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

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General discussion

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GENERAL DISCUSSION

South Africa accounted for 15.2% of the global human immunodeficiency virus (HIV) infected children (0-14 years) [1] and 5.6% of the global tuberculosis burden in children in 2016 [2, 3]. The sheer magnitude of the HIV and tuberculosis epidemics has stimulated the development of innovative means of delivering healthcare [4]. South Africa has the largest HIV program in the world [5] with 55% coverage of antiretroviral treatment (ART) for children (0-14 years) [6]. Overall tuberculosis treatment coverage in South Africa was similar at 54% [2]. Tuberculous meningitis is the most severe complication of tuberculosis and mainly affects young children [7]. Although in-hospital treatment is regarded the norm [8], short intensified treatment at home, under certain conditions, is a viable alternative to in-hospital treatment of children with drug-susceptible tuberculous meningitis [8, 9]. With increasing access to care, it is important to understand factors associated with positive treatment outcome such as adherence. In addition, it is crucial to evaluate interventions specific to resource-constrained environments that aim to improve paediatric adherence to ART [10] and tuberculosis treatment [11].

In this thesis, various aspects of treatment for children in a home-based setting were investigated. Children with HIV infection and children with tuberculous meningitis were central and provide a diverse population with different healthcare structures, treatment regimen, duration of treatment and effect of the condition on daily functioning. In order to provide a structured understanding of our findings, we use images based on the theory driven realist evaluation approach [12]. These figures were adjusted from the originals and imply an outcome is generated by a mechanism being triggered in a particular context through an actor when an intervention is implemented [13]. This chapter will review the main findings, their implications for practice and discuss future research directions.

I. Home-based treatment of paediatric HIV infection

Part I of this thesis focussed on home-based treatment of paediatric HIV infection. In **chapter 2** we used multiple measures and definitions to describe adherence in children and discussed factors affecting their adherence (child, caregiver, clinical and socio-economic characteristics). **Chapter 3** focused on disclosure of HIV status to the child and associated factors (child, caregiver, clinical and socio-economic characteristics) related to the disclosure process.

Main findings

Adherence depended on definition and measure and ranged between 20.3-54.7% for pill count, and 79.6-89.1% for self-report. In addition, 66.7% of children were virally suppressed and 92.1% had a CD4 count >500 copies/mm^3. Figure 1 provides an overview of the initial situation (children receiving home-based ART through an outpatient clinic) and the mechanisms we identified (child, caregiver, clinical and socio-economic characteristics) which affect a particular outcome (adherence) within the context of this study.

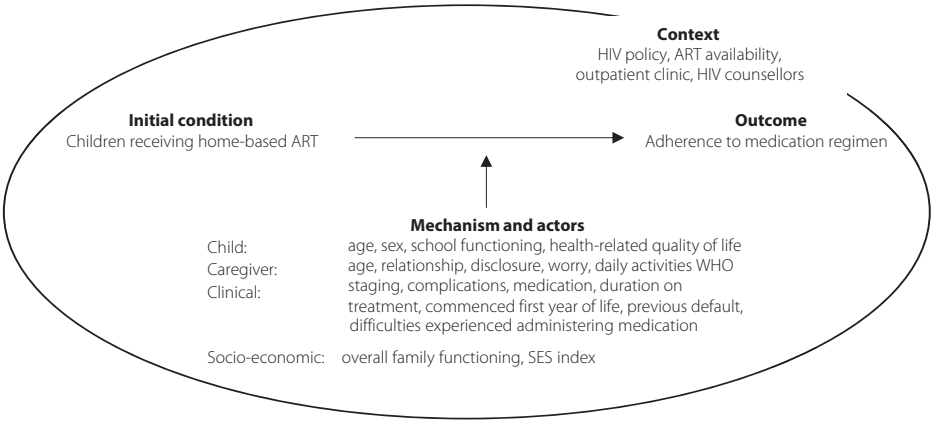

Figure 1. Configuration of adherence in home-based ART setting

HIV status of the child was disclosed to 23.7% of the children older than 3 years (14.7% were partially disclosed and 8.9% were fully disclosed). Figure 2 provides an overview of the initial situation (children receiving home-based ART through an outpatient clinic) and the mechanisms we identified (child, caregiver, clinical and socio-economic characteristics) which affect a particular outcome (disclosure) within the context of this study.

