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Anxiety and depression symptoms as risk factors for non-adherence to antiretroviral therapy in Brazil

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Abstract

Depression and anxiety are common among HIV-infected people and rank among the strongest predictors of non-adherence to antiretroviral therapy (ART). This longitudinal study aimed to assess whether symptoms of anxiety and depression are predictors of non-adherence among patients initiating ART at two public referral centers (n=293) in Belo Horizonte, Brazil. Prevalence of severe anxiety and depression symptoms before starting ART was 12.6% and 5.8%, respectively. Severe anxiety was a predictor of non-adherence to ART during follow-up period (RH=1.87; 95% CI=1.14–3.06) adjusted for low education, unemployment, alcohol use in the last month and symptoms of AIDS; while a history of injection drug use had borderline statistical significance with non-adherence. These findings suggest that using a brief screening procedure to assess anxiety and depression symptoms before initiating ART help identify individuals for interventions to improve adherence and quality of life.

Keywords

anxiety; depression; psychiatric symptoms; non-adherence; antiretroviral therapy

INTRODUCTION

Psychiatric symptoms are common among people with chronic illnesses, including HIV/AIDS (WHO, 2001; WHO, 2003). They can contribute to non-adherence to antiretroviral therapy (ART) and, consequently, to poor immune and virological response (Evans et al., 2002), progression to AIDS (Paterson et al., 2000), worse quality of life (Carballo et al., 2004; Tostes et al. 2004) and higher costs related to health care utilization (Acurcio et al., 2006; Ford et al., 2004). Symptoms of anxiety and depression, in particular, have been found to be strong predictors of non-adherence to antiretroviral therapy (Chesney, 2004;

Molassiotis et al., 2002; Turner, 2002; Tucker et al., 2004; Spire et al. 2002). Tucker et al. (2003) have pointed out that individuals with depression, generalized anxiety or panic disorder were approximately two times more likely to be non-adherent than those without a psychiatric disorder. Brazil has a unified national health system which provides free and universal access to ART and care of HIV-positive individuals. By the end of 2007, more than 180,000 people were receiving antiretroviral medications provided by the Brazilian government (Brasil 2008), and yet, there is no study which evaluated anxiety and depression as predictors of non-adherence in Brazil.

During 2001–2002, we conducted a cohort study, the ATAR (Adherence to Antiretroviral Therapy) Project, whose main objective was to determine the incidence and determinants of non-adherence to ART among HIV infected adult (≥ 18 years old) patients initiating treatment in Belo Horizonte, Brazil, a large urban area with approximately 2.5 million inhabitants (Bonolo et al., 2005). Participants, who were required to be ART-naïve, were recruited in the two main public health referral centers for HIV/AIDS, which provided care for more than 90% of all reported AIDS cases in the city at that time. ATAR Project included one baseline interview at the same day patients received their first prescription for ART and three follow-up interviews at the first, fourth and seventh months thereafter. Baseline data included sociodemographic, clinical and behavioral characteristics, while adherence to ART was evaluated at each follow-up visit. In addition, quality of life and presence of anxiety and depression symptoms were assessed at baseline and at the second follow-up visit, i.e., four months after the start of ART.

Our preliminary analysis of the cross-sectional baseline data ($n=386$) reviewed a high prevalence of moderate to severe symptoms of anxiety (35.8%) and depression (21.8%) among these HIV-infected patients before initiating ART (Campos et al. 2006). Female gender, low education, lack of health insurance, psychotherapy attendance, difficulty in accessing health service and exposure category to HIV infection (men who had sex with men and injection drug use) were independently associated with anxiety. Female gender, lack of health insurance, low individual monthly income, living alone, and lack of sexual partner in the last month were independently associated with depression.

We also found a high cumulative incidence of non-adherence to ART during the entire seven month follow-up period (36.9%) (Bonolo et al., 2005). Multivariate analysis indicated that unemployment, alcohol use, adverse reactions, number of pills, switch in ART regimen and a longer time between the HIV test result and the first prescription were predictors of non-adherence. However, symptoms of anxiety and depression present at the baseline visit were not taken into account in that analysis.

