PSYCHOLOGICAL AND BEHAVIORAL OUTCOMES ASSOCIATED WITH STRESSFUL OR TRAUMATIC LIFE EVENTS AMONG HIV-INFECTED PERSONS WITH DEPRESSION

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ABSTRACT

Julie K. O’Donnell: Psychological and behavioral outcomes associated with stressful or traumatic life events among HIV-infected persons with depression
(Under the direction of Brian W. Pence)

Stressful or traumatic life events (STLEs) are common among HIV-infected individuals (particularly individuals who also have depression) and may affect both behavioral outcomes such as adherence to antiretroviral (ARV) therapy, and psychological outcomes such as suicidal ideation. The associations between 1) STLEs and ARV adherence, and 2) STLEs and suicidal ideation were examined among 289 US-based participants active in the SLAM DUNC study between 7/1/2011 and 9/1/2013, a randomized controlled trial of the effect of evidence-based decision support for depression treatment on ARV adherence. Participants received monthly telephone calls to assess STLEs and pill count-based ARV adherence, and three-monthly telephone calls to assess suicidal ideation, for up to 12 months. 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. In Aim 1, 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 (prevalence ratio (PR) (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.

Participants assessed in Aim 2 experienced a mean of 2.36 overall STLEs (range: 0-12) in the previous month. Every additional STLE was associated with an increase in suicidal ideation prevalence of 22% (PR (95% confidence interval (CI)): 1.22 (1.01, 1.48)), and every additional severe STLE with an increase in prevalence of 70% (PR (95% CI): 1.70 (1.01, 2.87)). STLEs were associated with increased prevalence of experiencing SI, which is an important risk factor for suicide attempts and completions. STLEs were common in this population of HIV-infected adults with depression, and they were associated with negative behavioral and psychological outcomes.
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CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

Persons living with HIV/AIDS (PLWHA) face a number of challenges related to their infection, including but not limited to life-long use of antiretroviral (ARV) medications, HIV-related stigma, and opportunistic infections. Depression is also very common, affecting upwards of 20% of PLWHA, in comparison to 12-13% of the general population. More attention has been paid recently to stressful or traumatic life events (STLEs) among PLWHA, which are common in this population, and may have important implications for various psychological and behavioral outcomes. STLEs include moderately and severely stressful events such as death or illness of family or friends; difficulties with relationships, finances, or employment; legal trouble; threats to personal and/or home safety; and housing instability, as well as more traumatic events such as physical or sexual assault. Both types of events are experienced more often by PLWHA than by the general population, in part due to the overlap of HIV infection and economic and other disadvantages that are often related to such events.

STLEs may negatively impact both psychological and behavioral outcomes among individuals with HIV and depression. STLEs can disrupt routines such as medication adherence. The association between STLEs and poor ARV adherence has been investigated, however, studies have exclusively used self-reported ARV adherence, which may be subject to misclassification due to poor recall and social desirability bias. Unannounced, telephone-based pill counts have been shown to provide valid, accurate measures of adherence, and thus may allow for a more accurate assessment of the relationship between adherence and STLEs. In terms of psychological outcomes, suicide is the most severe complication of depression, and suicidal ideation (SI) is highly prevalent among HIV-infected persons with depression. Depression and SI are also more prevalent among persons with chronic
diseases, such as HIV, than among the general population.\textsuperscript{1,5,13,14} In a population of individuals with both depression and HIV, therefore, SI can be a major concern, and quantifying its association with STLEs would be informative for targeted interventions aimed at preventing completed and attempted suicide.

The overall goal of this research was to examine the association between STLEs and a behavioral and a psychological outcome among persons with both HIV infection and depression. Data from the Strategies to Link Antidepressant and Antiretroviral Management at Duke, UAB, NOC, and UNC (SLAM DUNC) Study, a multi-site randomized controlled trial of a depression management intervention for HIV patients, was used to look specifically at the longitudinal association between STLEs and (1) antiretroviral adherence and (2) suicidal ideation. The central hypotheses were that STLEs would be positively associated with: (1) poor ARV adherence and (2) suicidal ideation. Specifically, the following aims were addressed:

**Aim 1: Assess the association between STLEs and ARV adherence, measured using telephone-based pill counts, among PLWHA with depression.**

*Rationale:* Previous studies have investigated the association between STLEs and poor self-reported ARV adherence, but most have used cross-sectional information or long recall periods for both stressful events and adherence, and no studies have used pill count data to measure adherence.

*Hypothesis:* Increasing number and severity of STLEs would be positively associated with poorer ARV adherence.

*Secondary analysis:* Compared results obtained using telephone-based pill counts and self-report to measure adherence, as a sensitivity analysis.
Aim 2: Examine the association between STLEs and SI among PLWHA with depression.

Rationale: This association has not been studied extensively, especially in this population, and given the prevalence of both STLEs and SI, the results could provide important information for providers hoping to intervene on predictors of suicide.

Hypothesis: Increasing number and severity of STLEs would be positively associated with SI.

Secondary analyses: Assessed modification of the association between STLEs and suicidal ideation by a priori identified potential modifiers, including stress coping style and self-efficacy.
CHAPTER 2: BACKGROUND AND SIGNIFICANCE

Background

Stressful or traumatic life events (STLEs) are common among persons living with HIV/AIDS (PLWHA), and present challenges for their care and treatment.\textsuperscript{7-9,15} Childhood and lifetime trauma, abuse, and stress,\textsuperscript{7,16} as well as ongoing traumatic and stressful experiences and life chaos,\textsuperscript{8,9,15} are commonly reported among PLWHA and are associated with negative HIV-related clinical and behavioral outcomes. STLEs include moderately and severely stressful and traumatic events such as death or illness of family or friends; difficulties with relationships, finances, or employment; legal trouble; threats to personal and/or home safety; housing instability; and physical and sexual assault. Both types of events are experienced more often by PLWHA than by the general population, in part due to the overlap of HIV infection and economic and other disadvantages that are often related to such events.\textsuperscript{9}

Studies have described the high burden of stressful and traumatic life events experienced by PLWHA. Data from the Coping with HIV/AIDS in the Southeast (CHASE) Study has been used in several analyses to assess the frequency of these events and their association with adverse outcomes. In this study, both lifetime history and incidence of moderately and severely stressful events, as well as more traumatic events, were fairly common. More than half of the participants had experienced some form of sexual or severe physical abuse in their lifetime; 30% experienced such abuse before the age of 13.\textsuperscript{7} In the same sample, during 27 months of follow-up, participants reported medians of nine incident stressful events and three incident severely stressful events; incident stressful events were associated with both antiretroviral (ARV) non-adherence and virologic failure.\textsuperscript{9} Also in the CHASE sample, participants experienced medians of three lifetime traumatic events and three recent stressful events.\textsuperscript{16}
Finally, 91% of CHASE participants reported experiencing at least one incident stressful event over a nine-month period and 61% reported experiencing at least one incident severely stressful event; it was predicted that 100% and 97% of participants would experience at least one incident stressful and severely stressful event, respectively, during three years of follow-up.\textsuperscript{15} A secondary, cross-sectional analysis of data from a randomized trial found HIV-infected participants at 13 clinical sites throughout the US experienced a mean of 5.6 STLEs per month; financial problems were the most common STLEs, followed by unemployment.\textsuperscript{17} A small, cross-sectional study of 105 HIV-infected men and women in a southern US state found that participants had experienced a mean of 3.15 STLEs in the prior six months.\textsuperscript{10}

The experience of moderate to severe STLEs is associated with negative outcomes. In the CHASE study, increasing numbers specifically of traumatic events were associated with increased mortality rates.\textsuperscript{16} Associations between STLEs and other negative clinical and behavioral outcomes, such as decreased ARV adherence, virologic failure, and increased risky sexual behavior, have been identified among PLWHA.\textsuperscript{18,19} A different study, of HIV-uninfected young men who have sex with men, found that increased risk of substance use was associated with recent financial and health-related stressful events, and sexual risk-taking was associated with recent health- and partner-related stressors.\textsuperscript{20}

A health-related behavior that is critical for HIV-related outcomes among PLWHA is adherence to ARV medications. Highly active ARV therapy was introduced in 1996 and has been effective in lowering – and suppressing, as the ultimate goal – viral load, and in reducing morbidity and mortality among PLWHA.\textsuperscript{21-25} ARV treatment may fail, however, resulting in elevated viral load and poor clinical outcomes. Inadequate ARV adherence can lead to drug resistance and treatment failure.\textsuperscript{26-28} For many years, ≥95% adherence was believed necessary for viral load suppression and prevention of drug resistance.\textsuperscript{23} This threshold, however, was defined early in the era of highly active ARVs, when unboosted protease inhibitor (PI)-based regimens were the most common. More recent evidence with the
current boosted PI and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens suggest that virologic suppression can be reliably sustained at lower adherence levels,\textsuperscript{29,30} and that the adherence-virologic suppression relationship is monotonic, especially for NNRTI-based regimens.\textsuperscript{27,31}Regardless of the definition of “adequate” adherence, however, it is clear that high ARV adherence is necessary to achieve viral suppression, maintain health, and avoid developing drug resistance.\textsuperscript{27,29-31}

As ARV treatment is initiated earlier in the course of infection, and life expectancies for PLWHA increase, people are taking ARVs for longer periods of time; it is therefore increasingly important to understand barriers to long-term adherence. For many years, initiation of treatment was determined by clinical indicators; CD4 count has been the most commonly-used indicator.

Recommendations have been to initiate ARV therapy at CD4 counts ranging from ≤200 cells/mm\(^3\) in 2006 to ≤350 cells/mm\(^3\) in 2010, for example.\textsuperscript{32} More recently, however, even earlier initiation of ARVs has been shown to reduce sexual transmission of the virus, in addition to contributing to improved clinical outcomes for the individual receiving treatment.\textsuperscript{24} The WHO has updated its guidelines regarding the timing of ARV therapy initiation, now recommending that it be initiated at a CD4 count ≤500 cells/mm\(^3\) or at the time of diagnosis, regardless of disease stage, in certain cases (e.g. serodiscordant couples).\textsuperscript{33} Early initiation means that individuals will be on ARVs for longer periods of time than if they started treatment based on clinical indication of more advanced disease, which generally happens later in the course of infection. This results in longer periods of time during which adherence must be maintained; specifically, periods during which disease stage is less severe and symptoms are often absent. Adherence may be lower and more variable during less severe stages of HIV, due to lack of perceived need for treatment.\textsuperscript{34} Therefore, in order to fully realize the benefits to the health of the individual receiving treatment, as well as the transmission reduction benefits of early ARV initiation, predictors of and barriers to adherence must be understood.
STLEs can cause disruptions to the routines of those experiencing them, and for PLWHA, this may result in interruptions in their ARV adherence. The association between STLEs and ARV adherence has been investigated; higher numbers and greater severity of events are associated with poorer adherence.\textsuperscript{9,10,18,35} Studies assessing this association, however, have exclusively used self-reported ARV adherence, which may be subject to misclassification due to poor recall and social desirability bias; it is often biased upward.\textsuperscript{36} As a result of the upward bias, it is likely to be less variable and therefore it can be more difficult to assess changes over time and factors associated with such changes. Unannounced, telephone-based pill counts have been shown to provide valid, accurate measures of adherence,\textsuperscript{11} and are more sensitive to changes in adherence over time;\textsuperscript{36} they may thus allow for a more accurate assessment of the relationship between STLEs and ARV adherence. Studies have also predominantly used lifetime measures of STLEs, or long recall (≥9 months) for incident or more proximal events.\textsuperscript{7,9,10,15,35,37} This may weaken associations with STLEs, if study participants fail to accurately report their experiences. Cumulative lifetime STLEs and STLEs in the distant past have demonstrated associations with HIV-related outcomes, in particular ARV adherence, but more recent and ongoing STLEs might be more strongly related to certain outcomes.

An important psychological outcome of concern among PLWHA is suicidal ideation (SI). SI, which encompasses passive thoughts that life is not worth living and that an individual wishes to be dead, and active plans to act on such thoughts,\textsuperscript{38,39} is one of the strongest and most proximal risk factors for suicide attempts and completions. As a leading cause of death worldwide, suicide presents a significant public health concern.\textsuperscript{40} SI is strongly associated with depression,\textsuperscript{39,41-44} which is more common among persons with chronic diseases, such as HIV, than among the general population.\textsuperscript{13} Upwards of 20% of HIV-infected individuals are affected by depression, compared to 12-13% of the general population.\textsuperscript{16} Given its strong association with depression, therefore, it is not surprising that SI is also more common among PLWHA than the general population. Lifetime prevalence of SI in an HIV-
infected population was 26%,45 in comparison with an estimated 16% in the general US population.46 Given its relative high prevalence in a population of HIV-infected individuals with depression, SI is an important outcome to understand in order to both improve quality of life and prevent suicide attempts and completions.

