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## ASSOCIATION BETWEEN SMOKING, CRACK COCAINE ABUSE AND THE DISCONTINUATION OF COMBINATION ANTIRETROVIRAL THERAPY IN RECIFE, PERNAMBUCO, BRAZIL

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### SUMMARY

Despite the effectiveness of combination antiretroviral therapy in the treatment of people living with HIV/AIDS (PLWHA), nonadherence to medication has become a major threat to its effectiveness. This study aimed to estimate the prevalence of self-reported irregular use of antiretroviral therapy and the factors associated with such an irregularity in PLWHA. A cross-sectional study of PLWHA who attended two referral centers in the city of Recife, in Northeastern Brazil, between June 2007 and October 2009 was carried out. The study analyzed socioeconomic factors, social service support and personal habits associated with nonadherence to antiretroviral therapy, adjusted by multivariable logistic regression analysis. The prevalence of PLWHA who reported irregular use of combination antiretroviral therapy (cART) was 25.7%. In the final multivariate model, the irregular use of cART was associated with the following variables: being aged less than 40 years (OR = 1.66, 95%-CI: 1.29-2.13), current smokers (OR = 1.76, 95%-CI: 1.31-2.37) or former smokers (OR = 1.43, 95%-CI: 1.05-1.95), and crack cocaine users (OR = 2.79, 95%-CI: 1.24-6.32). Special measures should be directed towards each of the following groups: individuals aged less than 40 years, smokers, former smokers and crack cocaine users. Measures for giving up smoking and crack cocaine should be incorporated into HIV-control programs in order to promote greater adherence to antiretroviral drugs and thus improve the quality of life and prolong life expectancy.

**KEYWORDS:** AIDS; Adherence; Antiretroviral therapy; Associated factors.

### INTRODUCTION

Although the number of new HIV infections has declined globally by 19% over the past decade and the access to antiretroviral therapy in low- and middle-income countries has increased, HIV infection rates are increasing in several countries in Eastern Europe and central Asia, notably among injecting drug users and their sexual networks<sup>29</sup>. Access to antiretroviral treatment (ART) has been primarily responsible for prolonging and improving the lives of people living with HIV/AIDS (PLWHA), with Brazil, being the first developing country to implement the universal distribution of these drugs<sup>8,18</sup>. Consequently, nonadherence to the use of antiretroviral drugs is the greatest risk for a non-effective response to treatment and the possibility of spreading resistant viruses<sup>25,27</sup>. Moreover, poor adherence is one of the factors that may lead to a lower CD4 cell count, higher plasma viral RNA levels and delayed immune recovery, with progression of the disease that can lead to death<sup>11</sup>.

In the treatment of chronic disease, the degree of adherence is always influenced by a number of different factors: characteristics of the individual, characteristics of the disease, social support network (family and friends) and factors related to the health service, such as difficulties in

accessing it, and the relationship of the health team/individual<sup>12</sup>. Amongst the characteristics of the individual, habits such as alcoholism, drug abuse and irregular use of antiretrovirals<sup>21</sup> place the individual at further risk of secondary infections. Furthermore, studies have shown that the quantity of pills is also an important factor that influences the rate of adherence<sup>8,11</sup>.

For the treatment of HIV infection to be effective, several authors recommend an adherence level of at least 95% of the prescribed drugs to decrease the chance of viral resistance<sup>6</sup>. However, recent studies indicate that for boosted protease inhibitors an adherence level greater than 80% would be equally effective<sup>16</sup>.

Different methods have been employed in order to measure adherence to antiretrovirals, without a consensus gold standard. Due to their simplicity and the low costs involved, methods that use self-reports are widely used, and studies have demonstrated an association between the measure of self-reported adherence to antiretrovirals and HIV plasma viral load (with odds ratios and hazard ratios on the order of 2.0), making it possible to use this strategy in the conduct of PLWHA<sup>26,30</sup>.

The aim of this study was to identify the prevalence of the factors

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associated with the irregular use of antiretroviral drugs in people living with HIV, with special emphasis on socioeconomic factors and life habits, intending thereby to identify the groups at greatest risk so as to develop new strategies that set out to minimize the problem.

