Risk Factors for Medication Non-Adherence in an HIV Infected Population in the Dominican Republic

Julian Harris[1], **Mara Pillinger**[2], **Deborah Fromstein**[3], **Bayardo Gomez**[4], **Ivelisse Garris**[5], **Peter A. Kanetsky**[6], **Pablo Tebas**[7], and **Robert Gross**[6,7,8]

[1]Department of Medicine (Resident), Brigham & Women's Hospital, Harvard Medical School

[2]School of Arts & Sciences, University of Pennsylvania

[3]Department of Medicine (Resident), University of Washington

[4]Health Promotion & Human Solidarity Center (CEPROSH), Puerto Plata, Dominican Republic

[5]Galvan Health Center, Santo Domingo, Dominican Republic

[6]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, USA

[7]Penn Center for AIDS Research (CFAR), Center for Education and Research on Therapeutics, University of Pennsylvania, Philadelphia, PA, USA

[8]Division of Infectious Diseases, University of Pennsylvania, Philadelphia, PA, USA

Abstract

High levels of medication adherence are central to HIV treatment success. Barriers to medication adherence may differ by cultural setting. We aimed to determine risk factors for medication non-adherence in HIV infected individuals in the Dominican Republic. Adherence was measured in 300 individuals using a visual analog scale assessing the prior month and dichotomized at 95%. High levels of adherence were reported by 228 (76%). Risk factors for non-adherence included heavy alcohol use: 2.5 times odds (95% CI: 1.4-4.5), having children: 2.2 times higher odds (95% CI: 1.1-4.9) and perceptions of less social support related to adherence: 2 times higher odds (95% CI: 1.1-3.6). Culturally appropriate interventions are needed to address alcohol use, which is common in this setting. Parenting may represent a competing demand on time and resources and be an adherence barrier. Self-reported perceived lack of adherence support may be a useful marker for need for adherence interventions.

Introduction

The benefits of high adherence rates are well known and consistent across settings and include increased virologic response and lower rates of resistance, morbidity, mortality, and improved survival [1-4]. Concerns that poor adherence in resource poor settings would lead to increased resistance globally have been countered by studies in Africa demonstrating adherence rates that meet or exceed those in wealthy countries [5]. Examples of excellent adherence in resource-poor settings have advanced the moral and policy debates on the issue of antiretroviral availability. However, in resource poor countries, as in wealthier nations, clinically important non-adherence remains troublingly prevalent [6].

Corresponding Author: Robert Gross, MD MSCE, Associate Professor of Medicine (ID) and Epidemiology, Center for Clinical Epidemiology and Biostatistics, Blockley Hall, 804, 423 Guardian Drive, Philadelphia, PA 19104-6021, USA, Tel 215-898-2437, grossr@mail.med.upenn.edu.

Risk factors for non-adherence in wealthier countries include depression [7], active drug and alcohol abuse [8,9], social instability [10], and low literacy [11]. In contrast, studies of risk factors in resource-poor settings have focused on access to antiretrovirals [12] and food [12-14]. Few studies have investigated the barriers to adherence to antiretrovirals in Caribbean nations, some of which are middle income countries. These countries have fewer, but persistent, resource constraints when compared with the larger umbrella of lower-income countries.

The Dominican Republic, a country with a population of 9.5 million in which 42.2% of the population lives below the national poverty line [15] has an estimated HIV prevalence of 1%. However, among commercial sex workers and their clients, prevalence rates range from 2.5-12%,–depending on the location, with heterosexual sex representing the major mode of transmission [16]. Large-scale provision of antiretroviral therapy was introduced in 2004 in the Dominican Republic with antiretroviral drugs supplied by the government and distributed by government and non-governmental organization clinics. In order to provide tailored interventions aimed at increasing adherence, risk factors for non-adherence must first be assessed. Therefore, we set out to determine barriers to adherence to antiretroviral therapy in the Dominican Republic.

Methods

Study setting and participants

We conducted a cross-sectional study between June 2004-December 2005 in two clinics in the Dominican Republic, one each in Puerto Plata (Grupo Clara, CEPROSH a non-profit AIDS treatment and social support organization) and Santo Domingo (Centro Sanitario, a government health clinic). Participation was offered during clinic visits by clinical research staff to all HIV infected individuals ≥18 years of age receiving any antiretroviral therapy. Informed consent and interviews were conducted in Spanish. The study was approved by the University of Pennsylvania Committee on Studies Involving Human Beings and the local ethics boards in the Dominican Republic.

