Pediatric adherence to antiretroviral therapy in resource-poor settings: challenges and future perspectives

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The HIV pediatric epidemic in low-income countries is still growing with an increasing impact on children. By the end of 2007, more than 2 million children under 15 years of age worldwide were living with HIV, 90% in sub-Saharan Africa. In that year alone, 370,000 children were newly infected and 270,000 died. AIDS has become one of the leading causes of mortality among children under the age of 5 years in developing countries [101]. In the absence of combination antiretroviral therapy (cART), 52% of children infected with perinatally acquired HIV infection will die by the age of 2 years [1].

Numerous studies have confirmed the clinical efficacy and feasibility of cART in HIV-infected adults in Africa [2,3] but, to date, resources and programs targeting HIV-infected children in resource-poor settings remain limited. Even though the use of cART to treat children has increased in recent years in sub-Saharan Africa, less than 15% of children needing cART in Africa currently receive it [102]. It is estimated that more than 780,000 children are in need of cART in low- and middle-income countries [103]. When made accessible, treatment for children in this context has proved highly effective [4]. Studies have found the survival probability at 12 months for children on cART to be more than 95% in settings in sub-Saharan Africa [5] and Asia [6]. Education and adherence counseling are therefore essential components of cART and adherence in HIV-infected children is critical to the success of cART.

Specificities & challenges of pediatric cART adherence

The issue of adherence in children requires particular attention because of its specificities in comparison to adults as:

- Children may not be aware of their HIV status;

- Younger children depend on caregivers for receiving drugs;
- According to their age, adherence issues differ in terms of the cognitive development, level of maturity and feelings of the children;
- There are currently very few adequate pediatric formulations, raising palatability difficulties;
- There is often difficulties in the family structure with fewer adults/parents to care for the infected child (orphans and vulnerable children);
- The frequent lack of healthcare professionals with adequate childcare competencies.

Currently, several arguments are in favor of the early and systematic initiation of antiretroviral treatment among HIV-infected children at the earliest convenience to improve their survival, as reported in the Children with HIV Early Antiretroviral Therapy (CHER) Trial [7]. This led to a revision of the WHO pediatric guidelines in 2008 recommending that HIV-infected infants are treated systemically, irrespective of their clinical stage [104]. In low-income countries, it is crucial to assess public health strategies of early HIV diagnosis and lifelong cART targeted to HIV-infected infants. This early initiation of cART in infants also raises questions concerning long-term effects in terms of safety, efficacy and resistance, but also adherence.

Successful treatment of HIV requires drug adherence rates of 95% [8]. Even moderate non-adherence to cART is associated with compromised health status and significant disease progression [9]. On the contrary, good adherence minimizes the likelihood of developing resistance to a particular drug or class of drugs [10], a factor of great importance in resource-limited settings with few treatment options.

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Although adherence in adults has been well documented in developed and developing countries [11,12], less attention has been given to cART adherence among children. The need for near-perfect adherence to lifelong therapy from an early age has been identified as a major challenge in the administration of cART to HIV-infected children in a context where there is a crucial lack of accessibility to antiretroviral drugs [13].

Sustaining high rates of adherence in pediatric care is challenging for children receiving the treatment, their caregivers, as well as healthcare providers. Drug regimens include multiple medicines that may have complex dosing schedules often requiring that patients take numerous pills multiple times a day with specific timing and food restrictions or requirements and adverse effects resulting in poor tolerability [13]. Furthermore, discrimination and stigma may prevent caregivers from disclosing the child's HIV status with family members or others [14].

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Assessing adherence to pediatric cART

Regardless of the benefits of cART in treating pediatric HIV infection, estimates of adherence to cART have been reported to be suboptimal amongst children within high-income countries [15]. This is largely dependent on the definition of adherence, the method used to assess it and the study setting [16].

■ Methods of measurement

There have been several different methods to measure pediatric cART adherence in resource-limited settings, including self or caregiver reports [17–19], pill counts [20], pharmacy records [21], clinic attendance [22], therapeutic drug monitoring [23] and directly observed therapy [24]. Very few studies have compared clinical indicators (viral loads or CD4 counts) with measured adherence [5], or used electronic drug monitoring as a measure of adherence in this context [25]. It is difficult to estimate cART adherence in children with precision since the measurement methods are not standardized. Data from studies of pediatric cART adherence fail to provide definitive guidelines or to identify any gold standard in terms of assessment methods.

The limitations of any single assessment strategy suggest possible benefits of using multiple methods. It is often recommended to

associate the patient's and/or caregiver's declaration of adherence with virological outcomes [26]. Collecting information on adherence from multiple sources of information has also been suggested; nevertheless, few studies have validated adherence assessment strategies [18].

It is notable that because varying definitions of adherence among studies and different quantifying adherence strategies have been used, it has not been possible to produce a pooled estimate on pediatric adherence in developing countries. How adherence is assessed, how optimal adherence is defined (cut off points of 90, 95 or 100) and how findings are reported have varied considerably between studies.

