**The Pediatric Infectious Disease Journal Publish Ahead of Print**

**DOI: 10.1097/INF.0000000000000065**

# Short Intensified Treatment in Children with Drug-Susceptible Tuberculous Meningitis

Ronald van Toorn, FCP[1], H. Simon Schaaf, MD[1], Jacoba A. Laubscher, BCOMM[2], Sabine L. Elsland, MSc[1,3], Peter R. Donald, MD[1], and Johan F. Schoeman, MD[1]

Department of Pediatrics and Child Health[1], Stellenbosch University and Tygerberg Children's Hospital, Western Cape, South Africa. Biostatistics Unit[2], Medical Research Council of South Africa, Tygerberg, Cape Town. Department of Pediatric Infectious Diseases, Immunology and Rheumatology[3], University Medical Centre, Amsterdam, The Netherlands.

**Corresponding author:** Ronald van Toorn, Department of Pediatrics and Child Health, Stellenbosch University, PO Box 19063, Tygerberg, 7505, South Africa. Tel: +27 21 938 9113 Fax nr: +27 21 938 4858 E-mail: vtoorn@sun.ac.za

**Key words**: Pediatric, Children, Tuberculous meningitis, Treatment

**Sources of support:** None

**Abbreviated Title:** Short Intensive Treatment of Tuberculous Meningitis

**Running Head:** Tuberculous Meningitis

**Abstract**

**Background:** The World Health Organization recommends 12-months treatment (2RHZE/10RH) for children with tuberculous meningitis (TBM). Studies evaluating length of antituberculous treatment for TBM report similar completion and relapse rates comparing 6-months treatment with 12-months treatment.

**Methods:** A prospective evaluation to determine whether short course intensified treatment (6 RHZEth for HIV-uninfected and 9RHZEth for HIV-infected) is sufficient and safe in children with drug-susceptible TBM.

**Results:** Of 184 children with TBM, median age 58 months and 90 (49%) male, 98 children (53%) presented at stage II TBM, 64 (35%) at stage III TBM and only 22 (12%) at stage I TBM. Ninety (49%) children were treated at home after the first month of therapy; all others received their full treatment in hospital. The HIV prevalence was 14% (22/155 children tested). Antituberculosis drug-induced hepatotoxicity occurred in 5% (8 out of 143 children tested) all tested negative for viral hepatitis; in all 8 cases the original regimen was restarted without recurrence. After treatment completion, 147 (80%) children had a good outcome, 7 (3.8%) died. There was no difference in outcome between HIV-infected and HIV-uninfected children who completed treatment (p=0.986) nor between TBM-hydrocephalic children who were medically treated or shunted (p=0.166).

**Conclusion:** Short intensified treatment is safe and effective in both HIV-infected and HIV-uninfected children with drug-susceptible TBM.

## Introduction

Recent World Health Organization (WHO) guidelines recommend that children with tuberculous meningitis (TBM) should be treated with two months of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB) followed by 10 months of INH and RMP[1]. As the WHO has to consider the circumstances under which TB will be treated world-wide, this long duration of treatment was a compromise between the importance of preventing relapse and the unavailability of certain drugs (e.g. ethionamide) and an unwillingness to give pyrazinamide for more than two months in many settings. (personal communication Peter Donald)

However, a recent review found that all existing trials assessing antituberculosis treatment for TBM had limited power, poor methodology and used varying treatment regimens with conflicting results[2]. The studies reviewed reported similar completion and relapse rates when 6 months therapy with at least INH, RMP, and PZA was compared with longer treatment regimens, suggesting that 6-month therapy for TBM may be sufficient. Shorter treatment regimens are cheaper, less labor-intensive and may improve patient compliance.

This study describes local experience with intensive short-course antituberculosis treatment of at least 6-months duration in a large cohort of children with drug-susceptible TBM over a 4-year period. The aim was to demonstrate non-inferiority of our short-course intensive regimen compared with other published treatment regimens.