The high prevalence of anxiety and depression symptoms at baseline, the high incidence of non-adherence observed over time, and the absence of published data in Brazil regarding psychiatric symptoms as predictors of non-adherence to ART led us to the current study. Since establishing good adherence to ART at the outset of treatment is related to long-term adherence and good clinical outcomes (Carrieri et al. 2003), we were interested in knowing whether the presence of severe anxiety and depression symptoms at the time of initiating ART would predict subsequent non-adherence. If so, these findings would have important clinical implications for psychiatric screening and treatment of patients initiating ART in HIV care settings.

METHODS

Participants

This prospective concurrent analysis is part of the ATAR Project, described above in the introduction. For the current analysis we included only participants who completed the anxiety and depression assessment at baseline and also returned for at least one follow-up visit during the study period. Pregnant women were excluded since many were taking ART for only a limited time to prevent mother-to-child transmission. All participants were recruited immediately after receiving their first ART prescription from May 2001 thru May 2002 in two public health referral centers for HIV/AIDS in Belo Horizonte: 1) Infectious and Parasitic Diseases Training and Reference Center, from the City Health Department, and 2) Eduardo de Menezes Hospital, from the State Health Department.

Measures

Adherence—Adherence was self-reported and data were obtained by face-to-face interviews by trained staff members using a semi-structured questionnaire during follow-up visits. Participants were asked about the number of doses taken of each prescribed medication during the three days prior to the interview. Adherence was calculated as the number of doses taken in the last three days divided by the number of doses prescribed, and multiplied by 100. Analysis was performed using a dichotomous indicator of adherence with a threshold of 95%, based on the evidence that optimal virologic success declines rapidly in patients taking fewer than 95% of their prescribed doses (Paterson et al., 2000). In the present analysis we sought to observe only the first episode of non-adherence along the three follow-up visits.

Psychiatric symptoms—Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). This scale has been validated in many countries, including Brazil, and has adequate psychometric characteristics such as internal consistency, discriminating validity and reliability (Bjelland et al., 2002; Botega et al., 1998; Botega et al., 1995). The HADS was specifically developed for the screening of symptoms of anxiety and depression among patients with organic conditions. Therefore, it does not include somatic symptoms (e.g. fatigue, insomnia, tachycardia, dyspnea), which could overestimate the occurrence of anxiety and depression secondary to organic pathologies.

The HADS contains 14 items distributed in two constructs, anxiety and depression. The items constituting the depression subscale are based on the anhedonic state and the main items are loss of interest in activities, inability to laugh or to be cheerful, and pessimistic thoughts. The main anxiety items assessed were inner tension, worry, and presence of panic attacks. Participants were classified regarding the level of symptoms of anxiety and depression according to Zigmond and Snaith (1983): score over 14 as severe anxiety/depression, 11–14 as moderate, 8–10 as mild or “subclinical” and under 8 as absence of symptoms of anxiety/depression. The scale was applied at baseline interview, i.e. before initiating ART, and questions refer to the previous week. For the present analysis, depression and anxiety scores were analyzed separately and participants scoring above 14 on either subscale were considered as severe cases of anxiety or depression. This threshold was based on previous studies that described acceptable sensitivity and specificity at this level (Bjelland et al., 2002; Herrmann, 1997).

Other exposure variables—We adjusted our analyses by sociodemographic characteristics (gender, age, education, income, employment, health insurance and housing); behavioral data (use of condoms, tobacco, alcohol and illicit drugs in the prior month and

lifetime injection drug use); clinical characteristics (signs and symptoms of AIDS, CD4+ cell count and HIV viral load), and psychiatric variables (psychotherapy attendance, continuous use of other medications in addition to ART and anxiolytic/antidepressant use during follow-up). These variables were assessed using the semi-structured questionnaire at baseline interview, except for the variable use of anxiolytic/antidepressant medication during follow-up, which included data collected during the interview at the follow-up visits. Condom use was defined as regular when participants reported using condoms on all occasions of anal and vaginal sex in the last month, and irregular when not using them on such occasions. Finally, clinical data including signs and symptoms of AIDS (Centers for Disease Control and Prevention, 1992), CD4+ cell count and HIV viral load were collected from medical charts during the entire period of follow-up.