Implications for practice

Paediatric ART failure is an under-recognized issue that receives inadequate attention in the field of paediatrics and within HIV treatment programmes. Clinicians are often uncertain how to assess adherence of HIV-infected children and their caregivers, as well as how to provide structured adherence support at the time of treatment failure. Too often, proper basic adherence counselling is only provided once the child is failing on treatment [14].

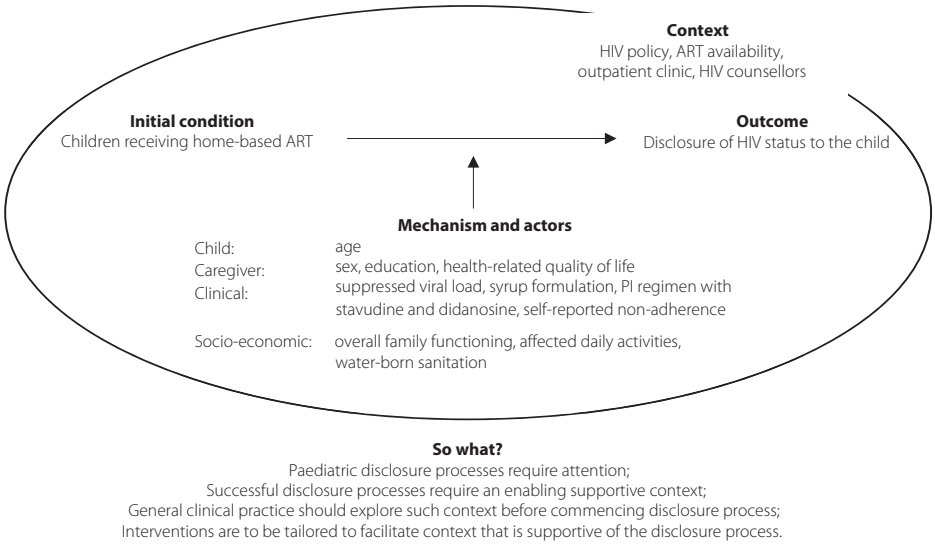

Figure 2. Configuration of disclosure of HIV status to a child receiving ART in a home-based setting

Adherence is a dynamic process [11] which is affected by health system challenges [15] and clinical, child, caregiver and socio-economic characteristics [16, 17]. This process requires routinization of participatory behaviour, which is deeply embedded in, and shaped by complex social and material context [12]. Our findings contribute to the understanding of this context providing opportunities for change, to guide clinical practice and policy strategies.

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 could explain the difference between caregiver reported adherence and pill counts. A study in the Western Cape Province of South Africa identified the pervasiveness of traditional gender roles. These are defined as women who stay at home, deal with household chores, care for family and be submissive to men and men on the other hand have the power in the home, go out to work as breadwinners and are the decision makers of a family [18]. Translating these roles to children, daughters are expected to be at home and are assumed to carry responsibility for their own treatment (high caregiver-reported adherence), where sons are outdoors playing and assumed to require more involved caregiver guidance with regard to their treatment (high pill counts). Physicians, counsellors and others involved in the care of children with HIV infection should be aware of this and take the social constructs of gender roles into consideration when addressing adherence. When the healthcare provider aims to address adherence based on pill counts (a common measure used in clinic) it is important to consider the expectations of the caregiver which may be different for their sons compared to the daughters.

Not only the measure of adherence but also the definition used can guide the correct interpretation of medication-taking behaviour. We found pill count levels as high as 192% which is an indication the family is experiencing difficulties such as vomiting and having to re-administer the dose, or the social desirability of maintaining high pill counts (e.g. disposing of pills). When using overall average pill counts without considering upper limits, potential difficulties are not picked up during clinic visits and remain unaddressed.

We identified a correlation between problems experienced administering medication and adherence measures. In a clinical setting, changing the question from 'did your child take the medicine', to 'what difficulties did you experience administering medication' could provide a better indication of adherence and at the same time create the opportunity to address the actual problems that are preventing optimal adherence. Monthly clinic visits represent a convenient and appropriate time to discuss potential difficulties and will reduce social-desirable answers and stigmatisation.

