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Nonadherence as four-day antiretroviral therapy interruptions: Do depression and race/ethnicity matter as much in the modern antiretroviral therapy era?

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Abstract

HIV+ White, Latino, and African Americans (N = 1,131) completed a survey advertised on social media to re-examine the effect of depressive symptoms (via the Patient Health Questionnaire; PHQ-9) and race/ethnicity on antiretroviral therapy nonadherence (defined as past 3-month, four-day treatment interruption). An adjusted logistic regression showed a 15% increase in odds for a treatment interruption per 1-unit increase on the PHQ-9. The effect of depressive symptoms on nonadherence was greater for Latinos (OR=1.80, p<.05), but not for African Americans, compared to Whites. The benefits of modern ART (e.g., simpler, forgiving to minor lapses) may not circumvent the effect of depressive symptomatology.

Keywords

Adherence; Antiretroviral Therapy; Depression; Latinos; Race/Ethnicity

Introduction

Disparities in antiretroviral therapy (ART) adherence among Latinos and African Americans in the U.S. persist for variety of reasons [1, 2], as does depression as a predictor of ART nonadherence [3, 4]. However, because newer ART regimens have greater potency, are better tolerated, and simplified, minor lapses in adherence now pose less of a risk for virologic failure [5–9].

Newer ARTs require an updated study of the depression-adherence relationship. For example, if depression is associated with missed ART doses, it depends on the duration of the lapse in adherence [6, 10, 11]. Missing one dose each week over four weeks is less risky when compared to missing four consecutive days of doses, although the calculated average adherence over this timeframe would be the same (i.e., 4 doses missed in past 4 weeks) [6]. Furthermore, viral load (VL) suppression has been observed with adherence levels ranging from 54% through 100%, an effect related to ART drug class [7–9, 12]. Therefore, interpreting an association between depression and adherence depends on how adherence is

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defined. In some cases, when the average number of doses missed, or artificial thresholds such as below 90% are used, self-reported nonadherence may not accurately represent a proxy for poorer clinical outcomes with newer, more forgiving regimens [7]. Thus, using a 4-day treatment interruption (i.e., nonpersistence, drug holidays) may better capture the missed dose pattern and signal that a gap in therapeutic coverage occurred [6].

This study examined depressive symptoms and race/ethnicity as a predictor of four-day ART treatment interruptions using data from social media users living with HIV. The primary hypothesis was that a treatment interruption would be more likely for participants with greater depressive symptoms, versus less; an effect moderated by race and ethnicity. The secondary hypothesis was that a treatment interruption would be associated with a detectable VL.

Methods

Cross-Sectional Study Design and Procedures

The data in this study come from a parent study that developed a novel strategy to help people living with HIV (PLWH) overcome barriers to research participation [13]. The study was advertised on social media sites, including Facebook, Twitter, and Craigslist, and targeted users who had self-reported interest or “liked” social media pages devoted to topics of HIV/AIDS, lesbian, gay, bisexual, transgender or queer, men who have sex with men, and HIV co-morbidities, such as tuberculosis, and unprotected sex. A Facebook Fanpage, with a link for the study, was created to disseminate HIV news articles, study announcements, and available HIV resources. Advertisements were also posted on message boards, the Twitter accounts of popular HIV/AIDS organizations, and on Craigslist discussion links. The link to the study directed all individuals to a website where they were screened for eligibility. Participants then completed the consent process and a one-time survey of demographic information, ART adherence, HIV clinical outcomes, and psychosocial factors. A research assistant managed the survey and weekly social media advertisements throughout the study period. The inclusion criteria were: 1) 18 years or older, 2) living with HIV, 2) and living in the U.S. To reduce repeat or fraudulent responses, only 1 Internet Protocol (IP) address was allowed per survey, no monetary incentives were provided, and no identifying information was obtained. Surveys were completed in English and the University of California, San Francisco Institutional Review Board approved this study.

