Stressful and traumatic life events as disruptors to antiretroviral therapy adherence

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ABSTRACT

Stressful and traumatic life events (STLEs) are common among HIV-infected individuals and may affect health behaviors such as adherence to antiretroviral (ARV) therapy, with important implications for treatment outcomes. We examined the association between STLEs and ARV adherence among 289 US-based participants enrolled between 7/1/2010 and 9/1/2013 in a study of depression treatment for HIV-infected patients. Participants received monthly telephone calls to assess STLEs and pill count-based ARV adherence. Inverse probability of observation weighting was combined with multiple imputation to address missing data. Participants were mostly male (71%) and black (63%), with a median age of 45 years. Median monthly adherence was 96% (interquartile range (IQR): 85–100%). Participants experienced a mean of 2.48 STLEs (range: 0–14) in the previous month. The presence of ≥2 STLEs was associated with a mean change in adherence of −3.67% (95% confidence interval (CI): −7.12%, −0.21%) and decreased likelihood of achieving ≥95% adherence (risk ratio (95% CI) = 0.82 (0.71, 0.95)). For each additional STLE, the mean adherence change was −0.90% (95% CI: −1.79%, 0.00%). STLEs were associated with poorer ARV adherence, including decreased likelihood of adhering to ≥95% of ARV doses. This level of adherence has a critical role in regimen effectiveness and prevention of resistance.

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Introduction

Persons living with HIV/AIDS (PLWHA) face a number of challenges related to their HIV infection, including life-long use of antiretroviral (ARV) medications, HIV-related stigma, and opportunistic infections. Depression is also common, affecting upwards of 20% of PLWHA in the USA (Bing et al., 2001; Burack et al., 1993; Ickovics et al., 2001; Kilbourne, Justice, Rabeneck, Rodriguez-Barradas, & Weissman, 2001; Lyketsos et al., 1993; Lyketsos, Hutton, Fishman, Schwartz, & Treisman, 1996), in comparison to 12%–13% of the general population (Kessler et al., 2003). More attention has been paid recently to stressful and traumatic life events (STLEs) among PLWHA, which are common in this population (Whetten et al., 2006; Wong, Sarkisian, Davis, Kinsler, & Cunningham, 2007), and may have important implications for psychological, behavioral, and other outcomes. STLEs include moderately or severely stressful or traumatic events such as death or illness of family or friends; difficulties with relationships, finances, or employment; legal trouble; threats to safety; housing instability; and physical or sexual assault. STLEs are experienced more often by PLWHA than by the general population, in part due to the predominance of HIV infection among populations experiencing economic and other difficulties that are often related to such events (Mugavero et al., 2009).

Previous studies of STLEs have documented their high prevalence and association with negative clinical and behavioral outcomes. In the *Coping with HIV/AIDS in the Southeast* (CHASE) study, HIV-infected participants reported medians of nine incident stressful events and three incident severely stressful events over two years (Mugavero et al., 2009). Increasing numbers specifically of traumatic events were associated with higher rates of unprotected sex, worse medication adherence, increased emergency department use and hospitalization, accelerated HIV disease progression, and increased mortality rates (Leserman et al., 2007;

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Mugavero et al., 2009; Pence, Mugavero, et al., 2012). In a separate, cross-sectional study of HIV-uninfected young men who have sex with men, recent financial- and health-related stressful events were associated with increased risk of substance use, and recent health- and partner-related stressors were associated with sexual risk-taking (Wong, Kipke, Weiss, & McDavitt, 2010).

One important HIV-related outcome that STLEs may affect is adherence to ARV medication. STLEs can cause disruptions to routines, and for PLWHA, such disruptions may result in decreased ARV adherence. Adequate ARV adherence is necessary to achieve viral suppression, maintain health, and avoid developing drug resistance (Bangsberg, 2006; Bangsberg, Moss, & Deeks, 2004; Maggiolo et al., 2007; Shuter, Sarlo, Kanmaz, Rode, & Zingman, 2007). Two prior studies examined the association between STLEs and self-reported ARV adherence and found that increased frequency and greater severity of events were associated with poorer adherence (Leserman, Ironson, O'Cleirigh, Fordiani, & Balbin, 2008; Mugavero et al., 2009). Both studies relied on self-reported ARV adherence and long recall periods for STLEs, which may have affected exposure and outcome measurement accuracy.