Data analysis

Cumulative and person-time incidences for non-adherence were estimated. For both measures, the numerator was the number of participants who reported taking less than 95% of the prescribed doses of antiretroviral drugs during the three days before the interview. The denominator was the number of participants who completed the HADS and returned for at least one follow-up visit and the sum of the times contributed by each individual, respectively. Time was defined as the number of days between the date of baseline interview and the date of follow-up visit indicating the first observance of non-adherence or the date of the last follow-up visit for those considered to be adherent.

Cox's proportional hazard model was used for both univariate and multivariate analysis (Cox and Oakes, 1984). The magnitude of the association between severe anxiety and severe depression and the first observed episode of non-adherence to ART was estimated by the relative hazard (RH) with 95% confidence interval, adjusting for other selected exposure variables. The level of significance considered was 0.05. Dose-response trend of the outcome in different categories for anxiety and depression (mild to severe) was assessed by Mantel's trend test (Mantel, 1963).

Those variables that showed association with non-adherence in the univariate analyses with a p-value less than 0.20 were selected to start multivariate modeling. Sequential deletion was conducted until a final model, which included variables showing statistical significance level of less than 0.05, was obtained. Proportional hazard assumption was assessed by checking the parallelism of the log-log survival curves and the Schöenfeld test (Hosmer and Lemeshow, 1999).

RESULTS

Among the 406 participants recruited for ATAR project, 346 (85.0%) completed the HADS at baseline and returned for at least one follow-up visit during the study period. After excluding 53 women on ART because of pregnancy, 293 (72.0%) individuals were eligible for this analysis. No statistically significant differences were observed between participants in our sample and those lost to follow-up (n=60) regarding non-adherence reports registered in medical charts (p-value=0.983). Almost half of the participants had three follow-up visits (n=143; 48.8%), while 77 (26.3%) and 73 (24.9%) had only one and two visits, respectively.

As shown in Table I, a majority of the participants were men (65.9%) over 35 years of age (52.9%), and heterosexual sexual contact (70.7%) was the predominant mode of HIV exposure. A large proportion had low education or income, were unemployed and had no health insurance. Poor living conditions (e.g. living in one-room residence or slum areas) were reported by 26.6% of the sample. Sociodemographic characteristics of the study population were similar to AIDS cases reported to the Ministry of Health nationally

(Rodrigues-Júnior and Castilho, 2004). Approximately 28.0% reported using condoms regularly in the prior month while a large proportion (56.0%) was not sexually active. Use of alcohol, tobacco and illicit drugs in the last month and lifetime injection drug use were reported by 37.9%, 34.5%, 8.5% and 5.8% of the participants, respectively.

It should be noted that many had initiated ART relatively late in the course of their disease, as indicated by the high proportion of patients with symptoms and/or with at least one AIDS-defining condition (53.9%) and a high proportion of patients with CD4+ cell count $\leq$ 200 cells/mL (42.3%). Median HIV-viral load was 103,500 copies/mL. Most of the prescribed antiretroviral regimens at baseline were two nucleoside reverse transcriptase inhibitors (NRTI) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) (51.5%), followed by two NRTIs plus one protease inhibitor (PI) (42.4%), two NRTI plus one PI combined with Ritonavir (5.8%). These prescribed regimens are in accord with the Brazilian treatment guidelines at the time of the data collection (Brasil 2000).

Overall, 151 (51.5%) and 119 (40.6%) patients had symptoms of mild to severe anxiety or depression, respectively. Mild, moderate or severe anxiety occurred among 15.7%, 23.2% and 12.6% of the patients, respectively, while symptoms of mild, moderate or severe depression were present in 19.1%, 15.7% and 5.8%, respectively (Table I).

