Adherence to Antiretroviral Drug Therapy in Children with HIV/AIDS in Jamaica

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ABSTRACT

Objective*: We aimed to describe the adherence patterns to antiretroviral therapy (ART) in a cohort of HIV-infected children.*

Methods*: Between the periods May to October 2005, 63 HIV-infected children and their caregivers recruited consecutively at four Paediatric Infectious Disease Clinics in Greater Kingston and St Catherine, Jamaica, were interviewed. Adherence was defined as no missed doses in the last four days. Biomedical markers and factors associated with adherence were explored.*

Results*: Global adherence level was 85.7% (54/63) and was significantly higher for children in residential care (approaching 100%) compared to 76.3% for children in family care (*p *= 0.008). Children had median age 7.9 years (range 0.8 – 19.4 years) and 57% were male. Median duration on ART was 18.3 months (range 0.1 – 123.8 months). Median CD4 count and per cent available for 95.2% (60/63) and 92.1% (58/63) children were 440 cells per µL (IQR 268-897 cells/µL) and 24.9% (IQR 15.6–42.7 %), respectively. Median viral load was 9.60 x 10^3 copies/ml (IQR 0.05 x 10^3 – 52.50 x 10^3) with 16% (10/63) having viral loads # 50 copies/ml. Children in residential care (n = 26), receiving directly observed therapy had higher CD4 counts (*p *= 0.006) and CD4 per cent (*p *# 0.001). Factors associated with non-adherence were primarily caregiver related, especially long work hours (*p *= 0.002) and nausea as a side effect of ART (*p *= 0.007). Non-adherence was positively correlated with missing clinic appointments (r = 0.342,* p *= 0.009) and increasing age of child (r = 0.310,* p *= 0.013).*

Conclusion*: In resource-limited settings, psychosocial factors contribute significantly to non-adherence and should complement biomedical markers in predicting adherence to antiretroviral therapy in children.*

Adhesión a la Terapia con Medicamento Antiretroviral en Niños con VIH/SIDA en Jamaica

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RESUMEN

Objetivo: *Este trabajo tiene por objeto describir los patrones de adhesión a la terapia antiretroviral (TAR) en una cohorte de niños infectados por el VIH.*

Métodos: *Entre los períodos de mayo a octubre de 2005, se entrevistaron 63 niños infectados con el VIH y las personas a cargo de su cuidado, reclutados consecutivamente en cuatro clínicas pediátricas de enfermedades infecciosas en Greater Kingston y Saint Catherine, Jamaica. La adhesión fue definida en términos de las dosis no perdidas en los últimos cuatro días. Se exploraron los marcadores y factores biomédicos asociados con la adhesión.*

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Resultados: *El nivel de adhesión global fue de 85.7% (54/63) y fue significativamente más alto para niños en cuidados residenciales (cerca de 100%) en comparación con el 76.3% de los niños en cuidado familiar (*p = *0.008). La edad promedio de los niños fue de 7.9 años (rango 0.8 – 19.4 años) y el 57% eran varones. La duración promedio del TAR fue de 18.3 meses (rango 0.1 – 123.8 meses). El conteo medio de CD4 y el porciento disponible para el 95.2% (60/63) y el 92.1% (58/63) de los niños fueron 440 células por μL (IQR 268-897 células/μL) y 24.9% (IQR 15.6 – 42.7 %), respectivamente. La carga viral media fue 9.60 x 10^3 copias/ml (IQR 0.05 x 10^3 – 52.50 x 10^3) con 16% (10/63) con cargas virales # 50 copias/ml. Los niños en cuidado residencial (n = 26), que recibían terapia directamente observada, tuvieron conteos más altos CD4 (*p = *0.006) y porciento de CD4 (*p # *0.001). Los factores asociados con la no adhesión estuvieron fundamentalmente relacionados con el encargado del cuidado, especialmente largas horas de trabajo (*p = *0.002) y náuses como un efecto colateral de TAR (*p = *0.007). La no adhesión fue correlacionada positivamente con los turnos médicos perdidos (r = 0.342,* p = *0.009) y el aumento de la edad del niño (r = 0.310,* p = *0.013).*