The current study examined the longitudinal association between STLEs and ARV adherence, measured monthly by pill counts, among adults in the Southeastern USA with HIV and depression. Unannounced, telephone-based pill counts have been shown to provide valid, accurate measures of adherence (Kalichman et al., 2007), and are more sensitive than self-report to adherence changes over time (Lee et al., 2007). Pill counts may, therefore, allow for a more accurate assessment of the relationship between STLEs and ARV adherence. Likewise, recent STLEs may be more strongly related to current ARV adherence than STLEs measured over longer recall periods. We hypothesized that higher numbers and severity of STLEs would be associated with poorer ARV adherence, and that improved measurements of both STLEs and adherence would yield stronger associations than those found in prior studies.

Methods

Study sample

Data for this study came from the *Strategies to Link Antidepressant and Antiretroviral Management at Duke University, the University of Alabama-Birmingham, Northern Outreach Clinic (Henderson, NC), and the University of North Carolina-Chapel Hill* (SLAM DUNC) Study, a randomized, controlled trial testing the effect of evidence-based decision support for depression treatment on ARV adherence, which has been described previously (Pence, Gaynes, et al., 2012). The study population comprises adult (age 18–65 years) HIV-infected patients with depression attending infectious disease clinics at the study sites. Participants enrolled between 1 July 2011 and 30 September 2013 were eligible for the current analysis; data on STLEs were collected during this period. Participants were followed for up to one year following enrollment, receiving up to 12 monthly pill count calls. The number of calls completed depended on attrition and timing of enrollment relevant to collection of STLE data and the end of the study. Study procedures were approved by the Institutional Review Boards at the University of North Carolina at Chapel Hill, Duke University, and the University of Alabama at Birmingham.

Measures

Stressful and traumatic life events

STLEs were assessed during monthly telephone calls with participants using the Life Events Survey (LES) (Leserman et al., 2008; Sarason, Johnson, & Siegel, 1978), modified to include those events considered moderately or severely stressful or traumatic based on prior research (Leserman et al., 2002, 2005). Participants were asked whether they had experienced any of 46 events, from within nine categories, during the prior month. STLE categories were: (1) romantic relationship changes; (2) estrangement from family; (3) death or serious illness of family member or close friend; (4) major illness, injury, or hospitalization; (5) employment difficulties; (6) financial difficulties; (7) legal difficulties; (8) life transitions; and (9) safety concerns (e.g., physical attacks, feeling unsafe). The total number of STLEs reported at each time point (monthly) was summed for each participant and coded discretely. The exposure was also dichotomized, to indicate experiencing at least the study population median number of STLEs vs. less than the median number, during the month prior. Additionally, the most potentially severe STLEs (divorce/separation, death/illness of immediate family member, major financial problems, time in jail, and sexual and/or physical assault) were combined, based on prior work (Mugavero et al., 2009), to create a second discretely-coded variable. The severe-only total was dichotomized to indicate one or more severe STLEs vs. zero during the past month.

Antiretroviral adherence

ARV adherence was measured by monthly, unannounced, telephone-based pill counts and recorded as a continuous percentage. Adherence was calculated as the observed

number of pills taken since the last count divided by the expected number of pills taken since the last count. The observed number of pills taken was the number of pills present at the current count, subtracted from the number present during the previous count, after accounting for pills gained (e.g., dispensed) and lost (e.g., thrown away) in the interim. The expected number of pills taken was the prescribed daily number of pills, multiplied by the number of days since the previous count. Both the observed and expected number of pills were summed across all ARV medications prior to dividing. Values of adherence <0% ($n = 20$) or >200% ($n = 1$) were discarded as outside the range of plausibility.

Secondary analyses explored (1) dichotomous coding of "adequate" (≥95%) vs. "inadequate" (<95%) adherence (Lima et al., 2009, 2008), and (2) differences between pill count-based and self-reported adherence. Self-reported adherence was measured at baseline (in-person) and every three months thereafter (by telephone) during structured research interviews, with the following questions: (1) "Over the past month, how much of the time have you taken all of your HIV/AIDS medications?" and (2) "Over the past month, how much of the time have you missed or skipped taking your HIV/AIDS medications?" Responses, ranging from 0%to 100%, were averaged (after reverse-coding the second question) to get a measure ranging from 0% to 100%. As self-reported adherence was measured every three months, while STLEs were measured every month, the average number of STLEs was calculated for each three-month time period. Self-reported adherence was also dichotomized at 95%, as above.

