuropathy; hypersensitivity reactions; optic neuritis; arthralgias; CNS changes; drug induced lupus; diarrhoea; cramping	300 mg once daily	<30 kg: 7-15 mg/kg; ≥30 kg: 4 to 6mg/kg
Pyrazinamide	PO	>90	None	~10	90-100	Hepatic hydrolysis (4-14% excreted unchanged) Excretion: urine (~70%)	9-10	None significant	25 mg/kg; 2 months	Gout (hyperuricaemia); arthralgias; hepatotoxicity; rash; photosensitivity; gastrointestinal upset	25–35 mg/kg per dose three times weekly	30–40mg/kg
Ethambutol	PO	75-80	None	20-30	20-30	Hepatic oxidation (85% excreted unchanged) Excretion: urine (~60%); faeces (~20%)	3-4	None significant	15–25 mg/kg; 2 months	Retrobulbar neuritis	15–25 mg/kg/dose, 3 times weekly	15–25mg/kg
Rifabutin	PO	50	Decreased rate of absorption	85	50	Hepatic (extensive) Excretion: urine (53%); faeces (~30%)	45± 17	P450 inducer	5mg/kg; 12 months	Similar to rifampicin; rashes/skin discolouration (bronzing or pseudojaundice); anterior uveitis; arthralgias	No dosage adjustment necessary	5–10mg/kg
Rifapentine	PO	70	None	98	-	Hepatic (75% excreted unchanged) Excretion: faeces (70%); urine (17%)	13	P450 inducer	600mg once weekly; 12 months	Similar to rifampicin	No dosage adjustment necessary	450mg once weekly if <45 kg
Second-line												
Streptomycin	IV; IM	~0	n/a	35	Low	Mostly unmetabolized Excretion: urine	5-6	Loop diuretics	15 mg/kg	Nephrotoxicity (kanamycin = amikacin > streptomycin); ototoxicity; vestibular toxicity; electrolyte abnormalities - hypokalaemia, hypocalcaemia, hypomagnesaemia	12–15 mg/kg/dose, 2–3 times weekly	20–40mg/kg
Kanamycin	IV; IM	~0	n/a	~0	10-20	Mostly unmetabolized Excretion: urine	2.5	Loop diuretics	15 mg/kg; intensive phase	Similar to streptomycin	12–15 mg/kg/dose, 3 times weekly	15–30mg/kg
Amikacin	IV; IM	~0	n/a	0-11	10-20	Mostly unmetabolized	2-3	Loop diuretics	15mg/kg; intensive phase	Similar to streptomycin	12–15 mg/kg/dose	15–30mg/kg