Measures

Age, gender, race, and CD4 count were collected by interview and chart review. The remaining data were drawn from responses to the AIDS Clinical Trials Group (ACTG) barriers to adherence questionnaire, including educational level, employment status, alcohol use, illicit drug use, route of acquisition, number of children, number of patient's children living in the residence, and the Perceived Stress Scale [17].

Adherence over the prior month was assessed separately for each antiretroviral using a self-report visual analog scale (VAS) [18]. Adherence was considered optimal if it was reported to be 95% or more. Within individual, adherence was the same for each medication and thus each participant was categorized based on this single value.

Barriers to adherence were assessed by self-report using the standard Spanish language Adult AIDS Clinical Trials Group (ACTG) barriers to adherence questionnaire and an *ad hoc* questionnaire that was translated and backtranslated to ensure validity. Barriers assessed by the ACTG questionnaire included forgetting, being away from home, running out of medications, feeling too busy, feeling too ill, wanting to avoid side effects, being unable to carry out instructions, experiencing a change in routine, feeling well (i.e., no need), feeling depressed, falling asleep, feeling medications harmful, and feeling that the medications are too numerous.

The ad hoc questionnaire assessed whether the following factors had prevented patients from coming to the clinic to pick up their anti-retroviral medications: the frequency of the visits, conflicts with work, arranging transport from home to the clinic, paying the fare to travel from home to the clinic, waiting time to see the clinician, too sick to come to clinic, and difficulty finding someone to care for your children.

Excessive alcohol use was defined as an average of two or more drink per day or five or more drinks per episode for women and an average of three or more drinks per day or six or more drinks per episode for men [19]. Satisfaction with family support and adherence support were assessed using the ACTG barriers to adherence questionnaire which asks::#1) In general, how satisfied are you with the support that you have received from your friends and family? Very unsatisfied, a little unsatisfied, somewhat satisfied, or very satisfied and #2) How much do your friends or family members help you with remembering to take your medications? None, very little, some, or a lot. For the question on family support, "unsatisfied" and "very unsatisfied" were grouped and "satisfied" and "very satisfied" were grouped. For the question on adherence support, "none" and "very little" were grouped and "some" and "a lot" were grouped.

Analysis

Categorical variables were compared between adherent and non-adherent participants using Chi-squared tests and continuous variables were compared using Wilcoxon rank sum tests. We assessed for confounding between adherence and risk factors for non-adherence with logistic regression adding secondary variables to the models. Separate models were constructed for each risk factor of interest. Potential confounders were chosen for each model based on their association with either adherence or the risk factor of interest with a p value <0.05. We declared confounding to be present and retained those confounders in the final models if the point estimate of the association between the main exposure variable and adherence differed by 15% or more from the unadjusted analyses. Effect modification was assessed by including interaction terms in the logistic regression models.

We based the desired sample size on the potential association between difficulty in reaching the clinic and adherence. Projecting 80% power to detect a 20% difference in the proportion of individuals with good adherence with a type 1 error rate of 0.05 and a prevalence of difficulty in reaching the clinic as high as 50%, we estimated a required samples size of 300.

Results

We enrolled 300 patients between July 2004 and November 2005, 62% from Puerto Plata and 38% from Santo Domingo. Of those enrolled, 289 (96%) were on triple antiretroviral therapy including 149 (50%) on zidovudine, lamivudine, and nevirapine, 55 (18%) on stavudine, lamivudine, and nevirapine, 38 (13%) on zidovudine, lamivudine, and efavirenz, 17 (6%) on stavudine, lamivudine, and efavirenz, 6 (2%) on zidovudine, lamivudine, and indinavir, 6 (2%) on zidovudine, lamivudine. and nelfavinr and the remainder on other protease inhibitors. The median number of times that participants were taking antiretroviral medications per day was 2 with a range of 1-3 with 96% of participants on twice daily regimens. The most recent median CD4 count obtained from clinic charts was 105 cells/cm3 (IQR=44-192) which was obtained a median of 434 days (IQR 223-521) prior to the study visit. The majority of individuals 133 (96%) reported being heterosexual.