Additional covariates

Covariates used in the analysis were sex, age, depressive severity, HIV care self-efficacy, stress coping style, HIV-related physical symptoms, HIV status disclosure, employment status, and drug and/or alcohol abuse. Sex and age were assessed at study enrollment. Depressive severity, HIV care self-efficacy, stress coping style, HIV-related physical symptoms, HIV status disclosure, and employment status were measured at enrollment and every three months thereafter. Depressive severity was measured with the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960, 1980; Zimmerman, Chelminski, & Posternak, 2004), and coded discreetly (range: 0–50) (Hamilton, 1960). HIV-related self-efficacy was measured using the managing depression/mood, managing symptoms, communicating with health care provider, getting support/help, and managing fatigue subscales of the HIV Self-Efficacy questionnaire (Shively, Smith, Bormann, & Gifford, 2002). Stress coping style was assessed with the Brief COPE instrument (Carver, 1997; Carver, Scheier, & Weintraub, 1989), and physical symptoms were measured using the HIV Symptom Inventory (Bing et al., 2001). Disclosure of HIV status to (1) close friends/family and (2) everyday acquaintances was measured separately with four-point Likert scales ("All," "Most," "Some," or "None") and was included as ordinal variables. Employment was dichotomized to indicate employed vs. not. Any abuse or dependence of drugs and/or alcohol was assessed at enrollment and at six- and twelve-month follow-up interviews with the alcohol/substance dependence and abuse sections of the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997).

Statistical analysis

The main exposure-outcome association was assessed using a linear model with robust variance to account for repeated observations on participants, yielding an estimate of the mean difference in past-month percent adherence. To address missing covariate values among completed contacts, multiple imputation by chained equations (MICE) was employed for all variables included in the analysis (White, Royston, & Wood, 2011). Ten cycles of imputation were carried out per imputed dataset; 50 datasets were imputed and analyzed. To address potential selection bias arising from uncompleted contacts, inverse probability of observation weights (IPOWs) were calculated for the inverse probability of completing a given contact conditional on predictors of contact completion, using a logistic model (Moodie, Delaney, Lefebvre, & Platt, 2008; Seaman, White, Copas, & Li, 2012). Baseline and time-updated variables found to be statistically significantly associated (at alpha = 0.05) with completion in bivariable analyses were included in the model. The IPOWs were stabilized by the marginal probability of contact completion and used to weight the final exposure-outcome model.

In analyses with dichotomous coding of the ARV adherence outcome, a Poisson model with robust variance was used instead of a linear model (and in place of a log-binomial model due to model convergence issues (Yelland, Salter, & Ryan, 2011)), to yield an estimate of the risk ratio (RR) for ≥95% adherence. All other analyses followed the approach described above.

Results

Study population

Two-hundred eighty-nine participants enrolled in the SLAM DUNC study while STLEs were being measured. The majority of the study sample (71%) was male, black (63%), non-Hispanic (96%), and single (78%). The median

Table 1. Study sample characteristics, Southeastern USA, 2010–2013 ($n = 289$).

Variable	*n* (%)	Median (IQR)	Missing
Sex			0
Male	205 (71)		
Female	84 (29)		
Age		45 (38–51)	0
Marital status			2
Married/cohabitating	62 (21)		
Single	225 (78)		
Race			0
White	94 (33)		
Black	181 (63)		
Other	14 (5)		
Ethnicity			0
Hispanic	13 (4)		
Non-Hispanic	276 (96)		
Education			3
Less than HS grad	40 (14)		
High school grad	110 (38)		
More than high school	136 (47)		
Monthly household income ($)		1000 (674–1752)	18
Log-10 income ($)		3 (2.83–3.24)	
Currently employed	76 (26)		3
Years since HIV diagnosis		11 (4–17)	11
Baseline log10-viral load		1.67 (1.59–2.31)	11
Baseline viral load 50+	90 (32)		
Baseline CD4 count		539 (326–789)	14
Baseline depression score		21 (15–25)	36
Baseline self-reported adherence		98 (85–100)	26

(interquartile range [IQR]) age was 45 (38–51), and participants reported contracting HIV, on average, 11 years prior to study enrollment. Eighty-five percent of participants had at least a high school-level education and 26% were employed at enrollment. Self-reported past-month ARV adherence was high at enrollment, with a median (IQR) of 98% (85–100%) adherence (Table 1).

Participants completed, on average, five monthly telephone interviews (IQR: 1–8); the number of interviews completed ranged from zero to 12. Of the total possible 2634 monthly interviews, 1412 (54%) were completed and included in analyses. Among completed contacts, 3373 STLEs were reported, for a mean of 2.48 events per month; the number of STLEs experienced in a month ranged from 0 to 14, and the median (IQR) was 2 (1–4). Six hundred seventy-eight severe STLEs were reported, or 0.50 events per month. Financial difficulties were most commonly reported, with 1.24 events/month, followed by illness/injury/hospitalization of the participant (0.31 events/months) and death/serious illness of family member/friend (0.25 events/month). Legal troubles were reported least often (0.04 events/month) (Table 2). Across all contacts, pill count-measured median (IQR) ARV adherence was 96% (83%–100%).