## METHODS

The study was conducted in Recife, a city in northeastern Brazil, with an estimated population of 1,561,659 inhabitants. This cross-sectional study was carried out in June 2007 and October 2009, with people living with HIV/AIDS aged 18 years and over, who attended two HIV referral centers in the state of Pernambuco (Hospital Correia Picanço and Hospital Universitário Oswaldo Cruz), which attend around 60% of the state's patients. Individuals were invited to participate in the study either during routine consultations and/or hospitalization. Those who agreed to take part gave informed consent and were then interviewed by trained professionals who used a questionnaire developed specifically for this study. Hospitalized patients who could not answer the questionnaire due to their clinical condition were excluded from the study.

The dependent variable was the self-reported irregular use of combined antiretroviral therapy (cART), categorized in 'yes' - when patients reported a discontinuation of treatment at some point on their own - and 'no'.

The independent variables were classified as: demographic (age and race), socioeconomics (marital status, social service support, head of household's income), how long the patient has been aware of being HIV positive, life habits (alcoholism and drug abuse). Information regarding the use of cART was collected from medical records.

Users of illicit drugs (crack cocaine and cocaine) fell into the following categories: non-users; intermittent (intermittent users who had abstained during the past year) and current users (who had been using during the past year).

The criteria adopted for alcohol consumption was based on the number of drinks per day, according to the definition of alcohol consumption patterns approved by the Centers for Disease Control

and Prevention (CDC)<sup>7</sup>. Patients were questioned about their alcohol consumption in the previous three months. Patients were classified as abstainers or light drinkers (non-drinkers or less than two drinks per day for men and one drink for women), and heavy drinkers (more than two drinks per day for men and more than one drink per day for women).

The Student's t-test was used to compare the mean scores of the independent samples and variance was tested with Levene's test. All variables associated with the irregular use of cART in the univariate analysis with a *p*-value of less than 0.20 were included in the multivariate analysis, using logistic regression and Odds Ratio (OR) with a confidence interval of 95%. The variables whose association with the event was statistically significant (*p* < 0.05) remained in the final multivariate model. The software used was Stata 11.2 (Stata-Corp LP, College Station, TX). The study is part of a cohort, which has been carried out in two research centers, and was approved by the Ethics and Research Committee of the Centro de Ciências da Saúde da Universidade Federal de Pernambuco.

## RESULTS

In the period from June 2007 to October 2009, 1815 PLWHA were interviewed, of which 1432 (78.9%) were taking cART. Of these, 52 (3.6%) did not answer the question referring to the irregular use of treatment, and were therefore excluded from the study. The study sample was made up of 1380 patients with a mean age of 40.6 years (18-80) and a median age of 40.0 years; 64.1% were male and 79.1% had a monthly family income of less than two minimum wages. The majority (84.7%) lived in the metropolitan region of Recife. The prevalence of people who reported irregular use of cART was 25.7%. Among people who reported irregular use of cART, 42% had stopped taking the pills in the two weeks preceding the study interview.

A comparison of the mean ages, CD4 cell count and HIV viral load at the time of the interview revealed an association between self-reported irregular use of cART, being under 40 years old and a lower CD4 cell count (Table 1).

Table 1 shows the frequency distribution of the studied factors and the

**Table 1**

Frequencies and univariate analysis of the association between characteristics of people living with HIV/AIDS and the irregular use of antiretroviral treatment, Recife, Pernambuco, Brazil, 2009

	Irregular use of ART (case)		Regular use of ART (control)		Crude OR (CI)	<i>p</i>
	n	%	n	%		
<b>Age</b>						
Years (mean)	38.8		41.3			<b>0.001*</b>
<b>Age</b>						
≥ 40 years	157	21.39	577	78.61	1.0	
< 40 years	198	30.65	448	69.35	1.62 (1.27 - 2.07)	<b>0.000</b>
<b>Total</b>	<b>355</b>	<b>25.72</b>	<b>1025</b>	<b>74.28</b>		
<b>Sex</b>						
Female	138	27.88	357	72.12	1.0	
Male	217	24.52	668	75.48	0.84 (0.65 - 1.08)	<b>0.171</b>
<b>Total</b>	<b>355</b>	<b>25.72</b>	<b>1025</b>	<b>74.28</b>		

Table 1 (continuation)