						Excretion: urine					after dialysis 2–3 times weekly	
Capreomycin	IV; IM	~0	n/a	0-10	-	Mostly unmetabolized Excretion: urine	5.2-6.8	Loop diuretics	15mg/kg; intensive phase	Similar to streptomycin	12–15 mg/kg/dose 2-3 times weekly	15-30mg/kg
Levofloxacin	PO; IV	~100	None	24-38	70-80	Mostly unmetabolized (>95% excreted unchanged) Excretion: urine (87%)	6-8	QT prolongation	10–15 mg/kg; throughout treatment	Nausea; bloating; headache; dizziness; insomnia; tremulousness; tendon rupture; arthralgias; QTc prolongation; hypo/hyperglycaemia; hepatotoxicity	750–1000 mg/dose, 3 times weekly	<5y: 15–20mg/kg; >5y: 10–15mg/kg
Moxifloxacin	PO; IV	90	None	50	70-80	Hepatic (45% excreted unchanged) Excretion: urine (~70%); faeces (~30%)	11.5-15.6	QT prolongation	400 mg; throughout treatment	Similar to levofloxacin	No dosage adjustment necessary	No established dose
Ethionamide	PO	~100	None	~30	80-90	Hepatic (<1% excreted unchanged) Excretion: urine	2-3	Isoniazid; cycloserine	15–20 mg/kg; throughout treatment	Gastrointestinal upset and anorexia; metallic taste; hepatotoxicity; gynaecomastia; hair loss; acne; impotence; menstrual irregularity; reversible hypothyroidism; neurotoxicity	No dosage adjustment necessary	15–20mg/kg
Cycloserine	PO	65-90	Slight decrease	~0	80-90	Mostly unmetabolized Excretion: urine	10	Isoniazid; ethionamide	10–15 mg/kg; throughout treatment	CNS toxicity (inability to concentrate; lethargy; seizure; depression; psychosis; suicidal ideation); peripheral neuropathy; skin changes (lichenoid eruptions; Stevens-Johnson syndrome)	250 mg once daily; or 500 mg, 3 times weekly	10–20mg/kg
Linezolid	PO; IV	~100	-23% with high-fat meals	31	70	Mostly unmetabolized Excretion: urine	4.5-5.5	Serotonergic agents	600 mg; throughout treatment	Myelosuppression; diarrhoea; nausea; optic/peripheral neuropathy; lactic acidosis.	No dosage adjustment necessary	<11y: 10mg/kg three times daily; >11y: 10mg/kg twice daily
Bedaquiline	PO	Unknown	Increase	>99	Likely poor (limited data)	Hepatic oxidation (<1% excreted unchanged) Excretion: urine	24 (terminal: 4-5 months)	P450 inducers/ inhibitors QT prolongation	400mg; 2 weeks then 200mg three times per week; 6 months	Arthralgia; dizziness; headache; hyperuricemia; insomnia; myalgia; nausea; pruritus; vomiting; QTc prolongation	No dosage adjustment necessary	No established dose
Delamanid	PO	25-47	Increase	>99	No human data	Albumin > hepatic metabolism Excretion: stool; urine (<5%)	30-38	P450 inducers/ inhibitors QT prolongation	200mg; 6 months	Headache; dizziness; nausea; paraesthesia; QTc prolongation	No dosage adjustment necessary; limited data	6-12y: 100mg
Pretomanid	PO	Unknown	Increase	93	No human data	Unknown	16-20	Possible QT prolongation	No established dose	Not established	N/A	No established dose

Table 2. Anti-tuberculosis drugs used in TBM treatment.[146, 180-183] PO = oral administration; IV = intravenous; IM = intramuscular.

Table 3. Summary of clinical studies investigating intensified antimicrobial treatments for TBM

