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Factors associated with lack of antiretroviral adherence among adolescents in a reference centre in Rio de Janeiro, Brazil

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Summary

The objective of this study was to describe the adherence to antiretroviral therapy (ART) among adolescents followed-up in Rio de Janeiro. This cross-sectional study included all adolescents (aged 10–19 years) followed at Instituto de Puericultura e Pediatria Martagão Gesteira and Hospital Universitário Clementino Fraga Filho. Adherence was determined by self-report (number of missed ART doses in three days prior to the interview). Adherence was categorized as taking $\geq 95\%$ of the ARTs (adherent), or $< 95\%$ (non-adherent). Variables related to demographics and treatment were evaluated and if P value ≤ 0.15 , they were selected for a logistic regression analysis. One hundred and one adolescents were interviewed. The mean time on ART was 91 months and the mean adherence was 94% of this, 21 were non-adherent, and 80 adherent. The risk factors associated with non-adherence were: if the patient was not concerned about ART, odds ratio (OR) ≥ 3.47 (95% confidence interval [CI] ≥ 1.13 –10.68); if they do not carry an extra dose of ART, OR ≥ 6.63 (95% CI ≥ 1.73 –25.47); if a health-care worker taught them how to take ART, OR ≥ 0.27 (95% CI ≥ 0.08 –0.93). Adherence among adolescents was higher than expected. Factors associated with lack of adherence were: interviewees being unaware of ARTs and lack of commitment to the treatment. Interventions involving these factors must be evaluated.

Keywords

HIV; antiretroviral; adherence; adolescent; Brazil

INTRODUCTION

Lack of adherence to antiretroviral therapy (ART) is one of the main causes for failure of the treatment worldwide and one of the main concerns when providing ARTs to developing countries. There is evidence that 95% or more of adherence to ARTs are associated with better virological and immunological outcomes.^{1,2} In a three-year cohort study that followed-up 120 adolescents, only 24% were able to reach and maintain an undetectable viral load. The main variable associated with this poor response to ART was lack of adherence to therapy.³

Several factors were identified as being associated with the lack of adherence in developed nations. Although some of these factors could be generalized to every population, such as medication for adverse events, number of pills taken daily, age and presence of depression; some of them could not, as they were associated with socio-economic conditions as well as cultural issues.^{4–6}

Adolescents are likely to present a lack of adherence to chronic medications, such as ARTs,^{3,7} and since highly active ART has transformed the human immunodeficiency virus (HIV) infection from a near-uniformly fatal disease into a chronic, manageable illness, children are

surviving AIDS and reaching adolescence.⁸ It is also noteworthy that HIV infection rates are still rising among adolescents.⁹

In Brazil, a large-scale public health programme, consisting of the distribution of free-of-charge antiretroviral drugs to all HIV-infected individuals who fulfill the criteria established by an independent advisory committee, was implemented in 1996. At present, this programme provides treatment to over 130,000 Brazilians with HIV infection. Drugs are distributed from over 400 dispensary units around the country and treatment is monitored through a national network of laboratories that perform CD4 lymphocyte counts and HIV RNA plasma viral load (VL) measurements.¹⁰

The Hospital Universita'rio Clementino Fraga Filho (HUCFF) and Instituto de Puericultura e Pediatria Martaga~o Gesteira (IPPMG) are university-based hospitals; both are reference centres for HIV/AIDS care for children, adolescents and adults in the state of Rio de Janeiro. Over 350 HIV-infected children/ adolescents have been followed-up in these centres since 1996, and there was no special intervention-focused adherence promotion for ART during the study period.

The main objective of this study is to assess the causes for the lack of adherence in adolescents, who are heavily experienced in ARTs, from a middle-income developing country.

METHODS

Study design

Cross-sectional

Study setting and data collection: The study was conducted in two outpatient clinics in Rio de Janeiro, Brazil. These clinics are located in two teaching hospitals affiliated to the Universidade Federal do Rio de Janeiro: IPPMG and HUCFF.

Subjects were HIV-1 seropositive adolescents (aged 10–19 years old) who had been on ART for at least two months. Exclusion criteria were pregnancy, inability to understand or cooperate with protocol requirements, ongoing psychiatric disorders and apparent intoxication from illicit drugs and/or alcohol at the time of the enrolment visit.

Patients were approached for participation in this study while waiting for their appointments in the waiting room of the participating clinics. Following informed consent, subjects underwent an interview on a structured questionnaire, which included their personal and demographical information, their sexual behaviour and social variables. Variables commonly reported to be associated with adherence to therapy were included in the questionnaire. One study investigator, who was unaware of the patients' clinical data at the time, conducted all the interviews. Later, data were taken from the medical records that included details about prescribed ART medications and plasma HIV RNA levels. HIV-1 plasma RNA was measured using NucliSens (BioMe'rieux SA, Mercy-l'Etoile, France/ Organon Teknika).