## Materials and Methods

### Setting

Tygerberg Children's Hospital (TCH), a referral hospital in the Western Cape province (WC) of South Africa, provides specialized care to half the province's 1.2 million children. A recent

pediatric meningitis survey identified TBM as the commonest form of bacterial meningitis in the WC [3].

**Study population and TBM definition**

All children admitted consecutively to TCH with TBM from 1 January 2006 through 31 December 2009, aged 0-13 years, were included in the study. Children with multidrug-resistant TB (MDR-TB; i.e. resistance to at least INH and RMP) were excluded but INH-monoresistant TBM cases were included. A definite diagnosis of TBM was made when *Mycobacterium tuberculosis* was cultured from cerebrospinal fluid (CSF) and /or polymerase chain reaction (PCR) for *M. tuberculosis* tested positive in CSF. In all other cases, the diagnosis was "probable TBM" based on clinical signs of meningitis in the presence of characteristic CSF findings (macroscopically clear, pleocytosis usually with lymphocyte predominance, elevated protein, and reduced glucose). In addition, 2 of the following criteria were required: other clinical specimens culture-positive for *M. tuberculosis* and/or positive TB histology, a positive tuberculin skin test, a chest radiograph compatible with TB, a cranial computerized tomography (CT) or magnetic resonance imaging compatible with TBM, growth failure with crossing of weight-for-age percentiles or finally, household contact with sputum smear-positive pulmonary TB.

TBM stage was classified as TBM stage 1 (Glasgow Coma Scale [GCS] 15 with no focal signs), TBM stage II (GCS 11-14 or GCS 15 with focal neurology) or TBM stage III (GCS< 11)

**Treatment of TBM**

Local practice is to treat TBM with a short, intensive 4-drug regimen consisting of daily INH 20 mg/kg (maximum 400mg daily), RMP 20 mg/kg (maximum 600mg daily), PZA 40 mg/kg

(maximum 2g daily) and ethionamide (ETH) 20 mg/kg (maximum 750mg daily), all given in a single daily dose, for 6 months duration. HIV-infected children, however, are treated for 9 months because of perceived slower response to treatment. Prednisone 2 mg/kg/day (maximum 60 mg/day) is given for the first month of treatment and gradually discontinued over the next 2-weeks. If the child's isolate of *M. tuberculosis* or that of the source case is resistant to any of the drugs used or if the child deteriorates clinically on this regimen, alternative anti-TB treatment is considered. Treatment of INH-monoresistant TB involves the addition of a fluoroquinolone and terizidone with treatment for 9-months. Air-encephalography is used to distinguish between communicating and non-communicating types of obstructive hydrocephalus. Institutional preference is to treat non-communicating hydrocephalus by ventriculo-peritoneal shunting (VPS) or endoscopic third ventriculostomy (ETV), whilst communicating hydrocephalus is treated medically with diuretics (acetazolamide 50 mg/kg per day and furosemide 1 mg/kg per day) during the first month of therapy to expedite normalization of intracranial pressure.

Once clinically stable, the child is medically evaluated and the family is screened by a social worker to determine suitability for home-based therapy [4]. Definite exclusion criteria for home-based treatment included: no reliable caregiver; insufficient income and support network; regular visits to TB-clinic not possible and no other DOT supporter available; MDR-TB or untreated household TB source case [4]. Caregivers of eligible patients were offered the choice of either in-hospital or home-based treatment.

During the 6-months home-based therapy, the mother and child were reviewed monthly assessing the clinical well-being of the child, adherence to treatment and adverse effects.

**Evaluation for adverse effects**

Local practice is to perform liver function tests [serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin] on admission and during the first 2 weeks of treatment. Thereafter children are observed clinically for symptoms of hepatotoxicity (jaundice, abdominal pain, new onset nausea and vomiting).