Caregivers ensured medication was taken when the condition directly affected daily life. Non-disclosure and difficulties administering medication negatively affected adherence and viral suppression. On the other hand, well-functioning families and families with high SES provide a context supportive of adherence. In order to identify and address non-adherence before the child's health deteriorates, it is important to explore the availability of such a supportive context, possible gaps in the support structure and opportunities for change.

Disclosure of an HIV diagnosis is an important means to improve HIV care [19-21], however, research is needed to implement age- and culture-appropriate disclosure in resource limited settings [19]. Literature describes factors influencing disclosure including child characteristics (age, understanding) and caregiver characteristics (educational level, openness about own HIV status, beliefs about children's capacities and fear) [19]. In chapter 3 we describe the minority of HIV infected children know their own status, which demonstrates an urgent need to address disclosure thoughtfully and proactively in long-term disease management. When children do well on treatment, caregivers feel less need to disclose their HIV status. 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. For the disclosure process to be beneficial, an enabling supportive context is important.

Implications for research

Any research on paediatric adherence should include multiple measures of adherence in order to provide a comprehensive understanding of the actual medication taking behaviour. Gender roles within the configuration of paediatric adherence provides an opportunity for

further exploration in order to develop healthcare practice that supports the individual's needs.

When studying (paediatric) adherence using measures such as pill count, it is important to define an upper level and not merely consider the average pill count. Average pill counts could suggest good medication-taking behaviour when caregivers actually experience difficulties which then remain unaddressed. Most studies define adherence by low limit pill counts (more pills returned than expected based on prescription and number of days passed). However, to our knowledge there are no studies that define adherence using an upper limit (less pills returned than expected based on prescription and number of days passed). The reason for the pills 'lost' can provide valuable insight in understanding medication taking behaviour and guide adherence support.

Valuable focus for future research includes the validation of healthcare provider-caregiver conversation on difficulties experienced with giving medication as a measure of adherence. We hypothesise that changing the phrasing will provide a better indication of adherence and at the same time will provide an understanding of the actual problems which can now be addressed.

Although adherence was high when the condition directly affected daily life, opportunities for change should be identified before the condition impacts daily functioning. To ensure generalizability of data we suggest doing similar research in other settings with other conditions.

When developing interventions supporting the disclosure process, focus should be on facilitating an enabling context. In addition, interventions with the aim to introduce the disclosure process should include children who have such context in place.

II. Home-based treatment of paediatric tuberculous meningitis

Part 2 of this thesis focussed on home-based treatment of paediatric tuberculous meningitis. **Chapter 4** introduces the health-belief model to support the understanding of barriers and facilitators of adherence in children treated at home for tuberculous meningitis and their caregivers' perceptions. In **chapter 5** we evaluated the costs and cost-effectiveness of home-base treatment versus in-hospital treatment for tuberculous meningitis in children.

Main findings

Caregivers showed good appreciation of the adverse effects of noncompliance and benefits obtained from taking treatment in the home environment. Figure 3 provides an overview of the initial situation (children receiving home-based treatment for tuberculous meningitis) and the mechanisms we identified (caregiver, clinical and socio-economic characteristics)

which affect a particular outcome (adherence) within the context of this study.

Societal costs (including healthcare, informal care, lost-productivity costs and costs in other sectors) 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 (90.9% versus 84.5%) and family impact-scores (94.8% versus 73.1%).

