Depression and Response to Antiretroviral Therapy in the Dominican Republic

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Abstract

**Background:** Depression is common in HIV-infected patients and may affect response to Antiretroviral Therapy (ART). We analyzed anonymized data from the DR’s major non-governmental ART clinics to estimate the prevalence of and characteristics associated with Clinically-significant Depressive Symptomatology (CSDS) in Dominican Republic (DR) ART patients, and its impact on response to ART.

**Methods:** We performed a cross-sectional analysis of data obtained by questionnaires screening for CSDS, ART adherence, and food insecurity in a convenience sample of non-acutely ill ART patients seen in the collaborating clinics in 20 workdays in May-June 2013. Demographic characteristics and most recent CD4+ T-lymphocyte counts and plasma HIV-RNA levels (“viral loads”) were obtained by medical record review. Factors associated with CSDS and poor ART response were identified by comparing prevalence of CSDS and ART failure by patient characteristics.

**Results:** Of 205 patients, 61 (29.8%) met criteria for CSDS. CSDS prevalence was higher among residents in bateyes (sugarcane plantation-worker barracks) (100%) than in those residing elsewhere (26.9%; p<0.001) and in patients reporting food insecurity (52.2%) than in those denying it (18.8%; p<0.001). Patients taking ART for less than 36 months were more likely to have CSDS (38.6%) than those with longer ART duration (23.8%; p=0.02). Proportions of patients with viral suppression were higher in: females (64.9%) than males (48.8%; p=0.02); patients with ART for over 36 months (66.0%) versus those with shorter ART duration (47.0%; p=0.009); patients reporting perfect (63.4%) versus imperfect adherence (42.3%; p=0.009), and patients without CSDS (64.0%) versus those with CSDS (40.0%; p=0.002). When controlled for perfect ART adherence, ART duration, and gender in logistic regression, CSDS was independently associated with decreased likelihood of viral suppression (OR=0.4; 95% confidence interval=[0.2-0.8]; p=0.006).

**Conclusions:** CSDS is associated with ART failure even when controlled for adherence. Depression treatment may improve ART response and patients’ quality of life.

**Keywords:** HIV; Depression; Antiretroviral therapy; Adherence; Viral suppression; CD4+; T-lymphocyte count; Dominican republic; Batey; Caribbean

**Abbreviations**

ART: Antiretroviral Therapy; CDF: Clínica De Familia La Romana; CSDS: Clinically Significant Depressive Symptomatology; DR: Dominican Republic; IDEV: Instituto Dominicano de Estudios Virológicos

**Introduction**

Over 75% of the estimated 250,000 HIV-infected persons in the Caribbean, the second most HIV-affected region in the world after Sub-Saharan Africa, live in Hispaniola, the island shared by Haiti (60%) and the Dominican Republic (DR) (18%) [1]. In the DR, rapid uptake of antiretroviral therapy (ART) has resulted in 78%-80% ART coverage for HIV-infected persons with CD4+ T-lymphocyte (CD4) counts less than 350 cells/ml (i.e., meeting criteria for ART for their own health). As in other low and middle-income countries advances associated with ART scale-up in the DR and the psychosocial challenges faced there have increased interest in improvement of other neglected healthcare services, including mental health [2-9].

Depression and other mental and neurologic disorders constitute 13% of the global burden of disease, surpassing cardiovascular disease and cancer [10]. After low back pain, depression was the leading cause of years lived with a disability; because of its association with suicide and heart disease, it also contributed to mortality [11]. Depression is common in persons with HIV infection [12-15]. It has reportedly been associated with progression of HIV-related immunosuppression [16-18] and poor adherence and response to ART [19-23], although studies have not consistently observed associations of depression with biomarkers of HIV progression [24,25]. Depression treatment and remission have reportedly improved immunologic status, ART
adherence and possibly viral suppression [26-29]. Conversely, HIV-related cytokine elevation and monoaminergic function decline may promote development of depression [30].