In resource-limited settings, pediatric cART adherence assessment is often restricted to the patient caregiver (as a proxy) or child/youth self-report and pill counts because of financial constraints [17]. Self-reported/caregiver adherence tends to overestimate the prevalence of adherence due to social desirability or recall bias factors [27]. In this sense, Farley *et al.* found self-report to be unreliable when compared with electronic measurement [28].

More objective measures of adherence such as unannounced pill count and medication event monitoring system (MEMS) tend to be more sensitive to lapses in adherence [9,18]. However, such measures are not feasible in resource-limited settings with large-scale programs. Davies *et al.* showed that although clinic-based medication measures may not be as sensitive as unannounced home-based measures or MEMS monitoring to detect poor adherence, they are still strongly predictive of virological response [29].

■ Level of adherence

Despite its importance in ensuring treatment success, a limited number of studies have been carried out among HIV-infected children concerning adherence to cART in resource-poor settings to date [17–19]. In a systemic review from low-income countries, Vreeman *et al.* presented estimates of cART adherence ranging from 49 to 100%, with the majority of studies reporting an adherence of greater than 75% [30]. In addition, recent prospective studies have highlighted that good adherence to cART in resource-poor settings is achievable with 80–90% of children obtaining average medication return adherence greater than 95%, resulting in 84 and 80% virological suppression at 6 and 12 months, respectively [6,29].

Correlates & determinants of pediatric adherence to cART in resource-poor settings

In order to facilitate adherence to cART and to improve outcomes of cART in HIV-infected children it becomes necessary to identify correlates and factors that influence adherence and determine possible interventions to improve cART adherence in children.

Several studies have recently been reported that describe the benefits of adherence and have identified nonadherence factors in children in resource-poor settings [17,19]. Specific findings vary from study to study, which is, in part, due to the different samples and measures used.

Child adherence is thwarted by multiple barriers including individual and broader structural factors related to patient and family/caregiver, medication and healthcare delivery systems [31]. Knowing and understanding these factors is helpful in identifying where and how to improve adherence to cART amongst children.

■ Family/caregiver correlates

Family/caregiver correlates are crucial to pediatric adherence because infants and younger children depend almost entirely on a caregiver to administer medication [9]. Various studies in resource-limited settings have confirmed the crucial role the caregiver has in pediatric cART adherence. Characteristics of the child's familial and socioeconomic environment has been shown to be significantly associated with nonadherence, including low parental education and disorganized families [32]. Furthermore, caregiver psychosocial factors, such as presence of anxiety, depression, fear of disclosure of HIV-positivity to family members, the perception and belief in the efficacy of the treatment, dosing self-efficacy, knowledge of the disease and cART, along with the financial burden and associated costs of medical treatment, have been identified as significant predictors of child adherence [17,27]

Regarding patient correlates, age (especially infancy and adolescence), refusal of treatment, knowledge of HIV status, clinical stage and changes in health status have also been identified as relevant issues in relation to adherence to cART in pediatric patients [33]. A study in Uganda identified complete disclosure and strong parental relationships as factors related to good adherence [19]. In addition, structural factors such as poverty and stigma were identified barriers to adherence. Complete parental disclosure helps to motivate HIV-infected children to

understand HIV infection and to make sense of disease-related experiences and the importance of adherence [34].

For adolescents, issues such as body modifications induced by puberty, authority problems, depression, aggressiveness and accession to sexuality are only some of the difficulties that will increase the problem of adherence. This a critical period with potential adherence fatigue leading to treatment failure [35].

An estimated 15 million children are orphaned as a result of HIV, with 80% of these orphans living in sub-Saharan Africa [101]. Contextual factors such as orphan status (child who lost one or both parents) may influence pediatric adherence to cART. Prior research concerning orphan status and its association with cART nonadherence has been inconsistent [33,36,37]. In a recent study in Uganda, orphans were more likely to initiate cART at an older age than non-orphans [38]. There is a need to better understand the relationship between pediatric cART adherence and the complex context of the death of one or both parents, and target those at risk for non-adherence so as to ensure timely cART access.

■ Medication-related factors

Proposed medication- or treatment-related factors that likely complicate pediatric adherence include complex regimens, high pill burden, complex dietary considerations, storage requirements and long-term toxicity. Other factors to consider are the characteristics of the available formulations of drugs such as taste, size of pills, availability of liquid formula, storage requirements and adverse effects [31]. To date there are a limited number of antiretrovirals approved worldwide for pediatric use, and these related factors become crucial in determining child's adherence to cART.

■ Healthcare delivery system related factors

The healthcare system has an important role in determining adherence. Decentralization of pediatric HIV care treatment from third-line health services to district level and the provision of a continuum of services within a family approach are major challenges to improve coverage of pediatric cART in resource-poor settings. This requires monitoring medication adherence, providing strategies to enhance adherence as well as establishing a reliable drug distribution system. Trust and communication with health providers as well as using directly observed therapy

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or watching children taking therapy have been reported to improve adherence [24]. These interventions require trained and committed healthcare staff and time to be spent with patients and their caregivers. Further data are needed to evaluate the long-term sustainability of this approach.