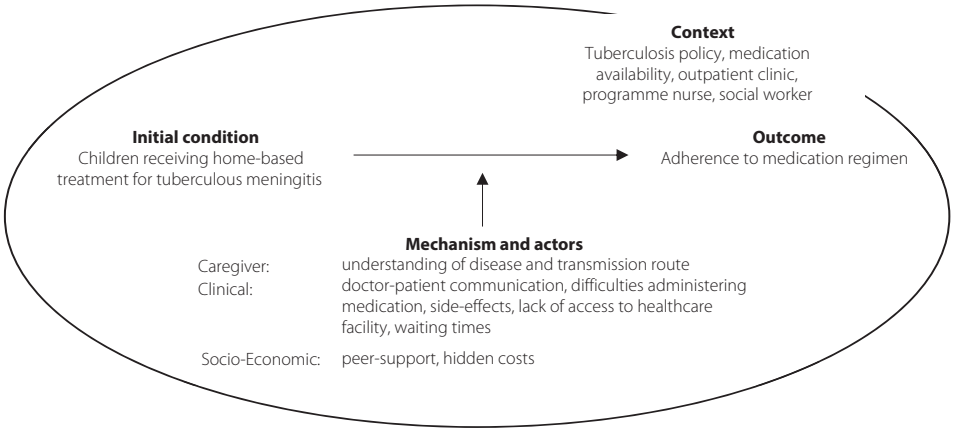

Figure 3. Configuration of home-based treatment of tuberculous meningitis

Implications for practice

Tuberculous meningitis is the most lethal form of tuberculosis [22] and uninterrupted treatment is essential to improve clinical symptoms, limit disease progression, terminate transmission, and prevent the emergence of drug resistance [23]. Previous studies showed that completion of treatment for tuberculous meningitis can be successful in a home-based setting [8] and can achieve positive clinical outcomes similar to in-hospital treatment with no loss to follow-up [9]. Our studies add an in-depth understanding of tuberculous meningitis treatment in the home-based setting and show caregivers respect the importance of, and do maintain high levels of adherence. Home-based treatment is a cost-effective alternative for in-hospital treatment. Children on home-based treatment compared to in-hospital treatment have better health-related quality of life and family functioning while reducing overall societal costs. Provided a strict selection procedure [8, 9], we recommend the implementation of home-based treatment as part of standard

care for tuberculous meningitis. This will require a dedicated programme nurse at each outpatient clinic involved with treatment of tuberculous meningitis and a structured follow-up system to ensure children remain on treatment until completion. When difficulties in the treatment process occur at home, policies should be in place with an accessible track to readmit the child for in-hospital completion of treatment. The following factors should also be considered within the new context when implementing the program at scale: communication and information provision (e.g. the caretakers' understanding of the condition and treatment is crucial), existing hospital structures (e.g. limited waiting times), opportunities to facilitate peer support and assessing hidden costs. Only when the program is well embedded in the system and has the full commitment of the healthcare providers involved, implementation at scale will be successful.

Implications for research

Home-based treatment of children with tuberculous meningitis, which was evaluated in part II of this thesis, is a unique program which was originally developed as an intervention. To make an intervention transferable, a part of the configuration is selected to become the 'intervention' and the other parts become 'context'. This process is important because the selection made determines what is expected from the context in which an intervention is supposed to function [24]. In the studies described in this thesis we have identified certain crucial elements that make up the intervention and assumptions of context required for the intervention to work. Future research should not only focus on monitoring and evaluation (adherence and clinical outcome) after incorporation of this program within existing policies. For successful implementation of intervention at scale (Nationwide within South Africa), future research can contribute by identifying the conditions of this new context required for the intervention to work.

III. Treatment-support intervention

Part 3 brings together both populations studied in the previous chapters. **Chapter 6** evaluates a treatment-support intervention, which was developed in collaboration with a diverse group of stakeholders involved with the care of children with HIV infection or tuberculous meningitis in a home-based setting.

Main findings

The low-cost, cultural friendly treatment-support intervention combined adherence-education (information brochure), -reinforcement (sticker-puzzle), and -monitoring (calendar). The 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. Figure 4 provides an overview of the effect of the treatment-support intervention on the initial situation (children receiving home-based treatment for HIV infection or tuberculous meningitis) and the mechanisms that affect a particular outcome within the context of this study.