Anti-TB drug induced hepatotoxicity (ADIH) severity was classified according to WHO adverse drug reaction terminology [5]: grade 1 (mild): ALT <2.5 times upper limit normal (ALT 51-125 U/L); grade 2 (mild) ALT 2.5-5 times upper limit normal (ALT 126-250U/L); grade 3 (moderate): ALT 5-10 times upper limit normal (ALT 251-500 U/L); grade 4 (severe): ALT >10 times upper limit normal (ALT >500 U/L). First-line treatment (with liver enzyme monitoring) is continued in asymptomatic children with WHO grade 1 hepatotoxicity. Children who developed more severe degrees of liver toxicity are commenced on liver-friendly regimens which include amikacin, ofloxacin, ethambutol and terizidone (terizidone for good CSF penetration). Once the liver enzymes have normalized, stepwise re-challenge with first-line drugs is attempted. Nausea and vomiting was considered significant if vomiting occurred for more than 2 consecutive days and where intervention such as administering ETH in the evenings or anti-emetics was required. Combination antiretroviral therapy (cART) consisting of stavudine, lamivudine and efavirenz was initiated as soon after HIV diagnosis as possible.

**Outcome**

After treatment completion, motor function, intelligence, vision and hearing were tested. Developmental quotient (DQ) was measured by Griffith's developmental scales. Patients were grouped as "normal" (DQ: > 80), "mild intellectual impairment" (DQ: 50–80), or "severe

intellectual impairment" (DQ: <50). Vision and hearing were classified as normal, impaired and blindness or deafness.

Neurological outcome was divided into 4 categories: (1) normal, including normal intelligence, motor function, vision, and hearing; (2) mild sequelae, including mild intellectual impairment, hemiparesis, and impaired vision and/or hearing; (3) severe sequelae, including severe intellectual impairment, quadriparesis, blindness, and/or deafness; and (4) death. Clinical outcome was defined as "good" in the case of normal outcome or mild neurological sequelae and defined "poor" in the case of severe neurological sequelae or death.

**Relapse rate**

Patients who remained disease free (any form of TB) for a period of more than two years after treatment completion were considered cured. Relapse rate was determined by telephonic contact with the child's caregiver at least two years after therapy completion or if the patient was reviewed in our neurology outpatient clinic after this time. The caregiver was requested to confirm the child's identity by date of birth and questions were asked relating to the child's clinical well-being and scholastic performance. If the caregiver expressed any concern, clinical review in neurology outpatients was offered.

**Statistical analysis**

Outcome was categorized into good (normal/mild) and poor (severe/death) outcome. Bivariate associations with outcome were assessed by either the Chi-squared test or Fisher's exact test (categorical variables) or an ANOVA (continuous variables). A p-value <0.05 was indicative of statistical significance. Logistical regression was used to assess the association between outcome

("good" is reference) and either type of hydrocephalus or HIV infection. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). A multinomial logistic regression was used to assess the association between outcome (normal as reference, mild and severe/death) and where the patients were treated (home-based as reference versus in-hospital), adjusted for the stage of the disease. Results were expressed as relative risk ratios with 95% CI.

**Ethics**

Ethical approval (N11/07/244) was obtained from the Stellenbosch University Human Research Ethics Committee.

**Results**

Table 1 demonstrates the demographics, TBM staging, clinical features, selected diagnostic tests and outcome of 184 consecutive children less than 13 years of age with TBM.

All children with stage I TBM had a good outcome compared with 97% with stage II disease and 47% with stage III disease. There was no difference in outcome after completion of treatment between HIV-infected and HIV-uninfected children (OR 1.01, 95%CI 0.34-2.96, p=0.986). The overall mortality prior to completion of anti-TB therapy was 3.8% (7 of 184 children). All 7 children who died were moribund on admission (stage III disease) and three children died within 8-days of starting treatment. Cranial CT on admission revealed extensive bilateral basal ganglia infarction (suggesting brainstem involvement) in all seven cases; only one of those who died was HIV-infected.