Published							
Author	**Year**	**Country**	**Trial design**	**N**	**Drug regimens tested (daily doses)**	**Duration of intervention**	**Outcomes** **Clinical / Pharmacokinetic**
Alvarez-Uria[74]	2013	India	Observational cohort (100% HIV-positive)	A=138 B=65	***prior standard of care (A)****:* R 450mg, H 300mg, Z 1500mg, E 800mg ***compared with intensified regimen (B):*** LVX 750mg, ETD 750mg, Z 1500mg, R 900mg, H 600mg	7 days (IQR 6-9)	***Clinical:*** 21.5% (95%CI 7.3-35.7%) absolute reduction in 12 month mortality with regimen B ***PK:*** No PK data
Ruslami[61]	2013	Indonesia	RCT Phase II Factorial design (12% HIV-positive)	60	***First randomisation:*** R 450mg PO or 600mg IV ***Second randomisation:*** M 400mg or 800mg or E 750mg Standard doses of Z and H used in all participants	14 days	***Clinical:*** Reduction in 6-month mortality in IV rifampicin recipients (aHR 0.42; 95%CI 0.2-0.9). No increased toxicity ***PK:*** 3-fold increase in plasma $AUC_{0\text{-}24h,}$ C_{max} and CSF C_{max} with 600mg IV rifampicin
Heemskerk[80]	2016	Vietnam	RCT Phase III (43% HIV-positive)	A=409 B=408	*Standard of care (A):* R 10mg/kg, H 5mg/kg, Z 25mg/kg, E 20mg/kg *Intensified regimen (B):* R 15mg/kg, LVX 20mg/kg H 5mg/kg, Z 25mg/kg, E 20mg/kg	8 weeks	***Clinical:*** No reduction in mortality overall (HR 0.94; 95%CI 0.7-1.2, P=0.66). Subgroup analysis of isoniazid-resistant TBM found that intensified therapy was significantly associated with improved survival (HR 0.34, 95% CI 0.15 to 0.76, p=0.01)[23] No increased toxicity. ***PK:*** PK data awaited
Dian[79]	2017	Indonesia	RCT Phase II 3 arm, parallel group (10% HIV-positive)	A=20 B=20 C=20	A: R 450mg (standard dose, ~10mg/kg) B: R 900mg (double dose, ~20mg/kg) C: R 1350mg (triple dose, ~30mg/kg) Standard dose H, Z and E used in all arms	30 days	***Clinical:*** Six month mortality: 7/20 (35%), 9/20 (45%), 3/20 (15%) in arms A, B and C respectively (p=0.12) No increase in grade 3 or 4 AEs ***PK:*** 3 and 5-fold higher total plasma exposures with double and triple dose rifampicin. Proportional increases in CSF concentrations.
Sun[120]	2014	China	Retrospective cohort (HIV-negative)	A=17 B=16	A: Standard of care B: Standard of care plus adjunctive LZD 600mg twice daily	32 days (median)	***Clinical:*** Those who received LZD had more rapid resolution of coma and normalisation of temperature as well as higher CSF glucose and lower CSF white cell count. AEs limited: 12.5% in LZD group (including myelosuppression (n=1) and optic neuropathy (n=1), both resolved on discontinuing LZD) ***PK:*** no PK done
Thwaites[99]	2011	Vietnam	RCT Phase II 4 arm, parallel group	A=15 B=16 C=15 D=15	A: Standard of care (SOC) B: SOC plus CIP C: SOC plus LVX D: SOC plus GFX	270 days	***Clinical:*** Worse outcomes amongst participants with low or high plasma or CSF exposures, rather than intermediate exposures (U-shaped exposure-response) ***PK:*** CSF penetration (ratio CSF $AUC_{0\text{-}24h}$:plasma $AUC_{0\text{-}24h}$) greatest for levofloxacin (0.74, 95%CI 0.58-1.03).
Yunivita[76]	2016	Indonesia	RCT Phase II, Open-label, three-arm, two-period (20% HIV-positive)	A=11 B=9 C=10	A: R 750 mg (~17mg/kg) B: R 900 mg (~20mg/kg) C: R 600 mg i.v.	14 days	***Clinical:*** The study focused on pharmacokinetics and safety/ tolerability and was not designed or powered to study outcome or relationships between exposures and outcome. ***PK:*** 750 mg and 900 mg resulted in similar total exposures to rifampicin in plasma as compared with 600 mg IV, but peak plasma concentrations remain higher with i.v. administration.
upcoming or current TBM clinical trials of intensified therapy							
Trial name	**start**	**Country**	**Trial design /population**	**Sample size**	**Regimens to be examined**	**Duration of intervention**	**Outcome measures**

RifT study ISRCTN42218549	2018	Uganda	Phase II RCT 3 arm, parallel group (95-100% HIV-positive)	60	A: Standard of care R (R ~10mg/kg) B: Intravenous R 20mg/kg C: Oral R 35mg/kg H, Z and E given at standard doses in all arms	8 weeks	1. PK parameters in plasma and CSF (C_{max}, AUC, T>MIC) 2. Safety 3. 8 and 24-week mortality 4. Functional status (Rankin scale) at 2 and 24 weeks 5. Incidence of TBM-IRIS
TBM-KIDS NCT02958709	2018	India Malawi	Phase II RCT paediatric	120	A: high dose R (standard dose H, Z, E) B: high dose R and levofloxacin (standard dose H and Z) C: standard of care	8 weeks	1. PK parameters (plasma, CSF) 2. Functional outcome (Modified Rankin Scale) 3. Safety 4. Neurocognitve (Mullen Scales of Early Learning)
Simple NCT03537495	2018	Indonesia	Phase II RCT	36	Rifampicin 1350mg (~30mg/kg) with A: no LZD B: LZD 600mg daily C: LZD 1200mg daily H, Z and E given at standard doses to all participants	14 days	1. PK parameters in plasma and CSF 2. Safety 3. Clinical response 4. Neurological response 5. Mortality 6. Blood and CSF inflammatory response
Harvest	2019	Indonesia South Africa Uganda	Phase III RCT 2 arm, parallel design	600	A: Standard of care B: R 1500mg (Asia) or 1800mg (Africa), equivalent to ~35mg/kg. H, Z and E given at standard doses	8 weeks	1. 6 month survival time 2. Time to normalisation of consciousness (GCS 15) 3. Neurocognitive outcomes 4. safety and tolerability endpoints 5. PK-PD endpoints 6. Cost effectiveness
ACTG A5384	2019	TBD	Phase II RCT 2 arm, parallel design	300	A: 2 months $R_{35}H_{10}LZD_{1200}Z$, 4 months $R_{35}H_{10}$ B: Standard of care	6 months	1. 18 month survival time 2. Modified Rankin scale at week 12, 24, 26, 48 and 72 3. Grade 3-5 adverse events 4. Neurocognitive function 5. Time to GCS=15 6. Pharmacokinetic parameters
R = rifampicin, H= isoniazid, Z = pyrazinamide, E = ethambutol, ETD = ethionamide, CIP = ciprofloxacin, GFX = gatifloxacin, LVX = levoflozaxin, LZD = linezolid, M = moxifloxacin							