Only 19 (6.5%) and 31 (10.6%) of the participants reported regular use of antidepressant and/or anxiolytic medications and psychotherapy attendance (individual or group therapy) at the time of baseline interview, respectively. Among those with symptoms of severe anxiety ($n=37$) and depression ($n=17$), only 6 (16.7%) and 3 (18.7%) patients were using antidepressant and/or anxiolytic medications. Similarly, only five (13.5%) of those with severe anxiety and none with severe depression were on psychotherapy at baseline interview. Only 9.8% ($n=29$) of our sample reported the use of antidepressant and/or anxiolytic medications during follow-up, i.e., after the assessment of psychiatric symptoms at baseline and before the assessment of non-adherence.

Non-adherence

The overall cumulative incidence of non-adherence was 37.2%, while the incidence rate was 0.21/100 person-days. The mean time of follow-up was 175 days (median: 204 days). The majority of episodes of non-adherence occurred in the first follow-up visit ($n=60$; 55.0%), followed by the second ($n=33$; 33.9%) and third visits ($n=12$; 11.1%).

The univariate analysis indicated an increased risk for non-adherence for those patients with severe symptoms of anxiety (RH=2.28, 95% CI=1.44–3.58; $p < .01$) (Table II). However, there was no indication of statistical association between severe depression and non-adherence. In this analysis, we also found an increased risk for non-adherence among those who were women, had lower education, had lower individual monthly income or no income, were employed in a fixed job schedule or unemployed, had no health insurance and lived in poor housing conditions. Similarly, lifetime injection drug use, irregular condom use and alcohol use in the previous month and smoking up to 10 cigarettes a day indicated an increased risk for non-adherence. It should be mentioned that illicit drug use indicated a greater risk for non-adherence, but with a borderline significance. Finally, those participants who had a CD4+ cell count greater than 200 cells/mL or were asymptomatic for AIDS had an increased risk of non-adherence to ART.

After taking into account potential confounders, multivariate analysis indicated that symptoms of severe anxiety were independently associated with non-adherence (RH=1.87, 95% CI=1.14–3.06; $p < .05$). Also, low education, unemployment, alcohol use in the previous month and no signs and symptoms of AIDS were independent risk factors for non-

adherence to ART, while lifetime injection drug use had a borderline significance ($p=.063$). The proportional hazards assumptions were satisfied according to both methods and no violation was verified (Schöenfeld test=2.09; degree of freedom=7; $p=.955$).

DISCUSSION

To our knowledge this is the first cohort study that assesses whether anxiety and depression symptoms predict non-adherence to ART among patients initiating ART in Brazil. Both participating centers were the main public health referral services for HIV/AIDS in Belo Horizonte representing approximately 90% of the reported AIDS cases under care in the city during the study period and were similar to the AIDS cases reported nationally (Rodrigues-Júnior and Castilho, 2004).

We found a high prevalence of anxiety and depression symptoms using the HADS. Although this is not a diagnostic scale, it is a useful screening measure for the presence of symptoms of anxiety and depression (Hermann, 1997) and it has been extensively applied and validated in different settings. However, comparability with other studies that assessed psychiatric symptoms in different populations using the HADS is difficult because of methodological differences across the studies such as study design, population, criteria used for defining anxiety and depression, and availability of data for each level of symptoms. Nevertheless, the prevalence of symptoms of anxiety and depression in our sample (51.5% and 40.6%, respectively) was consistent with the findings of many of these studies. Using the HADS, Crawford et al. (2001) described a prevalence of 33.2% and 11.4% of mild to severe symptoms of anxiety and depression, respectively, in a representative sample of the general adult UK population ($n=1,792$), while Olsson et al. (2005) found 28.8% of anxiety and 18.5% of depression symptoms in a sample of 1,781 patients in a primary care setting in Norway. Although there are no published general population representative data using the HADS in Brazil, this scale has been used in several studies of other medical conditions. The occurrence of symptoms of mild to severe anxiety and depression varied among patients with hematological malignancies (20.5% and 16.8%, respectively) (Santos et al. 2006) or with multiple sclerosis (35.7% and 17.9%, respectively) (Mendes et al. 2003), and among pregnant adolescents (23.3% and 20.8%, respectively) (Freitas and Botega 2002), or adult inpatients admitted to a general hospital (20.5% and 33.3%, respectively) (Botega et al. 1995). Our results are also consistent with studies that used the HADS in HIV-infected populations, with rates varying from 27.3% to 70.3% for anxiety and from 32.0% to 45.5% for depression (Au et al. 2004; Cohen et al. 2002; Cove and Petrak, 2004; Lambert et al. 2005). The only study using the HADS among HIV-infected populations in Brazil found 36.8% and 30.3% of mild to severe anxiety and depression symptoms, respectively, in a sample of HIV-infected women (Tostes et al. 2004). Finally, we also found a higher prevalence of symptoms of anxiety compared to depression and this finding is consistent with other studies that used the HADS to assess psychiatric symptoms among HIV-infected patients (Cohen et al. 2002; Cove and Petrak 2004; Lambert et al. 2005; Tostes et al. 2004).

