Article

DETERMINANTS OF ADHERENCE TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY AMONG HIV-INFECTED CHILDREN IN RWANDA

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ABSTRACT

Introduction: Adherence to antiretroviral therapy (ART) among HIV-infected children is influenced by numerous socio-economic, clinical, spiritual and psychological factors. Interrupted adherence can result in resistance to first-line ART. In such cases, patients may infect others with resistant virus strains and they may require a significantly more expensive second-line ART regimens, which are more difficult to procure and more difficult for patients to access. Thus, ART adherence influences not only individual and population outcomes, but also has significant implications for long-term healthcare financing. It is essential to determine and address the factors that impact a patient's likelihood to adhere to ART.
Objective: This study investigates factors that are associated with HIV-infected children's adherence to highly active antiretroviral therapy (HAART) in Rwanda.
Methods: Five health facilities were visited in August 2005. Each health facility was treating HIV-infected children who had been receiving HAART for at least 12 months. Participants included children under 15 years who were treated with HAART for at least 12 months at the selected health facilities. A standard questionnaire was employed for each caregiver participant and administered in his or her home. Non-adherence was defined as missing at least one dose of ART during a 12 month period of HAART treatment.
Results: Among the study participants 59% were girls and 41% were boys. Thirty-four percent of children had missed at least one dose of HAART in the past 12 months; forgetfulness (38%) and change in treatment routine (27%) were the most common reasons for missing doses. Caregivers who were members of an association for people living with HIV or AIDS (PLWHA) were more likely to be adherent than those who were not (p=0.031). The more time it took for children to be served at health centers, the less likely they were to be adherent (p=0.043). Finally, caregivers who were satisfied with the health care their children were receiving had children who were more likely to be adherent, compared to those caregivers who were unsatisfied (p=0.001).
Conclusion: In order for Rwanda to increase full pediatric adherence to HAART, it must review the national counseling protocol to provide caregivers and children with tools to combat forgetfulness; it must sensitize child caregivers to join associations of PLWHA; and it must promote improved "customer care" practices at health centers.

Keywords: Antiretroviral therapy, pediatric, Rwanda, adherence

RESUME

Introduction: L'adhérence à la thérapie antirétrovirale hautement active (TARHA) chez les enfants infectés par le VIH est influencée par des facteurs socio-économiques, cliniques, spirituels et psychologiques. La non adhérence peut entraîner une résistance à la TARHA de première ligne. Dans de tels cas, les patients peuvent infecter les autres personnes avec des souches de virus résistantes et nécessiter la mise sous une TARHA de deuxième ligne, beaucoup plus coûteuse, plus difficiles à obtenir et plus difficile d'accès pour les patients. Ainsi, l'adhérence à la TARHA influence non seulement les résultats individuels, mais a également des implications importantes pour la santé publique et les financements des soins de santé à long terme. C'est pourquoi il est essentiel de déterminer et de trouver une solution aux facteurs qui influencent négativement l'adhérence d'un patient à la TARHA.
Objectif: Cette étude examine les facteurs qui sont associés à l'adhérence des enfants infectés par le VIH à la TARHA au Rwanda.
Méthodes: Cinq établissements de santé ont été visités en août 2005. Chacun des établissements de santé avait traité des enfants infectés par le VIH qui avaient reçu une TARHA pendant au moins 12 mois. Les participants a l'étude comprenaient des enfants de moins de 15 ans qui ont été traités par TARHA pendant au moins 12 mois dans les établissements de santé sélectionnés. Un questionnaire standard a été utilisée pour chaque gardien - parent participant et été administré a domicile. La définition de la non adhérence est d'avoir manqué au moins une dose du traitement antirétroviral durant 12 mois de traitement HAART.
Résultats: Parmi les participants à l'étude 59% étaient des filles et 41% étaient des garçons. Trente-quatre pour cent des enfants avaient manqué au moins une dose de TARHA au cours des 12 derniers mois; oubli (38%) et le changement dans la routine de traitement (27%) sont les raisons les plus communes de non adhérence. Les enfants qui ont des gardiens - parents membres d'une association de personnes vivant avec le VIH ou le SIDA (PVVIH) sont plus susceptibles d'être adhérentes que ceux qui ne le sont pas (p = 0,031). Plus le temps d'attente de services à l'enfant dans les centres de santé était long, moins l'enfant était adhérant (p = 0,043). Enfin, l'adhérence des enfants était plus grande quand les gardiens - parents qui étaient satisfaits des soins de santé donnés à leurs enfants que lorsqu'ils n'étaient pas satisfaits (p = 0,001).
Conclusion: Pour que le Rwanda puisse augmenter l'adhérence a la TARHA chez les enfants, il faut revoir le protocole de consultation nationale à fournir aux gardiens - parents et aux enfants des outils pour lutter contre l'oubli; il faut sensibiliser les gardiens - parents des enfants à s'affilier a une association de PVVIH; et il faut favoriser l'amélioration du "service à la clientèle" dans les centres de santé.

