Home-based treatment of children with HIV infection or tuberculous meningitis in South Africa

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Summary

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Summary

The studies described in this thesis provide a comprehensive understanding of adherence to ART, disclosure of HIV status to the child, home-based treatment of tuberculous meningitis and we determined the cost-effectiveness of home-based treatment of this program compared to in-hospital treatment. In addition, a treatment-support intervention was developed, implemented and evaluated in collaboration with a diverse group of stakeholders involved with the care for children with HIV infection and tuberculous meningitis.

Chapter 1 is the general introduction to this thesis. South Africa is considered a middle-income country in terms of its economy, however, has health outcomes that are worse than those in many lower income countries. The country's history has had a pronounced effect on the health of its people, and the health policy and services of the present day. There are strategic plans in place to address the HIV and TB pandemics in particular, however there is inadequate capacity to deliver critical healthcare interventions.

South Africa has the largest paediatric HIV program in the world. Although South Africa has guidelines and strategic plans in place that address adherence, this information is not specifically tailored to children. Many patients experience difficulties following treatment recommendations. Poor adherence to long-term therapies severely compromises the effectiveness of treatment making it a critical issue in population health, both from the perspective of quality of life and of health economics. Understanding the factors associated with paediatric adherence can help inform clinical practice, strategies and policies to improve adherence. In addition, increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments. To date, the extent of disclosure of HIV status to children and adolescents and context facilitating their disclosure process has received little attention, although widely perceived to be important. For children and young adolescents, disclosure is the first step in a successful transition to manage their own HIV care. In-hospital treatment of children with tuberculous meningitis is not a feasible option in many resource-poor countries such as South Africa. Home-based treatment has shown to be a viable alternative under certain conditions. The cost-effectiveness of home-based treatment compared to in-hospital treatment had not yet been evaluated. The difference in healthcare structure, treatment regimen, duration of treatment and effect of the condition on daily functioning between HIV infection and tuberculous meningitis provided for a diverse population to study paediatric home-based treatment.

Chapter 2 describes a comprehensive analysis of factors associated with adherence in children with HIV infection. We included 195 children aged 2 to 13 years. Adherence depended on definition and measure which ranged between 20-55% for pill count, and 80-

89% for self-report. In addition, 67% of children were virally suppressed and 92% had a CD4 count >500 copies/mm3. We found that boys were less adherent according to caregiver self-report, girls were less adherent according to pill count. The social construct of gender roles seems to affect the measure of adherence within a paediatric population which needs to be taken into account when addressing adherence in clinical practice, research and when developing interventions.

Non-adherence was not merely defined by low pill counts; upper levels were as high as 192% and should therefore be considered when defining adherence both in clinical practice and in a research setting. Caregivers ensured medication was taken when the condition directly affected daily life. On the other hand, well-functioning families and families with high SES provide a context supportive of adherence. Non-disclosure and difficulties administering medication negatively affected adherence and viral suppression. Monthly clinic visits represent a convenient and appropriate time to address these difficulties and can resolve these problems while reducing socially desirable answers and stigmatisation.

In **chapter 3** we investigated disclosure of HIV status to the child and aimed to provide a comprehensive analysis of factors associated with disclosure. For this study, we included 190 children from the population described in **chapter 2**, who were three years and older. The HIV status was disclosed to 24% of the children (partial disclosure 15%, full disclosure 9%). Disclosure was strongly associated with older age of the child. When children do well on treatment, caregivers feel less need to disclose. Well-functioning families, with higher educated caregivers and children from households with better SES, provided an environment enabling and promoting disclosure. Non-disclosure can indicate a sub-optimal social structure which could negatively affect adherence and viral suppression. Low disclosure amongst young children demonstrates an urgent need to address disclosure thoughtfully and proactively in long-term disease management. For the disclosure process to be beneficial, an enabling supportive context is important. Families within such context provide a great opportunity for future interventions.

Barriers to adherence and caregiver perceptions of home-based treatment of tuberculous meningitis are discussed in **chapter 4**. A qualitative study describes 11 in-depth semi-structured interviews based on the principles of the health belief model. Caregivers showed good appreciation of the adverse effects of non-adherence and benefits obtained from taking treatment in the home environment. Barriers of adherence identified included poor understanding of the disease and transmission route, difficulty with medication administration and side effects, lack of access to the healthcare facility, long waiting times and hidden costs of transportation. Improved doctor–patient communication, information brochures, structural changes to hospital settings, provision of financial and peer support all contribute to optimal tuberculous meningitis home-based treatment.