	Irregular use of ART (case)		Regular use of ART (control)		Crude OR (CI)	p
	n	%	n	%		
<b>Skin color</b>						
White	92	25.34	271	74.66	1.0	
Non-white	263	25.86	754	74.14	1.03 (0.78 - 1.35)	<b>0.847</b>
<b>Total</b>	<b>355</b>	<b>25.72</b>	<b>1025</b>	<b>74.28</b>		
<b>Alcohol intake</b>						
Heavy drinker	225	23.61	728	76.39	1.0	
Light drinker or abstainer	130	30.44	297	69.56	1.42 (1.10 - 1.83)	<b>0.007</b>
<b>Total</b>	<b>355</b>	<b>25.72</b>	<b>1025</b>	<b>74.28</b>		
<b>Smoking status</b>						
Never smoked	133	21.28	492	78.72	1.0	
Former smoker	97	26.08	275	73.92	1.30 (0.97 - 1.76)	<b>0.083</b>
Current smoker	125	32.64	258	67.36	1.79 (1.34 - 2.39)	<b>0.000</b>
<b>Total</b>	<b>355</b>	<b>25.72</b>	<b>1025</b>	<b>74.28</b>		
<b>Use of cocaine</b>						
Never used	311	25.04	931	74.96	1.0	
Intermittent users**	37	29.84	87	70.16	1.27 (0.85 - 1.91)	<b>0.243</b>
Current users	7	58.33	5	41.67	4.19 (1.32 - 13.3)	<b>0.015</b>
<b>Total</b>	<b>355</b>	<b>25.76</b>	<b>1023</b>	<b>74.24</b>		
<b>Use of crack</b>						
Never used	319	24.79	968	75.21	1.0	
Intermittent users**	22	32.84	45	67.16	1.48 (0.88 - 2.51)	<b>0.141</b>
Current users	14	56.00	11	44.00	3.86 (1.73 - 8.59)	<b>0.001</b>
<b>Total</b>	<b>355</b>	<b>25.74</b>	<b>1024</b>	<b>74.26</b>		
<b>Can read and write</b>						
Yes	317	26.05	900	73.95	1.0	
No	37	24.03	117	75.97	0.90 (0.61 - 1.33)	<b>0.589</b>
<b>Total</b>	<b>354</b>	<b>25.82</b>	<b>1017</b>	<b>74.18</b>		
<b>Monthly income of head of family</b>						
≥ 2 minimum wages	55	22.36	191	77.64	1.0	
< 2 minimum wages	251	26.96	680	73.04	1.28 (0.92 - 1.79)	<b>0.144</b>
<b>Total</b>	<b>306</b>	<b>26.00</b>	<b>871</b>	<b>74.00</b>		
<b>Marital status</b>						
Married	64	22.38	222	77.62	1.0	
Other***	291	26.60	803	73.40	1.26 (0.92 - 1.71)	<b>0.146</b>
<b>Total</b>	<b>355</b>	<b>25.72</b>	<b>1025</b>	<b>74.28</b>		
<b>Social service support</b>						
Lives with family or partner	282	25.59	820	74.41	1.0	
Lives alone or in a shelter	73	26.26	205	73.74	1.03 (0.77 - 1.39)	<b>0.820</b>
<b>Total</b>	<b>355</b>	<b>25.72</b>	<b>1025</b>	<b>74.28</b>		
<b>City of residence</b>						
Recife	148	26.86	403	73.14	1.0	
Other	204	24.97	613	75.03	0.91 (0.71 - 1.16)	<b>0.433</b>
<b>Total</b>	<b>352</b>	<b>25.73</b>	<b>1016</b>	<b>74.27</b>		
<b>CD4 baseline</b>						
cells/mm <sup>3</sup> (mean)	383.9		446.1			<b>0.002*</b>
<b>Viral load baseline</b>						
copies/mL (mean)	29,501.7		18,114.7			<b>0.198*</b>

\* Student's t test; \*\* Users who have abstained during the past year; \*\*\* Separated, divorced, widowed or single.