**STLEs may serve as triggers for suicidal thoughts and may therefore lead to an increase in SI in an HIV-infected population with depression that is already susceptible to such thoughts.** Many studies have assessed the relationship between STLEs and SI; however, they have mainly been conducted among children or adolescents, or in countries other than the US. In a 2014 review, 38 studies of the relationship were identified; 27 of those found a positive association between STLEs and SI.47 The strength and precision of the estimates of association varied widely, however, and several methodological differences were present. The authors concluded that no firm inferences could be made from the results of the various studies, and that future research including longitudinal assessments of STLEs in brief time frames immediately preceding measurements of SI would greatly benefit the existing literature. Neither the studies included in the review, nor any other identified studies of the association between STLEs and SI, have been carried out among PLWHA with depression. Quantifying this association in such a population would provide important information for health care providers, in order to intervene on important predictors of SI in this population that may not have been otherwise assessed during routine appointments.

**Interventions could be targeted to increase provider awareness of STLEs, and to improve coping skills to mitigate their effects, in order to improve outcomes.** 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, independent of overall psychological well-being.48 Other studies have found that expressive writing about stressful and traumatic events being experienced, especially writing from a third-person approach, was associated
with greater cognitive engagement, fewer days of activity restriction, and improved health status.\textsuperscript{49,50} Similar interventions, focused on reducing the incidence of and/or developing skills to cope with STLEs, could be developed and targeted to HIV-infected populations.

**In summary, STLEs are commonly experienced by persons with HIV and depression, and they may be associated with important behavioral and psychological outcomes such as ARV adherence and SI. Interventions have been shown to be effective in reducing the incidence and mitigating the effects of STLEs in other populations and could therefore be targeted for a population of HIV-infected persons with depression.**

**Significance**

As described, stressful or traumatic life events are common among HIV-infected individuals,\textsuperscript{7-9,15} and have been associated with negative HIV-related clinical and behavioral outcomes such as ARV adherence\textsuperscript{9,10} and SI.\textsuperscript{47,51} ARV adherence and SI are outcomes with important implications for the health and well-being of PLWHA with depression. This research is therefore *significant* because it adds to the existing literature about the associations between STLEs and both ARV adherence and SI, using data from the SLAM DUNC study, which comprises HIV-infected individuals with depression. The most accurate, relevant, and sensitive measurements of STLEs, ARV adherence, and SI were used, and sophisticated analytic techniques were applied in order to properly address time-varying confounding by depressive severity and issues related to missing data. The outcomes of this scope of work are that (1) the association between STLEs and ARV adherence among PLWHA with depression are more precisely quantified and (2) the first assessment of the relationship between STLEs and SI among individuals with both HIV and depression has been carried out. Results of this work could be used in the development of targeted interventions aimed at reducing the incidence of and mitigating the effects of STLEs in this population.
Innovation

Prior studies have demonstrated that STLEs are negatively associated with ARV adherence; however, they have exclusively used self-reported ARV adherence.\textsuperscript{9,10,35} Self-reported adherence tends to be biased upwards,\textsuperscript{36} and is by definition capped at 100%, leading to reduced variability; associations may therefore be underestimated. Using a self-reported outcome introduces the possibility of dependent measurement error as well, when the exposure is also self-reported, as in the case of STLEs.\textsuperscript{52} Unannounced, telephone-based pill counts have been shown to provide adherence measurements that are not only valid,\textsuperscript{11} but also more sensitive than self-report to changes in adherence over time.\textsuperscript{36} As it comes from an actual medication count, there is no upper limit on the adherence value, and the possibility of both upward bias and dependent measurement error is reduced. While participants counted the pills themselves, adherence was calculated later and not shared with participants, making it difficult to falsify their counting in order to maintain higher adherence. This research used unannounced, telephone-based pill counts to obtain more accurate, sensitive measurements of ARV adherence than have been used in prior studies of its association with STLEs, thus leading to more valid, precise estimates of association.

Due to their design and the availability of data, prior studies have also failed to account for potential time-varying confounding by depression.\textsuperscript{9,10,35} If depression both affects subsequent STLEs and is affected by prior STLEs, and is associated with adherence, then it is both a mediator and a confounder of the relationship between STLEs and adherence. In order to obtain a marginal estimate of the full effect of STLEs (both through and independent of depressive severity) on adherence, without allowing for confounding by depressive severity, a marginal structural model approach can be used;\textsuperscript{53} none of the existing studies have taken this approach. For both study aims, we tested the hypothesis that depressive severity was acting as a time-varying confounder, in order to address this concern.
This research provides information about the relationship between STLEs and SI, which has largely gone unstudied in populations of HIV-infected individuals with depression. In all identified studies of the relationship, there are concerns about long recall periods for both STLEs and SI, and about temporality of the measures due to the often cross-sectional nature of the analyses.\textsuperscript{47,51} The identified studies also presented mixed results, with some finding evidence of a positive relationship and others finding no such evidence. Methodology varied widely among studies, and none of the existing studies were in HIV-infected populations. Given the relatively high prevalence of both STLEs and SI in individuals with both HIV and depression, in comparison with the general population, the association is of potential concern and likely more pronounced than that found in the identified studies. Our study provides the first assessment, to our knowledge, of this relationship in this population.

This research is \textit{innovative} because it used the most accurate available data to measure the relationship between STLEs and ARV adherence, and it provides the first information about the association between STLEs and SI in an HIV-infected population. In addition, this research made use of sophisticated analytical techniques to address the potential time-varying confounding by depressive severity of the relationships between STLEs and both ARV adherence and SI. Marginal structural models were used to account for confounding by depressive severity without losing any of the total effect of the exposure on the outcomes. Prior studies of these associations have not used such techniques, and thus the estimates of associations might have been biased.
CHAPTER 3: RESEARCH DESIGN AND METHODS

Overview

The overall objective of this research was to examine the relationships between stressful and traumatic life events (STLEs) and a psychological and a behavioral outcome among HIV-infected patients with depression. Data from the SLAM DUNC study, a randomized controlled trial testing the effect of measurement-based depression treatment on antiretroviral (ARV) adherence among HIV-infected individuals, were used to quantify the associations between STLEs and (1) ARV adherence and (2) suicidal ideation (SI) over up to 12 months of longitudinal follow-up. A repeated-measures approach was used to examine the hypotheses that STLEs are associated with poor ARV adherence (measured continuously) and with SI (measured dichotomously), accounting for correlation between measures taken on the same individuals over time. For both aims, the need for inverse probability weights to account for time-varying confounding of the associations by depressive severity was assessed, and weights were applied to analysis models when necessary.

Conceptual Model/Causal Diagram

The hypothesized relationships between STLEs and (1) ARV adherence and (2) SI are shown in the directed acyclic graph (DAG) in Figure 3.1 (full DAGs for both aims, including all hypothesized covariates, are found in Appendix 1). It was hypothesized that depressive severity functions as a time-varying confounder of the associations between STLEs and both ARV adherence and SI. Depressive severity at baseline can put participants at higher risk of experiencing some of the STLEs assessed during the subsequent time-period, for example, relationship and employment troubles. Since depressive
severity may also be associated with the outcomes of ARV adherence and SI, it may be acting as a confounder of the relationship between STLEs and these outcomes. STLEs that are experienced at a given point in time can also affect depressive severity at later time points, however, putting depressive severity on the causal pathway between STLEs and the outcomes and making it a potential time-varying confounder that is affected by prior exposure.

**Study overview and intervention description**

Data for this research came from the *Strategies to Link Antidepressant and Antiretroviral Management at Duke, UAB, NOC, and UNC (SLAM DUNC) Study*, a randomized, controlled trial that tested the effect of evidence-based decision support for depression treatment on ARV adherence. The study population comprised HIV-infected patients with depression attending the infectious disease clinics at Duke University; the University of Alabama at Birmingham (UAB); Northern Outreach Clinic (NOC) in Henderson, North Carolina; and the University of North Carolina (UNC) at Chapel Hill. Participants enrolled in the intervention arm had regular contact with a depression care manager who assessed their depression using standardized metrics and made evidence-based antidepressant treatment recommendations to the treating HIV medical provider. Participants in the control arm for the study received depression treatment as usual by their HIV providers. As study arm was randomized (and therefore independent of the exposure, STLEs), the proposed research did not need to take study arm into account, although the analyses did adjust for some factors that were expected to be affected by study arm. Variables that were considered for adjustment are shown in the full DAGs in Appendix 1.

**Study timeline and sample size**

Data were collected longitudinally over a maximum of 12 months of follow-up for each participant. Study enrollment began in April 2010 and ended in September 2013; follow-up continued
through April 2014. Participants enrolled between April and September 2013 were therefore followed for less than a full year. The STLE assessment was added to data collection for new and existing participants after the first year of the study, in July 2011; only participants still active in the study at that time or enrolled subsequently had data on STLEs and were eligible for inclusion in the current research. Out of the total 304 participants enrolled in the SLAM DUNC study, 289 were eligible to have data on STLEs and were followed for varying lengths of time of up to 12 months.

**Inclusion and exclusion criteria**

To enroll, individuals had to be adult patients (age 18-65 years at enrollment) with HIV attending the infectious disease clinics at Duke, UNC, NOC, or UAB who scored >9 on the Patient Health Questionnaire-9 (PHQ-9) depression screening instrument\(^5\) and also had a diagnosis of a current major depressive episode or dysthymia confirmed by the Mini International Neuropsychiatric Interview (MINI), a widely used psychiatric diagnostic instrument.\(^6\) Patients with a lifetime history of bipolar disorder or psychotic depressive, schizophrenic, schizoaffective, or other psychotic disorders (as determined by the MINI), who had current substance dependence that required inpatient detoxification or treatment, or who required immediate hospitalization for psychiatric disorders and/or acute suicidality, were ineligible for study participation. Patients who failed at least two adequate antidepressant trials, defined as ≥6 weeks at a moderate to high antidepressant dose for their current depressive episode, were also ineligible for the study.\(^7\)

**Analysis Plan for Aim 1: Stressful life events and antiretroviral adherence**

The primary goal of Aim 1 was to assess the association between stressful or traumatic life events (STLEs) and adherence to antiretroviral (ARV) medication, as measured by unannounced telephone-based pill counts. The hypothesis was that STLEs would be associated with poorer ARV
adherence. Secondary analyses focused on the alternative outcome of self-reported ARV adherence.

Previous studies demonstrated the negative association between STLEs and self-reported ARV adherence.\textsuperscript{9,10,18} Self-reported adherence is likely to be biased upward,\textsuperscript{36} however, with participants over-reporting adherence due to social desirability bias, resulting in less variability in the outcome. It was hypothesized that the strength of the association between STLEs and self-reported ARV adherence would be attenuated relative to the association between STLEs and pill count-based adherence.

**Exposure Assessment/Definition**

STLEs were the exposure of interest for both Aim 1 and Aim 2. STLEs were assessed during the monthly ARV pill count telephone calls using a modified version of the Life Events Survey (LES).\textsuperscript{10,59} Only those events from the LES considered moderately or severely stressful or traumatic based on prior research were included in this assessment.\textsuperscript{60,61} Participants were asked whether they had experienced any of 46 events, from within nine different categories, during the prior month. The categories were: romantic relationship changes; estrangement from family; death or major illness of a family member or close friend; major illness, injury, or hospitalization; employment difficulties; legal trouble; financial difficulties; life transitions; and safety concerns. Participants were also able to report additional STLEs that had not been covered by the LES; any event reported in this way was hand-reviewed and inclusion in the exposure was based on classification of the event as moderately or severely stressful or traumatic. The total number of STLEs reported at each time point was summed for each participant and coded discretely.

For the primary analysis with ARV adherence based on pill counts as the outcome, the unit of analysis was one month, since both pill counts and the LES were administered monthly (during the same telephone call). Self-reported adherence was measured every three months, however, and therefore for
this secondary analysis the exposure measure was defined as the average number of STLEs per month reported over each three-month period.

Outcome Assessment/Definition

The primary outcome for Aim 1 was ARV adherence, measured by unannounced, telephone-based pill counts and recorded as a continuous percentage variable, with, for example, 0% corresponding to zero adherence, or having taken no pills since the last count, and 100% corresponding to perfect adherence, or having taken all pills expected since the last count. Unannounced, telephone-based pill counts have been validated as an objective measure of adherence\textsuperscript{11} and have been shown to be more sensitive than self-report or pharmacy refill data to changes in adherence over time.\textsuperscript{36}

The pill counts were designed to be conducted monthly with each participant, and 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 pill count. The observed number of pills taken was based on the number of pills present at the current count, relative to the number present during the previous count and the number of pills that were gained or lost by the participant in the interim (e.g. new bottles, pills thrown away or lost). The expected number of pills taken was based on the number of days since the previous count, multiplied by the prescribed daily number of pills for each ARV. Losses and/or gains of pills since the previous count (e.g. due to medication received while in the hospital, or dropped pills that were not recovered) were also considered. Both the observed and expected number of pills were summed across all ARV medications prior to dividing. This measure of adherence represented an average value over the entire period between the current and previous pill counts. If a certain month’s pill count was missed, the next count was tied back to the last non-missing count if enough information was available; adherence was therefore calculated for the period between non-missing counts, which
could have been greater than one month. This adherence value was then applied to each month over which the value was calculated.