Missing data

Among completed contacts, multiple imputation was used to impute missing baseline values for 0.4% of employment data, 4% viral load, 5% CD4 count, 2% self-efficacy, and 0.5% SF12 mental functioning score. There was more substantial missing data for post-baseline variables. Pill count-measured ARV adherence was imputed in 15% of observations, employment status in 14%, and HIV status disclosure in 74%. For drug/alcohol abuse, coping style, self-efficacy, and HIV symptoms, values were imputed in 11% of observations.

In calculating the IPOWs, baseline predictors of completing interviews that were statistically significant at alpha = 0.05 were age, employment, viral load, CD4 count, self-efficacy, and SF12 mental functioning score. A time-updated variable indicating whether the previous month's pill count was completed was also included in the weighting model. The IPOWs had a mean (standard deviation) of 1.06 (0.50), and ranged from 0.58 to 5.35. These weights were applied to the 1412 completed observations, to account for the 46% of contacts that were not completed.

Table 2. Description of STLEs, Southeastern USA, 2010–2013 ($n = 289$).

	Incidence	
	Per person-month	Per person-year
Total # STLEs	2.48	29.76
Financial difficulties	1.24	14.88
Major illness, injury, or hospitalization	0.31	3.72
Death/illness of family member/friend	0.25	3.00
Employment difficulties	0.24	2.88
Safety concerns	0.12	1.44
Romantic relationship changes	0.11	1.32
Estrangement from family	0.10	1.20
Life transitions	0.08	0.96
Legal difficulties	0.04	0.48
Total # severe STLEs[a]	0.50	6.00

Note: STLEs = Stressful and traumatic life events.
[a]Includes: divorce/separation, death/illness of immediate family member, major financial problems, time in jail, and sexual and physical assault.

Primary outcomes

A greater number of past-month STLEs was associated with poorer past-month ARV adherence, after adjusting for confounding by drug/alcohol abuse, coping style, self-efficacy, employment, HIV symptoms, age, gender, and HIV status disclosure. One additional STLE experienced was associated with a mean difference (95% confidence interval (CI)) in ARV adherence of −0.99% (−1.89%, −0.09%), indicating that for each additional STLE, mean adherence decreased by nearly one percentage point (Table 3). A stronger association was observed when comparing participants with at least the median number of STLEs (2) to those with less than the median (mean difference = −3.67%, 95% CI = −7.12%, −0.21%). When limited to the most potentially severe STLEs, each

Table 3. Associations between STLEs and ARV adherence, pill count-based and self-reported, Southeastern USA, 2010–2013.

	Pill count-based adherence		Self-reported adherence	
	Mean % adherence difference (95% CI)	Adherence ≥95% RR (95% CI)	Mean % adherence difference (95% CI)	Adherence ≥95% RR (95% CI)
All STLEs				
Per 1-unit increase in number	−0.99% (−1.89%, −0.09%)	0.95 (0.90, 0.99)	−0.63% (−1.61%, 0.35%)	0.98 (0.94, 1.02)
≥2 vs. <2[a]	−3.67% (−7.12%, −0.21%)	0.82 (0.71, 0.95)	−1.63% (−5.16%, 1.91%)	0.91 (0.79, 1.05)
Severe STLEs				
Per 1-unit increase in number	−2.43% (−5.16%, 0.30%)	0.84 (0.74, 0.96)	−1.99% (−5.50%, 1.52%)	0.89 (0.77, 1.04)
Any vs. none	−3.03% (−6.41%, 0.35%)	0.80 (0.69, 0.94)	−3.45 (−6.33, −0.58)	0.84 (0.74, 0.96)

Note: STLEs = Stressful and traumatic life events; ARV = antiretroviral; RR = risk ratio; CI = confidence interval.
[a]2 = population median monthly number of STLEs.

additional event was associated with a more extreme mean difference of −2.43%; however, the 95% CI (−5.16%, 0.30%) spanned the null value of no difference. Experiencing any severe STLE vs. none was associated with a mean adherence difference (95% CI) of −3.03% (−6.41%, 0.35%). While these associations were modest in magnitude, they were relatively precisely estimated.

Secondary outcomes

When adherence was dichotomized, each additional past-month STLE was associated with decreased likelihood of ≥95% adherence in the past month, both overall (risk ratio (RR) = 0.95, 95% CI = 0.90, 0.99) and for severe STLEs (RR = 0.84, 95% CI = 0.74, 0.96). The decreases in likelihood of adherence were more marked for participants experiencing at least the median number vs. less than the median number of overall STLEs (RR = 0.82, 95% CI = 0.71, 0.95) and any severe STLE vs. none (RR = 0.80, 95% CI = 0.69, 0.94) (Table 3). The crude proportion of observations in which ≥95% adherence was achieved decreased with increasing number of STLEs (zero, one, two or more), both for overall and severe STLEs (Figure 1).