Conclusión: *En escenarios donde los recursos son limitados, los factores psicosociales contribuyen significativamente a la no adhesión y deben complementar los marcadores biológicos a la hora de predecir la adhesión a la terapia antiretroviral en niños.*

INTRODUCTION

Children comprise eight per cent of the estimated 22 000 persons living with the Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS) in Jamaica (1, 2). Within the Kingston Metropolitan Area, approximately 27% of these children are cared for within residential facilities and the rest receive family-based care (3). Globally, substantial expansion in antiretroviral access has occurred including in the Caribbean; however at the end of 2005, children represented at least 10 per cent of unmet treatment targets (4). Since 2003, there has been accelerated access to and increased uptake of highly active antiretroviral therapy (HAART) in HIV-infected children in Jamaica. This has been facilitated by funding *via* the Global Fund and the Clinton HIV/AIDS Initiative. Under the direction of the Kingston Paediatric and Perinatal HIV/AIDS Programme (KPAIDS) in collaboration with the National HIV/AIDS Programme, Ministry of Health, Jamaica, unified parallel treatment programmes for paediatric HIV have been established in the Kingston Metropolitan Area and strategic centres islandwide [through outreach and mentorship initiatives] (2). The initiation of antiretroviral therapy has contributed to improved outcomes in the paediatric cohort and there has been a strong emphasis on optimizing adherence (5).

Despite the impact of HAART, adherence remains a major challenge in children (6). The factors contributing to non-adherence are varied and include those associated with the medication regimen, socioeconomic factors, attending clinic appointments and caregiver-related issues (7). These have important implications for the evolution of drug resistance and increased HIV-related morbidity and mortality. It is therefore critical to measure and address non-adherence to minimize these problems. Although there are several modalities for assessing adherence, resource-limited settings, like Jamaica, have peculiar challenges including limited availability of objective biomedical markers.

Adherence rates are generally higher in controlled clinical trials than in other studies and range from 57% to 77% (8, 9). Although patients may take the total number of prescribed doses, up to 50% show significant fluctuation in dosing intervals. Various methods may be employed to measure patient adherence to antiretroviral therapy. These include directly observed therapy (10), blood drug concentration, electronic monitoring, pharmacy reporting, self-reporting, biomedical markers such as $CD4^+$ count and viral levels and adherence to clinic appointments. Self-report surveys that ask about missed doses within the last 1–4 days are more valid and reliable than surveys that ask respondents to remember a week or more ago (11). More objective methods like the biomedical markers may be combined with self-reporting in order to improve or assess accuracy of investigation. Questionnaires completed by caregivers are a useful tool for measuring adherence to ART in paediatric HIV-infected patients (9) and may correlate with virologic response to antiretroviral therapy (12, 13).

Adherence rates are similar in caregiver reporting, clinician perspective and pharmacy reporting (14). Researchers and clinicians could benefit from acquiring information on children's adherence from multiple sources, even though there is no significant difference between child and caregiver reporting, except that seen for older children (15). Predictors and correlates of adherence in children are generally similar to those in adult samples (16). But studies tend to concur that there is a need for ongoing and individualized support and information to families (17). Medical providers believe that the current limited availability of treatment options for paediatric HIV-infected patients pose major adherence challenges for families of these patients (18).

Purpose

Against the background of uniform protocol-driven management at established treatment centres, we aimed to des-

cribe the adherence patterns to antiretroviral therapy and explore factors contributing to non-adherence in a cohort of HIV-infected children attending the Paediatric Infectious Disease Clinics of the Kingston Perinatal and Paediatric HIV/AIDS Programme (KPAIDS) in Greater Kingston and St Catherine.

We anticipated that the data would inform on measures to limit non-adherence, thus delaying the development of viral resistance and treatment failure and the need for costly, less accessible second line therapy.