Table 2 demonstrates the disease complications and drug adverse effects of the 184 TBM children. None of the children with communicating hydrocephalus required VP shunting and their outcome after completion of therapy was similar to those children with non-communicating hydrocephalus who required VP shunting. (OR 0.55, 95%CI 0.23-1.28, p= 0.166)

Liver enzyme levels before initiation of treatment were normal in 75 (90%) of the 83 children tested; none with baseline abnormal liver functions had ALT levels higher than 2.5 times the normal upper limit. Only 8 (5.6%) of the 143 children who underwent liver enzyme testing during treatment experienced ADIH (grade 3 or 4 hepatotoxicity); viral hepatitis serology proved negative in all and none of the children were clinically jaundiced or had elevated serum bilirubin levels. The medium age of the ADIH children was 34 months (range 15-156 months) and the medium duration on therapy was 44 days (range 8 days -105 days). In all cases, change to liver-friendly regimens resulted in normalization of liver enzymes (medium duration 7 days, range 3-16 days) and the original regimen was restarted (stepwise) without recurrence. None of the 22 HIV-infected children on cART developed grade 3 or 4 hepatotoxicity. All 8 children with grade 3 or 4 hepatotoxicity experienced significant new onset vomiting. The prevalence of significant vomiting in children without ADIH was 6% (n=11). In these cases, substituting ethionamide with ethambutol (3 cases) or administering the ethionamide at night rather than in the morning solved the problem.

Table 3 demonstrates the duration of therapy and reasons for prolonged treatment (longer than 6 months) in the 177 TBM children who survived completion of therapy. Figure 1 illustrates the baseline and outcomes of the 184 TBM children who intended and received 6 months of treatment compared to those who required prolonged treatment because of other reasons. Table, Supplemental Digital Content 1, http://links.lww.com/INF/B704, demonstrates the

characteristics of home-based treatment versus hospital-based treatment of all children presenting with TBM by stage of disease. In-hospital treated TBM children had a higher risk of a poor outcome, after adjustment for the stage of disease (RR=4.55, 95%CI 1.46-14.15, p=0.009). No relapses were reported in 88 of the 90 children who completed home-based treatment. Two children on home-based treatment demised after completion of treatment; one had stage III disease and the other was HIV-infected (postmortems not performed). Fifty-one children were clinically reviewed in the neurology outpatient department two or more years after treatment completion. In all other cases, the caregiver(s) or patient him/herself reported clinical wellbeing. Five children who qualified for home-based treatment were readmitted for hospital-based treatment. Reasons for readmission include: development of non-related ocular myasthenia gravis, paradoxical enlargement of a tuberculoma, TB immune reconstitution inflammatory syndrome (IRIS), poor adherence and parental request (struggling to provide care). Of the 87 TBM children who survived in-hospital treatment we established that no relapses occurred in 52 children, but the caregivers of 29 children could not be contacted. Six children demised: five had previous stage III TBM and 4 of these (66%) were HIV-infected. Postmortems were not requested; death certificates stated either HIV infection or post-TBM complications. One child without stage III TBM died of HIV-related pneumonia more than two years after completion of therapy.



**Discussion**

Treatment response in TBM is judged by early morbidity, mortality and relapse rates[6].

The importance of early diagnosis and treatment is confirmed by the good outcome of stage I (100%) and II TBM (97%) cases compared with only 47% in stage III TBM. The overall

mortality of 3.8% at completion of treatment compares favorably with the median mortality rate of 33% (range 5-65%) reported in a recent review describing outcome in TBM treatment studies[2].

The WHO recommends that children with TBM should be hospitalized, preferably for at least the first 2-months of treatment[1]. Long-term in-hospital TBM treatment, however, is seldom feasible in resource-poor countries due to bed shortages and budgetary constraints. A previously conducted observational study at our hospital found that childhood TBM can be successfully treated at home, provided that patients are carefully selected and meticulously followed up by a dedicated health care team[7]. The efficacy of home-based treatment and our intensive short course anti-TB regimen is highlighted by the absence of relapses in the 88 children that completed home based TBM treatment (follow-up period 2-5 years). The fact that not a single patient was lost to follow-up in the home-based treatment group can be ascribed to the initial selection qualifying criteria for home-based treatment.