In **Chapter 5,** the societal costs and cost-effectiveness of home-based versus in-hospital treatment of paediatric tuberculous meningitis were described from a societal perspective using probabilistic analysis. Healthcare, informal care, lost-productivity costs and costs in other sectors, health-related quality of life and family impact were assessed during interviews with caregivers, children, medical staff and management. Societal costs of home-based treatment are lower compared to in-hospital treatment (USD3857 versus USD28043). Children treated at home have a better health-related quality of life (91% versus 85%) and family impact-scores (95% versus 73%). Home-based treatment is a highly cost-effective alternative for in-hospital treatment of drug-susceptible tuberculous meningitis.

Chapter 6 describes a randomised-controlled evaluation of a paediatric treatment-support intervention for home-based treatment of HIV infection (population described in **chapter 2 and 3**) and tuberculous meningitis (home-based treatment group described in **chapter 5)**. The intervention was developed based on qualitative research (**chapter 4)** and combined adherence-education (information brochure), -reinforcement (sticker-puzzle), and -monitoring (calendar). The low-cost, cultural friendly treatment-support intervention had beneficial effects on health-related quality of life, family functioning and caregiver disclosure of HIV status to the child. Treatment adherence was not significantly affected in both the HIV and tuberculous meningitis groups. The intervention resulted in an increased caregiver reporting of medication non-adherence and caregiver reporting of difficulties experienced with administering medication.

Chapter 7 reviewed the main findings and implications of these studies and provided recommendations for paediatric HIV and tuberculous meningitis care. The current home-based setting for treatment of HIV infection in children provides opportunities for improvement. It is important to address adherence to ART and the disclosure process of HIV status to children before the health of the child deteriorates. Recommendations for clinical practice, research and the development of interventions include the consideration of gender roles within the societal context, and defining adherence measured with pill count including upper limits. Monthly clinic visits represent a convenient and appropriate time to address difficulties administering medication (a good indication of adherence) and an opportunity to resolve these problems. The effect of the condition on the child's life, caregiver's life and family life affect paediatric adherence and the disclosure process. When ART is tolerated well, and no condition-related difficulties are experienced, the urgency to remain adherent or disclose the child's HIV status, are not as prominent. When daily life is affected by the condition, caregivers ensure medication is taken and children more likely receive disclosure. Well-functioning households and households with high SES provide a context supportive of treatment adherence, viral suppression and the disclosure process. For the disclosure process to be beneficial, an enabling supportive context is important.

Families within such context provide a great opportunity for future adherence and disclosure interventions. Healthcare provider-caregiver communication is crucial in the facilitation of good adherence behaviour, and successful disclosure process. High levels of adherence in a home-based setting for treatment of paediatric tuberculous meningitis are possible. Home-based treatment is highly cost-effective compared to in-hospital treatment. Provided a strict selection procedure, a structured follow-up system including a dedicated program nurse and with the commitment of the healthcare providers involved, we recommend the implementation of home-based treatment for tuberculous meningitis at scale. The treatment-support intervention enables an environment supportive of adherence and the disclosure process. We therefor recommend the use of the intervention to support home-based treatment for children embedded within existing treatment-support structures.

Samenvatting

De onderzoeken in dit proefschrift bieden een uitgebreide beschrijving van therapietrouw bij antiretrovirale therapie (ART) voor kinderen, het bespreken van de hiv-status met het kind, thuisbehandeling van tuberculeuze meningitis, en de kosteneffectiviteit van deze thuisbehandeling in vergelijking met ziekenhuisopname. In samenwerking met een diverse groep mensen die betrokken is bij de behandeling van kinderen met hiv of tuberculeuze meningitis hebben we een interventie ontwikkeld ter ondersteuning van deze behandeling en hebben we deze interventie geïmplementeerd en geëvalueerd.

Hoofstuk 1 is de algemene introductie van dit proefschrift. Zuid-Afrika wordt gezien als een land met een gemiddeld inkomen wat betreft de economie, maar de gezondheidsuitkomsten zijn slechter dan veel landen met een laag inkomen. De geschiedenis van het land heeft een nadrukkelijk effect gehad op de gezondheid van de bevolking en het huidige zorg- en servicebeleid. Hoewel strategische plannen bestaan die specifiek gericht zijn op de hiv en TB pandemie, beschikt het land niet over toereikende capaciteit om deze cruciale gezondheidszorg interventies te leveren.