**Table 2**

Multivariate analysis of the association between characteristics of people living with HIV/AIDS and the irregular use of antiretroviral treatment, Recife, Pernambuco, Brazil, 2009

	Crude OR		OR adjusted by the multivariate	
	OR (CI)	<i>p</i>	OR (CI)	<i>p</i>
<b>Age</b>				
≥ 40 years	1.0		1.0	
< 40 years	1.62 (1.27 - 2.07)	<b>0.000</b>	1.66 (1.29 - 2.13)	<b>0.000</b>
<b>Smoking</b>				
Never smoked	1.0		1.0	
Former smoker	1.30 (0.97 - 1.76)	<b>0.083</b>	1.43 (1.05 - 1.95)	<b>0.023</b>
Current smoker	1.79 (1.34 - 2.39)	<b>0.000</b>	1.76 (1.31 - 2.37)	<b>0.000</b>
<b>Use of crack</b>				
Never used	1.0		1.0	
Intermittent users*	1.48 (0.88 - 2.51)	<b>0.141</b>	1.20 (0.70 - 2.06)	<b>0.501</b>
Current users	3.86 (1.73 - 8.59)	<b>0.001</b>	2.79 (1.24 - 6.32)	<b>0.013</b>

\* Users who have abstained during the past year.

result of the univariate analysis of the association with the self-reported irregular use of cART.

Regarding the habits of the study population (Table 1), 69.1% were considered abstainers or light drinkers of alcoholic beverages; most participants had never used cocaine or crack cocaine (90.1% and 93.3% respectively); in relation to smoking, most individuals (54.7%) were current or former smokers, the majority (84.2%) having consumed cigarettes for 10 years or more.

In the multivariate analysis (Table 2), associations with the irregular use of cART in a statistically significant manner were, an age lower than or equal to 39 ( $p < 0.001$ ), a former smoker ( $p = 0.023$ ), currently smoking ( $p < 0.001$ ) and currently using crack cocaine ( $p = 0.013$ ).

## DISCUSSION

After adjusting the socioeconomic and social service support variables, the discontinuation of combination antiretroviral therapy was associated with the following variables: being aged less than 40 years, a former smoker or a current smoker and a crack cocaine user.

The prevalence of people who reported irregular use of cART was 25.7%. This prevalence was similar to the prevalence of non-adherence to treatment encountered in a number of studies in Brazil<sup>4,6,23,25</sup>. Most studies conclude that taking less than 90-95% of prescription drugs is an indication of non-adherence, unlike the present study, which evaluated individual patient responses to questions regarding the discontinuation of treatment at some point in time. Studies also show the importance of including additional resources to self-reporting, such as testing tablets, to provide a better evaluation of adherence<sup>22</sup>. Even without a consensus concerning the method of measuring this adherence, studies have indicated similar results of prevalence, demonstrating that the most appropriate method of certifying adherence to treatment was to question the patient directly. The strategy which uses, direct patient questioning, was chosen because it is easy to employ in everyday health

care. We are aware that adherence may be overestimated due to a fear of displeasing the interviewer, the health professional or physician (false negative response); however those who actually report poor adherence are probably expressing the truth (decrease in false positive response) and are an important group to intervene with. The option for the question on abandonment of treatment at some point, without the restriction to a length time before and after the interview, aimed to expand the knowledge of the problem. We recognize that in the systematic care to the patient, the definition of a time span would be crucial in the evaluation of the patient's response to treatment and in the selection of the best intervention to be adopted to change the patient's behavior. It would also minimize recall bias.

Most of the patients from this study were male and had a low monthly family income. These factors were related to poor adherence to antiretroviral treatment in another study<sup>12</sup>. Low socioeconomic status may be a proxy of several factors associated to nonadherence, such as difficulties in accessing the health system, difficulties involved in understanding the individual regarding his/her health situation, etc.<sup>26</sup>. Since the research involved a very low socioeconomic population, the study of the association of characteristics such as lifestyle, with the irregular use of cART, may be more specific to define the individual at risk.

Research has indicated that older patients have a better adherence to antiretroviral treatment<sup>15</sup>, which also reinforces the findings of this study. It is possible that, due to a better perception of their own health, older people tend to better assimilate the importance of treatment and the consequences of interrupting it. This data was also encountered in another study undertaken in Brazil, where being younger was related to low adherence to the treatment<sup>5</sup>.

Being a former smoker or a current smoker was associated with the discontinuation of combination antiretroviral therapy. Cigarette smoking has been associated with sexual behavior and drug abuse<sup>1,13</sup> and with a lower inclination to develop healthy behaviors related to

diet<sup>17,20</sup> and physical activity<sup>17</sup>. The same mechanism that predisposes all these behaviors may also lie behind, associated or not with these factors, a behavior less prone to adhere to medication. A study carried out by our group, in a cohort of people living with HIV/AIDS and under tuberculosis treatment, showed an association between smoking and the evasion of tuberculosis treatment<sup>19</sup>. The present study corroborates the findings of other authors who found an association between smoking and lower adherence to antiretrovirals<sup>4,24</sup>, either smoking alone or as part of a risky behavior profile. Depression has been thought of as a possible mediator between smoking and adherence to antiretrovirals<sup>28</sup> but this is not a finding common to all authors<sup>4</sup>.