Table 1 displays the association between the participant characteristics and non-adherence. Suboptimal adherence to antiretrovirals over the prior month was reported by 72 (24%) participants. Heavy alcohol consumption and having children were statistically significantly associated with non-adherence, each more than doubling the odds of non-adherence. Lack of

perceived family support and lack of perceived adherence support were both associated with non-adherence, each doubling the odds, although only the latter was statistically significant.

None of the other characteristics, including difficulty in getting to the clinic site were associated with non-adherence. In logistic regression models, there was no confounding of the relation between heavy alcohol consumption or having children with adherence. Further, there was no evidence that the association between having children and non-adherence differed for men or women (test for interaction, z=0.37, p=0.7). There was no evidence of differential associations between the risk factors and non-adherence by site of enrollment (data not shown).

Barriers to adherence are listed in Table 2. The median number of barriers self-reported by the non-adherent participants was 1 (interquartile range 1-3) with 9 (13%) participants reporting more than 5 barriers. The most commonly reported barriers were forgetting doses and being away and not able to take the medications.

Discussion

In this study we found self-reported non-adherence to antiretrovirals to be relatively common, which is consistent with findings both in wealthy and resource-poor countries. Heavy alcohol use was an important risk factor as has been found in other studies of HIV medication adherence[20,21]. Alcohol figures prominently in Dominican culture related in part to the colonial history of rum produced from local sugarcane. The 2003 World Health Survey examined the rate of heavy alcohol use among adults over 18 in the Dominican Republic finding that 15.7% of men and 3.5% for women met criteria for heavy drinking and 3.1% of men and 1.1% of women met criteria for hazardous drinking [16].

While alcohol use impairs judgment and may directly lead to missed doses, it may also be a response to other stressors which impinge on the structured behavior needed to maintain high levels of medication adherence. Unfortunately, to date, the results of interventions targeted at increasing adherence among patients with a history of alcohol abuse have been mixed and none have been conducted in the DR [22,23]. We also found that having children was associated with non-adherence. Prior research has shown that primary caregivers, particularly women, were at increased risk of non-adherence, presumably due to the competing needs of caring for children and the disruption of ones own routines that comes with providing care for others[24]. Interestingly, we did not find that this risk factor differed by gender despite the fact that women in the Dominican Republic, as in most parts of the world, continue to bear primary responsibility for childcare. The lack of a more pronounced effect of having children on antiretroviral non-adherence on women, compared to men, suggests that other factors related to having children, such as the competing costs of child care and self-care, may play a role [24]. We also found that non-adherent participants felt less supported by family and perceived having less support for adherence itself. These findings are consistent with prior work in other settings [25-27], and reinforce that having children may represent a competing demand and contribute to a lower level of self-care. As in most other settings, the most common reason participants ascribed to missing doses was forgetting. Running out of medications and being away from home were also common. Enhanced adherence support by a community health worker or treatment partner is a promising approach that may addresses the risk factors identified [28,29]. In nearby Haiti, community health workers, known there as *accompagnateurs*, have been used for over fifteen years to implement directly observed therapy for antiretroviral drugs and to provide psychosocial support to patients, resulting in higher rates of adherence than those traditionally observed in the U.S. [29]. Variants of this model, including the use of unpaid "treatment partners," have been used successfully in a number of other wealthy and

resource-poor settings from Boston, Massachusetts, to Kampala, Uganda [30-32] and warrant further testing in this setting.