Zuid-Afrika heeft het grootste hiv-behandelprogramma gericht op kinderen ter wereld. Hoewel Zuid-Afrika richtlijnen en strategische protocollen heeft om therapietrouw aan te pakken, is deze informatie niet specifiek toegespitst op kinderen. Het is voor veel patiënten moeilijk om de voorgeschreven behandeling nauwkeurig op te volgen. Inadequate therapietrouw bij langdurige behandeling brengt zowel de effectiviteit van de behandeling zelf als de volksgezondheid in gevaar en heeft effect op de kwaliteit van leven en de gezondheidseconomie. Een beter begrip van de factoren die een rol spelen bij therapietrouw bij kinderen kan helpen bij het informeren van klinische zorg, strategieën en beleid om therapietrouw te verbeteren. Wanneer interventies gericht op therapietrouw meer effectief zijn kan zelfs een groter gezondheidsvoordeel behaald worden dan met de verbetering van een specifieke medische behandeling. Tot op heden is weinig aandacht besteed aan het bespreken van de hiv-status met het kind (of puber) en de context waarin dit proces plaats vindt, hoewel dit algemeen als zeer belangrijk wordt beschouwd. Voor kinderen en pubers is dit proces de eerste stap in een succesvolle overgang naar het nemen van verantwoordelijkheid voor de eigen behandeling. Langdurige ziekenhuisopname voor kinderen met tuberculeuze meningitis is niet altijd mogelijk in landen met weinig middelen zoals Zuid-Afrika. Thuisbehandeling wordt onder bepaalde omstandigheden gezien als een goed alternatief. De kosteneffectiviteit van thuisbehandeling in vergelijking met ziekenhuisopname werd niet eerder geëvalueerd. Het verschil in zorgstructuur, behandelingsregime, duur van de behandeling en het effect van de aandoening op het dagelijks functioneren verschilt tussen hiv-infectie en tuberculeuze meningitis. Dit biedt de mogelijkheid om thuisbehandeling van kinderen te bestuderen in een diverse populatie.

Hoofdstuk 2 beschrijft een uitgebreide analyse van de factoren die een rol spelen in therapietrouw bij kinderen met hiv-infectie. We includeerden 195 kinderen in de leeftijd van 2 tot 13 jaar. Therapietrouw varieerde afhankelijk van de definitie en maat die gebruikt werd tussen 20 en 55% op basis van teruggebrachte medicatie en tussen 80 en 89% voor rapportage door de verzorger. Daarnaast was het virus onderdrukt bij 67% van de kinderen en had 92% een CD4-telling van >500 kopieën/mm3. Jongens bleken minder therapietrouw te zijn volgens de zelfrapportage van de verzorger, terwijl meisjes minder therapietrouw waren op basis van de teruggebrachte medicatie. De man-vrouw rolverdeling lijkt effect te hebben gehad op de uitkomst afhankelijk van de gekozen maat van therapietrouw en hier moet rekening mee gehouden worden in de klinische zorg, bij onderzoek en bij de ontwikkeling van interventies. Therapie-ontrouw bleek niet alleen gedefinieerd door te veel teruggebrachte medicatie (te weinig genomen pillen, een laag percentage), maar was in sommige gevallen zo hoog als 192%. Daarom zou zowel een ondergrens als een bovengrens gebruikt moeten worden bij het definiëren van therapietrouw als de maat gebaseerd is op teruggebrachte medicatie, zowel in de klinische zorg als bij onderzoek. Wanneer de aandoening direct effect had op het dagelijks leven zorgden de verzorgers van het kind ervoor dat de medicatie genomen werd. Daarnaast bieden goed functionerende gezinnen met een hogere sociaal economische status (SES) een context die therapietrouw bevordert. Wanneer de hiv-status niet met het kind besproken was en wanneer verzorgers moeilijkheden met het toedienen van medicatie ervaren, had dit een negatief effect op zowel therapietrouw als onderdrukken van de virale 'load'. Maandelijkse bezoeken aan de kliniek bieden een handig en geschikt moment om deze problemen aan te pakken en om sociaal wenselijke antwoorden en stigma te verminderen.