The DR has a high middle-income economy but most HIV-infected persons and those at highest risk (those of Haitian origin or descent and/or residing in bateyes [sugarcane plantation barracks]) endure poverty, discrimination [31-33] and possibly depression. We explored patterns of adherence and response to ART in DR patients, the scope and determinants of clinically-significant depressive symptomatology (CSDS) in this population, and CSDS’ impact directly (and indirectly through non-adherence) on viral and immunologic response.

Materials and Methods

This study used anonymized data from patients in the two non-governmental DR organizations with the highest numbers of adult ART patients (Instituto Dominicano de Estudios Virologicos [IDEV], in the DR capital, and Clínica de Familia La Romana [CDF], in the sugarcane-growing eastern region). They provided ART to 1,029 and 1,203, adults, respectively, two of only five clinics providing ART to more than 1,000 adults in 2013. Our target sample size was 9%-10% of ART patients in these clinics. Patients were selected for participation if they were aged over 18 years, had received ART for over 30 days, and/or residing in bateyes [sugarcane plantation barracks]) endure poverty, discrimination [31-33] and possibly depression. We explored patterns of adherence and response to ART in DR patients, the scope and determinants of clinically-significant depressive symptomatology (CSDS) in this population, and CSDS’ impact directly (and indirectly through non-adherence) on viral and immunologic response.

CSDS and food insecurity determinations were made based on responses to the Center for Epidemiologic Studies Depression Scale-20 (CESD-20) [34] and food insecurity two-question screening questionnaire [35] in interviews administered by clinic staff. The CESD-20 consists of 20 questions that ask whether the patient has experienced in the preceding seven days (rarely/never, a few times, occasionally, or almost all/all the time) symptoms or feelings suggestive of depression (e.g., “I thought that my life had been a failure,”) and indicators of non-depressed mood (e.g., “I felt optimistic about the future”). Responses were scored from 0-3 with increasing frequency of depressive or decreasing frequency of non-depressive emotions. The Food Insecurity Screening Question was: “In the last seven days, were there any days when there was not enough food for everyone at home to eat at least three times per day?” To measure adherence to ART, patients were asked how many doses of ART they had missed in the previous week, and one screening question from the Beliefs about Medicine Questionnaire [36] using a Likert scale: “Do you find that taking ART medications is difficult/problematic?”; options included very problematic, somewhat problematic, “so so,” virtually unproblematic, or not problematic at all. To assess ART response, baseline at (ART initiation) and most recent CD4+ T-lymphocyte (CD4) counts and quantitative HIV RNA (“viral load”) measurements were abstracted from medical records by clinic staff using standardized forms [37,38].

ART patients were characterized as having CSDS if their CES-D-20 score (range=0-60) was greater than 16 [34]. “Perfect” adherence was defined as reporting no missing doses in the previous week. Food insecurity was defined as answering “yes” to the screening question [35]. Patients were considered to have poorer attitudes towards adherence if they considered ART “very” or “somewhat” problematic/difficult. Viral suppression was defined as a viral load <40 copies/ml in the most recently obtained viral load [37]. Duration of ART at the time of viral load testing, and the time between most recent viral load and questionnaires were noted. In these clinics, once patients had over three consecutive undetectable viral loads over a 12-24 months period, viral loads were routinely repeated yearly. CD4 count response to ART varies considerably by CD4 count at ART initiation; an “optimal immunologic response” was defined as an increase in CD4 count greater than or equal to the lowest average CD4 count increases after 6, 12, and 24 months of ART (100, 150 and 250 respectively) [38,39]. CSDS, perfect adherence, food insecurity, considering ART problematic, viral suppression and optimal immunologic response were analyzed as categorical variables. After ensuring that clinicians were advised of data relevant to patient management, identifying information was stripped from the data and anonymized data were sent to FIU investigators.