Calculated adherence in theory should range from 0-100%; however, in practice it is possible to obtain estimates both above and below this range. Adherence values >100% could be due to 1) taking more pills than prescribed or 2) measurement error in the pill count. Values <0% can only be due to measurement error with the pill count. Measurement error could be due to losses and/or gains of pills that were not reported, entire bottles that were missed in between counts, or pills that the participant had in possession but did not report at either the prior or current count, for example. The data collection protocol included extensive probes about these issues in order to reduce measurement error, but error remains a possibility. The SLAM DUNC study discarded calculated adherence values <0% or >200% but did not discard values <200%; the same was done in the current research.

Studies of ARV adherence have mainly used a threshold of 95% adherence to indicate “adequate” adherence (i.e. adequate to suppress viral load and prevent ARV resistance); this threshold was largely defined during the early era of un-boosted PI-based regimens. More recent evidence with the current boosted PI- and NNRTI-based regimens suggest that virologic suppression can be reliably sustained at lower adherence levels, and that the adherence-virologic suppression relationship is monotonic, especially for NNRTI-based regimens. Therefore in primary analyses ARV adherence was kept as a continuous measure. Sensitivity analyses considered dichotomous adherence measures based on various thresholds to indicate adherent vs. non-adherent.

Covariate Assessment/Definition

Depressive severity, as both a potential confounder and a mediator of the relationship between STLEs and ARV adherence, was hypothesized to function as a time-varying confounder affected by prior exposure and thus assessed with the use of a marginal structural model (MSM) (described in further
It was measured with the Hamilton Rating Scale for Depression (HAM-D) at baseline and then every three months thereafter, during scheduled, telephone-based interviews with trained research interviewers. The HAM-D, the most widely used depressive severity measure in research settings, is a validated depression screening tool consisting of 17 open-ended sections assessing different facets of depressive symptoms, and refers to experiences during the past seven days.\textsuperscript{62-64} Scoring ranges from 0 to 50, and clinical categorization is as follows: 0-7 is normal, 8-13 is mild depression, 14-18 is moderate depression, 19-22 is severe depression, and 23 and above indicates very severe depression.\textsuperscript{63} Depressive severity was coded in this analysis as a discrete variable. Change in the total HAM-D score has been shown to correspond to clinically relevant changes in the underlying depression construct,\textsuperscript{65} and keeping the discrete coding (rather than categorizing) helped retain all of the information contained in the variable. Because it was only assessed every three months, with the exposure and outcome both assessed monthly, in order to use the most representative value for this time-varying confounder, the score closest in time to the measures of adherence and STLEs was used, even if it came from measurements taken after adherence and STLEs were obtained (e.g. for adherence at the two-month mark, the depression score from the three-month interview was used if it was closer in time than the baseline interview).

Other covariates that were assessed as potential confounders or effect measure modifiers included sex, age, drug and/or alcohol abuse, HIV care self-efficacy, stress coping style, HIV-related physical symptoms, HIV status disclosure, and employment status. Sex, as assessed at baseline, was used as a time-fixed dichotomous variable (male, female). Date of birth was obtained at the baseline interview, and used to calculate age at study entry; as all participants by definition aged one year or less during study participation, age at study entry was used as a time-fixed continuous variable.

Drug and alcohol abuse were assessed in person at baseline and at the six- and twelve-month telephone interviews with the alcohol/substance dependence/abuse sections of the MINI; the time
frame assessed at each time point was within the past twelve months. These sections resulted in ordinal scoring of no abuse/dependence, abuse, or dependence on alcohol and non-alcoholic psychoactive substances. The HIV Self-Efficacy scale was used to measure self-efficacy in, for example, avoiding/controlling depression, loneliness, and discouragement; taking medications properly; discussing/working out issues with medical providers; controlling physical symptoms; and dealing with fatigue. The scale consists of 34 examples of tasks, and participants rate how sure they feel that they could do each task on a scale from 1-10, with lower scores corresponding to feeling less sure and higher scores corresponding to feeling more sure. Stress coping style was assessed with the Brief COPE instrument, which contains 18 examples of coping strategies; participants use a four-point Likert scale to rate how often they use each strategy: “Not at all,” “A little bit,” “A medium amount,” or “A lot.” Self-efficacy and stress coping style were measured at baseline and at each three-monthly telephone interview; both were updated over time. Physical symptoms (HIV Symptom Inventory), employment status and extent of HIV status disclosure to friends, family, and acquaintances were also obtained at baseline and every three months. Physical symptoms were included as a discrete variable indicating the total number of symptoms reported, which was updated over time. Employment status was dichotomized to indicate employed vs. unemployed. Disclosure of HIV status both to close friends/family and to everyday acquaintances was measured separately with a four-point Likert scale for each inquiry: “All”, “Most”, “Some”, or “None” and was included as an ordinal variable that was allowed to change over time.

Secondary Outcomes

*Self-reported ARV adherence.* The SLAM DUNC study measured self-reported adherence in addition to pill count-based adherence, and thus the strength of the association between STLEs and adherence measured using pill count data could be compared to that obtained by using self-reported
adherence. Self-reported adherence was measured at baseline and every three months thereafter during structured research interviews (in-person at baseline and over the telephone for the rest), 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?” Participants were instructed to respond using a scale from 0% to 100%. The responses to these two questions were averaged (after reverse-coding the second question) as a measure of self-reported adherence ranging from 0-100%.

### Statistical Analyses

#### General Analysis Approach

To examine the hypothesis that STLEs are negatively associated with continuously-measured ARV adherence, a linear model with robust variance was used to account for repeated observations on participants, yielding an estimate of the mean difference in percent adherence. Under the hypothesis that the association between STLEs and ARV adherence is affected by time-varying confounding by depressive severity (Figure 3.1), standard approaches (e.g. inclusion on the right hand side of the regression equation) could not be used to control for depressive severity, since by doing so it would block part of the causal pathway of interest (from exposure to outcome through depression, see Figure 3.1). To deal with this time-varying confounding, inverse-probability-of-exposure weights could be applied to the model to estimate the parameters of a marginal structural model (MSM). The assumption that a MSM was necessary was examined by comparing models with and without the exposure weights, as well as by assessing the associations between STLEs and depression, and depression and adherence. With a continuously modeled exposure, as is the case with STLEs, a common approach to calculating the denominators of inverse probability weights is to recode the exposure into quantile bins, and to use ordinal logistic regression to obtain predicted probabilities of being in each
quantile.\textsuperscript{70} For total STLEs, the exposure was coded into deciles, and for severe STLEs into tertiles (due to the smaller range). For the dichotomously coded STLE exposures, logistic regression was used. In all cases, the weights were stabilized by the marginal probabilities of exposure. The stabilized weights were calculated according to Equation (1):

\[ SW_i = \frac{p(SLE_{ki})}{p(SLE_{ki}|D_{ki})} \quad (1) \]

where \( sw= \) stabilized weight, \( p= \) probability, \( D= \) depression, \( k \) indexes over time periods, and \( i \) indexes across individuals.

The estimates obtained from models with and without inverse-probability-of-exposure weights were nearly identical, suggesting that a MSM was not necessary to yield valid estimates. Analyses therefore proceeded under the assumption that the STLE-adherence relationship was not being affected by time-varying confounding by depression, and exposure weights were not used. The analysis model yielded an estimate of the mean percentage change in ARV adherence, given a one-unit increase in the number of STLEs experienced, while controlling for all potential confounders and adjusting for clustering due to making repeated observations on individuals over time.

**Secondary Analyses**

Secondary analyses focused on the alternative outcome of self-reported ARV adherence. Analyses for self-reported ARV adherence were conducted in largely the same way as analyses using pill count-measured ARV adherence, as both outcomes were on the same scale. Self-reported ARV adherence, however, was measured every three months; therefore, the total number of STLEs reported in each three-month period was divided by the number of times the exposure was measured (the number of pill count calls conducted) to obtain a mean monthly number of events for each three-month time period. Analyses again yielded an estimate of the mean percentage change in ARV adherence,
given a one-unit increase in the number of STLEs experienced, while controlling for all covariates and for
time-varying confounding by depression, and adjusting for clustering due to making repeated
observations on individuals over time.

Handling Missing Data

The amount of missing data in the SLAM DUNC study was non-trivial, and was not expected to
be missing completely at random; a complete-case analysis would therefore have likely introduced bias,
in addition to being inefficient due to losing power by excluding participants with partial data. To deal
with missing data, inverse-probability-of-observation weights were combined with multiple imputation,
therefore taking advantage of the efficiency of imputation, while avoiding the need to impute data
from completely missed study contacts. This utilized a three-step process: (1) calculation of weights, (2)
multiple imputation for observations to be included in the analysis, and (3) application of the weights to
each imputed dataset.

In the first step, inverse-probability-of-observation weights were calculated at the pill count
observation level. Each participant had a potential contact for each pill count that would have occurred
during the time they were under observation (up to 12 possible pill count contacts). The contact was
either completed or not (1=completed, 0=not completed, Table 3.1); any contacts not completed
resulted in missing exposure and outcome data. A missingness model was specified for the probability
that a contact was completed; only fully observed variables can be included in the model, so it included
variables measured at the baseline enrollment contact. In addition, a fully observed, time-updated
variable indicating whether the previous contact was completed was assessed. Variables that were
predictive of missing the pill count, as well as variables that were associated with both the exposure and
outcome, regardless of association with missingness, were included.
In the second step, for each observation with a completed pill count contact (e.g. rows 1 and 3-5 in Table 3.1), any missing data points were imputed. In the hypothetical data in Table 3.1, therefore, STLEs were imputed for the first record for ID 1, ARV adherence was imputed for the last record for ID 1, and both depressive severity and various other covariates were imputed for the first record for ID 2. To impute missing data points, multiple imputation using chained equations was used, which is a flexible way to implement multiple imputation when there is a non-trivial amount of missing data among variables of several different forms. It does not assume multivariate normal distribution of the variables being imputed; by imputing a series of sequential univariable models separately for each variable with missing data, it can accommodate different variable types (e.g. continuous, binary, ordinal, nominal).

To implement multiple imputation by chained equations, all missing values were first filled in by a simple random sampling, with replacement, from the observed values of each variable. The first variable, X1, was then regressed on all other variables. This regression was limited to participants with observed values of X1; simulated draws from the posterior predictive distribution of X1 were then used to fill in missing values of X1. The process was then repeated on the next variable, X2, and in turn for each variable with missing data. Imputation models included all variables that were considered for inclusion in the analysis model, i.e. both the exposure and outcome, as well as all covariates. Also included in imputation models were predictors of each variable being imputed, and predictors of missingness in each variable. To impute continuous variables, linear regression was used, after assessment of the functional form and potential transformation of the variables. Logistic regression was used to impute binary variables and multinomial regression was used for both nominal and ordinal variables.

Once each variable has been imputed, it constitutes a cycle; several cycles are customarily carried out in order to stabilize the results and produce an imputed data set. Within a cycle, variables
are imputed in increasing order of the number of missing values they contain. For this research, ten cycles were used per imputed dataset, and 50 datasets were imputed.

Finally, in the third step, the inverse-probability-of-observation weights were applied to the analysis model in each of the imputed datasets. The weighting rebalanced the data to ensure it was representative of the full sample, since the model was run only for the observations with completed pill counts.

In summary, only observations with completed pill count contacts were included in the analysis model. Any missing data points for included participants were imputed using multiple imputation by chained equations. Data points imputed were the exposure (STLEs), the outcome (ARV adherence), and all covariates (depressive severity, sex, age, drug/alcohol abuse, HIV care self-efficacy, stress coping style, HIV-related physical symptoms, HIV status disclosure, and employment status). In the assessment of the necessity of a MSM, the observation weights were combined with the exposure weights to generate one final set of weights, which was applied to the included sample to rebalance it to represent the full sample while adjusting for time-varying confounding by depressive severity.

**Sensitivity Analyses**

The primary analyses were guided by the assumption that depressive severity is a time-varying confounder of the relationship between STLEs and ARV adherence, thus necessitating the use of a MSM. This assumption was explored by measuring the associations between the three variables, in order to determine whether – and to what extent – depressive severity affects STLEs and ARV adherence and is affected by prior STLEs. These associations were measured directly to inform the assumption. A comparison of models was also carried out for further information, to determine whether the results differed when models did or did not include exposure weights.
Different dichotomous coding schemes for the outcome of ARV adherence were explored, in addition to the continuously-coded primary outcome. Adequate vs. inadequate adherence was defined using a threshold of 95%. We also explored the effect of truncating the continuously-measured adherence outcome at 100%, as the theoretical upper plausible limit.