In **hoofdstuk 3** onderzochten we het bespreken van de hiv-status met het kind en factoren die in dit proces een rol spelen. Bij deze studie includeerden we 190 kinderen van 3 jaar en ouder uit de populatie zoals beschreven in hoofdstuk 2. De hiv-status was met 24% van de kinderen besproken (gedeeltelijk 15% of volledig 9%). Of de status met het kind besproken wordt, was sterk afhankelijk van de leeftijd van het kind. Wanneer de behandeling goed verloopt en het goed gaat met het kind lijken verzorgers niet de noodzaak te ervaren om de hiv-status met het kind te bespreken. Families die goed functioneren, hoger opgeleide verzorgers en kinderen uit gezinnen met een hogere SES bieden echter een omgeving die het bepreken van hiv-status bevordert. Het niet bespreken van de hiv-status kan een indicatie zijn van een niet optimaal functionerende sociale omgeving wat tevens een negatief effect op de therapietrouw en virale onderdrukking kan hebben. De hiv-status wordt weinig met jonge kinderen besproken. Dit verdient dringend aandacht zodat het proces bedachtzaam en proactief in het lang termijn behandelplan opgenomen kan worden. Om dit goed te laten verlopen zodat het gesprek een gunstige uitkomst heeft, is een ondersteunende

context van belang. Gezinnen met een dergelijke ondersteunende structuur bieden een goede basis en gelegenheid voor het implementeren van toekomstige interventies.

Barrières voor therapietrouw en percepties van verzorgers van kinderen die thuisbehandeling voor tuberculeuze meningitis ontvangen worden besproken in **hoofdstuk 4**. Deze kwalitatieve studie beschrijft 11 semigestructureerd diepte interviews gebaseerd op het '*health belief model*'. Verzorgers toonden waardering voor de nadelige effecten van therapie ontrouw en goed begrip van de positieve effecten van het nemen van medicatie in de thuissituatie. Barrières voor therapietrouw waren onder andere een slecht begrip van de ziekte en transmissieroute, problemen met het toedienen van medicatie, bijwerkingen, gebrek aan toegang tot de gezondheidszorginstelling, lange wachttijden en verborgen transportkosten. Verbeterde communicatie tussen zorgverlener en patiënt, informatiebrochures, structurele veranderingen in de ziekenhuisomgeving, financiële en sociale ondersteuning kan bijdragen aan optimale thuisbehandeling van tuberculeuze meningitis.

In **hoofdstuk 5** beschrijven we de maatschappelijke kosten en kosteneffectiviteit van thuisbehandeling versus ziekenhuisopname voor de behandeling van tuberculeuze meningitis door middel van een probabilistische analyse vanuit een maatschappelijk perspectief. Gezondheidszorgkosten, informele zorgkosten, kosten door verloren productiviteit, kosten in andere sectoren, gezondheid gerelateerde kwaliteit van leven en familie-impact werden gemeten door middel van interviews met verzorgers, de kinderen, medisch personeel en management. De maatschappelijke kosten van thuisbehandeling zijn lager vergeleken met ziekenhuisopname (USD3857 versus USD28043). Kinderen die thuis behandeld werden hebben een betere gezondheid gerelateerde kwaliteit van leven (91% versus 85%) en 'family impact'-scores (95% versus 73%). Thuisbehandeling is een zeer kosteneffectief alternatief voor ziekenhuisopname bij de behandeling van tuberculeuze meningitis.

Hoofdstuk 6 beschrijft een gerandomiseerde gecontroleerde evaluatie van een interventie voor de ondersteuning van thuisbehandeling van hiv-infectie bij kinderen (populatie beschreven in **hoofdstuk 2** en **3**) en voor kinderen met tuberculeuze meningitis (populatie thuisbehandelgroep zoals beschreven in **hoofdstuk 5**). De interventie werd ontwikkeld gebaseerd op kwalitatief onderzoek (**hoofdstuk 4**) en combineert educatie (informatie brochure), 'reinforcement' (sticker-puzzel) en monitoren (kalender). Deze goedkope, cultuurvriendelijke interventie ter ondersteuning van de behandeling van kinderen had gunstige effecten op de gezondheid gerelateerde kwaliteit van leven, het functioneren van het gezin en het bespreekbaar maken van de hiv-status met het kind. Therapietrouw werd

niet significant beïnvloed door de interventie in de hiv-of tuberculeuze meningitis groep. De interventie zorgde voor een verhoogde rapportage door verzorgers van therapie-ontrouw en problemen die zij ervaren bij het toedienen van de medicatie.