Estimates of association between STLEs and self-reported ARV adherence were similar in direction and precision but attenuated compared to pill count-measured adherence (Table 3). All estimates using self-reported adherence were closer to the null than the estimates obtained using pill count-based adherence, except that of the mean difference in ARV adherence when comparing any severe STLE vs. none.

Discussion

In our study population, representing HIV-infected patients with depression in the Southeastern USA, a higher number of STLEs was associated with poorer ARV adherence, and in particular, lower likelihood of achieving or maintaining ≥95% adherence. Participants experiencing at least the median number of STLEs in a given month had 18% lower likelihood of ≥95% adherence in that same month, compared to those experiencing less than the median number. The association between STLEs and reduced adherence was similar when limited to the most severe STLEs.

STLEs were common, with participants reporting, on average, more than two events per month during follow-up of up to 12 months; number of events reported per month ranged from zero to 14 (median (IQR): 2

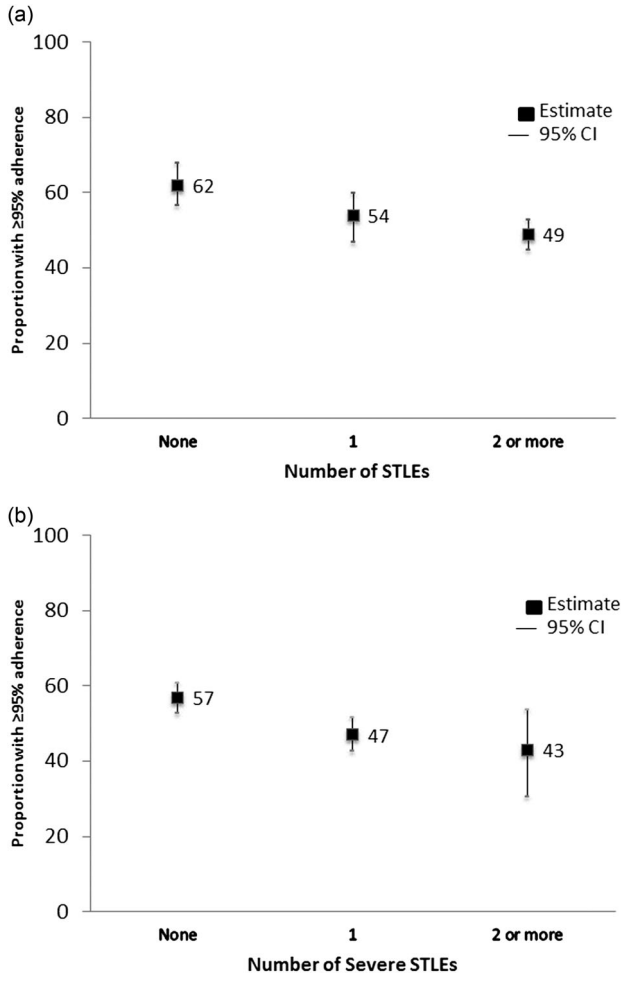

Figure 1. (a) Proportion with ≥95% ARV Adherence by Number of STLEs, Southeastern USA, 2010–2013. ARV = antiretroviral, STLE = stressful or traumatic life event. (b) Proportion with ≥95% ARV adherence by number of severe STLEs. ARV = antiretroviral, STLE = stressful or traumatic life event.

(1–4)). This high burden of STLEs, similar to that found in other studies (Leserman et al., 2008; Mugavero et al., 2009), emphasizes their potential impact on ARV adherence. The relatively modest difference in mean adherence of roughly 1% associated with one additional STLE implies that an individual experiencing ten STLEs in a given month could be expected to have 10% lower adherence than an individual experiencing no STLEs. Also, each additional STLE was associated with a 5% reduction in the likelihood of ≥95% adherence, and each additional severe STLE was associated with a 16% reduction. These results suggest that while the impact of STLEs on continuously measured adherence may be modest, it may be sufficient to reduce adherence below a critical threshold required for regimen effectiveness and prevention of resistance (Lima et al., 2009, 2008). The mean differences in adherence and the reductions in likelihood of ≥95% adherence were even more pronounced when comparing at least the median number of STLEs to less than the median, or any severe STLE vs. none.