Mots-clés: Thérapie antirétrovirale, pédiatrie Rwanda adhérence

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Introduction

In the last six years, with the "3 by 5" initiative and increased global solidarity to support universal access to HIV treatment, the landscape of pediatric HIV has changed dramatically. In Rwanda, with the commitment of the Minister of Health to universal access to ARVs and under the program led by the Center for Treatment and Research on AIDS, Malaria, Tuberculosis and Other Epidemics (TRAC Plus), 80% of children estimated to require highly active antiretroviral treatment (HAART) are now benefiting from treatment. The number of children on HAART in Rwanda has steadily increased from 468 to 6,676 between 2004 and 2009 (TRAC+ 2004-2009 reports). However, access to ART alone is not sufficient for optimal HIV care. Ensuring that children are adherent to therapy is crucial. In order for a child to reach and maintain an undetectable viral load, greater than 95% adherence to HAART is required. Furthermore, failure to reach this level of adherence can worsen a patient's health status and lead to disease progression and ART resistance. ,

A range of studies have investigated determinants of ART adherence, particularly in adult populations. In one literature review of twenty studies—primarily using data from North American and European patients—determinants most consistently associated with non-adherence included: symptoms and adverse drug side effects, psychological distress, lack of social or family support, complex HAART regimens, low patient self-efficacy, and inconvenience of treatment. By contrast, a qualitative study of HIV-infected patients in Uganda, Tanzania, and Botswana found that the main obstacles to optimal adherence were treatment-related costs (transportation, a lost day of work, registration fees at health facilities), long wait times at health facilities, stigma, and hunger and side effects during the initial stage of treatment. This exemplifies the wide range of factors associated with adherence and how they may differ according to context.

Adherence among HIV-infected adults in sub-Saharan Africa is higher than that among HIV-infected adults in other parts of the world, despite the greater financial and structural barriers that persons living with AIDS in sub-Saharan Africa often face. , Ware et al (2009) argue that adherence is high in sub-Saharan Africa because of the power and reliability of extended social networks to achieve desired ends; this is also referred to as "social capital." ,

Similarly, adherence rates are higher among children infected with HIV in sub-Saharan Africa, relative to pediatric ART adherence rates achieved in other parts of the world. However, in many resource-constrained settings, pediatric adherence is lower than adult adherence. This likely occurs because adults are generally autonomous and able to mobilize social networks to enhance their adherence. Children, on the other hand, are dependent others to mobilize social networks, to pay for transportation health facilities and consultations, as well as to obtain and take their medications. Thus, a child's relationship with his/her caregiver can either increase adherence or become a further barrier to it.