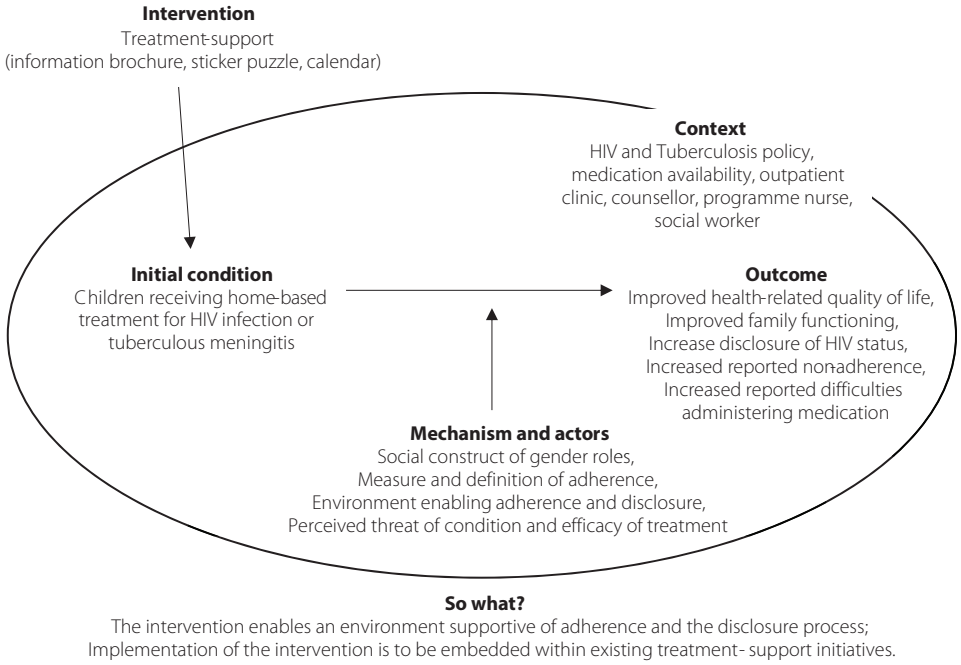

Figure 4. Configuration of the treatment support intervention as implemented in home-based treatment of HIV infection and tuberculous meningitis

Implications for practice

Clinicians are often uncertain how to provide structured adherence support and proper basic adherence counselling is only provided once the child's health is deteriorating [14]. Literature urges the need for well-designed evaluations of interventions to improve paediatric ART adherence [10, 25], in particular randomised controlled trials with specific focus on context and the effect of specific features of the intervention content on effectiveness [25].

Interventions designed to affect medication adherence, rely on the mechanism of suggestion to shape anticipatory behaviour. Anticipatory behaviour (medication

adherence) is embedded in and shaped by complex social and material context [12]. The intervention did not alter the range of elements that shape adherence. However, use of the intervention enabled an environment (health-related quality of life and family functioning) supportive of ART adherence and was facilitative of the disclosure process. In addition, the healthcare provider-caregiver communication benefits from the use of the intervention as non-adherence and difficulties experienced with administering medication were more likely reported when caregivers used the intervention.

The treatment-support intervention is a useful tool to support home-based treatment for children with HIV infection or tuberculous meningitis and has potential benefits in the support of treatment for other conditions. When upscaling the use of the intervention we advise to incorporate the intervention with existing local supportive material. Graphic stories for example provide a novel and creative way to learn and teach children about illness [26] and are a method we must take advantage of [27]. In both the HIV and tuberculous meningitis clinical setting, which are studied in this thesis, graphic stories such as MediKidz [28] are used and could guide the design of the sticker puzzle. This could facilitate the roll-out of the intervention and the commitment of clinics to incorporate and use it within their existing structures.

Implications for research

Better descriptions of what works for whom, in what context could stimulate mutual learning and more productive collaboration around interventions [24]. The current randomised effectiveness study could be supplemented with a qualitative study to further explore how children and their families in a specific context make use of the intervention. This understanding could facilitate successful implementation and amplify the beneficial effect of the treatment-support intervention. The intervention can be redesigned for different conditions and incorporated as part of existing treatment-support structures. Avenues for future research include evaluating the effect of the intervention on good healthcare provider-caregiver communication, the use of the intervention for conditions with general low levels of adherence, and the effect of the intervention on maintaining high levels of adherence for other conditions. The next step would be to clearly identify which elements make up the intervention and the assumptions about the context in which the intervention will be implemented before scaling up the use of the intervention for HIV infection, tuberculous meningitis and other conditions.