Different classifications of exposure were explored. The primary analysis incorporated all the STLEs assessed with the modified LES, to generate a discrete variable. Events were also limited, however, to determine whether results were sensitive to the severity of stressors experienced. By including only those STLEs considered “severe” (divorce or separation, death or major illness of an immediate family member, major financial problems, time in jail or prison, and sexual and physical assault), a second discretely coded exposure variable was created and assessed. Finally, both the primary exposure that included all STLEs and the severe-only STLE exposure were dichotomized into variables indicating at least the population mean number of events vs. less than the mean, and any event experienced vs. no events, respectively. The use of dichotomous exposures changed the calculation of weights for the MSM as described above.

**Statistical Power**

Statistical power was assessed using PROC POWER in SAS 9.3 (SAS Institute, Cary, NC). A 5% Type I error probability, with a two-tailed test, was used. The exposure was dichotomized (at the median value for number of STLEs per month) for power calculations; 65% of the study population was assumed to be exposed. Power to detect a 10-percentage point difference in adherence, based on an assumed pooled standard deviation of 25-29%, was calculated for the expected sample size.

Due to the need to account for repeated measures on individuals over time, the total expected sample size used in power calculations needed to be adjusted for clustering. The effective sample size (ESS) for clustered samples was calculated with Equation (2):
\[ ESS = \frac{(m \cdot k)}{DE} \quad (2) \]

In Equation (2), \( m \) refers to the number of observations per cluster, \( k \) is the number of clusters (here, participants), and \( DE \) is the design effect (a correction factor applied that takes into account the correlation between observations within a cluster). \( DE \) is calculated with Equation (3):

\[ DE = 1 + ((m - 1) \cdot \rho) \quad (3) \]

In Equation (3), \( \rho \) is the intracluster correlation coefficient, which can vary from 0 to 1.\(^{75}\)

The number of clusters (participants), \( k \), was expected to be 240. The average number of observations per cluster, \( m \), was assumed to be 5, to account for missed pill counts (resulting in fewer than the maximum 12 observations), and for the 40 expected participants with less than a year of follow-up (by design, fewer than 12 observations). Allowing \( \rho \) to vary between 0.5 and 0.9, assuming fairly high correlation of adherence measures among individuals, the ESS for this aim ranged from 261 to 400 (Figure 3.2). The upper and lower bounds of ESS were input into PROC POWER to represent the best- and worst-case scenarios.

Under these assumptions, the power to detect percent difference in adherence ranging from 0.07-0.13 is shown in Figure 3.3 for effective sample sizes of 261, 316, and 400, corresponding to sample sizes using the maximum, median, and minimum values of \( \rho \) that were assessed (0.9, 0.7, and 0.5), respectively. Even under the worst-case scenario of an ESS of 261, there was expected to be >80% power to detect 10% or greater change in adherence.

Limitations

The proposed research had several limitations. One limitation was the accuracy of both the exposure and outcome measurements. The exposure, STLEs, was measured via self-report during the telephone-based pill count assessments. As a self-reported measure, it was subject to measurement
error due to poor recall, as participants were asked to report on events experienced over the past month; events that happened at the beginning of the month might have been forgotten, or thought by the participant to have occurred in the previous month. The assessment of STLEs in the SLAM DUNC study improved upon similar exposure assessment in other studies by using a shorter recall period (one month).\textsuperscript{9,19} The trained interviewers repeatedly mentioned the timeframe while asking about each event, in order to anchor the period of recall only to the month preceding the assessment.

Participants might also have chosen not to report STLEs if they did not wish to disclose them, due to embarrassment, a wish for privacy, or other reasons.

The heterogeneity of the exposure may also have led to some measurement error, as the Life Events Survey (LES) that was used to measure STLEs comprised a diverse set of events. It is possible that associations with modifiers, confounders, and the outcome could have been of different strengths or even in different directions for different events. Sensitivity analyses addressed some of these limitations by varying the types of events included in the exposure. In addition, the exposure was measured discretely, as the total number of events experienced. This implied that each different type of event had the same marginal association with the relevant outcome. To make this more plausible, only events considered to be moderately to severely stressful or traumatic, based on prior studies, were included in the LES version used.\textsuperscript{60,61} In order to ensure greater consistency, the number of events experienced, rather than participants’ ratings of the severity of events, was used to measure the exposure, making for a more objective and consistent measurement.

The outcome, ARV adherence, may also have been measured with some error. The accuracy of the pill counts depends upon being able to account for all pills that were received and consumed by participants, but it is possible to miss some pills, or to count some pills more than once. This could happen due to participant error or intentional misreport, and it is impossible to differentiate. Efforts were made to reduce this type of error. Information about each bottle, including the prescription
number, the date that it was filled, and the number of refills remaining, was collected in an effort to track the continuity of bottles received. Participants were also asked to obtain refill histories from their pharmacy and provide them to study staff; information provided in the pill counts was verified and supplemented with these histories when available. Data collectors were trained not to provide feedback to participants during the call about their calculated adherence, in order to reduce any motivation to intentionally misreport pill counts.

The amount of missing data in the SLAM DUNC study was non-trivial. The missing data plan described above helped address this issue.

**Analysis Plan for Aim 2: Stressful life events and suicidal ideation**

The overall goal of Aim 2 was to examine the association between STLEs and suicidal ideation (SI). The hypothesis was that STLEs would be positively associated with report of suicidal thoughts. Secondary analyses focused on evaluation of modification of the relationship between STLEs and SI by variables identified *a priori*, including stress coping style and self-efficacy. Hypotheses for secondary analyses were that the positive association between STLEs and SI would be stronger among those with less adaptive coping styles and among those with low self-efficacy.

**Exposure Assessment/Definition**

The exposure for Aim 2, STLEs, was described in detail above. The Life Events Survey (LES) was used to assess the experience, during the previous month, of any events in the nine categories described above. For this aim, while the exposure was measured monthly at the time that pill count calls were conducted, the outcome of SI was measured every three months. The total number of STLEs reported in each three-month period was therefore divided by the number of times the exposure was measured (the number of pill count calls conducted) to obtain a mean monthly number of events for that time.
period. If more than three measures of STLEs were taken in a given time period, the three measures closest in time to the SI assessment were used. The mean number of STLEs was coded continuously and also dichotomized to indicate experiencing at least the population mean number of events vs. less than the mean. STLEs were also limited to the most potentially severe, coded both continuously and dichotomized as any vs. none.

Outcome Assessment/Definition

The outcome for Aim 2 was SI, measured with the Hamilton Rating Scale for Depression (HAM-D) during telephone interviews conducted every three months. The HAM-D, the most widely used depressive severity measure in research settings, consists of 17 open-ended sections assessing different facets of depressive symptoms experienced during the past seven days.62-64 The third section addresses SI with the following questions:

“During this past week, did you have thoughts that life is not worth living?”
“Did you think that you would be better off dead?”
“Have you had thoughts of hurting or killing yourself?”
“Have you actually tried to hurt yourself?”

Additional probes were asked based on the participant’s responses to these questions. Trained interviewers administered the HAM-D, and a protocol was in place to address active SI that was reported during interviews, if the safety of the participant was in question. Scores for the SI section range from 0-4 as follows: (0): No symptoms; (1): Feels that life is not worth living; (2): Wishes that s/he were dead, or had thoughts about hurting self; (3): Suicidal ideas of gesture (has a plan, or begins suicide attempt but stops); (4): A suicide attempt during the past week. Responses falling between two scores were scored conservatively (given the lower score) by the interviewers. For the primary analysis, the outcome was dichotomous: any suicidal ideation (score >0) vs. none (score of 0).

The HAM-D is able to differentiate between passive SI (thoughts of being better off dead, without intent to act on those thoughts) and active SI (thoughts of actually harming or killing oneself,
with or without a definite plan). Using a dichotomous outcome of any SI vs. no SI introduced the assumption that STLEs affect all types of SI in the same way. This assumption might not be plausible in all cases, as active SI might be expected to be associated with more extreme exposures. The vast majority of SI, however, was passive; it should therefore have posed minimal issues to have included all SI as one outcome, while retaining the greatest statistical power as a result of having more overall outcomes. Sensitivity analyses explored sensitivity of results to different coding of the outcome, including separation of passive and active SI.

Covariate Assessment/Definition

Depressive severity was assumed to function as a time-varying confounder of the association between STLEs and SI, in the same way as described for Aim 1. For Aim 2, however, since it was measured every three months at the same time as SI, the HAM-D score from each three-monthly interview was used; it was not necessary to “borrow” scores from other time points. The HAM-D score was recalculated to exclude the section that covers SI, in order to avoid overlap with the outcome; resulting in a possible range of 0 to 46.

Sex, age, drug/alcohol use, HIV-related physical symptoms, HIV-care self-efficacy, stress coping style, and employment status were also covariates that were considered as confounders in the analysis for Aim 2; measurement and coding of these variables were described under Aim 1, and were identical for this aim. In addition, psychiatric comorbidities and mental health function status were assessed. Psychiatric comorbidities were measured with the MINI at baseline, and include dysthymia, mania, panic disorder, specific phobias, obsessive-compulsive disorder, generalized anxiety disorder, drug and alcohol abuse and dependence, psychotic disorder, and post-traumatic stress disorder. All comorbidities were combined and then dichotomized to indicate presence/absence of any comorbidity. Mental health functioning was measured at baseline and at six- and twelve-month follow-ups using the using the Short
Form-12, scored continuously on a 0–100 scale (with higher numbers indicating greater functionality; US population mean=50, one standard deviation=10).\textsuperscript{76,77} 

Potential Modifier Assessment/Definition 

Modification of the relationship between STLEs and SI was assessed in secondary analyses. Potential modifiers included stress coping style and self-efficacy. Measurement and scoring of these variables were described above. Both potential modifiers were dichotomized in order to assess the exposure-outcome relationship within strata of the modifier. The Brief COPE instrument for measuring stress coping style includes items related to adaptive (e.g. acceptance, getting emotional support) and maladaptive (e.g. drug/alcohol use, denial) strategies for coping with stress. A dichotomous variable was created to indicate high adaptive vs. low adaptive coping style, using a score of 2.5, which is the midpoint of the scoring range, as the cut-off. Scores of 2.5 or above indicated high adaptive coping while scores below 2.5 indicated low adapting coping. Likewise, self-efficacy on the module relating to mood, support, and fatigue was dichotomized at a score of five (the midpoint of the scoring range); scores of five or above indicated high self-efficacy and below five indicated low self-efficacy.

Statistical Analyses 

General Analysis Approach 

To examine the hypothesis that STLEs are positively associated with dichotomously-measured SI, we used Poisson models with robust variance (instead of a log-binomial model due to model convergence issues\textsuperscript{78}), adjusted for repeated observations among participants. Under the hypothesis that the association between STLEs and SI is affected by time-varying confounding by depressive severity (Figure 3.1), inverse-probability-of-exposure weights were applied to estimate the parameters of a MSM as described under Aim 1. MSMs were used for the primary analyses; however, as in Aim 1,
the assumption that they were necessary was examined in sensitivity analyses. This model yielded an estimate of the increase in prevalence of SI, given a one-unit increase in the number of STLEs experienced, while controlling for all covariates and for time-varying confounding by depression, and adjusting for clustering due to making repeated observations on individuals over time.

The same assumptions, and justifications for making the assumptions, that are necessary to make when using MSMs, described in Aim 1, hold for this aim: assumptions of exchangeability, consistency, and positivity.79

Again with this aim, there was the same continuously-modeled exposure of STLE, and thus as described in Aim 1, total STLEs were coded into deciles, and severe STLEs into tertiles (due to the smaller range), and ordinal logistic regression was used to obtain probabilities of exposure for calculating the weights.70 For the dichotomously coded STLE exposures, logistic regression was used. In all cases, the weights were stabilized by using the marginal probabilities of exposure for the numerators. The denominators included the probabilities of exposure conditional on baseline, lagged, and current values of SI and depressive severity; current and lagged values of STLEs; baseline and current values of HIV-related symptoms and drug/alcohol use; baseline age, gender, and psychiatric comorbidities; and interview month. Restricted cubic splines were used for modeling the continuously-measured variables (lagged STLEs, depressive severity, HIV-related symptoms, and age), and interview month was modeled using indicator variables for each of the 3-, 6-, 9-, and 12-month interview periods.