Measures

Descriptive Information—Basic demographic information (age, sex, and education), education, income, and self-reported CD4+ cell counts [14] at most recent clinic visit were collected.

Covariates—Self-reported daily alcohol use and binge-drinking frequency items from the Alcohol Use Disorders Identification Test [15], past three-month stimulant use (crack, cocaine, methamphetamines) [16], past three-month opiate use [16], and ART regimen complexity (coded as 0-once-daily or 1- twice-daily/greater than twice-daily) were collected.

Predictors—1) Depressive symptoms were assessed with the Patient Health Questionnaire (PHQ-9) [14]. Total PHQ-9 scores are presented for descriptive purposes but somatic symptoms of depression were omitted in the regression analysis as they may confound with disease/side-effect symptoms [17]. 2) Race and ethnicity was assessed with two dummy-coded variables. Latinos and African Americans were compared to Whites (i.e., the referent group).

Outcomes—1) Treatment interruptions were defined as missing all ART doses over a four-day period at least once in the past three months (1 = treatment interruption, 0 = no treatment interruptions). [6] 2) Self-reported VL test results at most recent clinic visit was coded as 0 = undetectable, 1 = detectable. [14]

Statistical Analyses

Statistical analyses were run using IBM SPSS V.19 software. Basic descriptive statistics were used to characterize the total sample. For the primary hypothesis, a multiple logistic regression was used. First, we ran an Unadjusted Model to collect effect size estimates without any covariates. Second, we ran an Adjusted Model that included the covariates of age, use of stimulants, and regimen complexity [19], which were selected based on preliminary bivariate associations observed in the sample. We then entered the race/ethnicity variables (Latinos vs. Whites, African Americans vs. Whites), PHQ-9 depressive symptom score, and the interaction term (i.e., moderation analysis) of race/ethnicity by PHQ-9 score. We used the identical analysis for our secondary hypothesis. Unstandardized coefficients were entered into a Microsoft Excel program to calculate and plot probabilities of our outcome in the moderation analysis [20, 21].

Results

Descriptive Statistics

A full list of descriptive statistic for Whites, Latino, and African American participants is in Table 1 (N = 1,131 participants). For all racial/ethnic groups, PHQ-9 depressive symptom mean scores were nearly equivalent and in the mild severity category. About 20% of Latinos and African Americans, and 11.7% of Whites had at least one treatment interruption in the past three months and >60% of all participants were on a once-daily dosed ART regimen.

Inferential Statistics

Unadjusted Model. For the total sample, a one-unit increase on the PHQ-9 was associated with a 17% increase in the odds of reporting a treatment interruption (*OR* = 1.17, 95% CI [1.10–1.24], $p < .001$). Latinos had twice the odds of a treatment interruption (*OR* = 2.02, 95% CI [1.25–3.27], $p = .004$), compared to Whites. The difference between African Americans and Whites reached a marginal level of statistical significance (*OR* = 1.63, 95% CI [0.90–2.97], $p = .10$). Adjusted Model: An increase in the odds for a treatment interruption was associated with stimulant use (*OR* = 1.91, 95% CI [1.09–3.33], $p = .02$) and nearly associated with regimen complexity (*OR* = 1.50, 95% CI [.99–2.26], $p = .051$). Age was negatively associated with odds of treatment interruption (*OR* = 0.97, 95% CI [.96 – .99], $p = .01$).

The effect size for the PHQ-9 depressive symptom score in the adjusted model dropped from 17% to 15% (*OR* = 1.15, 95% CI [1.08–1.23], *p* = .001). Latinos had nearly twice the odds of a treatment interruption compared to Whites (*OR* = 1.80, 95% CI [1.07–3.00], *p* = .03) and no differences emerged between African Americans and Whites (*OR* = 1.39, 95% CI [0.74–2.61], *p* = .31). Lastly, the race/ethnicity variable moderated the effect of depressive symptoms on treatment interruptions in Latinos versus Whites (*OR* = .43, 95% CI [.26 – .74], *p* = .002) but not between African Americans and Whites (*OR* = 0.61, 95% CI [0.32–1.18], *p* = .15]. To visualize the moderation effect, estimates were used from a separate adjusted regression model with only Latino and White participants. In Figure 1, the probability of a treatment interruption was greater for Latinos compared to Whites at lower levels of depressive symptoms (See Figure 1), while at higher levels no differences emerged. For the secondary hypothesis, a treatment interruption was associated with a detectable VL (*OR* = 1.75, 95%CI [1.13–2.71], *p* = .01), after adjusting for the covariates described above.