Our results add to the existing evidence that ongoing STLEs may interfere with ARV adherence among PLWHA. Prior studies have demonstrated this association, but have exclusively used self-report to measure adherence, and long recall periods for STLEs (Leserman et al., 2008; Mugavero et al., 2009). This is the first study showing the association between STLEs measured monthly over time and pill count-based ARV adherence. Pill counts have been shown to be more sensitive to changes in adherence over time than self-reported measures (Lee et al., 2007), and the measurement of both STLEs and adherence at the same point in time over short recall periods allowed us to capture more proximal associations of STLEs with adherence.

We found an attenuation of estimates of association when ARV adherence was measured by self-report, compared to pill counts. This might be due in part to reduced variability of the measurement, as self-reported adherence tends to be skewed upwards; however, it is likely also due to the improved accuracy of using the more objective measure of unnannounced pill counts. Telephone-based pill counts have been shown to be as accurate as researcher-performed pill counts (Kalichman et al., 2007).

Previous studies have also used dichotomous outcomes to indicate adherent vs. non-adherent, based on report of missing ARV doses. The 5% reduction in risk of ≥95% adherence in our study is lower than both the 10% increase in non-adherence (OR = 1.10, 95% CI = 1.04, 1.16) in one study assessing missed doses over the past seven days (Mugavero et al., 2009), and the 36% increase in non-adherence (OR = 1.36, 95% CI = 1.13, 1.63) in a study using missed doses in the prior two weeks as the outcome (Leserman et al., 2008). The use of risk ratios instead of odds ratios in those studies may account for some of the difference. In our study there was an 11% reduction in odds of ≥95% adherence (data not shown). Our continuous pill count measure allowed us to additionally assess differences in adherence not tied to a somewhat arbitrary adherent/non-adherent cut-point.

Strengths of this study include the continuous pill count measure of adherence, monthly assessments of both adherence and STLEs, and the availability of a comprehensive set of potential confounders for inclusion in multivariable models. One important limitation was the low retention rate during follow-up and the resulting large amount of missing data. Rather than conduct a complete-case analysis, we used a combination of multiple imputation and inverse probability of observation weighting, based on observed predictors of missingness, to address the potential for selection bias arising from these missing data. We cannot exclude the possibility, however, that missingness could also be a function of unobserved characteristics, and in particular could be associated both with higher numbers of STLEs and with lower adherence. If this were the case, the present analysis would likely have underestimated the actual association of STLEs with poor adherence, but overestimation is possible as well. There is also the possibility of misspecification of the weighting model, the imputation model, or both.

Interventions should be targeted to increase provider awareness of STLEs, and to improve patient coping skills to mitigate negative effects of STLEs, in order to improve ARV adherence. One study found that participants receiving a quality-improvement intervention, aimed at increasing the proportion of patients receiving appropriate depression treatment, experienced fewer STLEs than those in usual care (Sherbourne et al., 2008). Other studies found that expressive writing about STLEs being experienced was associated with greater cognitive engagement, fewer days of activity restriction, and improved health status (Andersson & Conley, 2013; Smyth, Stone, Hurewitz, & Kaell, 1999). Other such interventions, focused on reducing the incidence of and/or developing skills to cope with STLEs, could be developed and potentially integrated with direct ARV adherence support strategies.

STLEs are common and potentially impactful, especially among persons managing both medical and mental health diagnoses. While some STLEs are unavoidable (e.g., death/illness), others (e.g., relationship problems, employment issues) might be mitigated through management of depressive symptoms and/or

working with outside help, such as a social worker. In either case, raising awareness of the frequency and impact of STLEs among HIV providers, and developing interventions to prevent or alleviate their negative impacts could help in maximizing the clinical benefits of HIV treatment.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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References

Andersson, M. A., & Conley, C. S. (2013). Optimizing the perceived benefits and health outcomes of writing about traumatic life events. *Stress and Health*, *29*(1), 40–49. doi:10.1002/smi.2423

Bangsberg, D. R. (2006). Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clinical Infectious Diseases*, *43*(7), 939–941. doi:10.1086/507526

Bangsberg, D. R., Moss, A. R., & Deeks, S. G. (2004). Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *Journal of Antimicrobial Chemotherapy*, *53*(5), 696–699. doi:10.1093/jac/dkh162

Bing, E. G., Burnam, A., Longshore, D., Fleishman, J. A., Sherbourne, C. D., London, A. S., … Shapiro, M. (2001). Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*, *58*(8), 721–728. doi:10.1001/archpsyc.58.8.721

Burack, J. H., Barrett, D. C., Stall, R. D., Chesney, M. A., Ekstrand, M. L., & Coates, T. J. (1993). Depressive symptoms and CD4 lymphocyte decline among HIV-infected men. *JAMA-The Journal of the American Medical Association*, *270*(21), 2568–2573.