Secondary Analyses – Modification Assessment

The association between STLEs and SI was assessed separately, following the general analysis approach described above, within strata of both of the a priori-identified potential effect measure modifiers: coping style, and self-efficacy. Interactions between the exposure and time-varying covariates cannot be modeled with MSMs, so only the baseline values of the potential modifiers were assessed.53
Differences in the estimates of effect obtained were compared across strata of each potential modifier qualitatively, and Wald chi-square homogeneity tests were conducted with a term for interaction between STLEs and the given modifier included in the model.

Handling Missing Data

The same general approach to handling missing data that is described in Aim 1 was followed for this aim. A different inclusion rule was used, however, to determine which observations were included in the analyses (and therefore for which observations missing data were imputed). Observations in which the quarterly interview (during which the outcome, SI, is measured) was completed were included; the data were weighted to account for the exclusion of other observations. Any missing data for included observations were imputed. The variables included in imputation models differed slightly from those in Aim 1; variables included the exposure of STLEs and the outcome of SI, as well as the covariates and potential modifiers described above. For further stabilization of the inverse-probability-of-observation weights, a lagged variable for the exposure (continuously-measured STLEs) was included in both the numerator and denominator.

Sensitivity Analyses

As described in Aim 1, the necessity of a MSM to assess the relationship between STLEs and SI was examined. Alternate coding of the outcome of SI was explored. This included nominal coding that differentiated between no SI (score of 0 on the SI section of the HAM-D), passive SI (score of 1 or 2), and active SI (score of 3 or 4).
**Statistical Power**

Statistical power was assessed using PROC POWER in SAS 9.3 (SAS Institute, Cary, NC). A 5% Type I error probability, with a two-tailed test, was used. The exposure was dichotomized (at the median value for number of STLEs per month) for power calculations; 65% of the study population was assumed to be exposed. Twenty percent of the unexposed are assumed to experience the outcome, suicidal ideation, based on available data to date. Power to detect a prevalence ratio ranging around 2.0, a conservative estimate based on the only similar study available, was calculated for the expected sample size. The effective sample size (ESS) was calculated based on Equations 2 and 3 above; here, however, the number of observations per participant, m, was assumed to be three on average (out of four possible observations, corresponding to the interviews conducted at three, six, nine, and 12 months post-enrollment). Again using 240 expected clusters (participants) and allowing the intracluster correlation coefficient, ρ, to vary between 0.5 and 0.9, the ESS ranged from 257 to 360 (Figure 3.4). These sample sizes were input into PROC POWER.

Under these assumptions, the power to detect prevalence ratios (PRs) ranging from 1.7-2.3 is shown in Figure 3.5 for effective sample sizes of 257, 300, and 360, corresponding to the minimum, median, and maximum sizes obtained with the given range of ρ. At least 80% power was expected with each ESS for a PR of at least 2.0, and for an ESS of 360 at all PR values of at least 1.7.

**Limitations**

Aim 2 used the same exposure of STLEs as Aim 1 and thus the same limitations surrounding the exposure applied; as described above, there may have been exposure measurement error due to poor participant recall or intentional misreporting of the exposure. The exposure was also a heterogeneous mixture of STLEs, which may have led to inaccurate estimations of associations. This again was explored in sensitivity analyses, with different coding variations for the exposure.
For this aim, the possibility of dependent measurement error was a potential concern since the exposure, STLEs, and the outcome, SI, were both measured by participant self-report. There could have been factors that affected measurement error in both cases similarly, leading to biased estimates. In order to minimize the possibility of measurement error, the interviewers collecting information about SI were trained extensively and there was ongoing review of both the administration and scoring of the questions to ensure consistency across and within interviewers. The telephone-based setting as well as familiarity with interviewers who called each month should help minimize misreport of STLEs by participants due to embarrassment or fear of negative consequences.
Figure 3.1. Simplified directed acyclic graph for the associations between STLEs and the outcomes

Figure 3.2. Effective sample size over varying correlation values: Aim 1

Figure 3.3. Power to detect varying mean difference over different ESS: Aim 1
Figure 3.4. Effective sample size over varying correlation values: Aim 2

Figure 3.5. Power to detect varying prevalence ratios over different ESS: Aim 2

Table 3.1. Example of 1st three observations for two participants

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CHAPTER 4: RESULTS

Aim 1: Stressful and traumatic life events as disruptors to antiretroviral therapy adherence

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 US,\textsuperscript{1,5,69} in comparison to 12-13% of the general population.\textsuperscript{80} More attention has been paid recently to stressful and traumatic life events (STLEs) among PLWHA, which are common in this population,\textsuperscript{7,8} 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 personal or home 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.\textsuperscript{9}

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, during 27 months of follow-up, HIV-infected participants reported medians of nine incident stressful events and three incident severely stressful events.\textsuperscript{9} 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.\textsuperscript{9,16,81} 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.\textsuperscript{20}

Adherence to ARV medication is one important HIV-related outcome that STLEs may affect. 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.\textsuperscript{27,29-31} 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.\textsuperscript{9,10} Both studies relied on self-reported ARV adherence and long recall periods for STLEs, which may have affected the accuracy of exposure and outcome measurements.

The current study examined the longitudinal association between STLEs and ARV adherence, as 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,\textsuperscript{11} and are more sensitive than self-report to changes in adherence over time.\textsuperscript{36} 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. 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 July 1, 2011 and September 30, 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 or Traumatic Life Events. STLEs were assessed during monthly telephone calls with participants, using a modified version of the Life Events Survey (LES). Events from the LES considered moderately or severely stressful or traumatic based on prior research are included in this assessment. 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, regardless of category, 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. 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, to create a second discretely-coded variable. The severe-only total was dichotomized to indicate one or more severe STLEs vs. zero.
Antiretroviral Adherence. ARV adherence was measured by 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., bottles dispensed) and lost (e.g., pills 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, and 2) differences between pill count-based and self-reported adherence. Self-reported adherence was measured at baseline and every three months thereafter during structured research interviews (in-person at baseline and by telephone post-baseline), 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 to these two questions, ranging from 0%-100%, were averaged (after reverse-coding the second question) to get a measure ranging from 0-100%. 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; as all participants by definition aged one year or less during study participation, the enrollment value was
retained throughout. 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). Scoring of the HAM-D ranges from 0 to 50, and depressive severity was coded discretely. 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. Stress coping style was assessed with the Brief COPE instrument, which contains 18 examples of coping strategies; participants used a four-point Likert scale to rate how often they used each strategy: “Not at all,” “A little bit,” “A medium amount,” or “A lot.” Physical symptoms were measured using the HIV Symptom Inventory to indicate the total number of symptoms. 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. Drug and alcohol use were 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; a single variable indicating any abuse or dependence of drugs and/or alcohol, vs. none, was created.

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 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. 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. 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), to yield an estimate of the prevalence ratio (PR) for ≥95% adherence. All other analyses followed the approach described above.

In sensitivity analyses, marginal structural models were used to assess whether depressive severity was acting as a time-varying confounder, affected by prior exposure, of the relationship between STLEs and ARV adherence. Weights for the inverse probability of STLEs were calculated, multiplied by the IPOWs, and applied to analysis models. Effect estimates were compared to those resulting from the primary analysis models that assumed no time-varying confounding by depressive severity.

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 (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 all 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 2,634 monthly interviews, 1,412 (54%) were completed and included in the final analysis sample. Among the completed contacts, 3,373 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. Age was available for all participants. 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 1,412 completed observations, to account for the 46% of contacts that were not completed.
**Primary outcomes**

A greater number of STLEs was associated with poorer 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 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. An experience of 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 STLE was associated with decreased likelihood of ≥95% adherence, both overall (prevalence ratio (PR)=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.

**Sensitivity analyses**

To assess whether depressive severity was functioning as a time-varying confounder of the STLE-adherence relationship, we compared the above results to results using a marginal structural model obtained by combining weights for the inverse probability of STLEs with the IPOWs. Effect estimates were not qualitatively different from the main model in either strength or precision, suggesting that depressive severity does not need to be considered as a time-varying confounder in this analysis.

**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 ≥95% adherence. Participants experiencing at least the median number of STLEs in a given month had 18% lower likelihood of ≥95% adherence, compared to those experiencing less than the median number. This association was similar when limited to the most severe STLEs, contrary to our hypothesis that increasing severity of events would be associated more strongly with poor adherence.

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 (1-4)). This high burden of STLEs, similar in magnitude to that found in other studies, 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, the impact may be sufficient to reduce adherence below a critical threshold of adherence required for regimen effectiveness and prevention of resistance.\textsuperscript{82,83} 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.\textsuperscript{9,10} This is the first study to show 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,\textsuperscript{36} 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, in comparison to pill counts. This might be due in part to an increase in variability of the measurement, as self-reported adherence tends to be skewed upwards; however, it is likely also due to improved accuracy as a result of using a more objective measure. While participants counted the pills themselves, adherence was calculated later and not shared with participants, making it difficult to falsify their counting in order to maintain higher adherence. Telephone-based pill counts have been shown to be as accurate as researcher-performed pill counts.\textsuperscript{11}

Previous studies have also used dichotomous outcomes to indicate adherent vs. non-adherent, based on report of missing doses of ARVs. The 5% reduction in prevalence 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,\textsuperscript{9} 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. The use of prevalence ratios instead of odds ratios, as those studies used, 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 the negative effects of STLEs, in order to improve ARV adherence. One study found that, independent of overall psychological well-being, 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. 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. Other such interventions, focused on
reducing the incidence of and/or developing skills to cope with STLEs, could be developed for HIV-infected populations 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.
<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Median (IQR)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>205 (71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>84 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>45 (38-51)</td>
<td></td>
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</tr>
<tr>
<td>Marital status</td>
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<td></td>
</tr>
<tr>
<td>Married/cohabitating</td>
<td>62 (21)</td>
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<td></td>
</tr>
<tr>
<td>Single</td>
<td>225 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>White</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>181 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
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<td>Ethnicity</td>
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<tr>
<td>non-Hispanic</td>
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<td>Education</td>
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<td></td>
</tr>
<tr>
<td>Less than high school grad</td>
<td>40 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school grad</td>
<td>110 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than high school</td>
<td>136 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly household income ($)</td>
<td>1000 (674-1752)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Log-10 income ($)</td>
<td>3 (2.83-3.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently employed</td>
<td>76 (26)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Years since HIV diagnosis</td>
<td>11 (4-17)</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Baseline log10-viral load</td>
<td>1.67 (1.59-2.31)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Baseline viral load 50+</td>
<td>90 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count</td>
<td>539 (326-789)</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Baseline depression score</td>
<td>21 (15-25)</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Baseline self-reported adherence</td>
<td>98 (85-100)</td>
<td></td>
<td>26</td>
</tr>
</tbody>
</table>
### Table 4.2. Description of STLEs, Southeastern USA, 2010-2013 (n=289)

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

STLEs = Stressful and traumatic life events

*Includes: divorce/separation, death/illness of immediate family member, major financial problems, time in jail, and sexual and physical assault
Table 4.3. Associations Between STLEs and ARV Adherence, Pill Count-Based and Self-Reported, US, 2010-2013

<table>
<thead>
<tr>
<th></th>
<th>Pill Count-Based Adherence</th>
<th></th>
<th>Self-Reported Adherence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean % adherence difference (95% CI)</td>
<td>Adherence ≥95% PR (95% CI)</td>
<td>Mean % adherence difference (95% CI)</td>
<td>Adherence ≥95% PR (95% CI)</td>
</tr>
<tr>
<td><strong>All STLEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit increase in number</td>
<td>-0.99% (-1.89%, -0.09%)</td>
<td>0.95 (0.90, 0.99)</td>
<td>-0.63% (-1.61%, 0.35%)</td>
<td>0.98 (0.94, 1.02)</td>
</tr>
<tr>
<td>≥2 vs. &lt;2*</td>
<td>-3.67% (-7.12%, -0.21%)</td>
<td>0.82 (0.71, 0.95)</td>
<td>-1.63% (-5.16%, 1.91%)</td>
<td>0.91 (0.79, 1.05)</td>
</tr>
<tr>
<td><strong>Severe STLEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit increase in number</td>
<td>-2.43% (-5.16%, 0.30%)</td>
<td>0.84 (0.74, 0.96)</td>
<td>-1.99% (-5.50%, 1.52%)</td>
<td>0.89 (0.77, 1.04)</td>
</tr>
<tr>
<td>Any vs. none</td>
<td>-3.03% (-6.41%, 0.35%)</td>
<td>0.80 (0.69, 0.94)</td>
<td>-3.45 (-6.33, -0.58)</td>
<td>0.84 (0.74, 0.96)</td>
</tr>
</tbody>
</table>

STLEs=Stressful and traumatic life events; ARV=antiretroviral; PR=prevalence ratio; CI=confidence interval
*2=population median monthly number of STLEs
Figure 4.1. Proportion with ≥95% ARV Adherence by Number of STLEs

Figure 4.2. Proportion with ≥95% ARV Adherence by Number of Severe STLEs
Aim 2: Suicidal Ideation after Stressful or Traumatic Life Events

Introduction

Suicidal ideation (SI), whether passive (thoughts that life is not worth living or that an individual wishes to be dead) or active (plans to act on such thoughts), is one of the strongest and most proximal risk factors for suicide attempts and completions. SI is strongly associated with depression, and both SI and depression are more common among persons with chronic diseases, such as HIV, than among the general population. A population of persons with both HIV and depression, therefore, may be at particularly high risk for experiencing SI. Identification of risk factors and triggers for SI in this population would allow for targeted interventions aimed at reducing the incidence of SI and, as a result, suicide attempts and completions.