Data were entered and analyzed using Epi Info for Windows 3.5.4 (Atlanta, GA) [40]; 95% confidence intervals (95%CIs) were used to assess precision of prevalence estimates. Prevalence ratios (PRs) were used to assess the strength of association between independent and dependent variables. Significance testing was done using 95%CIs of prevalence ratios and Fisher’s exact or Chi square tests. PRs>1.0 and <1.0 indicated greater and lower likelihood of the outcome variable (e.g. viral suppression) occurring in patients who had the independent variable (e.g. female sex). Medians were compared for continuous variables using the Kruskal-Wallis test for two groups, which has no assumption of normality [40]. P values<0.05 and 95% CIs that did not include 1.0 indicated that differences between groups achieved statistical significance.

Analyses of characteristics associated with CSDS and viral suppression were stratified by potential confounders. The Breslow-Day test was used to assess whether associations were homogenous across strata (suggesting no interaction between stratification and independent variables) or not homogenous (suggesting interaction); p-values from the Breslow-Day Chi-square were used to determine whether PRs differed significantly by stratum [40]. To control for confounding, logistic regression was used to assess the relationship between CSDS and failure to achieve viral suppression, controlled simultaneously for all other variables associated with ART failure.

The Florida International University Institutional Review Board reviewed the protocol for this data analysis and concurred that it did not meet the criteria for human participant research.

Results

Data from 205 patients, of whom 103 (50.7%) were female, were analyzed. Median age was 39.3 (range=19-72) years. Sixty-seven (32.7%) reported “food insecurity”; 145 (70.7%) reported perfect ART adherence. ART duration ranged from one to 130 months (median=54 [IQR=32-130] months), and was longer among women than men (median=60 versus 47 months; p=0.009); 61/205 (29.8%; 95% CI=23.6%-36.5%) had CSDS. CSDS did not vary by sex, age, or ART regimen at the time of questionnaire. Median time on ART was lower in patients with CSDS than in others (median=45 vs. 60 months; p=0.053). Eight of 205 reported residing in bateyes. CSDS prevalence was higher in batey residents than in others (8/8 [100%] vs. 53/297 [26.9%]; p=0.001), in food insecure than non-food insecure patients (35/67 [52.2%] vs. 26/138 [18.8%]; p=0.001), and in patients treated with ART for less than 36 months than those with longer ART duration (32/83 [38.6%] versus 29/122 [23.8%]; p=0.02).
Patients with CSDS were more likely to describe ART use as very or somewhat “problematic” (23/61 [37.7%]) than patients without CSDS (28/144 [19.4%]; PR=1.9; 95% CI= 1.2-3.1, p=0.006) but were no less likely to report perfect adherence; 186 had a viral load 1-130 months after ART initiation (median=59, IQR=36-87 months). This viral load was the most recent available, obtained 1-13 months before the questionnaires. Viral loads ranged from <40 to 809,456 copies/ml. Median was <40 (IQR=<40-223) copies/ml; 76.3% had viral loads <400 copies/ml. Median ART duration for patients with viral suppression was longer than for those without viral suppression (66 versus 46 months; p=0.002).