Outcome measures: Non-adherent patients were defined as: failed to take or administered incorrectly (missing dose or incorrect dose), 95% of the antiretroviral drugs prescribed in the three days prior to the interview. In order to validate the adherence measures, we assessed the last viral load measurement before the interview and stratified the value into two groups: those with a viral load ,1000 copies/mL and those with .1000 copies/mL. Both the groups were compared with the self-reported adherence.

Statistical analysis: Data analysis was performed using Stata version 8.0 statistical software (Stata Corp., College Station, TX, USA). Univariate analysis was performed using independent t-test (for variables with a normal distribution) or Wilcoxon (Mann-Whitney) two sample test (for variables which did not follow the normal distribution). The chi-square test was used to evaluate associations for categorical variables (or Fisher exact test if 20% or more of the table cells had an expected value of five or lower). Variables with a P value ≤ 0.15 were included in the multivariate analysis.

A main-effects logistic regression model was fitted using the stepwise maximum likelihood estimation technique. The level of significance for the removal of a variable with backward regression was 0.10. Interactions were assessed using the 22 log likelihood ratio test to compare models with and without interactions. The Pearson's chi-square goodness-of-fit test, as well as the Hosmer-Lemeshow test, were used to evaluate the fitness of the model.

Self-reported adherence validation. To validate our measurements of adherence, we compared the mean patients' self-reported adherence (independent t-test) with their last viral load measurement ≥ 1000 or ≤ 1000 copies/mL (on an average six months before/after the interview).

Ethical considerations: This study was reviewed and approved by the Instituto de Puericultura e Pediatria Martaga~o Gesteira and the Hospital Universita'rio Clementino Fraga Filho's Ethical Committees.

Role of the funding source: Those who sponsored this study had no role to play in its design, sample and data collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

RESULTS

During a six-month period, 106 patients were asked to participate in this study and, following written informed consent, 102 (96%) patients were enrolled. Four patients did not wish to participate and were not enrolled. One patient refused to answer questions related to his adherence to ARTs, and was excluded from the study.

The patients aged between 10 and 19 years of age (average 13 years old), 47 (46%) were male, 71 (70%) were treated at IPPMG and 22 (22%) were not yet aware of their HIV status. All had been using ARTs for a long period (average 91 months, from two to 192 months). The mean self-reported adherence in our study was 94% (ranged from 44 to 100%). The mean self-reported adherence among those with viral load (VL) ≥ 1000 copies/mL was 97% and 89% among patients with VL ≤ 1000 copies/mL ($P = 0.05$). Twenty-one patients (21%) were classified as non-adherents (self-reported adherence $\leq 95\%$) and 80 (79%) as adherents.

The demographic data, stratified by adherents and non-adherents, are shown in Table 1. Variables associated with being non-adherent to the therapy in the univariate analysis were used in the multivariate analysis (Table 2).

DISCUSSION

Several studies showed that self-reported adherence overestimated actual adherence, using a medication event monitoring system as the gold standard.^{1,11,12} In our sample, we used self-reported adherence and compared it with an indirect measurement of adherence (VL) in an attempt to validate the former.

Mean of self-reported adherence in our study was 94%, a level consistently higher than that observed in developed countries: 57.6% among intravenous drug users in Spain,¹³ 69.2% across seven cities in the USA¹⁴ and 84% in Italian children; however, none of them studied adolescents who were mostly vertically infected and were being treated for a long time (on average, 91 months). Although these levels are higher than that expected, the most important findings of this study are the aspects related to non-adherent individuals, which must be reliable.¹⁵

In our questionnaire, we explored possible causes of non-adherence related to the patients' daily routine. In the multivariate analysis, patients who were not concerned about the therapy or did not carry extra doses of ARTs while out of the house reported worse adherence. We believe that this finding reflects patients who were not involved in their treatments and who did not try to fit them into their routine, which is one of the basic steps towards adhering to any new behaviour, based on the behaviour modification model.¹⁶ We believe that questions related to the patient's commitment, such as those used in this study, must be introduced to any questionnaire that evaluates ART adherence, and any intervention to improve adherence in adolescents must stimulate this commitment.