Discussion

In a large sample of HIV+ White, Latino, and African Americans online social media users, depressive symptoms (cognitive and affective symptoms only) were associated with missing four consecutive days of ART in the past three months, even with a majority (>60%) of the sample on once-daily dosed ART. The effect of depressive symptoms on ART nonadherence was greater for Latinos compared to non-Latino Whites at lower levels of depressive symptoms, but unexpectedly not greater for African Americans as hypothesized. The data suggest that adherence to a more simplified, potent and better-tolerated ART regimen remains associated with even mild self-reported depressive symptoms, especially among Latinos.

This data showed four-day treatment interruptions to occur relatively frequently. Approximately 20% of Latinos and African Americans reported having at least one treatment interruption in the past three months. This finding adds to the depression-adherence literature because it documents depressive symptoms and a pattern of missed doses, which is less commonly used as an adherence outcome. Few have investigated factors associated with adherence as several consecutive days of missed ART doses [22] and we support moving in this direction. Conceptually, consecutive missed doses are problematic because it signifies that gaps in therapeutic coverage are occurring. As was demonstrated in the data, a four-day treatment interruption was associated with a self-reported detectable VL.

Latinos had a greater probability of a treatment interruption compared to Whites at the same low level of depressive symptoms, but this difference diminished at higher levels. This result is not surprising as greater depressive symptomatology likely impairs all groups similarly. However, the disparity at lower levels could indicate that even mild symptoms related to sadness, guilt, or decreased pleasure can interfere with the ability to overcome social, cultural and structural barriers to adherence and health-promoting behavior. Evidence shows that Latinos underutilize mental health service for reasons such as restriction from publicly funded insurance programs, or Spanish language barriers [23]. Mild depressive symptoms may diminish the motivation to travel to acquire medication or alternatively exacerbate the difficulty of overcoming a language barrier in medical care or psychotherapy [24–25].

Unexpectedly, differences between African American and Whites reached a marginal level of statistical significance; thus, we are cautious about drawing conclusions, as this may be an issue of limited statistical power.

Implications and Limitations

As single-dose daily regimens become the norm in the U.S., we must re-examine the measurement of adherence and predictors of nonadherence. However, regarding HIV patient education, we unequivocally support the continued messaging of maintaining high levels of adherence. Newer therapies now have greater potency and challenge the assumption that near-perfect adherence is necessary to achieve an undetectable VL [6]. For this reason, nonadherence as consecutive treatment interruptions may better capture the risk for virologic failure. Despite advancements in ART, mental health problems among PLWH continue to be a significant public health challenge. We need culturally-appropriate mental health programs that are integrated into HIV primary care to streamline access to mental health services and reduce disparities.

This study and its findings must be interpreted in light of some limitations. First, all data were self-reported, but participants reported treatment interruptions anonymously and with no incentive to do so. Second, because we investigated percentages of nonadherence rather than adherence levels, the threat to validity is lessened given the tendency to overestimate adherence. That is, self-reported nonadherence can be a high specificity indicator of adherence problems, which was the focus of this study [26]. However, if the social desirability effect was present, then there was an underestimation of the true estimate of treatment interruptions. Second, the study was open to all PLWH, but the sample consisted mostly of gay/bisexual males, and only a small percentage (less than 5%) was female. Additionally, the majority of the sample had high levels of education and use of social media. Thus, it may not be representative of, or generalizable to, all gay male communities and women. Third, we did not find that African Americans have a greater likelihood of nonadherence compared to Whites, which may have been due to statistical power. Fourth, in our secondary hypothesis and due to the self-report format, we could not verify the chronological order of when the most recent VL test was conducted and when the treatment interruption occurred in the past three months. Thus, we only interrupt the result as an association between a treatment interruption and VL. Lastly, because we could not physically collect HIV biomarkers, the evidence for the effect of treatment interruptions on VL cannot be taken as conclusive or definitive. A future validation study is needed.