Stressful or traumatic life events (STLEs), which are common among persons with HIV, may trigger suicidal thoughts and lead to an increase in SI in HIV-infected populations with depression already susceptible to such thoughts. STLEs include events related to relationship changes; estrangement from family; health concerns; death or illness of family or friends; financial, legal, or employment difficulties; safety concerns; and life transitions. The high burden of STLEs in populations of HIV-infected adults has been demonstrated in prior studies. HIV-infected participants in the Coping with HIV/AIDS in the Southeast (CHASE) study reported medians of nine incident stressful events and three incident severely stressful events over two years of follow-up. A secondary, cross-sectional analysis of data from a randomized trial found HIV-infected participants at 13 clinical sites throughout the US experienced a mean of 5.6 STLEs per month; financial problems were the most common STLE, followed by unemployment. A small, cross-sectional study of 105 HIV-infected men and women in a southern US state found that participants had experienced a mean of 3.15 STLEs in the prior six months.

These and other studies among persons with HIV have identified associations between STLEs and negative clinical and behavioral outcomes, such as decreased medication adherence, virologic
failure, and increased sexually risky behavior, but SI as an outcome has not been examined previously in this population. While a relationship between STLEs and increased SI has been found in other studies, this has mainly been studied among children or adolescents, or in countries other than the US, and methodological differences have led to varying results and conclusions.\textsuperscript{47,51,85} No existing studies have examined this relationship among adults with both HIV and depression. The current study was carried out to examine the association between STLEs and SI over one year of follow-up among adults in the Southeastern US with HIV and depression while accounting for time-varying confounding of the association by depressive severity.

Methods

Study Sample

Data for this study came from the \textit{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.\textsuperscript{54} The study population is made up of adult (age 18-65 years) HIV-infected patients with depression who attended the infectious disease clinics at Duke University; the University of Alabama at Birmingham (UAB); Northern Outreach Clinic (NOC) in Henderson, North Carolina; and the University of North Carolina at Chapel Hill (UNC). The present analysis is restricted to participants under observation between July 1, 2011 and March 31, 2014. This time period corresponds to when data on STLEs were collected. All study procedures were approved by the Institutional Review Boards at UNC, Duke University, and UAB.
**Measures**

*Suicidal Ideation.* SI was measured with the Hamilton Rating Scale for Depression (HAM-D) during telephone interviews conducted at enrollment and at three, six, nine, and twelve months post-enrollment. The HAM-D, the most widely used depressive severity measure in research settings, consists of 17 open-ended sections assessing different facets of depressive symptoms experienced during the past seven days.\(^{62-64}\) The third section addresses SI by asking whether the individual has 1) had thoughts that life is not worth living, 2) had thoughts that s/he would be better off dead, 3) had thoughts of hurting or killing himself/herself, and/or 4) actually tried to hurt or kill himself/herself. Additional probes were asked based on the participant’s responses to these questions. One score is obtained from the four questions and additional probes of the SI section, and ranges from 0-4 as follows: (0): no symptoms; (1): feels that life is not worth living; (2): wishes that s/he were dead, or had thoughts about hurting self; (3): suicidal ideas of gesture (has a plan, or began suicide attempt but stopped); (4): a suicide attempt during the past week. Responses falling between two scores were scored conservatively (given the lower score) by the interviewers. Scores were dichotomized to indicate any suicidal ideation (score >0) vs. none (score of 0).

*Stressful and Traumatic Life Events.* STLEs were assessed during monthly telephone calls with participants using a modified version of the Life Events Survey (LES).\(^{10,59}\) Only those events from the LES considered moderately or severely stressful based on prior research are included in this assessment.\(^{60,61}\) Participants were asked whether they had experienced any of 46 events, from within nine different categories, during the prior month. STLE categories were: 1) romantic relationship changes; 2) estrangement from family; 3) death or major illness of a family member or close friend; 4) major illness, injury, or hospitalization; 5) employment difficulties; 6) financial difficulties; 7) legal difficulties; 8) life transitions; 9) safety concerns. To match the quarterly assessments of SI, the monthly average of STLEs was determined by summing the number of STLEs reported during the quarter for each participant and
dividing by the number of completed assessments in that quarter (to account for missed assessments).
The three most recent measures were used in instances in which there were more than three measures in a given period. This average was coded continuously, and also dichotomized to indicate experiencing at least the study population median number of STLEs vs. less than the median number. Additionally, based on prior work, STLEs limited to the most severe events (divorce or separation, death or major illness of an immediate family member, major financial problems, time in jail, and sexual and physical assault) were combined to create both continuous (number of severe events) and dichotomous (any vs. none) variables.

Additional Covariates. Depressive severity was measured with the HAM-D\(^{62-64}\) at baseline and every three months thereafter, during scheduled, telephone-based interviews. Scoring of the HAM-D ranges from 0 to 50; however, scores were recalculated to exclude the SI section, resulting in scores ranging from 0 to 46. Coding of scores was kept continuous to retain information.

Other covariates used in the analysis were age, sex, drug and/or alcohol abuse or dependence, HIV-related physical symptoms, mental health functioning, CD4 count, psychiatric comorbidities, HIV-care self-efficacy, stress coping style, and employment status. Sex and age were assessed at study enrollment. Drug and alcohol dependence and abuse were assessed at baseline and at six- and twelve-month follow-ups with the alcohol and substance dependence and abuse sections of the Mini International Neuropsychiatric Interview (MINI), a widely used psychiatric diagnostic instrument. A single variable indicating any abuse or dependence of drugs and/or alcohol, versus none, was also created. HIV-related physical symptoms were measured at baseline and every three months using the HIV Symptom Inventory\(^{69}\) to indicate the total number of symptoms, coded discretely. Mental health functioning was also measured at baseline and at six- and twelve-month follow-ups using the Short Form-12, scored on a 0-100 scale (with higher numbers indicating greater functionality; US population mean=50, one standard deviation (SD)=10).\(^{76,77}\) CD4 count was measured at baseline and at six and
twelve months post-baseline. Psychiatric comorbidities were measured at baseline using the MINI, and
dichotomized to indicate any comorbidity (e.g. dysthymia, anxiety disorder) other than depression vs.
none. HIV-related self-efficacy was measured at baseline and every three months 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.\textsuperscript{66} Also at baseline
and every three months, stress coping style was assessed with the Brief COPE instrument, which
contains 18 examples of coping strategies; participants used a four-point Likert scale to rate how often
they used each strategy: “Not at all,” “A little bit,” “A medium amount,” or “A lot.”\textsuperscript{67,68} Employment
status was assessed at baseline and every three months thereafter; in analyses it was dichotomized to
indicate employed vs. unemployed.

\textit{Statistical Analysis}

The associations between each coding of STLEs and SI were estimated using Poisson models
with robust variance (instead of a log-binomial model due to model convergence issues\textsuperscript{78}), accounting
for repeated observations among participants. These models yielded estimates of the prevalence ratio
of experiencing SI associated with higher numbers of STLEs. To deal with non-trivial amounts of missing
data, multiple imputation was combined with inverse-probability-of-observation weighting.\textsuperscript{71,72} Among
completed interviews, missing values for all variables included in analyses were imputed using multiple
imputation by chained equations.\textsuperscript{73} Ten cycles of imputation were carried out per imputed dataset; 50
datasets were imputed and analyzed. After imputation, to address potential selection bias due to
excluding uncompleted contacts, inverse-probability-of-observation weights were calculated for the
inverse probability of completing a given interview conditional on measured covariates, using a logistic
model. 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 inverse-probability-
of-observation weights were stabilized by the marginal probability of interview completion.
Depressive severity was theorized to act as both a time-varying confounder and mediator of the relationship between STLEs and SI over time. Depression may increase the incidence of certain STLEs (e.g., employment, financial, and legal difficulties) and also increase the risk of SI, suggesting that an estimate that does not account for confounding by depression would be biased (see Figure 1, arrows a and e). However, STLEs would be expected to affect SI in part by leading to depression. This observation implies that (subsequent) depression is a mediator of the STLE-SI relationship and an analysis that adjusts for time-varying depression would block part of the causal pathway (Figure 1, arrows b and c), leading to a biased estimate of the total effect of interest. To remove bias due to time-varying confounding by prior depression while avoiding blocking the pathway through subsequent depression, inverse-probability-of-exposure weights were calculated, for the inverse probability of exposure to STLEs. Applying these weights to the analysis models allowed us to break the association between prior depressive severity and STLEs, corresponding to arrow a in Figure 1, without blocking the mediating pathway from STLEs through subsequent depressive severity to SI (arrows b and c).

In the inverse-probability-of-exposure weight calculation, the denominator probabilities were conditional on baseline and lagged SI; lagged STLEs; current, baseline, and lagged depressive severity; and current and baseline confounders of the STLE-adherence relationship. Logistic regression was used to calculate the inverse-probability-of-exposure weights for the two dichotomous outcomes, while ordinal logistic regression was used to calculate the weights for continuously-coded exposures, categorized into deciles (for overall STLEs) and tertiles (for severe STLEs). All exposure weights were stabilized by the marginal probabilities of exposure. The inverse-probability-of-exposure weights were combined by multiplication with the inverse-probability-of-observation weights to create final (“full”) weights for each observation, which were applied to the analysis models. In sensitivity analyses, to assess any effects of extreme weights on the magnitude and precision of estimates, the full weights were truncated at the 1st and 99th percentiles. To assess the extent to which time-varying confounding
affected the estimates, these models were compared to multivariable models that adjusted for all inputs into the weighting models but did not use the weights themselves.

Results

Study Population

Two hundred eighty-nine participants were enrolled in the SLAM DUNC study while STLEs were being measured. Most participants (70%) were male, 62% were black, and 97% were non-Hispanic. The median (interquartile range [IQR]) age was 45 (37-51), and participants reported contracting HIV, on average, 11 years prior to study enrollment. Eighty-seven percent had at least high school-level education, 78% were single, and 27% were employed at enrollment. Eighty-five (34%) participants reported any SI at the baseline interview; the vast majority of these, 83 participants, had a score of one or two, corresponding to passive SI (Table 1).

Participants completed between zero and four (the maximum possible number) interviews after enrollment (median=2, IQR=0-3). Five hundred six (49%) of the total possible 1,041 quarterly interviews were completed and therefore included in analyses. The 289 participants reported a total of 2,270 STLEs, a mean of 2.36 events per month; the number of STLEs experienced in a month ranged from 0 to 12, with a median (IQR) of 2 (0-4). Four hundred fifty-seven severe STLEs were reported, a mean of 0.48 events per month. Financial difficulties were most commonly reported, with 1.23 events/month, followed by illness, injury, or hospitalization of the participant (0.27 events/month) and employment difficulties (0.25 events/month). Legal troubles were reported with the least frequency (0.03 events/month) (Table 2).

Missing Data

Age, sex, baseline marital status, and psychiatric comorbidity data were available for all participants. Multiple imputation was used to impute missing baseline values for <1% of alcohol
dependency and adaptive coping; 1% of employment status; 2% of self-efficacy, SF12 mental functioning and HIV-related symptoms; 5% of SI; 6% of HAM-D; and 13% of CD4 count values. For post-baseline variables, values were imputed for <1% of SI and HAM-D, 1% of HIV-related symptoms, and 7% of drug and/or alcohol abuse or dependence.

In calculating the inverse-probability-of-observation weights, baseline predictors of completing interviews were age, employment, CD4 count, self-efficacy, SF12 mental functioning score, alcohol dependence, and adaptive coping. A time-updated variable indicating whether the previous contact was completed was also included in the weighting model. For additional stabilization, lagged STLE variables were added to both the numerators and denominators of the weights. Cubic splines for all continuous variables were also included in the denominators. These weights all had means close to one and tight ranges (Table 3).

**Exposure and Full Weights**

The inverse-probability-of-exposure weights for the continuous, overall STLE exposure had a mean of 0.95 (SD=1.57) and a range of 0.09 to 85.82. The combined inverse-probability-of-observation/inverse-probability-of-exposure weights, or “full weights,” had a mean of 0.96 (SD=1.73) and range of 0.08 to 82.36 for the overall, continuous STLE exposure model. Weights for the other exposure measures were similarly well-behaved (Table 3).