More importantly, we found that symptoms of severe anxiety at the time of initiating ART were significant predictors of non-adherence to ART. Two-thirds of the patients with severe anxiety were non-adherent within the follow-up study period. Similar results have been observed in other studies in other settings although anxiety was assessed using diagnostic procedures different from HADS (Blanco et al. 2005; Molassiotis et al. 2004; Tucker et al., 2003). One recently published study of 198 patients initiating ART linked higher predicted probability of psychiatric morbidity, including any mood, anxiety or substance abuse disorder, and delayed achievement of virologic suppression and overall virologic failure (Pence et al. 2007). However, no other study has assessed the relationship between anxiety and early adherence to ART. Furthermore, in subsidiary analyses we found a significant

trend of non-adherence when comparing those with mild, moderate or severe anxiety to those without anxiety (RH=1.27, RH=1.31 and RH=2.57, respectively; Mantel's Chi-square=12.02, $p < .01$).

It is of concern that, although patients scored in the severe range for depression and/or anxiety, only a small proportion of them were receiving mental health treatment such as antidepressant and/or anxiolytic medications and psychotherapy. This indicates a potential inadequacy of mental health attention for HIV-infected patients in these two public health referral centers for HIV/AIDS in Brazil. Patients experiencing symptoms of severe anxiety at the time of ART initiation could benefit from intervention (i.e. counseling, diagnosis, and pharmacological and non-pharmacological treatment) established soon in the treatment course, with the potential to improve adherence to ART.

Although we did not find a statistical association between severe depression and non-adherence in either univariate or multivariate analyses, clinicians should pay attention to depression symptoms among patients initiating ART since other studies have shown there to be an association (Ammassari et al. 2004; Baford et al. 2005; Blanco et al. 2005). Our results could be partially explained by a lack of statistical power, because of the low number of participants with severe depression ($n=17$) in our study. Spire et al. (2002) also found no association between baseline depression among patients initiating ART and non-adherence to ART ($n=445$). However, they showed that an increase in symptoms of depression during the first four months of treatment was a risk factor for non-adherence ($p < .01$). This suggests that it is important to monitor the evolution of symptoms of depression when patients initiate ART and not just rely on what is reported at the time of ART initiation (Spire et al., 2002).

Previous researches have suggested that heavy drinking may pose a threat to adherence (Braithwaite et al. 2005; Cook et al. 2001; Lucas et al. 2002). However, our findings also indicate that any recent (past month) alcohol use was also a potential predictor of non-adherence to antiretroviral medications, after controlling for other confounding variables, such as psychiatric symptoms and injection drug use. It is possible that alcohol use may be a strategy used by some patients to cope with stressful events such as having to initiate ART (Arnsten et al. 2002), which can have negative effects on adherence. Medical providers should be able to refer these patients for proper counseling early in the course of treatment.

We also found that patients who were asymptomatic with HIV-related physical symptoms were at increased risk for non-adherence. This has been seen in other chronic illnesses as well (Miller, 1997). Patients often report that they feel it is unnecessary to keep taking medications when they have no symptoms of illness from their disease, especially when the medication causes unwanted side effects. It is important for physicians and other healthcare providers to consistently emphasize, in their ongoing communication with patients, the importance of maintaining high levels of adherence to their treatment even when the disease itself is not causing any physical problems. It is also important that providers help patients manage uncomfortable side effects associated with their treatment.