HAART adherence is a crucial issue in caring for HIV patients. Interrupted adherence can result in resistance to first-line ART. In such cases, patients often must switch to significantly more expensive second-line regimens which are more difficult to procure and more difficult for patients to access. Switching to second-line therapy as a child results in a more costly lifetime ART regimen, and is a major financial concern and human resource burden for the Government of Rwanda (GOR). Furthermore, the future spread of drug-resistant strains of HIV would increase the number of patients on second-line therapy, exacerbating the financial consequences of non-adherence. For these reasons, among others, the GOR needs to better understand the dynamics that influence pediatric adherence to ART, so that health interventions can address these factors. Health care providers must also be equipped with the tools to help their young patients and families ensure high adherence to HAART. This study aims to identify the factors associated with adherence and non-adherence to pediatric HAART in Rwanda.

Methodology

This study was multi-centric and cross-sectional. It was conducted from July 2005 to December 2005.

Selection Criteria

Selection criteria for health facilities included Ministry of Health-accredited public health facilities that had provided HAART to more than 10 children for at least 12 months by August 2005. Five health facilities met these criteria: 2 health centers (Kimironko and Kicukiro), one district hospital (Kabgayi), one reference hospital (CHU Butare), and the outpatient clinic of TRAC Plus in Kigali.

The sample size was calculated from an estimated prevalence of non-adherence of 30±10% reported in other studies. , , Inclusion criteria for participants were: all children under 15 years who were treated with HAART for at least 12 months prior to the commencement of the study. A total of 88 children met the selection criteria.

Study Design

This study measured HIV-infected children's adherence to HAART through caregivers' report of missed doses over the course of the preceding 12 months. Our definition of adherence is consistent with a study describing "full

adherence" as those who never missed any doses and "non-adherence" as those who missed at least one dose.

Data collection

All participants were interviewed in their respective homes with the consent of their caregiver.

Two questionnaires were designed for this study; one was designed for caregivers and one was designed for parents. The questionnaires were administered during home visits. Data points in the questionnaire included: the socio-economic status of the children and their caregivers; and problems faced by caregivers (e.g. time waiting at health facility; distance to health facility; financial wellbeing). The semi-structured interviews were oral and administered by a trained medical student.

Data Analysis

Our study involved quantitative and qualitative analysis. SPSS 10.1 for Windows was used for quantitative analysis.

Ethics Approval

Approval from the Scientific Committee of the National University of Rwanda was obtained.

Results

Demographic, socioeconomic, clinical and health care characteristics

Of the 88 children surveyed, 59% of the children were female and 41% were male. Twenty-two percent (n=19) were less than 6 years old, 57% (n=50) were between 6 and 12 years old, and 22% (n=19) were between 12 and 15 years old. Eight percent were paternal orphans, 13% were maternal orphans, and 31% were double orphans, while 47% had both parents alive. 24% of all children surveyed were not in school at the time of the survey, however only approximately 2% of those children were of schoolgoing age. Most of the children's caregivers had some formal schooling; only 14% (n=12) of caregivers had no schooling. Thirty-one percent (n=27) of caregivers had reached primary school, 33% (n=29) had reached secondary level, 5% (n=4) had reached university level, and 18% (n=16) had professional training. Nearly 40% (n=34) of caregivers were unemployed. Of the caregivers who participated in this study, 52% (n=46) had not disclosed their children's HIV status to them. When caregivers were asked about their own HIV status, 69% (n=61) said they were HIV positive, 11% (n=10) stated that they were HIV negative, and 19% (n=17) did not know their status. Sixty-eight percent of caregivers belonged to associations for people living with HIV/AIDS (PLWHA).

Participants lived at varying distances from the health facility where they received HAART: 75% (n=66) lived within five kilometers, 22% (n=19) lived between five and ten kilometers away, and 3% (n=3) lived more than 10 kilometers away.