This study had several limitations. Although the visual analog scale measure of adherence has been associated with virologica response, self-reports tend to overestimate adherence [33]. However, we chose a high cutoff for adherence (95% or greater) to address this issue. Also, the one-month time period assessed is a brief window on the dynamics of adherence behavior [34]. It is likely that periods of non-adherence are more common than can be detected over any one month period. Yet, we still found non-adherence to be relatively common. We did not have virological response data since it was only sporadically assessed in this setting. However, we know from many other studies that non-adherence is clinically crucial and that occult treatment failures are likely to be occurring in at least a subset of these participants. Resistance and transmission of resistant virus are the appropriately feared sequelae. While they have been previously validated, the Spanish-language version of the ACTG questionnaire on barriers to adherence and the Visual Analog Scale were not specifically validated in the DR. We also employed an ad hoc questionnaire which was simply translated and backtranslated as a measure to improve validity. Of note, all questionnaires were reviewed with Dominican physicians and HIV counselors. The instrument was also piloted with a small sample of Dominican patients prior to the initiation of the study. All of these reviewers felt that the Spanish used in the instrument was simple and clear and no difficulties with the instruments were reported during data collection. Finally, our study was limited to two centers in the Dominican Republic and may not be generalizable to all sites providing care. However, while the centers differed markedly in some regards (one run by a non-governmental organization and the other a government clinic) the findings were consistent between sites.

In conclusion, we found non-adherence to antiretroviral drugs to be common in the Dominican Republic. Several risk factors for non-adherence emerged including heavy alcohol use, having children, and the self-perception of lack of adherence support. Interventions targeting non-adherence, particularly focused on alcohol use, are needed in this setting. Further exploration of the issue of having children is warranted to determine if any modifiable factors can be identified for interventions to improve adherence. Development of culturally appropriate interventions for alcohol abuse should remain a high priority to prevent antiretroviral treatment non-adherence and treatment failure.

Acknowledgments

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Table 1
Associations Between Participant Characteristics and Non-Adherence

	Adherent N=228	Non-adherent N=72	Odds Ratio (95% Confidence Interval), test statistic, p value
Female sex	122 (53%)	43 (61%)	1.3 (0.8-2.4), χ^2= 1.1, p=0.30
Age <35 years	32 (46%)	37 (54%)	1.5 (0.8-2.6), χ^2=0.8, p=0.18
Less than high school education	165 (73%)	54 (77%)	1.3 (0.6-2.5), χ^2=0.47, p=0.50
Having children	162 (71%)	63 (86%)	2.2(1.1 -4.9), χ^2=4.9, p=0.03
Employed	103 (45%)	38 (53%)	1.4 (0.76-2.4), χ^2= 1.2, p=0.30
Heavy alcohol use	60 (26%)	34 (47%)	2.5 (1.4-4.5), χ^2= 11.1, p<0.001
Perceived lack of family support	28 (12%)	14 (20%)	1.7 (0.8-3.7), χ^2=2.4, p=0.12
Perceived lack of adherence support	92 (41%)	40 (58%)	2.0 (1.1-3.6), χ^2=6.4, p=0.01
Difficulty in reaching clinic	26 (37%)	70 (31%)	1.3 (0.7-2.3), χ^2=0.7, p=0.4

Table 2

Comparison or Reasons for Missing Doses Between Adherent and Non-Adherent Participants Reporting Any Missed Doses

	Adherent N=199	Non-Adherent N=71	Test, test statistic, p value
Forgetting	20 (10%)	29 (41%)	X^2=33.4, p<0.001
Being away from home	19 (10%)	22 (31%)	X^2=18.7, p<0.001
Running out of medications	10 (5%)	15 (21%)	X^2= 16.0, p<0.001
Feeling too busy	7 (4%)	12 (17%)	X^2=14.3, p<0.001
Feeling too ill	6 (3%)	11 (16%)	X^2= 13.8, p<0.001
Wanting to avoid side effects	6 (3%)	10 (14%)	X^2=11.5, p=0.001
Unable to carry out instructions (e.g., take with food)	7 (4%)	8 (11%)	X^2=6.1, p=0.01
Change in routine	7 (4%)	7 (10%)	X^2=4.4, p=0.04
Feeling well (i.e., no need)	5 (3%)	6 (9%)	X^2=4.9, p=0.03
Feeling depressed	5 (3%)	6 (9%)	X^2=4.7, p=0.03
Falling asleep	5 (3%)	5 (7%)	X^2=3.1, p=0.08
Avoiding notice of taking medications	2 (1%)	5 (7%)	X^2=7.5, p=0.006
Feeling medications harmful	1 (1%)	1 (1%)	X^2=0.6, p=0.5
Feeling number of medications too many	2 (1%)	1 (1%)	X^2=0.08, p>0.5