The prevalence of ADIH in the study population who underwent liver function testing was 5.6% and only 4.3% developed symptomatic ADIH. In most resource-poor countries with high TB burden, liver function tests cannot be routinely performed. In those situations one has to rely on clinical symptoms of hepatotoxicity, such as jaundice, abdominal pain, nausea and vomiting. Of interest was that none of the children with ADIH developed jaundice or had elevated serum bilirubin levels. This is much lower than the incidence of abnormal liver functions (52.9%) and jaundice (10.8%) reported in a recent literature review of 717 TBM children.[7] All of the children who developed ADIH experienced new onset vomiting, which suggests that it is a more reliable clinical marker of hepatotoxicity compared with clinical jaundice. Reported risk factors for ADIH in children are female sex, slow acetylator status,

malnutrition, disseminated TB disease and pre-existent liver disease [7]. The low prevalence of ADIH could be attributed to the high frequency of fast acetylator status (approximately 60%) in the study population.[8] Baseline liver function testing also did not demonstrate evidence of pre-existent liver disease. Whether HIV-infected children with TBM have an increased risk of ADIH is not determined; overlapping drug toxicities, drug-drug interactions and malnutrition are factors likely to increase the risk of ADIH in HIV-infected TBM children. However, none of the HIV-infected children in the study developed ADIH. Studies from developing countries report high rates of infectious viral hepatitis in children with suspected ADIH [11]. Viral hepatitis serology proved negative in all study children with ADIH. This can partly be attributed to universal hepatitis B vaccination policy in South Africa since 1995. Although ADIH occurred within the first 2 months of treatment in six of the eight children, the remaining two children developed ADIH during their final month of treatment confirming that ADIH can occur at any time during treatment.[11]

Whether intensified treatment improves the outcome of TBM is still to be determined. A recent Indonesian adult TBM study reported a 50% reduction in 6-month mortality without any increase in toxicity when high-dose intravenous RMP (13 mg/kg/day) was given for the first two weeks of treatment[9]. Our experience is that high oral dose RMP (20 mg/kg/day) for 6-9 months duration is well tolerated by children.

The rational for using ETH as 4$^{th}$ drug in the regimen is that it has good CSF penetration (healthy and inflamed meninges) compared with streptomycin (20% in inflamed meninges only) or EMB (25-50% in inflamed meninges only)[10]. This is important as tuberculomas may occur in the absence of meningeal inflammation. Another advantage is that INH-monoresistant TBM may be overcome when ETH and PZA are used continuously together with RMP for a 6 month

period. This was confirmed by a recent study which reported no differences in outcome between children with INH-monoresistant TBM and those with drug-susceptible TBM.[11] The inclusion of ETH should therefore be considered in areas with high INH monoresistance (> 4% in primary TB cases) or in resource limited settings where drug resistance rates are unknown[11]. Use of ETH is also preferable to the use of an aminoglycoside with poor CSF penetration and considerable risk of hearing loss[12]. The most frequent adverse effect observed during treatment with ETH is nausea and vomiting. Our experience is that almost all children respond favourable to administration of ETH at night separately from the other anti-TB medications. Recent studies found the prevalence of ETH-induced hypothyroidism (20-50%) to be more common than previously recognized in children on second-line anti-TB drugs including ETH[13, 14]. Regular screening of thyroid functions is therefore indicated in TBM children on prolonged or high dose ETH.

Management of TBM in the setting of HIV is complex. Additional treatment considerations for HIV-infected children include the timing of initiation of cART and the potential for drug-drug interactions. The optimal time to initiate cART in children with HIV-associated TBM is unknown[15]. We will usually delay cART by 2-4 weeks to reduce the risk of TB-IRIS.[16] Therapy is also prolonged for an additional 3 months in HIV-infected cases because of perceived slower response to treatment. The similar result in outcome between HIV-infected and uninfected children at completion of treatment can be attributed to the benefits derived from cART and/or longer treatment duration of TBM.

Limitations of the study include the inability to contact the care-givers of the 29 children in the hospital-based treatment group and the fact that it was not a randomized controlled study comparing longer/shorter treatment regimens or home-based versus hospital-based treatment.

We believe that short intensified chemotherapy is sufficient and safe in HIV-infected and HIV-uninfected children with drug susceptible TBM. Home-based treatment can be recommended for the management of childhood TBM following adequate screening, counseling and support.