SUBJECTS AND METHODS

Setting

Confirmed HIV-infected children and adolescents are followed three-monthly at the Paediatric Infectious Diseases Clinics of the KPAIDS Programme. Clinical management is guided by standardized evidence based protocols and pertinent investigations (haematological, biochemical, immunological, microbiological and radiological) and treatment (anti-infectives, prophylaxis and antiretroviral agents) are offered to all patients as the need arises. Monitoring methods include interval history, physical examination, nutritional, growth and development assessments and addressing adherence to prophylaxis and antiretroviral agents (2, 5, 19). Prior to the initiation of antiretroviral therapy (ART), caregivers and children are counselled to (i) assess their readiness for ART, (ii) educate about the goal, practical considerations, administration, and adverse effects of ART, and (iii) identify and address potential barriers to treatment success. Using the multidisciplinary team (doctors, nurses, pharmacists, social workers and adherence counsellors), ongoing adherence monitoring and evaluation are conducted at each ambulatory encounter and through telephone follow-up calls. Team consultations are convened to discuss and propose solutions for challenging situations.

Study Design

This was a cross-sectional study to determine the level of adherence to ART and associated factors, document reasons for non-adherence, explore the relationship between self-reporting and other adherence monitoring mechanisms utilized by the programme and to formulate strategies for further intervention among this paediatric cohort.

Procedure

Sixty-three children and their caregivers were recruited consecutively by convenience sampling as they accessed services at four Paediatric Infectious Diseases Clinics in Greater Kingston and St Catherine, Jamaica (University Hospital of the West Indies, Bustamante Hospital for Children, the Comprehensive Health Centre and Spanish Town Hospital). Patients received no prior notification that they may be asked questions about how they take their medications and were informed about the study by the clinic nurse at the time of ambulatory visit. Patients who were known to be non-compliant with clinic appointments and hence at greatest risk for negative outcome due to non-adherence to ART, were reminded of their clinic appointments by telephone, a strategy which was already being utilized by KPAIDS. They were not told that they may be asked questions about how they take their ART.

Informed consent and assent for children over seven years was obtained by an independent, trained interviewer following which a peer-reviewed 54-item questionnaire was administered. Older children were interviewed separately from caregivers to complete pertinent aspects of the questionnaire. Data, which were collected between the periods May to October 2005, included sociodemographic characteristics, caregiver/child health status, disclosure patterns, knowledge of antiretroviral therapy and reported adverse effects. Clinical, immunological and virological data were extracted from patient's medical records. Adherence data were obtained from caregivers and older children but there was no disaggregation of these data. Adherence was defined as no missed doses in the last four days.

Inclusion criteria were as follows: (1) confirmed diagnosis of HIV infection by a commercial enzyme-linked immunosorbent assay (ELISA) and confirmatory test (Western blot technique) in children between 18 months and 18 years of age, (2) clinical diagnosis of HIV infection in infants less than 18 months of age if symptomatic according to criteria for acquired immunodeficiency syndrome (AIDS) diagnosis based on the 1987 AIDS surveillance case definition (20) and/or confirmed by positive HIV polymerase chain reaction test (Roche® DNA AmplicorPCR test), (3) primary caregiver is biological parent, relative, adopted or foster parent or residential institution caregiver. Ethical approval for this study was received from the University of the West Indies/University Hospital of the West Indies, Faculty of Medical Sciences Ethics Committee.

Completed questionnaires were coded at the clinic to protect patient confidentiality. Data obtained from these questionnaires were compared with data from previously implemented mechanisms for monitoring adherence, most recent biomarkers in the past year where available (viral load, $CD4^+$ count and per cent), and documented compliance indicators: socio-economic status, family support, past history of adherence, understanding of doses, drug administration and side effects and the relationship between adherence and viral resistance. Data were analyzed using the Statistical Programme for the Social Sciences (SPSS) version 12.0. A p-value < 0.05 was considered statistically significant, except for multiple comparisons where a more rigorous p-value of < 0.01 was applied using the Bonferroni's method. Descriptive statistics were calculated for reasons of non-adherence. Student independent t-test was used to make comparisons between children in residential *versus* family-based care. Pearson's chi-squared, Fisher's Exact tests and Pearson's correlation were used to assess factors potentially

impacting adherence. These were further explored in logistic regression models using STATA version 9.0.