Hoofdstuk 7 evalueert de belangrijkste bevindingen en implicaties van de onderzoeken beschreven in dit proefschrift en biedt aanbevelingen voor de zorg van kinderen met hiv-infectie en tuberculeuze meningitis. Binnen de zorg voor kinderen met hiv-infectie is ruimte voor verbetering. Het is belangrijk om aandacht te besteden aan therapietrouw en het bespreken van de hiv-status met het kind voordat de gezondheid van het kind achteruitgaat. In een klinische setting, binnen onderzoek en bij de ontwikkeling van interventies moet rekening gehouden worden met de specifieke sociale context en de man-vrouw rolverdelingen daarbinnen. Bij het meten van therapietrouw door middel van teruggebrachte medicatie is het van belang om een bovengrens te definiëren. Maandelijkse kliniekbezoeken bieden een goede mogelijkheid om moeilijkheden bij het toedienen van medicatie aan de orde te stellen (dit is een goede aanwijzing voor therapietrouw) en tegelijkertijd het daadwerkelijke probleem aan te pakken. Het effect van de aandoening op het leven van het kind, de verzorger en het gezin zijn van invloed op therapietrouw en het proces waarbij de hiv-status met kinderen besproken wordt. Wanneer ART goed getolereerd wordt en geen aandoening-gerelateerde moeilijkheden ervaren worden, dan ontbreekt de noodzaak om het medicatie-regime strikt te volgen of de hiv-status met het kind te bespreken. Wanneer de aandoening echter direct effect heeft op het dagelijks leven, zijn verzorgers juist meer therapietrouw en word de hiv-status vaker met het kind besproken. Goed functionerende huishoudens met een hoge SES bieden een ondersteunende context voor therapietrouw, virale onderdrukking en het bespreekbaar maken van de hiv-status met het kind. Het proces waarbij de hiv-status besproken wordt met het kind kan alleen succesvol zijn wanneer een dergelijke ondersteunende structuur aanwezig is. Deze gezinnen bieden een ultieme mogelijkheid voor toekomstige interventies. Goede communicatie tussen zorgverlener en verzorger is cruciaal voor het faciliteren van therapietrouw en een succesvol proces waarbij hiv besproken wordt met het kind. Goede therapietrouw is mogelijk bij kinderen die thuisbehandeld worden voor tuberculeuze meningitis. Thuisbehandeling is zeer kosteneffectief in vergelijking met ziekenhuisopname. Het thuisbehandelprogramma voor kinderen met tuberculeuze meningitis raden we aan op schaal te implementeren wanneer een strenge selectie plaatsvindt, een gestructureerd zorgproces gevolgd wordt en toegewijde programmaverpleegkundigen en zorgverleners aanwezig zijn. De ontwikkelde interventie ondersteunt een structuur die therapietrouw bevorderd en de hiv-status van het kind bespreekbaar maakt. Wij raden daarom aan om deze interventie te implementeren binnen bestaande thuisbehandelprogramma's voor kinderen.

Additional publication

Short intensified treatment in children with drug-susceptible tuberculous meningitis

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ABSTRACT

Background: The World Health Organization recommends 12-month 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-month treatment with 12-month treatment.

Methods: A prospective evaluation to determine whether short-course intensified treatment (6 RHZEth for HIV-infected and 9RHZEth for HIVinfected) 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). Anti-TB drug-induced hepatotoxicity occurred in 5% (8 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.

BACKGROUND

Recent World Health Organization (WHO) guidelines recommend that children with tuberculous meningitis (TBM) should be treated with 2 months of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol followed by 10 months of INH and RMP [1]. As the WHO has to consider the circumstances under which TB will be treated worldwide, 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 PZA for >2 months in many settings (personal communication P.R.D.). However, a recent review found that all existing trials assessing anti-TB 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 labour-intensive and may improve patient compliance.

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

MATERIALS AND METHODS

Setting

Tygerberg Children's Hospital, a referral hospital in the Western Cape province of South Africa, provides specialized care to half the province's 1.2 million children. A recent paediatric meningitis survey identified TBM as the most common form of bacterial meningitis in the Western Cape province [3].