Table 1. Demographic and socioeconomic characteristics of children and caregivers

Characteristic	Number of children or caregivers	Percentage (%)
Sex		
Female	52	59
Male	36	41
Age		
Under 6 years	19	22
6-12 years	50	57
12-15 years	19	22
Orphan status		
Both parents alive	41	47
Paternal orphan	7	8
Maternal orphan	11	13
Double orphan	27	31
School status of child		
Attending school	67	76
Not attending school	21	24
Educational level of caregiver		
No schooling	12	14
Primary school	27	31
Secondary school	29	33
University level	4	5
Professional training	16	18
Child's HIV status disclosure		
Disclosed	42	48
Not disclosed	46	52
Caregiver's HIV status		
HIV positive	61	69
HIV negative	10	11
Not known	17	19
Caregivers' affiliation with association for PLWHA		
Member	60	68
Non-member	28	32
Distance from ART health facility		
Less than 5 kilometers	66	75
5-10 kilometers	19	22
More than 10 kilometers	3	3

Children were on a variety of ART regimens: 44% (n=39) of children received the D4T/3TC/NVP ARV combination, 25% (n=22) received the AZT/3TC/EFV combination, 21% (n=18) received the D4T/3TC/EFV combination, and 10% (n=9) received the AZT/3TC/NVP combination. Thirty-nine percent of children in our study reported side effects from their HAART regimen, including nausea (17%, n=15), pruritus (9%, n=8), vertigo (6%, n=5), anemia (3%, n=3), hepatitis (2%, n=2), and neuropathy (1%, n=1).

The childrens' conditions were staged according to the World Health Organization (WHO) HIV/AIDS clinical staging guidelines: 7% (n=6) were stage 1, 33% (n=29) were stage 2, 39% (n=34) were stage 3, and 22% (n=19) were stage 4.

Table 2. Clinical characteristics of participants

Characteristic	Number of children	Percentage (%)
ARV regimen		
D4T/3TC/NVP	22	25
AZT/3TC/EFV	18	21
D4T/3TC/EFV	9	10
AZT/3TC/NVP	9	10
Medication side effects		
Nausea	15	17
Pruritis	8	9
Vertigo	5	6
Anemia	3	3
Hepatitis	2	2
Neuropathy	1	1
WHO HIV/AIDS clinical stage		
Stage 1	6	7
Stage 2	29	33
Stage 3	34	39
Stage 4	19	22

Caregivers were also asked about their experiences at the health facilities where their children received HAART. Regarding wait times at health facilities, 24% (n=21) of caregivers and children had been seen by the health care practitioner within less than one hour, 47% (n=41) had to wait between one and two hours, 27% (n=24) waited between two and three hours, and 1% (n=1) waited more than three hours. Caregivers were asked about their satisfaction with the health care given to their children, and were given two options to choose from: "very satisfied," or "a little bit satisfied." Seventy-three percent (n=64) of caregivers indicated they were "very satisfied" with the care given to their children, while 27% (n=24) were only "a little bit" satisfied.

Table 3. Caregiver experiences at health facilities

Characteristic	Number of children or caregivers	Percentage (%)
Wait time at health facility		
Less than 1 hour	21	24
1 to 2 hours	41	47
2 to 3 hours	24	27
More than 3 hours	1	1
Caregiver satisfaction with care		
"Very satisfied"	64	73
"A little bit satisfied"	24	27

Child adherence to HAART

Thirty-four percent (n=30) of caregivers reported that their children missed at least one dose of HAART in the past twelve months. Ten percent (n=9) reported that their children had missed at least one dose of HAART in the preceding month. According to caregiver report, only two children (2%) had received incorrect doses of HAART at home. Of the caregivers who said that their children had missed at least one dose of HAART, forgetfulness (47%, n=14) was the most common reason, followed by a change in the treatment routine (33%, n=10), the child becoming sick (20%, n=6), lack of money (3%, n=1), and drug stock-out (3%, n=1).

Table 4. Children's adherence to HAART

Characteristic	Number of children	Percentage (%)
Adherence in past 12 months		
Missed at least 1 dose	30	34
Missed no doses	58	66
Adherence in past 1 month		
Missed at least 1 dose	9	10
Missed no doses	79	90
Reasons for missing dose(s), of those who missed dose in past 12 months (n=30)		
Forgetfulness	14	47
Change in treatment routine	10	33
Child was sick	6	20
Lack of money	1	3
Drug stock-out	1	3

Factors associated with adherence to HAART

Within our sample, three factors were found to have a statistically significant correlation with adherence, by chi-square analysis: (1) caregivers' affiliation with a PLWHA association, (2) the length of wait times at health facilities, and (3) caregiver satisfaction with the health care provided to their child children (Table 5).