Carver, C. S. (1997). You want to measure coping but your protocol's too long: Consider the brief COPE. *International Journal of Behavioral Medicine*, *4*(1), 92–100. doi:10.1207/s15327558ijbm0401_6

Carver, C. S., Scheier, M. F., & Weintraub, J. K. (1989). Assessing coping strategies: A theoretically based approach. *Journal of Personality and Social Psychology*, *56*(2), 267–283.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*, *23*, 56–62.

Hamilton, M. (1980). Rating depressive patients. *The Journal of Clinical Psychiatry*, *41*(12 Pt 2), 21–24.

Ickovics, J. R., Hamburger, M. E., Vlahov, D., Schoenbaum, E. E., Schuman, P., Boland, R. J., & Moore, J. (2001). Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: Longitudinal analysis from the HIV epidemiology research study. *JAMA-The Journal of the American Medical Association*, *285*(11), 1466–1474.

Kalichman, S. C., Amaral, C. M., Stearns, H., White, D., Flanagan, J., Pope, H., … Kalichman, M. O. (2007). Adherence to antiretroviral therapy assessed by unannounced pill counts conducted by telephone. *Journal of General Internal Medicine*, *22*(7), 1003–1006. doi:10.1007/s11606-007-0171-y

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., … National Comorbidity Survey, R. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA-The Journal of the American Medical Association*, *289*(23), 3095–3105. doi:10.1001/jama.289.23.3095

Kilbourne, A. M., Justice, A. C., Rabeneck, L., Rodriguez-Barradas, M., & Weissman, S. (2001). General medical and psychiatric comorbidity among HIV-infected veterans in the post-HAART era. *Journal of Clinical Epidemiology*, *54*(Suppl. 1), S22–S28.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H., … Dunbar, G. C. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry*, *12*(5), 224–231. doi:10.1016/S0924-9338(97)83296-8

Lee, J. K., Grace, K. A., Foster, T. G., Crawley, M. J., Erowele, G. I., Sun, H. J., … Taylor, A. J. (2007). How should we measure medication adherence in clinical trials and practice? *Ther Clin Risk Manag*, *3*(4), 685–690.

Leserman, J., Ironson, G., O'Cleirigh, C., Fordiani, J. M., & Balbin, E. (2008). Stressful life events and adherence in HIV. *AIDS Patient Care and STDs*, *22*(5), 403–411. doi:10.1089/apc.2007.0175

Leserman, J., Pence, B. W., Whetten, K., Mugavero, M. J., Thielman, N. M., Swartz, M. S., & Stangl, D. (2007). Relation of lifetime trauma and depressive symptoms to mortality in HIV. *American Journal of Psychiatry*, *164*(11), 1707–1713. doi:10.1176/appi.ajp.2007.06111775

Leserman, J., Petitto, J. M., Gu, H., Gaynes, B. N., Barroso, J., Golden, R. N., … Evans, D. L. (2002). Progression to AIDS, a clinical AIDS condition and mortality: Psychosocial and physiological predictors. *Psychological Medicine*, *32*(6), 1059–1073.

Leserman, J., Whetten, K., Lowe, K., Stangl, D., Swartz, M. S., & Thielman, N. M. (2005). How trauma, recent stressful events, and PTSD affect functional health status and health utilization in HIV-infected patients in the south. *Psychosomatic Medicine*, *67*(3), 500–507. doi:10.1097/01.psy.0000160459.78182.d9

Lima, V. D., Harrigan, R., Bangsberg, D. R., Hogg, R. S., Gross, R., Yip, B., & Montaner, J. S. (2009). The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*, *50*(5), 529–536. doi:10.1097/QAI.0b013e31819675e9

Lima, V. D., Harrigan, R., Murray, M., Moore, D. M., Wood, E., Hogg, R. S., & Montaner, J. S. (2008). Differential impact of adherence on long-term treatment response among naive HIV-infected individuals. *AIDS*, *22*(17), 2371–2380. doi:10.1097/QAD.0b013e328315cdd3

Lyketsos, C. G., Hoover, D. R., Guccione, M., Senterfitt, W., Dew, M. A., Wesch, J., … Morgenstern, H. (1993). Depressive symptoms as predictors of medical outcomes in HIV infection. Multicenter AIDS Cohort Study. *JAMA: The Journal of the American Medical Association*, *270*(21), 2563–2567.

Lyketsos, C. G., Hutton, H., Fishman, M., Schwartz, J., & Treisman, G. J. (1996). Psychiatric morbidity on entry to an HIV primary care clinic. *AIDS*, *10*(9), 1033–1039.