Study Population and TBM Definition

All children admitted consecutively to Tygerberg Children's Hospital with TBM from January 1, 2006, through December 31, 2009, aged 0–13 years, were included in the study. Children with multidrug-resistant TB (MDR-TB; ie, 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 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, two 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 or magnetic resonance imaging compatible with TBM, growth failure with crossing of weight-forage 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 400 mg daily), RMP 20 mg/kg (maximum 600 mg daily), PZA 40 mg/kg (maximum 2 g daily) and ethionamide (ETH) 20 mg/kg (maximum 750 mg 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/d (maximum 60 mg/d) 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 noncommunicating types of obstructive hydrocephalus. Institutional preference is to treat noncommunicating hydrocephalus by ventriculo-peritoneal (VP) shunting or endoscopic third ventriculostomy, whilst communicating hydrocephalus is treated medically with diuretics (acetazolamide 50 mg/kg/d and furosemide 1 mg/kg/d) 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 directly observed therapy supporter available and 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-month, home-based therapy, the mother and child were reviewed monthly assessing the clinical wellbeing of the child, adherence to treatment and adverse effects.

Evaluation for Adverse Effects

Local practice is to perform liver function tests [serum aspartate aminotransferase, 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 that include amikacin, ofloxacin, ethambutol and terizidone (terizidone for good CSF penetration). Once the liver enzymes have normalized, stepwise rechallenge with first-line drugs is attempted. Nausea and vomiting was considered significant if vomiting occurred for >2 consecutive days and where intervention such as administering ETH in the evenings or antiemetics 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 >2 years after treatment completion were considered cured. Relapse rate was determined by telephonic contact with the child's caregiver at least 2 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 wellbeing 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 χ^2 test or Fisher's exact test (categorical variables) or an analysis of variance (continuous variables). A P-value <0.05 was indicative of statistical significance. Logistic 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 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 <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 (odds ratios: 1.01, 95% CI: 0.34–2.96, P=0.986). The overall mortality before completion of anti-TB therapy was 3.8% (7 of 184 children). All seven children who died were moribund on admission (stage III disease) and three children died within 8-days of starting treatment. Cranial computerized tomography 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 1. Demographics, TBM Staging, clinical Features, Selected Diagnostic Tests and Outcome of 184 Consecutive Children <13 Years of Age With TBM

Characteristic	Number (%) Unless Specified
Age (median 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 polymerase chain reaction positive†
Treatment	
In-hospital treatment only	94 (51%)
Home-based treatment after stabilization	90 (49%)
Outcome (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 >2 years after treatment completion were considered cured, †CSF polymerase chain reaction testing for TB is not routinely performed.

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 noncommunicating hydrocephalus who required VP shunting (odds ratios: 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 >2.5 times the normal upper limit. Only eight (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 median age of the ADIH children was 34 months (range 15–156 months) and the median duration on therapy was 44 days (range 8–105 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 eight 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 ETH with ethambutol (three cases) or administering the ETH at night rather than in the morning solved the problem.

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> 500 U/L	2 (1.1%)
Significant nausea and vomiting*	19 (10.3%)

*Significant vomiting: vomiting occurring for >2 consecutive days and where separation of drug administration (ETH in the evenings) or additional treatment (antiemetics) was required. Of the 19 patients, 8 with significant vomiting had anti-TB druginduced 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 and 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	0 (0.0%)	-
		3 poor adherence		
9 months	11 (7.1%)	1 INH monoresistance	12 (57.1%)	-
		1 HIV-exposed uninfected		
		4 TB-immune reconstitution inflammatory syndrome		
		5 TB mass lesions		
12 months	2 (1.3%)	2 TB mass lesions	2 (9.5%)	2 TB mass lesions
15 months	0 (0.0%)	-	1 (4.1%)	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%)	-

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.

Table 3 demonstrates the duration of therapy and reasons for prolonged treatment (longer than 6 months) in the 177 TBM children who survived TMB upon completion of therapy. Figure 1 illustrates the baseline and outcomes of the 184 TBM children who intended and received 6 months of treatment compared with 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 (relative risk = 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; 1 had stage III disease and the other was HIV infected (post-mortems not performed). Fifty-one children were clinically reviewed in the neurology outpatient department ≥2 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 included: development of nonrelated ocular myasthenia gravis, paradoxical enlargement of a tuberculoma, TB immune reconstitution inflammatory syndrome, 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 four of these (66%) were HIV-infected. Post-mortems were not requested; death certificates stated either HIV infection or post-TBM complications. One child with stage III TBM died of HIV-related pneumonia >2 years after completion of therapy.