**Primary Outcomes**

Greater numbers of STLEs, both overall and severe, were associated with increased prevalence of experiencing SI. In the final weighted model, each additional STLE was associated with a 22% increase in prevalence of SI (prevalence ratio (PR): 1.22, 95% confidence interval (CI): 1.01, 1.48), while each additional severe STLE was associated with a 70% increase in prevalence of SI (PR: 1.70, 95% CI: 1.01, 2.87). Experiencing at least the median number of STLEs was not associated with an increased
prevalence of SI in comparison with experiencing less than the median (PR: 1.06, 95% CI: 0.58, 1.96).
Experiencing any severe STLE vs. none suggested an increased prevalence of SI (PR: 1.26, 95% CI: 0.69, 2.28) (Table 4).

Crude results were all further from the null than weighted results, while multivariable-adjusted results were all closer to the null (except for comparing at least the median number of STLEs to less than the median). Truncating weights at the 1st and 99th percentiles did not qualitatively changes the estimates for the continuously-measured exposures, but it did increase their precision, as expected. For the dichotomous exposures, however, the estimates were biased away from the null and were more precise than with the original weights.

Discussion

STLEs were common in this population of adults with depression and HIV in the Southeastern US, and associated with higher prevalence of experiencing SI. For each additional STLE per month there was a 22% increase in prevalence of SI, and for each additional severe STLE there was a 70% increase in prevalence of SI (Table 4). These prevalence ratios correspond to important increases in prevalence in a population in which SI was reported in 15% of observations with the median number of STLEs (2) and 17% of observations with the median number of severe STLEs (0.33).

Little is known about the burden of STLEs in this type of population of persons with both HIV and depression. The burden of STLEs in this sample was higher than that in HIV-infected populations without depression in similar settings (the Southeastern US), which might be expected under the hypothesis that depression can affect STLEs. While our participants experienced more than two STLEs per month, on average, and one severe STLE every two months, Mugavero, et al found a median of nine STLEs and three severe STLEs over nearly two years of follow-up, and Leserman, et al found a mean of roughly three STLEs in a six-month period. In a more nationally representative study of HIV-infected adults, however, the number of STLEs participants experienced per month was more than twice the
number our participants experienced. Similarly, the baseline burden of SI in this population was in line with that found in related populations. Badiee, et al. found a SI prevalence of 26% in an HIV-infected population (without depression), and Gaynes, et al. found a prevalence of 45% in depressed patients in primary care (HIV-uninfected).

In a review of the existing studies assessing the relationship between STLEs and SI, Liu, et al. present heterogeneous estimates of association that are mostly from studies of children or adolescents, or adults outside the US. None of the studies were conducted among HIV-infected persons. In a study of predictors of SI in a random sample of South Australians, Goldney, et al. found elevated risk of SI associated with experiencing a psychosocial event (RR: 2.21, 95% CI: 1.48, 2.38) and with experiencing a traumatic event (RR: 2.49, 95% CI: 1.49, 4.18). Both estimates are stronger than ours; however, these estimates are from univariate analyses and therefore might be exaggerated by confounding. In contrast to these estimates indicating a strong association, other studies found no association between STLEs and SI. The current study provides a methodologically rigorous assessment of the STLE-SI association to add to that literature, and provides the first known assessment of this relationship in an HIV-infected population.

The use of inverse-probability-of-exposure weights allowed us to account for time-varying confounding by depressive severity. As it was theorized to be both a mediator and a confounder of the STLE-SI association, we wanted our estimate of the total effect of STLEs on SI to include the portion that works through current depression while removing confounding from prior depression. Including concurrent and lagged depressive scores in the denominators of the exposure weights yielded marginal estimates of the associations of interest. The crude, unweighted estimates were all further from the null, which can be interpreted as being confounded upwards by prior depressive severity. The multivariable-adjusted estimates, also unweighted, were nearly all closer to the null than the weighted estimates, suggesting that adjusting for depressive severity not only blocked the confounding by prior
depressive severity but also blocked the mediating pathways through subsequent depressive severity. The weighted estimates thus allowed us to block confounding while allowing mediation, to obtain more accurate results.

A strength of this study was that STLEs and SI were measured close in time, and at multiple times over the course of follow-up, allowing for assessments of recent stressors and subsequent SI. This is an improvement over the measurement of most prior studies that have used cross-sectional measurement and/or long recall periods for measurement of STLEs. As both STLEs and SI were measured by self-report, there is the potential for dependent measurement error, but they were measured during different interviews and in different contexts, which should have helped avoid some of the possibility of bias.

The large amount of missing data resulting from low retention during follow-up in the SLAM DUNC study is a limitation of this study. To address it, 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. This approach should be less biased than a complete case analysis, and the two-pronged approach helped to mitigate the potential bias resulting from misspecification of models in either prong. There is, however, the possibility that missingness could also be a function of unobserved characteristics. If missingness were associated both with higher numbers of STLEs and with higher prevalence of SI, for example, the present analysis would likely have underestimated the actual association of STLEs with SI; however, overestimation is also a possibility. We also cannot exclude the possibility of misspecification of the weighting models, the imputation models, or both.

The inclusion of STLE and SI history in the denominators of the inverse-probability-of-exposure weights permitted us to estimate the association between the most recent STLEs (in the past three months) and current SI at each time point, independent of prior history. From the perspective of a
hypothetical randomized controlled trial, this would correspond to random assignment of STLEs over a three-month period and assessment of SI at the end of three months, repeated multiple times. The inverse of the reported PR could therefore be thought of as the impact on SI of an intervention to reduce STLEs over a three-month period.

SI was common in this population of HIV-infected adults with depression, and STLEs, which were also common, were identified as an important risk factor for SI. Efforts to reduce exposure to STLEs or to improve individuals’ skills for coping with STLEs could therefore help reduce SI. Studies have shown that interventions aimed at improving depression care and initiating expressive writing about STLEs were associated with fewer STLEs and improved health and quality of life, respectively. Other interventions focused on reducing the incidence of STLEs and developing skills to cope with STLEs could be developed for HIV-infected populations, which independently of STLEs are also more prone to depression and therefore to SI. Interventions could also focus on increasing provider awareness and assessment of STLEs to better target those patients at increased risk of SI to receive more intense support services. Overall, such efforts could play an important role in reducing SI, which is one of the strongest and most proximal risk factors for suicide attempts and completions.
Table 4.4. Study sample characteristics (n=289)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Median (IQR)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>204 (71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>85 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>45 (37-51)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Married/cohabitating</td>
<td>62 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>224 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>100 (35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>179 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-Hispanic</td>
<td>276 (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Less than HS grad</td>
<td>38 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school grad</td>
<td>110 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than high school</td>
<td>137 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly household income, $</td>
<td>1,000 (674-1,900)</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Monthly household income, log10</td>
<td>3.0 (2.8-3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently employed</td>
<td>77 (27)</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Years since HIV diagnosis</td>
<td>11 (4-17)</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>HIV RNA viral load, log10</td>
<td>1.4 (1.4-2.1)</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Viral load &lt;48 copies/mL</td>
<td>177 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count, cells/mm³</td>
<td>549 (331-784)</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Depression score</td>
<td>21 (15-25)</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Suicidal ideation*</td>
<td></td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Any (score &gt;0)</td>
<td>85 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>168 (66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>31 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>52 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Scores: 0=absent, 1=feels life not worth living, 2=Wishes that he/she was dead, or had thoughts about hurting self, 3=suicidal ideas of gesture, 4=suicide attempt in past week
Table 4.5. Description of Stressful or Traumatic Life Events (STLEs)

<table>
<thead>
<tr>
<th>Type of STLE</th>
<th>Per person-month</th>
<th>Per person-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial difficulties</td>
<td>2.36</td>
<td>28.32</td>
</tr>
<tr>
<td>Major illness, injury, or hospitalization</td>
<td>1.23</td>
<td>14.76</td>
</tr>
<tr>
<td>Employment difficulties</td>
<td>0.27</td>
<td>3.24</td>
</tr>
<tr>
<td>Death or illness of family member or friend</td>
<td>0.25</td>
<td>3.00</td>
</tr>
<tr>
<td>Safety concerns</td>
<td>0.24</td>
<td>2.88</td>
</tr>
<tr>
<td>Romantic relationship changes</td>
<td>0.10</td>
<td>1.20</td>
</tr>
<tr>
<td>Estrangement from family</td>
<td>0.09</td>
<td>1.08</td>
</tr>
<tr>
<td>Life transitions</td>
<td>0.08</td>
<td>0.96</td>
</tr>
<tr>
<td>Legal difficulties</td>
<td>0.06</td>
<td>0.72</td>
</tr>
<tr>
<td>Severe STLEs*</td>
<td>0.03</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Severe STLEs* includes: divorce or separation, death or illness of immediate family member, major financial problems, time in jail, and sexual and physical assault

Table 4.6. Weight Distribution

<table>
<thead>
<tr>
<th>Exposure Coding</th>
<th>Inverse-Probability-of-Observation Weights</th>
<th>Inverse-Probability-of-Exposure Weights</th>
<th>Full Weights*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Min, Max</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>All STLEs, continuous</td>
<td>1.02 (0.15)</td>
<td>0.78, 2.27</td>
<td>0.95 (1.57)</td>
</tr>
<tr>
<td>Severe STLEs, continuous</td>
<td>1.02 (0.16)</td>
<td>0.79, 2.21</td>
<td>0.99 (1.06)</td>
</tr>
<tr>
<td>All STLEs, dichotomous</td>
<td>1.02 (0.15)</td>
<td>0.84, 2.07</td>
<td>1.02 (1.53)</td>
</tr>
<tr>
<td>Severe STLEs, dichotomous</td>
<td>1.02 (0.16)</td>
<td>0.84, 2.24</td>
<td>0.98 (0.72)</td>
</tr>
</tbody>
</table>

*Product of inverse-probability-of-observation and inverse-probability-of-exposure weights
<table>
<thead>
<tr>
<th>STLEs</th>
<th>Suicidal Ideation PR (95% CI)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted</td>
<td>Weighted</td>
<td></td>
</tr>
<tr>
<td>All STLEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit increase</td>
<td>1.26 (1.17, 1.35)</td>
<td>1.04 (0.92, 1.19)</td>
<td>1.22 (1.01, 1.48)</td>
<td></td>
</tr>
<tr>
<td>≥2 vs. &lt;2*</td>
<td>2.81 (1.69, 4.65)</td>
<td>1.11 (0.70, 1.78)</td>
<td>1.06 (0.58, 1.96)</td>
<td></td>
</tr>
<tr>
<td>Severe STLEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit increase</td>
<td>2.34 (1.81, 3.01)</td>
<td>1.31 (0.83, 2.06)</td>
<td>1.70 (1.01, 2.87)</td>
<td></td>
</tr>
<tr>
<td>Any vs. none</td>
<td>2.55 (1.54, 4.23)</td>
<td>1.20 (0.71, 2.01)</td>
<td>1.26 (0.69, 2.28)</td>
<td></td>
</tr>
</tbody>
</table>

*2=population median monthly number of STLEs
STLEs=Stressful or traumatic life events, PR=prevalence ratio
Figure 4.3. Directed Acyclic Graph of the Relationship between Stressful or Traumatic Life Events, Depressive Severity, and Suicidal Ideation.
CHAPTER 5: DISCUSSION AND CONCLUSIONS

A growing literature has highlighted the high prevalence of STLEs among PLWHA,\textsuperscript{7,8} a population that already faces a number of challenges related to their infection, including but not limited to life-long use of antiretroviral (ARV) medications, HIV-related stigma, opportunistic infections, and depression. STLEs may have important implications for various psychological and behavioral outcomes; many associations with negative outcomes have been demonstrated.\textsuperscript{8,9,16,81}

The purpose of this dissertation was to examine the burden of STLEs among adults in the Southeastern US with both HIV and depression, and to assess the association of STLEs with the behavioral and psychological outcomes of ARV adherence and suicidal ideation. The following discussion summarizes, synthesizes, and interprets the key findings of both research aims that were separately summarized and discussed in previous chapters. Overall strengths and limitations are highlighted and addressed, and future research directions are discussed.

Summary of Findings

The data for this research came from the SLAM DUNC study, a randomized controlled trial testing the effectiveness of measurement-based depression treatment at improving ARV adherence among adults with HIV and depression in North Carolina and Alabama. Both of the specific aims were restricted to participants under observation in the study between July 1, 2011 and March 31, 2014, the time period during which data on STLEs were being collected. There were 289 participants available for each study aim, with multiple observations made over up to 12 months of follow-up; for Aim 1, this resulted in 2,634 possible monthly observations and for Aim 2, 1,041 possible 3-monthly observations, corresponding to the time frame for outcome measurements. In both datasets, the burden of STLEs was
high, with participants experiencing, on average, 2.48 events per month in Aim 1 and 2.36 events per month in Aim 2. In both aims, on average participants reported experiencing a severe STLE every two months.