Table 5. Chi-square test of proportion of non-adherence among children on HAART, by caregiver characteristics

Characteristic	Reported Adherence to HAART		P-value
	Missed at least 1 dose in past 12 months *n, (row % by variable)*	Missed no doses in past 12 months *n, (row % by variable)*	
Caregivers' affiliation with association for PLWHA			
Member	16 (26.7)	44 (73.3)	*0.031*
Non-member	14 (50.0)	14 (50.0)	
Caregivers' wait time at ART health facility at last visit			
< 1 hour	2 (9.5)	19 (90.5)	
1-2 hours	18 (43.9)	23 (56.1)	
2-3 hours	9 (37.5)	15 (62.5)	*0.043*
3-4 hours	1 (100)	0 (0)	
> 4 hours	0 (0)	1 (100)	
Caregiver satisfaction with health care			
Very satisfied	15 (23.4)	49 (76.6)	*0.001*
A little satisfied	15 (62.5)	9 (37.5)	

Children whose caregivers belonged to an association for people living with HIV/AIDS (PLWHA) were more likely to be adherent than those who had caregivers who were not members of an association for PLWHA (p=0.031). An increase in wait time at health facilities was associated with an increased likelihood of missing doses of HAART (p=0.043). A statistically significant correlation was found between caregivers' satisfaction with the health care provided to their children and missed doses of HAART (p=0.001); children of caregivers who were very satisfied with the health care given to the child were less likely to miss HAART doses compared to children of caregivers who were only a little bit satisfied. Other factors, such as medication side effects, cost, and parent employment status were included in the analysis but were not found to be statistically significant.

Discussion

In this sample of children living with HIV, 34% did not fully adhere to their ART regimens. This is consistent with several studies that found non-adherence rates of 30±10%.9, 10, 11 Caregivers of non-adherent children reported that missed doses were most often due to forgetfulness or changes in treatment routine.

Univariate analysis by chi-square test revealed three factors that were statistically significantly correlated with pediatric adherence to HAART: (1) caregivers' affiliation with a PLWHA association (p=0.031), (2) the length of wait times at the health facilities (p=0.043), and (3) caregiver satisfaction with the health care provided to the child (p=0.001). Thus, pediatric adherence was largely influenced by children's caregivers – their associations with support groups and their perceptions of care. Other studies have also shown the importance of social relations and social capital in promoting adherence to medications such as HAART.6,7 Our findings suggest that there were no significant barriers to adherence linked directly to the child's characteristics (age, sex, etc) or characteristics of the drugs, such as cost or side effects.

Although there is limited research on pediatric adherence to HAART in resource-limited settings, several studies have advanced this area of inquiry. As expected, not all studies align with our findings, highlighting the importance of identifying locally-defined factors that affect adherence. In recognizing these differences and similarities, health care implementers in resource-limited settings can more efficiently create and implement responses to issues of adherence.

For example, a study from Côte d'Ivoire on pediatric ART adherence found that missed doses were most commonly due to forgetfulness (40.5%), similar to our study findings. Children who received Efavirenz were also less likely to achieve full adherence, which was not supported by our study. Adherence was also interrupted by drug stock-outs at the central level. By contrast, drug stock-out was not a major factor associated with adherence in our study; only one caregiver out of 88 claimed drug stock-out as the reason for his/her child missing a dose of HAART. In a sample of HIV-positive children in Togo, only 42% adhered to their medication. In their multivariate analysis, imperfect adherence was more common among: female children, children living in a nuclear family environment instead of a shared compound, children receiving ART regimens other than an NNRTI-based regimen, and caregivers who perceived ARV administration as "too hard."