RESULTS

Adherence was significantly higher among children in residential care, approaching 100%, compared to 76.3% in family care (p = 0.008). Global adherence level was 85.7% (54/63). Children had median age of 7.9 years (range 0.8 – 19.4 years; IQR 4.8 – 10.6 years) and there were 36 males (57%). Seventy-nine per cent had severe disease by Centers for Disease Control and Prevention (CDC) classification and 81% were receiving first-line highly active antiretroviral therapy comprising zidovudine/lamivudine/nevirapine. The median duration on ART was 18.3 months (range 0.1–123.8 months; IQR 8.3–32.6 months). Median $CD4^+$ count and per cent, available for 95.2% (60/63) and 92.1% (58/63) children, were 440.0 cells per μL (IQR 268.5 – 897.0 cells/μL) and 24.9% (IQR 15.6–42.7%), respectively. Median viral load available for 51% (32/63) of participants was 9.60 x 10^3 copies/ml (IQR 0.05 x 10^3 – 52.50 x 10^3). Sixteen per cent (10/63) had viral load # 50 copies/ml. The median duration between commencing ART and viral load testing was 25.6 months (range 4.0–129.3 months). Duration on antiretroviral therapy, a potential confounder in this cross-sectional survey, was similar between children receiving family-based and residential care. Likewise, the age (p = 0.324), CDC categories (p = 0.384) and drug regimen were similar for the two groups (Table 1).

Table 1: Epidemiological and biomedical characteristics of Jamaican children on antiretroviral therapy

Mode of Caregiving	Median Age years (IQR) n = 63	Mean (SD) CD4 count (μL/ml) n = 60	Mean (SD) CD4 % n = 58	Mean (SD) Viral Load (cells/ml/10^3) n = 32	Mean (SD) duration of ART (days) n = 63	CDC category n = 63	
						CDC	Frequency (%)
Residential Care	7.7 (5.5–9.6)	887 (534)	38.4 (12.23)	50.0 (133.0)	732 (587)	A	2 (7.7)
						B	3 (11.5)
						C	21 (80.8)
Family Care	8.0 (4.8–14.3)	484 (540)	20 (12.6)	81.3 (196.5)	562 (458)	A	3 (8.1)
						B	5 (13.5)
						C	29 (78.4)
t-test	–	p = 0.006	p < 0.001	p = 0.596	p = 0.262	–	–

Children in residential care had significantly better $CD4^+$ counts (p = 0.006) and per cent (p < 0.001) although there was no statistically significant difference in viral load when compared to children in family care. The epidemiological and biomedical characteristics of the children on antiretroviral therapy are shown in Table 1.

Reasons for non-adherence to antiretroviral therapy were primarily caregiver-related. Due to frequently alternating staff caregivers in institutions, these factors were only analyzed for children in family care (n = 37). Main reasons included caregiver forgetting to administer medications (35%), change in caregiver's schedule (35%), running out of medications (30%) and child being away from home (27%) without caregiver putting measures in place to ensure adherence (Table 2). Caregiver hours worked (p = 0.007) and nausea as a side effect of ARVs (p = 0.011) appeared to be

Table 2: Reasons for non-adherence to antiretroviral medications in Jamaican children (n = 37)

Reason	Frequency (%)
Caregiver forgot	13 (35.1)
Change in caregiver schedule	13 (35.1)
Pills finish (ie family ran-out of drugs)	11 (29.7)
Caregiver busy	10 (27)
Child away from home	10 (27)
Antiretrovirals unavailable at pharmacy	7 (18.9)
Child feels down/ depressed	6 (16.2)
Child having side effects	6 (16.2)
Child can't swallow medications	6 (16.2)
Child sleeping	5 (13.5)
Child too ill	5 (13.5)
Antiretrovirals taste bad	5 (13.5)
Fear of having side effects	4 (10.8)
Antiretrovirals too much (*ie* too many pills, too much medicine to drink)	3 (8.1)
Antiretrovirals got lost	1 (2.7)
No privacy to take antiretrovirals	1 (2.7)

significantly associated factors (Table 3) and remained so with logistic regression analysis with p-values of 0.002 and 0.011 respectively (Table 4). Furthermore, when all potentially significant variables (except income) were analyzed in the same regression model, caregiver hours worked (p = 0.017) remained statistically significant and nausea remained marginally significant (p = 0.052). Since the presence of nausea was strongly associated with non-adherence both in children receiving residential and family care, it was always included in logistic regression models. Older age of child (p = 0.001) was also found to be correlated with non-adherence (Table 3).