Known	Implications	Evidence
Two to three-fold increased risk of death in HIV co-infection	• Drivers of increased mortality not well characterised and require further research • HIV-associated TBM in particular may benefit from intensified therapy	Thao [184] Marais [159]
Diagnosis more challenging: differential diagnosis is broader and CSF picture can be atypical	• Diagnostic algorithms for TBM have poor sensitivity and specificity in HIV co-infection • Delayed treatment initiation due to diagnostic uncertainty may be implicated in poor outcomes • Additional diagnostic tests such as urine TB-LAM may be useful in the diagnostic process for disseminated TBM	Checkley [2] Cresswell [133] Marais [159] Gupta-Wright [185]
ART initiation should be delayed til week 8 in TBM.	• Provide dose-adjusted fluconazole in cryptococcal antigenaemia and co-trimoxazole prophylaxis if CD4<200 • Increased pill burden and additional risk of liver toxicity, renal dysfunction and blood dyscrasias	DHHS Guidelines [142] Torok [19]
Increased risk of immune reconstitution inflammatory syndrome (IRIS)	• IRIS has 30% associated mortality • Complicates ART initiation and increases steroid requirements • Alternative host-directed therapies are required	Marais [159] Pepper [186]
Overlapping drug toxicities with ART e.g. liver injury, peripheral neuropathies, rash	• Significant drug related adverse events are 3.8-fold more likely in HIV-TB co-infection than TB mono-infection This includes drug induced hepatitis which occurs in 10% of HIV-negative and 20% of HIV-positive TB patients. • Individualised therapy to avoid or manage toxicity is challenging in resource-constrained settings (individually formulated drugs are not widely available) so TBM treatment is often interrupted. Interruption of anti-TB drugs in TBM correlates with death • Availability of safe and personalised treatment is particularly important at HIV-TBM	Heemskerk [80] Thwaites [14]
Increased risk of drug-interactions with ART	• **PIs**: risk of virological failure due to significant reduction in PI exposures with rifampicin co-administration. Rifabutin recommended instead of rifampicin, though not widely available and little data in TBM. In the absence of rifabutin or alternative ART some use double dose lopinavir/ritonavir, though side effects are considerable. • **INIs**: require dose-adjustment with increased pill burden and possible increase in toxicity • **NNRTIs**: nevirapine is contraindicated due to marked reduction in exposure with rifampicin co-adminstration, switch required. Efavirenz levels reduced, though not thought to be clinically significant.	McIlleron [141] www.hiv-druginteractions.org
Increased risk of disseminated TB disease, or HIV-related organ pathology and associated complications	• HIV-positive people frequently have disseminated TB at the time of TBM, including granulomatous hepatitis, which can worsen on initiating anti-tuberculous therapy. Medical course may be more complicated due to multi-system disease at baseline.	Coash [187] Katrack [136]
Unknown	**Implications**	**Evidence**
Use of adjunctive corticosteroids is not of proven benefit in HIV-associated TBM	• Corticosteroids can be potentially harmful in people with advanced HIV as they may exacerbate fungal infections and Kaposi's sarcoma. A randomised trial in Asia is currently evaluating the impact of adjunctive corticosteroids in HIV-TBM.	Thwaites [14] Prasad [188] Chabria [189] Beardsley [190] Donovan [191]
Driver of lower exposure to rifampicin in early days of TB treatment in HIV-infection are not known	• Undetermined whether HIV-related intestinal immune activation, HIV enteropathy, wasting or alteration in drug transporters are contributory factors in the observed lower rifampicin exposures in HIV, nor whether ART use can modify exposures. • Further pharmacokinetic studies in HIV-TBM are needed • Parenteral administration may be preferable in HIV	Stott [132] Vinnard 2017[24] McIlleron [141]
Unknown whether levels of other anti-tuberculous drugs are reduced in HIV co-infection	• Possible reduced clearance of pyrazinamide and isoniazid in HIV co-infected patients with high levels of immune activation	Vinnard [192] McIlleron [141]
Differential degree of meningeal inflammation in HIV-associated TBM	• Reduced meningeal inflammaton in HIV likely to result in reduced levels of antimicrobial drug penetration into CSF compartment	Cresswell [133] Nau [137]
Theoretical risk of strongyloides super-infection with high-dose corticosteroids	• Concurrent antihelminthic treatment may be required to prevent overwhelming strongyloides infection in endemic regions (albendazole or ivermectin). Trial underway in Asia.	Donovan [191]