**References**


1. World Health Organization. Rapid advice: treatment of tuberculosis in children. Geneva: World Health Organization, 2010. WHO/HTM/TB/2010.13
2. Woodfield J, Argent A. Evidence behind the WHO guidelines: hospital care for children: What is the most appropriate anti-microbial treatment for tuberculous meningitis? J Trop Pediatr 2008; 54(4):220-4
3. Wolzak NK, Cooke ML, Orth H, van Toorn R. The changing profile of pediatric meningitis at a referral centre in Cape Town, South Africa. J Trop Pediatr 2012; 58(6):491-5
4. Schoeman JF, Malan G, van Toorn R, Springer P, Parker F, Booysen J. Home based treatment of Childhood Neurotuberculosis. J Trop Pediatr 2009; 55(3):149-54
5. Tosmann A, Boeree MJ, Aarnoutse RE, de Lange WCM. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol 2008; 23; 192-202
6. Donald PR. The chemotherapy of tuberculosis meningitis in children and adults. Tuberculosis 2010; 90(6):375-92
7. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. Pediatr Rep. 2011, 16; 3(2):e16.
8. Schaaf HS, Parkin DP, Seifart HI et al.Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. Arch Dis Child 2005; 90 (6):614-8.
9. Ruslami R, Ganien AR, Dian S et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label randomized controlled phase 2 trial. Lancet Infect Dis 2013; 13(1):27-35.

10. Donald PR. Cerebrospinal fluid concentration of antituberculosis agents in adults and children. Tuberculosis 2010; 90:279-292

11. Seddon JA, Visser DH, Bartens M et al. Impact of drug resistance on clinical outcome in children with tuberculous meningitis. Pediatr Infect Dis J 2012; 31(7):711-6

12. Seddon JA, Thee S, Jacobs K et al. Hearing loss in children treated for multidrug-resistant tuberculosis. J Infect 2013; 66(4):320-9

13. Thee S, Zollner EW, Willemse M et al. Abnormal thyroid function in children on ethionamide treatment. Int J Tuberc Lung Dis 2011; 15(9):1191-3

14. Hallbauer UM, Schaaf HS. Ethionamide-induced hypothyroidism in children. South Afr J Epidemiol Infect 2011; 26(3):161-163

15. Marais S, Meintjies G, Pepper DJ, Dodd LE et al. Frequency, severity and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. Clin Infect Did. 2013; 56(3): 450-60

16. van Toorn R, Rabie H, Dramowski A, Schoeman JF. Neurological manifestations of TB-IRIS: a report of 4 children. Eur J Paediatr Neurol. 2012 Nov; 16(6):676-82.

Table 1: Demographics, TBM staging, clinical features, selected diagnostic tests and outcome of 184 consecutive children <13 years of age with tuberculosis meningitis

| **Characteristic** | Number (%) unless specified |
|---|---|
| **Age** (medium in months) | 58 months (3-156 months) |
| **Gender:** Female | 94 (51) |
| **Stage of TBM (n=184)** | |
| TBM Stage 1 | 22 (11.9) |
| TBM Stage 2 | 98 (53.3) |
| TBM Stage 3 | 64 (34.8) |
| Definite TBM | 16 (8.7) |
| Probable TBM | 168 (91.3) |
| **HIV status** (n=155 ) | (as % of those tested) |
| Uninfected | 128 (82.6%) |
| Infected | 22 (14.2%) |
| Exposed uninfected | 5 (3.2%) |
| Not tested | 29 |
| **Positive TB cultures** | (as % of those tested) |
| Gastric washings (155 tested) | 43 (27.7%) |
| Cerebrospinal fluid (136 tested) | 16 (11.8%) – 2 also PCR positive[#] |
| **Treatment** | |
| In-hospital treatment only | 94 (51%) |
| Home-based treatment after stabilization | 90 (49%) |
| **Outcome after end of treatment** | |
| Normal | 79 (42.9%) |
| Mild sequelae | 68 (36.9%) |
| Severe sequelae | 30 (16.3%) |
| Death | 7 (3.8%) |
| **Relapse rate of treatment survivors**[*] | |
| **Home-based treatment (n=90)** | |
| No relapses (cured) | 88 |
| Death | 2 |
| Lost to follow up | 0 |
| **In-hospital treatment (n=87)** | |
| No relapses (cured) | 52 |
| Death | 6 |
| Lost to follow-up | 29 |

Relapse rate*: Children who remained disease free (any form of TB) for a period of more than two years after treatment completion were considered cured.
Cerebrospinal fluid PCR testing# for TB is not routinely performed.