Patients treated with ART for <36 months, males and patients with CSDS or imperfect adherence were less likely to have viral suppression (Table 1). When stratified by ART duration the difference in likelihood of viral suppression by presence of CSDS was significant only in those receiving ART for 36 months or longer. When controlled in logistic regression for ART duration, perfect adherence, sex and describing ART as problematic CSDS was independently associated with decreased likelihood of viral suppression (OR=0.4; 95% CI=0.2-0.8; p=0.006).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%) with Viral Suppression</th>
<th>Prevalence Ratio (95%CI)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>CSIDS Present</td>
<td>22/ 55 (40.0)</td>
<td>0.62 (0.44-0.87)</td>
<td>0.002</td>
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<tr>
<td>Screening score not consistent with CSIDS</td>
<td>85/131 (64.9)</td>
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<thead>
<tr>
<th>Duration of ART</th>
<th>Number (%) with Viral Suppression</th>
<th>Prevalence Ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 36 months</td>
<td>39/ 83 (47.0)</td>
<td>0.71 (0.54-0.93)</td>
<td>0.009</td>
</tr>
<tr>
<td>36 months or more</td>
<td>68/103 (66.0)</td>
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<tr>
<th>Stratified by ART Duration</th>
<th>Number (%) with Viral Suppression</th>
<th>Prevalence Ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART for less than 36 months</td>
<td>12/ 32 (37.5)</td>
<td>0.7 (0.47-1.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>CSIDS not consistent with CSIDS</td>
<td>27/ 51 (52.9)</td>
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<tr>
<th>ART for 36 months or longer</th>
<th>Number (%) with Viral Suppression</th>
<th>Prevalence Ratio (95%CI)</th>
<th>p-value</th>
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<td>CSIDS not consistent with CSIDS</td>
<td>58/80 (72.5)</td>
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<th>Sex</th>
<th>Number (%) with Viral Suppression</th>
<th>Prevalence Ratio (95%CI)</th>
<th>p-value</th>
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</thead>
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<tr>
<td>Female</td>
<td>64/ 98 (65.3)</td>
<td>1.3 (1.03-1.7)</td>
<td>0.02</td>
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<tr>
<td>Male</td>
<td>42/ 86 (48.8)</td>
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<tr>
<th>Adherence to ART</th>
<th>Number (%) with Viral Suppression</th>
<th>Prevalence Ratio (95%CI)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Perfect</td>
<td>85/134 (63.4)</td>
<td>1.5 (1.1-2.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Less than perfect</td>
<td>22/ 52 (42.3)</td>
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Table 1: Characteristics, including clinically-significant depressive symptomatology (CSDS), associated with viral suppression* in antiretroviral therapy (ART) patients: overall and stratified by ART duration and adherence. *Analysis confined to 186 patients with at least one viral load after ART initiation, †95%CI=95% Confidence Interval, † from uncorrected Chi-square, ‡From Chi square for differing prevalence ratios by stratum.

At ART initiation, CD4 count ranged from 3-840 cells/mL (median=164; IQR=57-258); 85.6% of the 201 patients with CD4 counts at ART initiation had CD4 counts less than 350 cells/mL. Most patients’ CD4 counts at ART initiation (59.7%) were less than 200 cells/mL. Most recent CD4 counts available ranged from 49 to 1,439 (median=398; IQR=252-538) cells/ml and had been obtained in 192 patients 1-12 months prior to questionnaires, and 2-113 months since ART initiation. Change in CD4 count from the value at ART initiation to most recent value ranged from 361 cell/mL decrease to 971 cells/mL increase (median=268 cell/mL increase; IQR=125-402 cells/ml); 166 values were from patients who had had ART for at least six months when the CD4 count was obtained. CSDS was associated with a slightly lower likelihood of “optimal” immunologic response (24/49 [49%] in patients with CSDS versus 69/117 [59.0%] in patients without CSDS; PR=0.8 [0.6-1.1], p=0.23). However, in patients who had had ART for at least 24 months, those with CSDS were significantly less likely to have a CD4 count increase of over 200 cells (15/33 [45.4%]) than those without CSDS (65/94 [69.9%]; PR=0.65; 95%CI=0.44-0.97; p=0.01). In patients with ART for at least 24 months, median CD4 increase was significantly lower in patients with CSDS than in those without CSDS (173 versus 284 cells/mL; p=0.045).

Female patients had higher median CD4 counts at ART initiation than males (194 versus 132 cells/ml; p=0.02) and higher median CD4 count increases (255 versus 166 cells/ml; p=0.03). However, when stratified by CSDS, this sex-related CD4 count increase was seen only in patients without CSDS (median increases: females=272 cells/ml, males=191 cells/ml; p=0.01). In patients with CSDS, females did not have significantly higher median CD4 count increases (167 versus 130; p=0.39).