Interventions to promote pediatric adherence to cART in resource-poor settings

Even though there have been studies of factors related to adherence, very little work has been carried out to identify ways to improve cART adherence in children generally and in resource-poor settings in particular. In addition, limited information has been reported on the evaluation of adherence-promoting interventions. At present, a few feasible strategies to encourage and improve pediatric cART adherence that can be applied in resource-poor settings have been identified.

■ Interventions aimed to reduce the barriers to adherence

Simplifying treatment regimens when possible and tailoring cART regimens to the daily activities of the child and his/her family may enhance patient adherence to therapy [31]. Developing fixed-dose combinations and thus lowering pill burden that are appropriately formulated for children is a priority [39]. Palatable pediatric syrups and appropriate low-dose tablet formulations remain all too rare. There is an urgent need for the development of simplified pediatric antiretroviral regimens. With this aim, once-daily regimens are promising options that need to be developed [40].

Disclosure of HIV status to children over 6 years of age and implicating children in the decision-making process regarding therapy modifications has been reported to enhance the child's cooperation with treatment [17]. There is a need to assess the nature of the parental relationship and consider support activities aimed at caregivers on how to announce the serological status to the child [41].

■ Interventions aimed to support adherence

Before treatment begins, educating, counseling and giving continuous psychological and social support to parents and/or caregivers as well as patients is required through the implementation of programs to support adherence for HIV-positive children in need of cART [42]. Assessing regimen knowledge at periodic intervals to identify families at risk for nonadherence so that

educational interventions can be tailored toward this group and using directly observed therapy through involvement of community workers are some of the strategies that can result in improved pediatric adherence to cART [24].

Owing to expanding services for cART in resource-poor settings, there is a need to address severe human resource shortage. Task-shifting strategies (delegation of health service responsibilities from higher to lower cadres of healthcare staff) through the training of community health workers and lay counselors as adherence support workers should be considered. Recent implementation of this strategy has proved feasible in HIV-testing centers [43]. However, there will be a need to assure the provision of quality assurance through ongoing supervision. There is very limited evidence-based data on how task shifting influences the quality, safety, acceptability and impact of cART interventions in sub-Saharan Africa. Operational research in this field is still needed [44].

The establishment of a long-term relationship between children, families and clinic staff has been reported as a key intervention [45]. In this sense, adherence programs that include strategies to enhance and facilitate communication between the family and care providers can help overcome language and cultural barriers.

The high rates of HIV-positive caregivers indicates that it is imperative to transform the pediatric treatment model from child orientated to family orientated in order to protect the integrity of care giving structures. This family-orientated approach needs to be free of charge or associated with strategies to identify indigents, and able to support minimal financial needs [46].

During treatment, adherence should be repeatedly monitored and promoted whenever needed. Several psychosocial interventions such as disclosure or support groups could play a role; on the other hand, there are also different tools that could assist patients with taking treatment (e.g., pill boxes and calendars, among others).

Priorities for future research on pediatric cART in resource-poor settings

Promoting adherence is a multidisciplinary challenge that raises research and programmatic perspectives.

■ Research issues

Below are a number of directions that should be considered in future research on pediatric adherence to cART in resource-poor settings.

“The high rates of HIV-positive caregivers indicates that it is imperative to transform the pediatric treatment model from child orientated to family orientated in order to protect the integrity of care giving structures.”

- Systemic meta-studies that focus on African pediatric cART adherence should be encouraged. This might provide a more complete understanding of the problem of pediatric adherence;
 - As has been recommended by others [31], estimates of adherence need to be based on two or more assessment techniques. To date, the use of multiple measures of adherence is rare [18,29]. Therefore, comparison between self-report, objective measures and clinical indicators are needed to identify the most cost-effective assessment strategies [47]. In addition to this, standardization of assessment methods and definitions of adherence will facilitate the comparison of research results originating from resource-poor settings. A low-cost, reliable, replicable and easy-to-use tool is needed to measure adherence specifically in children in routine clinical follow-up;
 - Most studies have reported adherence correlates by cross-sectional designs. Future research should incorporate prospective studies to investigate the variability and consistency of adherence repeatedly over time, as well as predictors of short- and long-term adherence [25,29];
 - Currently, cART is mainly initiated during the advanced stages of HIV in African children. Recent data have shown the benefits of early cART in children [7]. There is an urgent need to evaluate early pediatric treatment adherence;
 - Simplification of long-term antiretroviral treatment relevant in children could focus on a once-daily strategy easier to maintain for a life-long treatment. This type of approach needs to be further investigated in infants and children.
- **Programmatic issues**
- A reliable tool of adherence that can be adapted to children less than 3 years of age, who are highly dependent on caregivers and need specific drug formulations is urgently needed.

Conclusion

With more than 2 million children under the age of 15 currently living with HIV, interventions to enhance pediatric cART adherence at the patient, family and healthcare level in low-income countries are an urgent priority. A major challenge for developing countries is adapting the healthcare infrastructure and models for the management of chronic diseases. Operational research that enhances our understanding of cART adherence will be critical.

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