Conclusion

In the modern ART era, depressive symptoms continue to have a critical impact on adherence across racial/ethnic minority groups living with HIV. We recommended that researchers and clinicians move towards measuring nonadherence as treatment interruptions to better capture the risk of HIV treatment failures.

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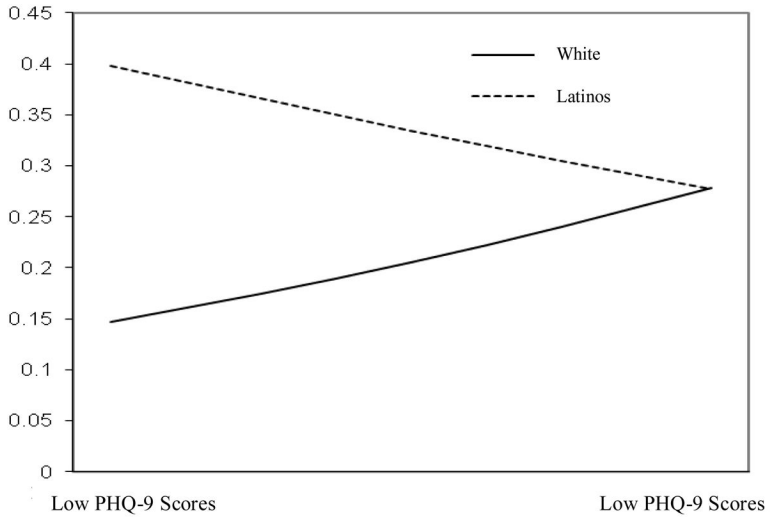

Fig. 1.

Visual representation of depressive symptoms-ethnicity (Latino versus Whites) interaction and probability of a treatment interruption. To illustrate the effect of depressive symptoms, the low and high indicators represent a plus/minus one standard deviation from PHQ-9 mean score.

Table 1

Participant characteristics (N = 1,131)

	Non-Latino Whites n = 880	Latinos n = 149	African Americans n = 102
	% or Mean (SD)	% or Mean (SD)	% or Mean (SD)
Age (Years)	47.07 (11.02)	42.41 (10.75)	42.52 (11.26)
Education			
< HS diploma	2.7	6.6	4.8
HS diploma or GED	26.2	25.8	31.8
Some College	25.9	28.0	28.2
College or higher	45.2	39.6	35.2
Income			
< $20,000	32.8	39.1	40.0
$20,000 to $39,999	25.3	23.7	29.6
$40,000 to $59,999	14.7	20.1	17.4
> $60,000	27.2	17.1	13.0
Depressive Symptoms			
PHQ-9 Total *	7.97 (6.14)	7.97 (6.38)	6.93 (6.42)
PHQ-9 Cognitive/Affective Score †	3.71 (3.06)	4.04 (3.26)	3.45 (3.08)
Past three-month Stimulant Use	9.3	6.0	12.3
CD4+ Cell Count	644 (359)	644 (298)	689 (415)
Undetectable Viral Load	86.5	90.9	76.7
Antiretroviral Therapy Regimen Complexity			
Once-daily	67.6	61.2	65.6
>Twice-daily	32.4	38.8	34.4
At least One 4-Day Treatment Interruption in Past 3 Months	11.7	20.8	19.6

Note.

*Patient Health Questionnaire-9.

†PHQ-9 score excluding somatic symptoms of depression.