For both study aims, there was substantial missing data, and we applied a relatively little-used strategy of combining inverse-probability-of-observation weighting with multiple imputation. This allowed us to take advantage of the efficiency of multiple imputation while avoiding the need to impute large swaths of data when entire study contacts were not completed. We were able to use all completed study contacts in analyses, which were weighted to account for the uncompleted contacts that were excluded, and only impute missing values on data points that were missing among the completed contacts, making the specification of imputation models simpler. The availability of a large number of covariates for inclusion in weighting and imputation models made the assumption that missing data were missing at random conditional on observed characteristics more plausible; however, it is possible that missingness was also a function of unobserved characteristics. If the latter were true, we hypothesize that missingness would be associated with higher numbers of STLEs, poorer adherence, and higher prevalence of SI, and that our analyses would therefore have underestimated the true associations.

We hypothesized that depressive severity was acting as a time-varying confounder, affected by prior exposure, of the relationships between STLEs and ARV adherence/SI, meaning that depressive severity was both a mediator and confounder of the relationships (Figure 3.1). In this type of situation, a marginal structural model approach can be used in order to break the association between depressive severity and STLEs, yielding marginal estimates of the associations between STLEs and the outcomes. In both research aims, the hypothesis that depressive severity was acting in this way was addressed by assessing the associations between depression and STLEs, and between depression and the outcomes, as well as by assessing changes in estimates of association when using or not using a marginal structural
model approach. In Aim 1, based on these tests, we concluded that a marginal structural model was not needed; however, in Aim 2 we concluded that it was necessary. Inverse-probability-of-exposure weights were created in order to break the confounding by depressive severity while maintaining its mediation role. The weights for all four exposures (total and severe-only STLEs, continuously measured and dichotomized) were well-behaved with means close to 1.0 and reasonable ranges (Table 4.6). The inverse-probability-of-exposure weights were combined by multiplication with the inverse-probability-of-observation weights, to yield final weights which were also well-behaved. The final weights were applied to the analysis models.

In the first research aim, we analyzed the association between STLEs and pill count-measured ARV adherence, both of which were measured monthly at the same study contact. A greater number of STLEs was associated with poorer ARV adherence. Each additional STLE experienced was associated with a mean difference (95% CI) in ARV adherence of -0.99% (-1.89%, -0.09%). The association was stronger when comparing participants with at least the median number of STLEs 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 additional event was associated with a more extreme mean difference of -2.43% (95% CI: -5.16%, 0.30%) and an experience of any severe STLE vs. none was associated with a mean adherence difference (95% CI) of -3.03% (-6.41%, 0.35%) (Table 4.3). Each additional STLE was also associated with decreased likelihood of ≥95% adherence, both overall (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 4.3). Results were attenuated toward the null when self-reported ARV adherence was used as the outcome.

In the second research aim, the outcome of interest was suicidal ideation. Greater numbers of continuously-measured STLEs, both overall and severe, were associated with increased prevalence of
experiencing SI. The inverse probability-weighted prevalence ratio for SI was 1.22 (95% CI: 1.01, 1.48) for each additional STLE, and 1.70 (95% CI: 1.01, 2.87) for each additional severe STLE. Neither experiencing at least the median number of total STLEs vs. less than the median, nor experiencing any severe STLE vs. none was associated with statistically significantly increased prevalence of SI (Table 4.7). We did not find the association to be modified by either self-efficacy or stress coping style, as estimates within strata of those variables were not qualitatively different, and interaction terms between STLEs and the variables that were added to the analysis models were not statistically significant.

Interpretation of Findings

The results of the first study aim contribute to the existing literature about the relationship of STLEs with ARV adherence among persons with HIV. We believe that by measuring adherence with monthly pill counts, and by assessing prior-month STLEs over time, we have improved upon the exposure and outcome measurements of prior studies, therefore obtaining more accurate estimates of the association. The 1% difference in adherence for each additional STLE that we found was modest, yet relatively precise and statistically significant. Given that, on average, participants experienced more than two STLEs each month, and the number of STLEs experienced ranged from zero to 14, this modest difference could end up having a big impact on overall adherence. Someone experiencing ten STLEs in a given month would be expecting to have 10% lower adherence than someone with no STLEs. Also, comparing the highest burden of STLEs to a lower burden (at least the mean number of STLEs vs. less than the mean), the mean difference in adherence was more extreme, at nearly 4%. Perhaps most importantly, the likelihood of achieving ≥95% adherence was reduced as the number of STLEs went up; each additional STLE was associated with a 5% reduction in the likelihood of ≥95% adherence, and experiencing at least the median number of STLEs with an 18% reduction. These reductions were even more marked when looking only at the most severe STLEs was associated with a 16% reduction. These results suggest that while the impact of STLEs on continuously measured adherence may be modest, the
impact may be sufficient to reduce adherence below a critical threshold of adherence required for regimen effectiveness and prevention of resistance.\textsuperscript{82,83} It is also possible that the modest mean difference is related to the overall high ARV adherence among participants. Across all study contacts, the median adherence was 96\% (IQR: 83-100\%); with such high adherence, there is little room to detect a difference. This type of “ceiling effect”\textsuperscript{90} has long been noted as a challenge in studying adherence.

We found, as hypothesized, that the estimates of association were attenuated towards the null, and in most cases no longer statistically significant (only two estimates were statistically significant), when ARV adherence was measured by self-report instead of pill counts. This is likely due to an even more pronounced ceiling effect and less variability in adherence, as the median adherence across study contacts was 100\% (IQR: 95-100\%). It is well-known that self-reported adherence tends to be biased upward;\textsuperscript{36} it is therefore not surprising that we found higher mean adherence and attenuated results when using self-report instead of pill counts, which are more objective due to calculation of adherence by investigators after the counts.

In the second study aim, in which we examined the relationship between STLEs and suicidal ideation, we obtained, to our knowledge, the first estimates of this association in a population of adults with both HIV and depression. Other studies have investigated this association; however, they have mainly been carried out in adolescent or general clinic populations, many times in foreign countries, and they have yielded mixed results.\textsuperscript{47} We found an elevated prevalence of experiencing SI with higher numbers of continuously measured STLEs, both overall (PR: 1.22) and when limited to the most severe events (PR: 1.70), but not for dichotomously measured STLEs. The 22\% increase in prevalence of SI for each additional total STLE and 70\% increase for every severe STLE is potentially even more significant when considering that 15\% of those with the median number of STLEs (2) and 17\% of those with the median number of severe STLEs (0.33) reported SI. As the numbers of STLEs increase above the medians, therefore, a substantial portion of the population would be expected to experience SI.
The use of inverse-probability-of-exposure weights in Aim 2, to address time-varying
confounding by depressive severity, allowed us to obtain more valid estimates of the association
between STLEs and SI. The inclusion of potential confounders, including depressive severity, in the
denominators of the weights, as well as history of both STLEs and SI, means that the STLE exposure in
each 3-month period more closely resembles random assignment than a usual observed exposure. The
inverse of the estimated prevalence ratios, therefore, correspond to the reduction in SI that could be
achieved by preventing STLEs. The crude estimates (weighted only by the inverse-probability-of-
exposure) were all further from the null than the inverse-probability-of-exposure-weighted estimates,
which we interpreted as being confounded upwards by prior depressive severity. In contrast, the
multivariable-adjusted estimates, also weighted only by the inverse-probability-of-exposure, were
nearly all closer to the null than the inverse-probability-of-exposure-weighted estimates. This suggests
that by adjusting for depressive severity, we blocked not only the confounding pathway through prior
depressive severity but also the mediating pathway through subsequent depressive severity. The
inverse-probability-of-exposure-weighted estimates thus allowed us to block confounding while
allowing mediation, to obtain estimates corresponding to the total effect of STLEs on SI.

In both study aims, we used a combination of inverse-probability-of-observation weighting and
multiple imputation to deal with missing data. This is a relatively novel missing data approach that has
been used sparingly with real (as compared to simulated) data. Our data were particularly well suited to
this approach, given that most of the missingness among the data was a result of missing entire study
contacts, and not due to missed or unanswered items within a given, completed contact. Using multiple
imputation alone, therefore, would have required imputing exposure, outcome, and covariate values for
missed contacts. With such a large amount of data being imputed, any misspecification of the
imputation models would potentially lead to bias in the resulting estimates of association. Instead, we
simply excluded missed contacts and used inverse probability weights to rebalance the included
(completed) contacts by how likely, based on measured characteristics, they were to be observed. Among the included contacts, the smaller amounts of missing data values were imputed. We have therefore provided one of the few real-world examples of the application of this missing data approach.

Taking the results of both study aims together, we have demonstrated that in this population of HIV-infected adults with depression in the US Southeast, STLEs are common and impactful. Along with other challenges facing individuals in this population, STLEs pose barriers to care and treatment, as they are associated with poorer ARV adherence. As adequate adherence is necessary to maintain health and prevent disease transmission, identification of and intervention upon its barriers is important. We have also shown that STLEs are associated with prevalence of SI, which is significant not only as a predictor of suicide attempts and completions, but also in its detrimental effect on quality of life. The magnitude of the impact of any given STLE might be relatively modest, but given how common they are, the overall effect can be quite meaningful.

**Future Research Directions**

In both study aims, our exposure of interest was moderately to severely stressful or traumatic life events, as measured by the Life Events Survey (LES). For all analyses, we focused on the total number of STLEs experienced, or on the total number of the most severe of the STLEs, based on prior work. It is plausible, however, that different events would be associated differently with the outcomes of interest. For example, both experiencing a fight with a romantic partner and experiencing the death of a parent counted equally as one event each in our analyses. It is likely, of course, that potential disruptions to ARV adherence and/or triggering of suicidal thoughts would be of different magnitude for these two types of events. As we did not assess how each event affected participants, however, we chose to use the most objective measure possible, and not make assumptions about the relative importance of individual events. A reasonable and interesting next step would be to examine individual STLEs, and/or the nine different categories of STLEs, separately in relation to ARV adherence and SI, to
determine which are relatively most strongly associated, and in which direction. This would inform interventions and further study, by identifying which events are the most impactful; those types of events could be targeted for prevention, or people experiencing those types could be targeted for interventions to help them cope with any negative effects.

As we found relatively high ARV adherence overall, it is possible that the modest differences in mean adherence by number of STLEs was a result of limited variability in the outcome. In an attempt to increase variability, our analyses could be done among those participants with lower baseline self-reported ARV adherence (e.g. less than 95%). The high adherence in our study population is likely related to the fact that most participants had been in established HIV care for some time at the time of study enrollment, and therefore in most cases had been taking ARVs for some time. Future research could focus more on acute infections, and the association between STLEs and ARV adherence as individuals are establishing care and their medication-taking routines; it is likely that, as patients are taking new medications and getting used to a routine, disruptions like STLEs would have more of an impact on their adherence.

Due to the distribution of SI in our study population, we were precluded from assessing the relationship between STLEs and ordinally-coded SI (none, passive, active). The vast majority of the SI reported across all study contacts was passive; we therefore were not able to assess whether STLEs were more associated with either more or less severe SI, or whether the relationship would be unchanged. This differentiation would be of interest from a clinical standpoint, as active SI would be more likely to lead to a suicide attempt than passive SI. Future studies, if the data allow, could aim to tease out any differences in the relationship depending on the passive vs. active status of reported SI. Greater variability in the distribution of SI scoring could potentially be obtained by recruiting individuals with more severe depression and/or history of SI or a suicide attempt.
Our results show that STLEs are associated with negative outcomes; development of interventions to reduce STLEs or to mitigate their effects would therefore likely lead to better outcomes. Such interventions could be randomized and studied in similar study populations to determine whether and to what extent they are successful. For example, an intervention could entail training of HIV providers in the assessment of STLEs and provision of a social worker or therapist to help patients work through the STLEs they are experiencing; the effect of the intervention on clinical outcomes and on subsequent number or severity of STLEs could be assessed.

Conclusions

STLEs are commonly experienced by HIV-infected persons with depression, and are associated with negative behavioral and psychological outcomes such as ARV adherence and depression, among others. In addition, the experience of STLEs on its own can be expected to decrease quality of life, independently of any outcomes. Interventions have previously been shown to both reduce the number of STLEs experienced and mitigate the negative impact of STLEs that are experienced. Similar interventions could be tailored to this type of population, and additional interventions could be developed, to reduce the burden and mitigate the consequences of STLEs, in order to improve physical and mental health and quality of life.
APPENDIX 1

Full DAG: STLEs and ARV Adherence
Full DAG: STLEs and Suicidal Ideation
REFERENCES