People who use drugs tend to be more socially vulnerable and have a chaotic, unstable lifestyle that influences the adherence to any type of chronic treatment<sup>8</sup>. The use of illicit drugs has been associated with both nonadherence and a decrease in the viral and immunologic responses to antiretrovirals<sup>18</sup>, the former also being a finding in the present study. Research has demonstrated that cocaine (including the crack variation) has an influence over the pathogenesis of AIDS, accelerating its progression and the risk of mortality, morbidity and an increased viral load<sup>9,10</sup>. For this group, an increase in the viral load may be related to nonadherence to the treatment, which may lead to viral resistance and subsequently to an immunological decline, thus favoring the HIV virus and its replication.

Studies show that direct administered antiretroviral therapy (DAART) in people living with HIV/AIDS who use drugs may improve adherence and thus improve the immune status of the individual<sup>2,3</sup>. Beyond DAART, other interventions such as counseling by motivational interviewing or video information, which is feasible in health care centers, improve adherence to antiretroviral treatment and maintain their efficacy three months later<sup>14</sup>.

Once adherence to treatment has been promoted through individual approaches and discussions by health professionals in the majority of the specialized services for treating PLWHA, differentiated attention towards smokers and crack users, as well as interaction with specific control programs, are central to good adherence to antiretroviral treatment and the consequent reduction of viral resistance.

This study has some constraints. We are aware that the strategy used to measure the use of illicit substances may not be very accurate as a participant who has experienced crack cocaine once in the previous 12 months, an occasional user and a drug dependent (who used crack cocaine in the same time span), are all classified as current users of crack cocaine, although usage patterns and possibly behavior differ. The constraint posed to the interpretation of our findings by the discontinuation of combination antiretroviral therapy being measured has already been mentioned. Finally, a major limitation of this study, because of its cross-sectional design, is that it is not possible to establish the temporal sequence between exposure and outcome and differentiate cause and effect. Nevertheless the results pointed to groups which should be monitored differentially because of their association with discontinuation of combination antiretroviral therapy.

Further studies, using a longitudinal design and more restricted definitions, could complement our findings.

## RESUMO

### Associação entre tabagismo e o uso de crack com a descontinuidade da terapia antirretroviral combinada em Recife, Pernambuco, Brasil

Apesar da eficácia da terapêutica antirretroviral combinada para o tratamento de pessoas vivendo com HIV/Aids, a não adesão aos medicamentos tem se tornado uma das maiores ameaças à efetividade dessa terapêutica. O objetivo desse estudo foi estimar a prevalência de uso irregular autorreferido da terapia antirretroviral e os fatores associados com essa irregularidade em pessoas vivendo com HIV. Foi realizado um estudo seccional de pessoas vivendo com HIV/Aids atendidas em dois centros de referência no Recife, Nordeste do Brasil, entre junho 2007 e outubro de 2009. Foram analisados os fatores socioeconômicos, de apoio social e de hábitos do indivíduo, ajustados através de análise de regressão logística multivariada. A prevalência de pessoas vivendo com HIV/Aids que relataram o uso irregular da terapia antirretroviral combinada (TARC) foi de 25,7%. No modelo multivariado final, o uso irregular da TARC esteve associado às seguintes variáveis: ter menos de 40 anos (OR = 1,66, IC95%: 1,29-2,13), fumantes (OR = 1,76, IC95%: 1,31-2,37) ou ex-fumantes (OR = 1,43, IC95%: 1,05-1,95) e ser usuário de crack (OR = 2,79, IC95%: 1,24-6,32). Medidas especiais devem ser direcionadas para cada um dos seguintes grupos: adultos com menos de 40 anos, fumantes, ex-fumantes e usuários de crack. Ações voltadas para a cessação do tabagismo e do crack devem ser incorporadas ao programa de controle dos infectados pelo HIV, visando promover a maior adesão aos antirretrovirais e, conseqüentemente, aumentar a expectativa e a qualidade de vida.

## COMPETING INTERESTS

The authors declared that there are no competing interests.

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