This analysis also found a greater risk for non-adherence among patients with lower education and unemployed. Despite free access to antiretroviral drugs and specialized care for HIV/AIDS, poor socioeconomic conditions can be barriers for good adherence in Brazil, as shown by others (Bonolo et al. 2005; Carvalho et al. 2003; Nemes et al. 2004; Pinheiro et al. 2002). Patients with low education may lack essential knowledge related to their treatment and health resources use (Falagas et al. 2008; Wolf et al. 2005). In addition, unemployment may influence the ability of patients to have adequate access (e.g. financial burden of public transportation) and use of health care facilities and the patient's quality of

life (Falagas et al. 2008; Melo and Guimaraes 2005). These issues may affect the accessibility to appropriate care and treatment as well as the patient's ability to adhere to ART.

Finally, while not a statistically significant association, there was a trend for an association between non-adherence and lifetime injection drug use. Thus, we highlight the public health importance of this finding. Other authors have demonstrated that injection drug use compromises adherence and long-term effectiveness of antiretroviral therapy. Injection drug users have been found to report confusion about the treatment regimen, difficulty integrating the regimen into their chaotic lifestyle, forgetfulness of medication intake, running out of medications before the next appointment, and negative perception regarding the effectiveness, side effects, and toxicity of antiretroviral therapy (Tucker et al. 2004).

Some limitations to this work should be considered. Self-report assessment of adherence may be subject to recall bias, inaccurate memory, social desirability bias, and may be problematic for individuals with cognitive impairment (Simoni et al., 2006; Wagner and Miller, 2004). Although self-reported adherence may overestimate the true adherence, compared to other more objective methods of assessment such as Medication Event Monitoring System and pill counts, it has demonstrated a robust pattern of association with HIV viral load (Arnsten et al., 2002; Gifford et al., 2000; Haubrich et al., 1999; Nieuwkerk and Oort, 2005; Simoni et al., 2006) and plasmatic levels of antiretroviral drugs (Murri et al., 2000). Also, self-report has advantages, such as its low cost and easy applicability in clinical practice, its high specificity, and the minimal participant burden (Simoni et al., 2006).

Another limitation was the use of HADS as the only psychiatric measure, since we did not have a diagnostic assessment. As stated earlier, this analysis is part of the ATAR Project, whose main focus was not psychiatric outcomes and therefore could not include a lengthier diagnostic assessment (Bonolo et al., 2005). We were interested in screening for symptoms of anxiety and depression in a non-psychiatric population, and the HADS has been validated in Brazil with adequate psychometric properties (Botega et al. 1995). The HADS can easily be applied by non-psychiatric health professionals in similar HIV/AIDS care treatment settings for screening purposes. As shown, self-assessment measurement of psychiatric symptoms can perform well in screening for anxiety and depression symptoms (Bjelland et al., 2002; Hermann 1997; Olsson et al., 2005), and our results have an important public health message with clinical implications for health care professionals and providers in the outset.

This study reports a high prevalence of psychiatric symptoms among patients initiating ART in these two HIV/AIDS referral centers in Brazil. We also found a high cumulative incidence of the first episode of non-adherence to ART during the first year of treatment. And the presence of symptoms of severe anxiety, in particular, was a good predictor of non-adherence to ART in this population. Although, we cannot directly attribute the non-adherence to ART in one, four and seven months of the follow-up to the anxiety and depression evaluated at the baseline interview, our data strongly suggests that people experiencing symptoms of severe anxiety are at increased risk for non-adherence within the first year of treatment and thus can potentially benefit from extra medical attention. Therefore, we advocate for the implementation of multidisciplinary strategies for the early assessment of psychiatric symptoms, early diagnosis of psychiatric disorders and provision for and specific pharmacological and non-pharmacological treatment, such as counseling, group or individual psychotherapy. Screening for psychiatric symptoms can be done routinely and in a relatively short period of time. If symptoms are present at the time of initiation of ART, patients can be referred for further evaluation and appropriate

interventions can be implemented to help improve adherence over time. It is particularly important to try to establish good adherence at the outset for people initiating ART since early adherence has been shown to be a good predictor of long-term adherence (Carrieri et al., 2003). Early non-adherence to ART can lead to rapid resistance, leaving patients in need of second-line therapy early in the course of treatment. Also, better adherence to ART can improve quality of life among people living with HIV/AIDS.