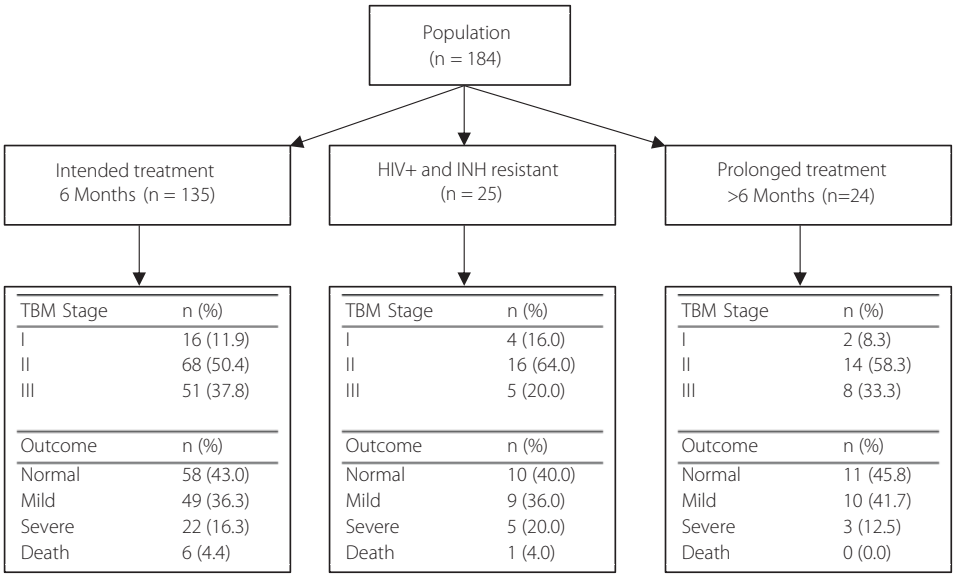

Figure 1. The baseline and outcomes of TBM children who intended and received 6 months of treatment; who intended and received 9 months of treatment and those who required prolonged treatment because of other reasons.

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 stage II TBM (97%) cases compared with only 47% in stage III TBM. The overall mortality of 3.8% at completion of treatment compares favourably 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 healthcare team [4]. 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 [9]. 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 6 of the 8 children, the remaining 2 children developed ADIH during their final month of treatment confirming that ADIH can occur at any time during treatment [9].

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/d) was given for the first 2 weeks of treatment [10]. Our experience is that high oral dose RMP (20 mg/kg/d) for 6–9 months duration is well-tolerated by children.

The rational for using ETH as 4th drug in the regimen is that it has good CSF penetration (healthy and inflamed meninges) compared with streptomycin (20% in inflamed meninges only) or ethambutol (25–50% in inflamed meninges only) [11]. 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.9 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 [9]. 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 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 immune reconstitution inflammatory syndrome [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 HIV-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 caregivers 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.

Conflict of interest

The authors have no funding or conflicts of interest to disclose.

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Sabine van Elsland was born on the 21st of February 1984 in Amersfoort, the Netherlands. She graduated from secondary school (VWO) at the RSG 't Slingerbos in Harderwijk in 2002. Travelling around the world for a year inspired her studies in general health sciences at the VU University of Amsterdam, The Netherlands. After completing a research internship at the Padjajaran University in Bandung, Indonesia she obtained her Bachelor degree in 2007. Her two-year research Master degree program in biomedical sciences (public health research and infectious diseases) involved a research internship at Wockhardt-Harvard HIV/AIDS research foundation in Aurangabad, India, as well as a research internship at the Stellenbosch University in Cape Town, South Africa. During her studies and after completion of her Master degree in 2009, she lectured at the VU university in Amsterdam at the department of biostatistics and the department of infectious diseases. She relocated to Cape Town, South Africa where she coordinated research programs at the Stellenbosch University in a collaboration with the VU University Medical Center, and from 2012 with the Desmond and Leah Tutu Legacy Foundation. Upon completion of her doctorate degree in 2018, she moved to London, United Kingdom to start a new position as external relationships and communications manager at Imperial College's MRC centre for global infectious disease analysis. Inspired by people, cultures and healthcare initiatives around the world, Sabine is passionate about contributing to sustainable knowledge translation.

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S.L. van Elsland, R.P.H. Peters, N. Grobbelaar, P. Ketelo, M.O. Kok, M.F. Cotton, A.M. van Furth (2018) Disclosure of HIV status to children in South Africa: a comprehensive analysis. Submitted.

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