Maggiolo, F., Airoldi, M., Kleinloog, H. D., Callegaro, A., Ravasio, V., Arici, C., … Suter, F. (2007). Effect of adherence to HAART on virologic outcome and on the selection of resistance-conferring mutations in NNRTI- or PI-treated patients. *HIV Clinical Trials*, *8*(5), 282–292. doi:10.1310/hct0805-282

Moodie, E. E., Delaney, J. A., Lefebvre, G., & Platt, R. W. (2008). Missing confounding data in marginal structural models: A comparison of inverse probability weighting and multiple imputation. *The International Journal of Biostatistics*, *4*(1), Article 13.

Mugavero, M. J., Raper, J. L., Reif, S., Whetten, K., Leserman, J., Thielman, N. M., & Pence, B. W. (2009). Overload: impact of incident stressful events on antiretroviral medication adherence and virologic failure in a longitudinal, multisite human immunodeficiency virus cohort study. *Psychosomatic Medicine*, *71*(9), 920–926. doi:10.1097/PSY.0b013e3181bfe8d2

Pence, B. W., Gaynes, B. N., Williams, Q., Modi, R., Adams, J., Quinlivan, E. B., … Mugavero, M. J. (2012). Assessing the effect of measurement-based care depression treatment on HIV medication adherence and health outcomes: Rationale and design of the SLAM DUNC Study. *Contemporary Clinical Trials*, *33*(4), 828–838. doi:10.1016/j.cct.2012.04.002

Pence, B. W., Mugavero, M. J., Carter, T. J., Leserman, J., Thielman, N. M., Raper, J. L., … Whetten, K. (2012). Childhood trauma and health outcomes in HIV-infected patients: An exploration of causal pathways. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*, *59*(4), 409–416. doi:10.1097/QAI.0b013e31824150bb

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1978). Assessing the impact of life changes: Development of the life experiences survey. *Journal of Consulting and Clinical Psychology*, *46*(5), 932–946.

Seaman, S. R., White, I. R., Copas, A. J., & Li, L. (2012). Combining multiple imputation and inverse-probability weighting. *Biometrics*, *68*(1), 129–137. doi:10.1111/j.1541-0420.2011.01666.x

Sherbourne, C. D., Edelen, M. O., Zhou, A., Bird, C., Duan, N., & Wells, K. B. (2008). How a therapy-based quality improvement intervention for depression affected life events and psychological well-being over time: A 9-year longitudinal analysis. *Medical Care*, *46*(1), 78–84. doi:10.1097/MLR.0b013e318148478d

Shively, M., Smith, T. L., Bormann, J., & Gifford, A. L. (2002). Evaluating self-efficacy for HIV disease management skills. *AIDS and Behavior*, *6*(4), 371–379.

Shuter, J., Sarlo, J. A., Kanmaz, T. J., Rode, R. A., & Zingman, B. S. (2007). HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*, *45*(1), 4–8. doi:10.1097/QAI.0b013e318050d8c2

Smyth, J. M., Stone, A. A., Hurewitz, A., & Kaell, A. (1999). Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis: A randomized trial. *JAMA-The Journal of the American Medical Association*, *281*(14), 1304–1309.

Whetten, K., Leserman, J., Lowe, K., Stangl, D., Thielman, N., Swartz, M., … Van Scoyoc, L. (2006). Prevalence of childhood sexual abuse and physical trauma in an HIV-positive sample from the deep South. *American Journal of Public Health*, *96*(6), 1028–1030. doi:10.2105/AJPH.2005.063263

White, I. R., Royston, P., & Wood, A. M. (2011). Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine*, *30*(4), 377–399. doi:10.1002/sim.4067

Wong, C. F., Kipke, M. D., Weiss, G., & McDavitt, B. (2010). The impact of recent stressful experiences on HIV-risk related behaviors. *Journal of Adolescence*, *33*(3), 463–475. doi:10.1016/j.adolescence.2009.06.004

Wong, M. D., Sarkisian, C. A., Davis, C., Kinsler, J., & Cunningham, W. E. (2007). The association between life chaos, health care use, and health status among HIV-infected persons. *Journal of General Internal Medicine*, *22*(9), 1286–1291. doi:10.1007/s11606-007-0265-6

Yelland, L. N., Salter, A. B., & Ryan, P. (2011). Performance of the modified poisson regression approach for estimating relative risks from clustered prospective data. *American Journal of Epidemiology*, *174*(8), 984–992. doi:10.1093/aje/kwr183

Zimmerman, M., Chelminski, I., & Posternak, M. (2004). A review of studies of the Hamilton depression rating scale in healthy controls: Implications for the definition of remission in treatment studies of depression. *The Journal of Nervous and Mental Disease*, *192*(9), 595–601.