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Table I
Descriptive characteristics of the study population

ATAR Project, Brazil, 2001–2003 (n=293).

Characteristics	n (%)
Sociodemographic	
Gender (male)	193 (65.9)
Age (>35 years old)	155 (52.9)
Education (< 8 years)	145 (49.5)
Individual monthly income:	
> US\$ 80	127 (43.3)
≤ US\$ 80	46 (15.7)
None	118 (40.3)
Employment:	
Non-fixed job schedule	57 (19.4)
Fixed job schedule	133 (45.4)
Unemployed	103 (35.1)
Health insurance (no)	221 (75.4)
Housing conditions (poor)	78 (26.6)
Exposure category for HIV infection:	
Heterosexual	207 (70.7)
Sex among men	62 (21.2)
Injection drug use	10 (3.4)
Blood transfusion	14 (4.8)
Behavioral	
Condom use in the last month:	
No sexual activity	164 (56.0)
Regular	82 (28.0)
Irregular	45 (15.3)
Injection drug use in lifetime (yes)	17 (5.8)
Illicit drug use in the last month (yes)	25 (8.5)
Alcohol use in the last month (yes)	111 (37.9)
Frequency of tobacco use per day:	
None	192 (65.5)
0 – 10 cigarettes	56 (19.1)
11 – 20 cigarettes	45 (15.4)
Clinical	
Signs and symptoms of AIDS (yes)	158 (53.9)
CD4+ cell count (cells/mL):	
≤ 200	124 (42.3)
> 200	103 (35.1)
Unknown	66 (22.5)
Viral load for HIV (copies/mL):	

Characteristics	n (%)
> 100,000	68 (23.2)
□ □ ≤ 100,000	68 (23.2)
Unknown	157 (53.6)
Psychiatric	
Symptoms of anxiety:	
None	142 (48.5)
Mild	46 (15.7)
Moderate	68 (23.2)
Severe	37 (12.6)
Symptoms of depression:	
None	174 (59.4)
Mild	56 (19.1)
Moderate	46 (15.7)
Severe	17 (5.8)
Psychotherapy attendance (yes)	31 (10.6)
Continuous use of other meds:	
None	165 (56.3)
Anxiolytic and/or antidepressant	19 (6.5)
Others	107 (36.5)
Anxiolytic/antidepressant use during follow-up:	
None	111 (37.9)
Yes	29 (9.8)
Other meds	151 (51.5)

Table II
Univariate analysis and multivariate analysis for the first episode of non-adherence
ATAR Project, Brazil, 2001–2003 (n=293).

Characteristics	Total n	Univariate Analysis			Multivariate Model	
		n (%) ^a	RH ^b	(95% CI) ^b	RH ^c	(95% CI) ^c
Sociodemographic						
Gender:						
Male	193	62 (32.1)	1.00		-	-
Female	100	47 (47.0)	1.50	(1.02–2.19) [*]		
Age (years):						
≤ 35	138	49 (35.5)	1.00		-	-
>35	155	60 (38.7)	1.10	(0.75–1.60)		
Education (years):						
≥ 8	148	41 (27.7)	1.00		1.00	
< 8	145	68 (46.9)	1.83	(1.24–2.69) ^{**}	1.71	(1.14–2.56) ^{**}
Individual monthly income:						
> US\$ 80	127	35 (27.6)	1.00		-	-
≤ than US\$ 80	46	21 (45.7)	1.86	(1.08–3.18) [*]		
None	118	52 (44.1)	1.72	(1.12–2.63) ^{**}		
Employment:						
Non-fixed job schedule	57	13 (22.8)	1.00		1.00	
Fixed job schedule	133	46 (34.6)	1.52	(0.82–2.82) [*]	1.50	(0.81–2.79)
Unemployed	103	50 (48.5)	2.40	(1.31–4.42) ^{**}	1.90	(1.01–3.57) [*]
Sociodemographic						
Health insurance:						
Yes	72	19 (26.4)	1.00		-	-
No	221	90 (40.7)	1.85	(1.12–3.03) [*]		
Housing:						
House/apartment	215	69 (32.1)	1.00		-	-
Poor conditions	78	40 (51.3)	1.68	(1.14–2.48) ^{**}		