This study showed that patients who were taught by a health-care worker (HCW) how to take ARTs, had better adherence. This demonstrates the importance of the patient–HCW relationship in order to guarantee a better adherence to ARTs, and underlines the importance of health education tools in patient care. This is in accordance with the reports of Rueda et al.¹⁷ who demonstrated that interventions seeking to improve the practical skills on how to take the ARTs, such as a HCW teaching the patients, were shown to improve adherence. Kalichman et al.¹⁸ also reported that education and health literacy were independently associated with adherence, even after adjusting for income, distress, and support.

In this research, we studied patients who were either aware or unaware of their HIV status. We used the same questionnaire, but did not mention HIV/AIDS on applying it to patients whose HIV status was unknown. Although we had some missed data on these patients, we opted to study them together to evaluate the role of knowledge of their HIV status on their adherence to ART.

In conclusion, the proportion of self-reported adherence in our unique population: heavily ART-experienced adolescents, was surprisingly better than other groups in developed countries, suggesting that heavily treated adolescents from middle-income developing countries are able to reach the desired adherence level. Variables related to patient–HCW relationship and education, and personal lifestyles were associated with better adherence to ARTs. These findings have important implications on developing nations that are considering providing increased access to ART for adolescents.

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Table 1

Demographic data, stratified by adherents and non-adherents

	Non-adherents = 21 (21%)			Adherents = 80 (79%)			Total = 101		
	No.	(%)	Mean (range)	No.	(%)	Mean (range)	P value	No.	(%)
Age (years)	-		12.89 (10–19)	-		13.37 (10–19)	0.37		13 (10–19)
Gender (Male)	11/21	(52)	-	36/80	(45)	-	0.55	47/101	(47)
Race (Caucasian)	5/21	(24)	-	26/80	(32)	-	0.44	31/101	(31)
Unit of treatment IPPMG	18/21	(86)	-	53/80	(66)	-	0.08*	71/101	(70)
Do not know their HIV status	8/21	(38)	-	14/80	(17)	-	0.04*	22/101	(22)
Drug use	2/21	(10)	-	2/80	(3)	-	0.14*	4/101	(4)
Alcohol use	2/21	(10)	-	14/80	(17)	-	0.37	16/101	(16)
Cigarette smoke	2/21	(10)	-	3/80	(4)	-	0.28	5/101	(5)
Sexually active	1/21	(5)	-	8/80	(10)	-	0.45	9/101	(9)
Education >8 years	1/21	(5)	-	8/79	(10)	-	0.45	9/100	(9)
Vertically infected	10/12	(83)	-	57/64	(89)	-	0.57	67/76	(88)
Does not have support	1/13	(8)	-	3/66	(4)	-	0.64	4/79	(5)
HCV taught them how to take ART	5/21	(24)	-	36/80	(45)	-	0.08*	41/101	(41)
Ever being in a support group	15/21	(71)	-	53/80	(66)	-	0.65	68/101	(68)
Patient never carries ART's while out	18/21	(86)	-	37/79	(47)	-	<0.01*	55/101	(55)
Time on ART (months)	-		101 (2–180)	-		89 (2–192)	0.32		91 (2–192)
Number of tablets/daily	-		9.30 (3–19)	-		9.11 (2–21)	0.87		9.10 (2–21)
Does not refill the prescription before ART finishes	4/21	(19)	-	3/79	(4)	-	0.02*	93/100	(93)
Patient is not concerned about ARTs	13/21	(62)	-	30/80	(62)	-	0.04*	43/101	(43)
When the patient feels bad, he/she stops ART	4/21	(19)	-	6/80	(8)	-	0.11*	10/101	(10)
Patient uses alarm to remind him herself to take ART	2/21	(10)	-	16/80	(20)	-	0.26	18/101	(18)
Patient has life plans	20/21	(95)	-	75/80	(94)	-	0.80	95/101	(95)

	Non-adherents = 21 (21%)			Adherents = 80 (79%)			Total = 101		
	No.	(%)	Mean (range)	No.	(%)	Mean (range)	P value	(%)	Mean (range)
VL - six months before/after the interview copies/mL			43,982 (undetectable – 690,000)			8208 (undetectable – 480,00)			10,923 (undetectable – 690,000)

ART = antiretroviral therapy, HCW = health-care worker, IPPMG = instituto de Puericultura e Pediatria Martagão Gesteira

* Variables included in the multivariate analysis

Table 2
Multivariate analysis of factors associated with non-adherence to ART

Variable	OR	P value	95% CI
Patient is not concerned about ARTs	3.47	0.03	1.13–10.68
Patient never carries ARTs while out	6.63	<0.01	1.73–25.47
HCW taught them how to take ART	0.27	0.07	0.08–0.93

HCW = health-care worker, CI = confidence interval, OR = odds ratio, ART = antiretroviral therapy