Table 3: Correlates of adherence among children on antiretroviral therapy receiving family care in Jamaica (n = 37)

Factors	*p*-value
Caregiver hours worked	0.007*
Last school attended by caregiver	0.136
Weekly household income	0.285
Caregiver employment	0.617
Caregiver work shifts	0.684
Caregiver on antiretroviral therapy	0.105
Caregiver's age†	0.297
Caregiver status	0.202
Caregiver's belief that antiretrovirals help child	0.352
Older age of child†	0.001*
Child's sex	0.177
Child's knowledge of status	0.160
Cannot name/ describe medications	0.024
Missing clinic appointments	0.018
Antiretroviral regimen	0.680
Child taking medications other than antiretrovirals	0.432
Caregiver-child pair knowledge of medication dosage	0.141
Nausea	0.011*
Vomiting	0.269
Dizziness	0.140
Pruritus	0.141
Weakness	0.244
Sleepiness	1.000
Abdominal pain	0.373
Headache	1.000
Other side effects	0.620
Disclosure of HIV status to neighbours	0.181
Disclosure of HIV status to church	0.815
Disclosure of child's HIV status to others	0.364
Disclosure of child's HIV status to school	0.797
Disclosure of child's HIV status to family	0.548

Chi-square test, Fisher's exact test, †Pearson's Correlation where appropriate;
*statistically significant ($p < 0.01$)

Caregiver-child pairs were interviewed to assess their knowledge of adherence and antiretroviral therapy. Ninety per cent (or more) of participants knew that no more than three doses of antiretrovirals (ARVs) should be missed each month, that ARVs should be taken at the same time everyday and that the ARVs should be continued even if the child feels better. However, 43% (16/37) of respondents did not demonstrate an appreciation of the need to stop all other ARVs if one finished before the others and 30% (11/37) failed to understand that non-adherence leads to viral resistance.

Viral load testing was available for just over 50% of children in this study and was obtained at a median of 25.6 months (IQR 4.0–129.3 months) after commencing ART. The primary reason for the unavailability of this marker of adherence was the prohibitive cost. Viral load was not significantly lower ($p = 0.596$) among children in residential care than those in family care (Table 1).

DISCUSSION

The level of adherence to antiretroviral therapy (85%) was good among the infected children in this cross-sectional study. Adherence level was significantly higher ($p = 0.008$) approaching 100%, among those children receiving care in residential facilities compared to 76.3% of those receiving family-based care. These findings are attributed to the support strategies implemented by the KPAIDS programme and include assessing patients' and their caregivers' readiness for ART, pre-ART counselling on dosing, side effects and implications of non-adherence, increased access to staff via mobile phone contacts, reinforcement by pharmacists and adherence counsellors. Adherence is further enhanced in children in residential care by directly observed therapy (DOT).

Table 4: Results of multiple logistic regression analysis for children on antiretroviral therapy receiving family care (n = 37)

Factors	Number Adherent (%)		Odds Ratio (95% CI)	P-value*
	Yes	No		
Working hours/week				
< 40	23 (82)	2 (22)	1.00 (referent)	0.002
$ 40	5 (18)	7 (78)	0.04 (0.004, 0.45)	
Caregiver education				
Primary and secondary	16 (57)	2 (25)	1.00 (referent)	0.045
Tertiary and vocational	8 (29)	2 (25)	0.44 (0.04, 5.15)	
Other	4 (14)	4 (50)	0.05 (0.003, 0.77)	
Weekly household income				
Low (< JAD $5000)	14 (56)	2 (25)	1.00 (referent)	0.127
High ($JAD $5000)	8 (32)	2 (25)	0.43 (0.04, 4.73)	
Unknown	3 (12)	4 (50)	0.10 (0.01, 1.08)	
Can name/describe ARVs				
Yes	26 (96)	5 (62.5)	1.00 (referent)	0.028
No	1 (4)	3 (37.5)	0.06 (0.004, 0.92)	
Nausea				
No	23 (82)	3 (33)	1.00 (referent)	0.007
Yes	5 (18)	6 (67)	0.11 (0.02, 0.59)	

*P values were obtained by likelihood ratio test using logistic regression models, and the presence of nausea was always included in the model as a covariate. When all variables in this table, except income, were analyzed in the same logistic regression model, only "working hours" was statistically significant ($p = 0.015$) and the presence of nausea was marginally significant ($p = 0.052$); (p values for school and name/describe ARVs were 0.317 and 0.331, respectively).