Characteristics	Total n	Univariate Analysis			Multivariate Model	
		n (%) ^a	RH ^b	(95% CI) ^b	RH ^c	(95% CI) ^c
Behavioral						
Condom use in the last month:						
No sexual activity	164	54 (32.9)	1.00		-	-
Regular	82	36 (43.9)	1.53	(0.91–2.58)		
Irregular	45	19 (42.2)	1.53	(1.00–2.34) *		
Injection drug use in lifetime:						
No	276	98 (35.5)	1.00		1.00	
Yes	17	11 (64.7)	2.20	(1.18–4.11) *	1.84	(0.97–3.50)
Illicit drug use in the last month:						
No	268	96 (35.8)	1.00		-	-
Yes	25	13 (52.0)	1.74	(0.97–3.10)		
Behavioral						
Alcohol use in the last month:						
No	182	58 (31.9)	1.00		1.00	
Yes	111	51 (45.9)	1.79	(1.23–2.61) **	1.87	(1.27–2.73) **
Frequency of tobacco use per day:						
None	192	67 (34.9)	1.00		-	-
0 – 10 cigarettes	56	26 (46.4)	1.70	(1.08–2.67) *		
11 – 20 cigarettes	45	16 (35.6)	1.12	(0.65–1.93)		
Clinical						
Signs and symptoms of AIDS:						
Yes	158	51 (32.3)	1.00		1.00	
No	125	56 (44.8)	1.50	(1.03–2.20) *	1.73	(1.18–2.55) **
CD4+ cell count (cells/mL):						
≤ 200	124	40 (32.3)	1.00		-	-
> 200	103	48 (46.6)	1.53	(1.00–2.33) *		
Unknown	66	21 (31.8)	0.90	(0.53–1.53)		
Viral load for HIV (copies/mL):						
> 100,000	68	27 (39.7)	1.00		-	-

Characteristics	Total n	Univariate Analysis			Multivariate Model	
		n (%) ^a	RH ^b	(95% CI) ^b	RH ^c	(95% CI) ^c
<i>≤ 100,000</i>	68	22 (32.4)	1.60	(0.91–2.81)		
<i>Unknown</i>	157	60 (38.2)	1.23	(0.76–2.01)		
Psychiatric						
Symptoms of anxiety:						
<i>None/Mild/Moderate</i>	256	85 (33.2)	1.00		1.00	
<i>Severe</i>	37	24 (64.9)	2.28	(1.44–3.58) **	1.87	(1.14–3.06) *
Symptoms of depression:						
<i>None/Mild/Moderate</i>	276	100 (36.2)	1.00		-	-
<i>Severe</i>	17	9 (52.9)	1.41	(0.71–2.79)		
Psychotherapy attendance:						
<i>No</i>	261	99 (37.9)	1.00		-	-
<i>Yes</i>	31	10 (32.3)	0.75	(0.39–1.43)		
Continuous use of other meds:						
<i>None</i>	165	59 (35.8)	1.00		-	-
<i>Anxiolytic/antidepressant</i>	19	7 (36.8)	0.84	(0.38–1.85)		
<i>Others</i>	107	42 (39.3)	0.95	(0.63–1.41)		
Anxiolytic/antidepressant use during follow-up:						
<i>No</i>	111	46 (41.4)	1.00			
<i>Yes</i>	59	9 (31.0)	0.53	(0.26–1.09)	-	-
<i>Other meds</i>	151	53 (35.1)	0.65	(0.44–0.97) *		

^aNumber and proportion of non-adherent participants in each variable category

^bCrude Relative Hazard and 95% confidence intervals

^cAdjusted Relative Hazard and 95% confidence intervals

** p < 0.01;

* p < 0.05

Schönfeld test for multivariate final model=2.09; degree of freedom=7; p=0.955