**Table 2: Disease complications and drug adverse effects of 184 TBM children**

| **Complication/Adverse effect** | Number (%) |
|---|---|
| **Hydrocephalus** | |
| No hydrocephalus | 75 (40.8) |
| Communicating hydrocephalus | 72 (39.1) |
| Non-communicating hydrocephalus | 37 (20.1) |
| * VP shunted | 34 |
| * Endoscopic third ventriculostomy | 3 |
| **Anti-TB drug-induced hepatotoxicity** | |
| **Not tested** | 41 (22.3) |
| Normal ALT< 50 U/L | 111 (60.4) |
| Grade 1 (Mild) ALT 51-125 U/L | 18 (9.8) |
| Grade 2 (Mild) ALT 126-250 U/L | 6 (3,2) |
| Grade 3 (Moderate) ALT 251-500 U/L | 6 (3.2) |
| Grade 4 (Severe) ALT> 500U/L | 2 (1.1) |
| **Significant nausea and vomiting *** | 19 (10.3) |

* **Significant vomiting**: vomiting occurring for more than 2 consecutive days and where separation of drug administration (ethionamide in the evenings) or additional treatment (anti-emetics) was required. Eight of the 19 patients with significant vomiting had anti-TB drug-induced hepatotoxicity.

**Table 3: Duration of treatment and reasons for prolonged treatment (>6 months) in the 177 TBM children who survived completion of therapy**

| Treatment duration | HIV negative & not tested (n = 156) | | HIV positive (n = 21) | |
|---|---|---|---|---|
| 6 months | 130 (83.3%) | - | 6* (28.6%) | - |
| 7 months | 6 (3.9%) | 6 ADIH | 0 (0.0%) | - |
| 8 months | 5 (3.2%) | 2 ADIH<br>3 poor adherence | 0 (0.0%) | - |
| 9 months | 11 (7.1%) | 1 INH mono-resistance<br>1 HIV-exposed uninfected<br>4 TB IRIS<br>5 TB mass lesions | 12 (57.1%) | - |
| 12 months | 2 (1.3%) | 2 TB mass lesions | 2 (9.5%) | 2 TB mass lesions |
| 15 months | 0 (0.0%) | - | 1 (4.8%) | 1 TB mass lesion |
| 17 months | 1 (0.6%) | 1 INH resistance with TB mass lesion | 0 (0.0%) | - |
| 18 months | 1 (0.6%) | 1 TB mass lesion | 0 (0.0%) | - |

TBM: Tuberculosis meningitis; ADIH: Antituberculosis drug-induced hepatotoxicity; INH: Isoniazid, TB mass lesion refers to either large Tuberculoma(s) or TB abscesses.

* All the HIV infected TBM children who were treated for 6 months had either stage I or stage II disease.