PI = protease inhibitors, INI = integrase inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors

Box 1. Implications of HIV coinfection in TBM

1. **Preclinical tools**
   - Molecular pharmacological research
   - Physiologically-based pharmacokinetic (PBPK) modelling
2. **Adaptive trial design**
3. **Integration of PK and PK-PD assessments**
4. **Tools for determination of CNS drug distribution**
   - PET imaging
   - Post-mortem measurement of drug in brain
   - Animal models
5. **Validated alternative endpoints**
   - Functional
   - Metabolomic
   - Proteomic

Box 2: Innovative research strategies and methodology

Table 4: Suggested intensified TBM regimen and administration for high resource settings

Individual drugs	Dose	Formulation	Administration
Isoniazid*	5 mg / kg p.o. or i.v.	tablet 200 mg or injection fluid 100 mg/ml, 3 ml	orally i.v. bolus: in 3-5 min i.v. infusion: add the dose to 100 ml NaCl 0.9%, administer within 0.5 h
Rifampicin*	30-35 mg/kg p.o or 15 mg/kg i.v. .	capsule (150 or 300 mg), tablet (600 mg) or powder for infusion fluid 600 mg (Rifadin®, Sanofi-Aventis)	orally i.v. infusion: dissolve 600 mg in 10 ml water for injection, add the correct dose to 250 ml NaCl 0.9%, administer in 1.5 h. Minimal volume is 100 ml, administration in 0.5 h.
Pyrazinamide*	30 mg / kg p.o.	tablet 500 mg	orally
Moxifloxacin*	600 mg p.o. or i.v.**	Tablet 400 mg or infusion fluid,1.6 mg/ml, 250 ml (Avelox®, Bayer)	i.v. infusion: infuse in no less than 1h. No dilution needed.
Optional fifth drug			
Linezolid*	600mg bd p.o. or i.v.	tablet 600mg, or infusion fluid, 2 mg/mL, 300 mL	orally, twice daily i.v. infusion: administer within 30-120 minutes, no dilution needed.
Amikacin	15 mg / kg i.v.	Injection fluid 250 mg/ml, 2 ml	i.v. infusion: add the dose to 100-200 ml NaCl 0.9%, administer in 0.5-1.0 h.
Other			
Dexamethasone	0·4 mg/kg i.v. (grade 2/3), or 0·3 mg/kg i.v. (grade 1) TBM	Dexamethasone disodium phosphate, 5 mg/ml, 1 ml	i.v. bolus: in 2-3 min i.v. infusion: add the dose to 50-500 ml NaCl 0.9%

This regimen is used in the intensive care unit at Radboud university medical centre, The Netherlands. All doses of drugs can be individualized by measurement of drug concentrations in plasma or CSF (Therapeutic Drug Monitoring, TDM)
*In patients without risk of malabsorption e.g. ileus medication can be given by mouth or by nasogastric tube in patients unable to take medication by mouth
** Higher dose of moxifloxacin is used to counteract the effect of rifampicin, which decreases the exposure to moxifloxacin by approximately 30% [100]
Of note, Intravenous compatibility of these drugs has not been tested, neither when combined in one infusion fluid nor when co-administered by Y-side. Only dexamethasone is compatible with amikacin infusion when administered through a Y-side. Therefore the drugs should be administered separate from each other and the injection port / infusion system should be flushed with NaCl 0.9% after each administration.

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