In a study from South Africa, confusion between multiple caregivers, children vomiting the medication, and financial constraints were factors associated with missed HAART doses. In our study, financial difficulties were not associated with adherence, which may be due to the availability of free ART and HIV follow-up care in Rwanda. Another study of pediatric ART adherence from Côte d'Ivoire found that the involvement of multiple caregivers in administration of the pills was correlated with non-adherence.

In a study from Uganda, children who did not know their serostatus were three times less likely to adhere to HAART as children who were aware of their HIV status. Caregivers described the informed children as being self-motivated to adhere to their medications; as such, both the child and the caregiver shared responsibility for ensuring the child's adherence. Children generally complied with their regimens if the caregiver-child relationship was strong, and did not if the caregiver-child relationships were unsupportive and lacked trust. These findings are particularly noteworthy, given that 52% of children in our study had not been told their HIV status. Further investigation of how disclosure influences ART adherence is required in the Rwandan context.

Our study found that caregiver satisfaction with care was associated with ART adherence. There is limited research on how patient satisfaction with care influences adherence in resource-limited settings and among pediatric populations. However, several studies among adult American populations have shown correlations between positive patient-provider interactions and ART adherence. , , In one qualitative study of HIV-positive patients, most patients cited a connection between the quality of their patient-physician relationship and their adherence to ART. A study of 620 HIV-positive patients in Boston showed that a higher quality of physician-patient relationships was related to improved adherence. The dimensions of the physician-patient relationship that were related to good adherence included patient ratings of: physicians' general communication, provision of HIV specific information, overall satisfaction with care, willingness to recommend the physician, trust in physician, and dialogue on adherence (the patient's rating of the physician's ability to understand and solve problems

with ART regimens). Another study of HIV-positive adults in four US cities showed a correlation between patient-rated positive patient-provider interactions and adherence self-efficacy (i.e. a patient's confidence in carrying out treatment plans); and both factors independently related to improved medication adherence. In multivariate regression analysis, however, only adherence self-efficacy was significantly associated with medication adherence, suggesting that adherence self-efficacy mediates the correlation between positive provider interactions and adherence to ART. Although our study linked general caregiver satisfaction with care to improved adherence, specific factors contributing to satisfaction were not examined. Additional questions to explore specific factors that contribute to caregiver satisfaction with care (e.g. communication skills of health care providers, cleanliness of facilities, etc.) would produce more actionable data, upon which health interventions could be planned.

Our study is an initial investigation into the factors that influence pediatric adherence to ART in Rwanda and highlight the need for further investigation in this domain. There were several limitations to our study. Adherence data relied on reporting by caregivers, which is subject to recall and response bias. Using a technique, such as pill counting, to measure adherence may have yielded more accurate results. Additionally, multivariate analysis of caregiver, patient, and health care characteristics would strengthen our study through the disaggregation of potentially confounding or co-varying variables. More detailed questions on patient and caregiver characteristics would also provide further insight into the dynamics affecting adherence.

Additional research is needed to further elucidate locally-defined best practices in supporting pediatric adherence to HAART. A more detailed exploration of patient judgments of care would help to determine how services could be improved to enhance patient satisfaction. Future studies at the community level are needed to better understand the reasons for which people choose not to join an association of people living with HIV/AIDS. Furthermore, additional studies with larger sample sizes would yield more robust data on the determinants of adherence among children.

Conclusion

In Rwanda, as is the case in the majority of Sub-Saharan Africa, the adherence rate to HAART is higher than in many parts of the world. , However, adherence rates may decline in the future if the social and organizational problems that lead to pediatric non-adherence are not addressed. This study sheds light on determinants of pediatric adherence to ART and has implications for steps Rwanda could take to improve treatment effectiveness. Potential steps to increase adherence may include: reviewing Rwanda's counseling protocols and providing caregivers and children with tools to combat forgetfulness; encouraging caregivers to join associations of PLWHA; promoting good "customer care" to improve patient and caregiver satisfaction with care; and innovations to reduce wait times at health facilities. By implementing these suggestions, Rwanda may enhance pediatric adherence to ART, thereby reducing future financial burden on the Government and, above all, improving the lives of children infected with HIV.

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