Non-adherence was primarily related to caregiver issues and reinforces the fundamental role of caregivers in influencing the overall outcome of children with HIV. Medication-related issues were less important except for the side effect of nausea especially when initiating ART. Biomarkers, such as viral load and $CD4^+$ count are useful indicators of adherence but the impact of temporally-related and immunologic factors in this cross-sectional study necessitate further investigation.

The greater level of adherence and immunologic status of children receiving residential care, relative to those in family care, underscores the positive impact of directly observed therapy. However, these benefits must be weighed against the value of the family social support system in enhancing the developmental outcome of children. A possible option for improving adherence in the family-based setting is developing a 'day-clinic' facility that provides multidisciplinary multifaceted holistic care to children on ART, similar to Early Childhood Day Care Centres in Kenya (21). Services could include educational, developmental, spiritual, social, medical care and directly observed antiretroviral therapy during mornings and afternoons; children would return home to their families in the evenings. The Multisystem Therapy (22) and similar approaches involving home visits, directly observed therapy and developmentally appropriate counselling are other options to explore in our setting (23). Improving adherence to antiretroviral therapy in paediatric patients requires innovative and multifaceted strategies on a sustained basis in order to improve the quality of life of these patients.

Self-reporting, the main approach in determining adherence levels in this study, may lead to over-reporting. However, the other parameters used to measure adherence provided support for the adherence levels observed. Children receiving residential-based care had significantly higher mean CD4 count, CD4 per cent and higher adherence levels than their peers who received family-based care. Viral loads were similar in both groups of children, despite higher CD4 markers in residential children. A study of 154 HIV-infected children in Uganda revealed no correlation between viral load and T-cell activation after controlling for CD4 count (25). Sub-threshold HIV antigen exposure, thymic dysfunction and variable T-cell maturity were suggested explanations.

Mellins *et al* noted that caregiver's HIV positive status was a predictor of non-adherence; however, this association was not seen in our study. Missing clinic appointments and side effects from ART, compounded by factors related to caregiver stress and developmental challenges particularly in older children, contribute to non-adherence to ART in Jamaican children. Strategies to enhance understanding of ART and improve social support systems could reduce the impact of non-adherence in our setting.

More definitive laboratory markers, such as plasma viral load, were not available for many participants due to resource constraints. The relatively low number of patients with available counts also limited statistical inferences. Cross-sectional studies of this nature do not capture trends in adherence over time and are limited in drawing conclusions regarding a cause-effect relationship of potential factors. Additionally, there was a wide age range in the children enrolled in the study; hence differences in developmental stage may influence adherence behaviour. It is possible that reporting bias by caregivers may have resulted in inflated adherence levels.

Adherence in this study was defined as missing zero doses in the last four days, as the accuracy of self-reporting improves with shorter recall intervals. Indeed, adherence levels were lower when participants were asked about taking their medications over longer recall intervals (data not shown). The relatively small sample size limits the generalizability of these findings, but provides valuable lessons for intensifying present adherence interventions.

In conclusion, increased access to paediatric antiretroviral therapy demands a concurrent systematic approach to innovative adherence strategies. In order to achieve the goal of maximal viral suppression and immune reconstitution, as well as overall social and developmental health, caregivers and older children must receive special focus in longitudinal adherence programmes. Factors impacting adherence are multidimensional and complex but it is prudent to consider social, developmental and biomedical issues when assessing adherence. Innovative translational and experimental research on adherence to ART based on sound theoretical knowledge and behaviour-change models will aid in ensuring a better quality of life for children with HIV/AIDS in Jamaica and similar resource-limited settings.

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