**Discussion**

Prevalence of CSDS was high in these ART patients (almost 30%), higher than the prevalence in normative populations (15%-19%) [34], and similar or somewhat higher than in other low and middle-income [12,13] and US populations [14,15], respectively. Overall, proportions of ART patients who reported excellent adherence and who had viral loads <400 copies per mm3 (both over 70%) are encouraging. Unlike
other studies of depression in low-and middle-income countries, CSDS did not appear to affect reported adherence to ART [19-21,23]. However, CSDS was associated with decreased likelihood of viral suppression, which has been less commonly reported worldwide, and not at all in the Caribbean. Importantly, the relationship between CSDS and failure to achieve viral suppression was strongest in subgroups that (in the absence of CSDS) had the best prospects for viral suppression: perfectly adherent patients with longer ART duration. The relationship remained statistically significant when controlled for sex, perfect adherence and longer ART duration. The emergence of CSDS as an independent risk factor for failure to achieve viral suppression when controlled for adherence supports the hypothesis, suggested by previous evidence, that physiologic processes associated with depression and depression treatment may directly affect viral replication [17,24,29].

The effect of depression on immunologic response was less striking. There is evidence that adults who initiate ART with CD4 counts 350 cells/ml or higher can achieve complete immune-reconstitution, continued increase in CD4 counts over years, and CD4 counts over 799 cells ml after seven years of ART [38]. However, such optimal immune response may be less likely in populations like ours where most patients initiated ART after profound immunosuppression. Because women have been offered HIV prenatal testing since 1999 in the DR even if asymptomatic [3] they were more likely to be diagnosed with HIV before severe immunosuppression than men, as reflected by their CD4 counts at ART initiation and CD4 count increases. However, this protective effect of female sex (and earlier ART initiation) declines among women with CSDS, suggesting that in persons who do not begin ART with severe immunosuppression, and may have a greater likelihood of optimal ART immune response [38] depression may impair their response to ART.

CSDS was strongly associated with factors (food insecurity and batey residence) linked to poverty in the DR, where over 40% of the population lives in poverty [41]. Poverty is much higher among HIV-infected adults who also experience considerable discrimination [3,31]. Batey residents and persons of Haitian origin or descent endure high levels of discrimination, low access to health care, poverty, and exclusion from many aspects of civil society [2,39]. Although they represent only 1.0%-1.5% of the DR population, with a seroprevalence rate of 3.2% [33] (greater than the DR adult seroprevalence of 0.7% [32] and the seroprevalence in Haiti [1]), they are over-represented (over 5%) of HIV-infected persons in the DR. In our data, only 8 (3.9%) ART patients were batey residents, even though CDF is located in an area with many bateyes, suggesting slightly less ART use by batey residents or batey residence under-reporting. However, even with this small number the impact of batey residence on CSDS was significant and striking, suggesting that batey residents may be at increased risk of depression.

The limitations of this study include its cross-sectional nature, which reduce certainty in assessing direction of causality. Reliance on self-report for adherence and attitudes towards medications is a limitation although there is little concern that patients may have exaggerated adherence or ease of ART because of the strong association between these and viral suppression. Because ART response biomarkers were not obtained at the moment of the questionnaires, the strength of associations between these and CSDS may have been lower than if they would have been performed simultaneously. However, several instruments use seven-day reports because these tend to stably reflect behaviors, emotions and conditions over time without sacrificing simplicity and increasing recall bias [34,35].

In conclusion, our data suggest that CSDS is common in ART patients and is associated with failure to achieve viral suppression even with perfect ART adherence, suggesting a role for depression treatment. Such treatment is no substitute for addressing aspects of patients’ life experiences that contribute to “reactive” depression [42,43]. Conversely, it should be recognized that antidepressant treatment is effective even in traumatized persons with excellent “cause” for depression [44]. Despite paucity of psychiatrists and psychologists in the DR [45,46], “task-shifting” ART scale-up experiences suggest approaches that can address mental health needs [8]. Promising antidepressant-use algorithms have been successfully integrated into HIV care in low-income settings [47]. The DR’s dramatic ART scale-up, achieved mostly by non-specialist physicians, may be a model for antidepressant treatment introduction.

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