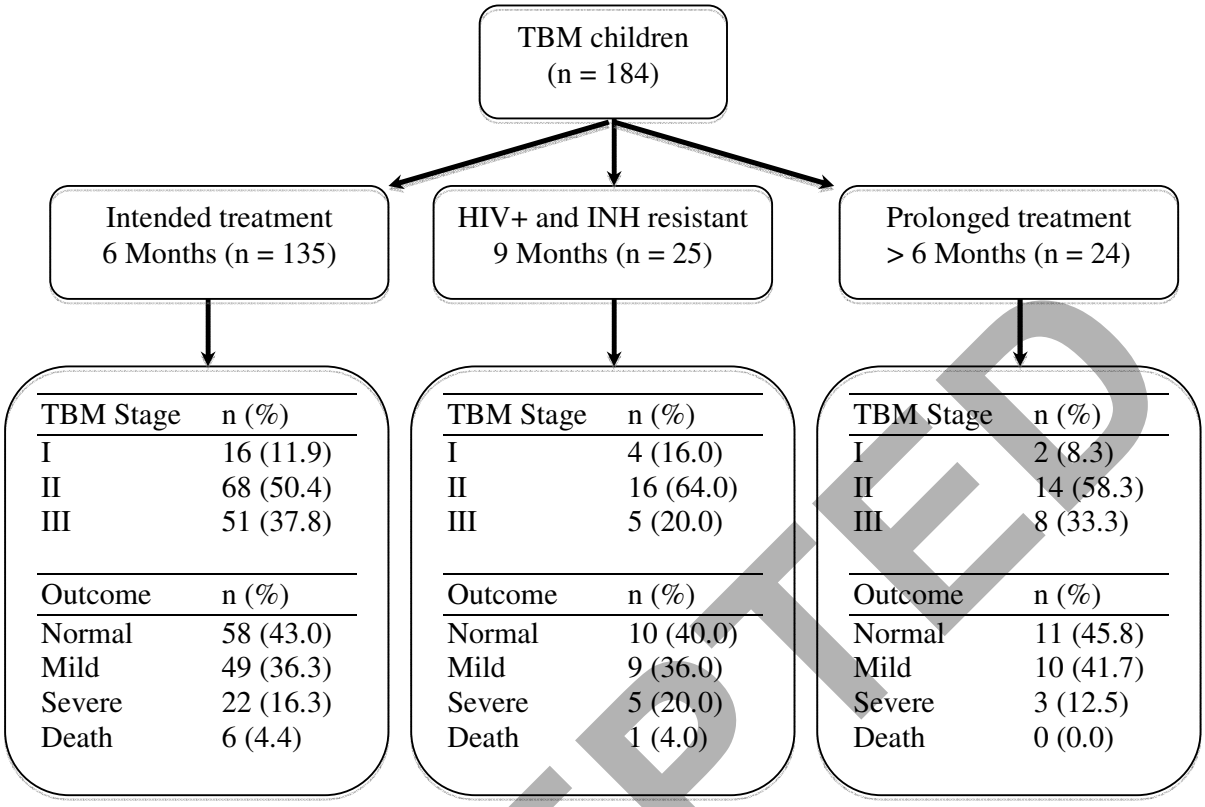


Figure 1: The baseline and outcomes of TBM children who intended and received 6 months of treatment; who intended and received 9 months of treatment and those who required prolonged treatment because of other reasons.

**SDC 1. Characteristics and outcome of home-based treatment versus hospital-based treatment of 184 consecutive children presenting with tuberculous meningitis by stage of disease**

| Characteristic/Outcome | **Stage1** n=22 (11.9%) | | **Stage 2** n=98 (53.2%) | | **Stage 3** n=64 (34.8%) | | Total |
|---|---|---|---|---|---|---|---|
| | Home | Hospital | Home | Hospital | Home | Hospital | |
| **Total** | 17 | 5 | 54 | 44 | 19 | 45 | 184 |
| HIV-infected (155) | 2 | 2 | 8 | 7 | 0 | 3 | 22 (14.2%) |
| Hepatotoxicity (143) | 2 | 0 | 2 | 1 | 1 | 2 | 8 (5.6%) |
| **Outcome** | | | | | | | |
| Normal | 16 | 4 | 29 | 26 | 1 | 3 | 79 (42.9%) |
| Mild sequelae | 1 | 1 | 24 | 16 | 14 | 12 | 68 (36.9%) |
| Severe sequelae | 0 | 0 | 1 | 2 | 4 | 23 | 30 (16.3%) |
| Death during treatment | 0 | 0 | 0 | 0 | 0 | 7 | 7 (3.8%) |
| Death after treatment completion | 0 | 1 | 1 | 0 | 1 | 5 | 8 (4.3%) |
| Lost to follow-up after treatment completion | 0 | 3 | 0 | 14 | 0 | 12 | 29 (15.7%) |