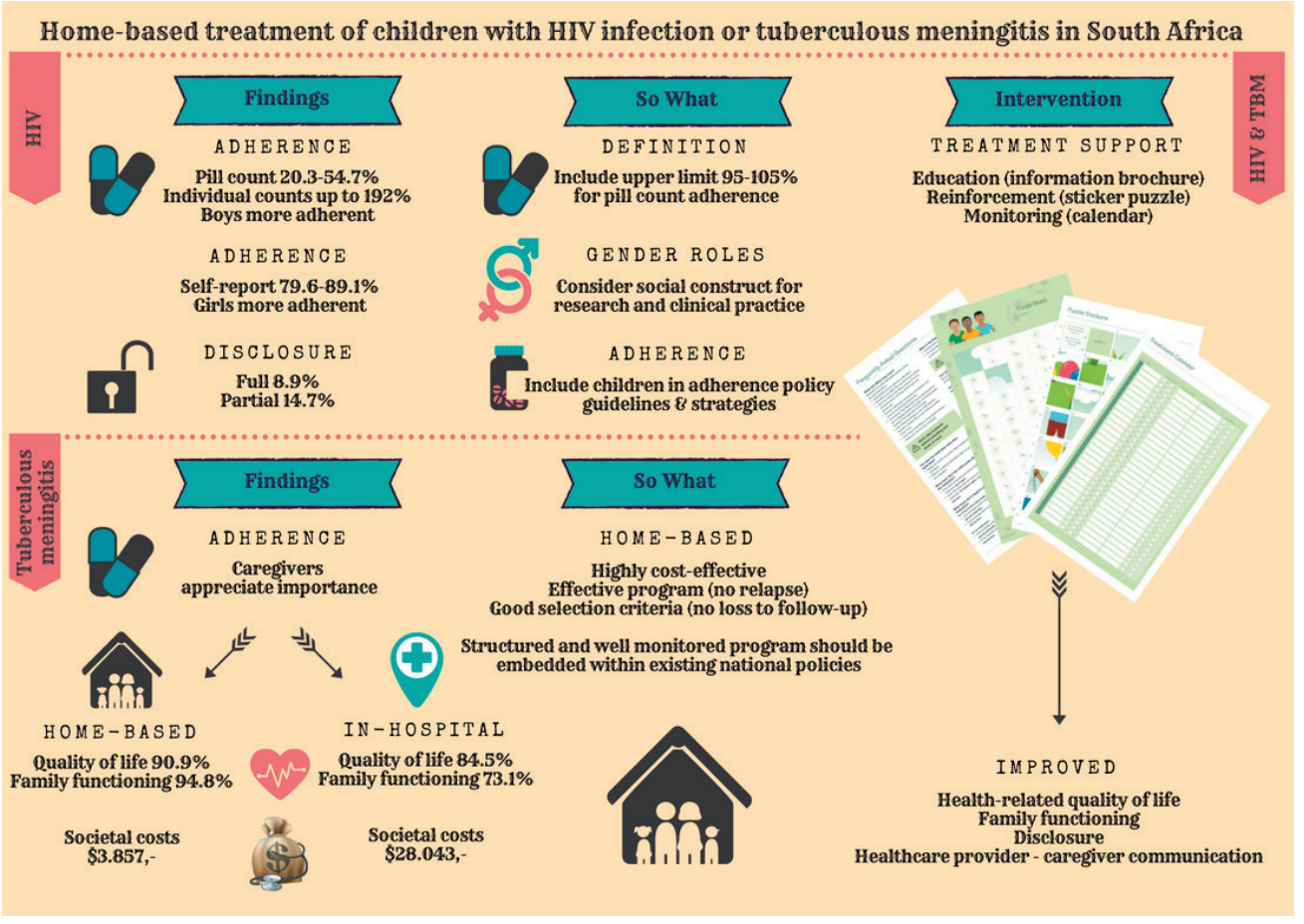

Figure 5. Infographic of main findings presented in this thesis

CONCLUSION

Figure 5 provides an overview of the main findings presented in this thesis. The current home-based setting for treatment of HIV infection in children provides opportunities for improvement. Although current policy guidelines discuss adherence, we recommend to include strategies tailored specific to children. It is important to address adherence to ART and the disclosure process of HIV status to children before the health of the child deteriorates. Doing so successfully in clinical practice, research or when developing interventions, requires the consideration of gender roles within the societal context. In addition, we recommend to define adherence using both lower and upper limits when using pill counts as the measure of choice. Caregiver-reported difficulties administering medication provide a good indication of adherence. Monthly clinic visits represent a convenient and appropriate time to address these difficulties while resolving the actual problem and reducing social desirable answers and stigmatisation. The effect of the condition on the child, caregiver 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. Good 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 and we therefore recommend the use of the intervention to support home-based treatment for children embedded within existing treatment-support structures.

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