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Alcohol-antiretroviral therapy interactive toxicity beliefs and daily medication adherence and alcohol use among people living with HIV

Jennifer A. Pellowski¹, Seth C. Kalichman², Moira O. Kalichman², and Chauncey Cherry²

¹Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University, Providence, RI

²Department of Psychology, University of Connecticut, Storrs, CT

Abstract

Alcohol-antiretroviral therapy (ART) interactive toxicity beliefs reflect perceived adverse outcomes of mixing alcohol and ART. Previous research has shown a significant relationship between alcohol-ART interactive toxicity beliefs and ART non-adherence, over and above other correlates of non-adherence such as HIV symptoms and frequency of alcohol use. Most past studies have collected data over extended periods and have not determined if alcohol use and missed medications occur at the day-level among people holding interactive toxicity beliefs. Previous daily analyses, however, have been limited by self-reported adherence and relatively short periods of observation. To address these gaps in the literature, men and women living with HIV in Atlanta, GA were enrolled in a 45-day observational cohort study. Daily alcohol use was collected using two-way interactive text message surveys and daily adherence was collected via the Wisepill device. Fifty-seven participants completed a measure of alcohol-ART interactive toxicity beliefs and contributed 2,565 days of daily data. Participants who endorsed high levels of interactive toxicity beliefs had significantly more days when they missed doses of medication. Alcohol-antiretroviral toxicity beliefs predicted missing doses of medication on days when participants were drinking and on days when they were not drinking. Multilevel multivariate regressions showed that these toxicity beliefs predicted daily missed doses of medication over and above quantity of alcohol consumed, depression and general medication concerns. This study replicates and extends previous literature and indicates the necessity of addressing alcohol-ART toxicity beliefs within adherence interventions.

Keywords

HIV; medication adherence; antiretroviral therapy; alcohol; toxicity beliefs

Antiretroviral therapies (ART) are effective in reducing human immunodeficiency virus (HIV) replication in HIV infected individuals to undetectable levels (Egger et al. 2002;

Correspondence concerning this article should be addressed to Jennifer A. Pellowski, PhD, Brown University, 121 South Main Street, 2nd Floor, Providence, RI, 02903, Phone: (860) 908-2406, jennifer_pellowski@brown.edu.

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European Collaborative Study, Patel, Cotina-Borja, Thorne, & Newell, 2007). However, these regimens require relatively high levels of adherence to render the benefits of these therapies and to prevent drug resistance (Kobin & Sheth, 2011; Viswanathan et al., 2015). Alcohol use is a significant barrier to ART adherence (Grodensky, Golin, Ochtera, & Turner, 2012). On a daily level, drinking alcohol is directly related to a greater likelihood of missing medications (Parsons, Rosof, & Mustanski, 2008). This relationship is often attributed to alcohol related cognitive impairments (Meyerhoff, 2001). However, recent research has found that this relationship may also be due to intentional non-adherence (Kalichman et al., 2013, 2015).

Alcohol-antiretroviral interactive toxicity beliefs reflect perceived adverse outcomes of mixing alcohol and ARTs. Previous research has shown a significant relationship between alcohol-ART interactive toxicity beliefs and ART non-adherence, over and above other correlates of non-adherence such as HIV symptoms and frequency of alcohol use (Kalichman et al., 2009; 2012). For individuals with liver disease and/or hepatitis C co-infection drinking while taking ART can modify liver drug metabolic rates leading to risk of drug resistance (Kresina et al., 2002). However, with the exception of individuals with compromised liver function, studies suggest that the benefits of sustained adherence to ART on viral suppression and immune system functioning outweigh the negative impacts of mixing alcohol and ART (Conen, et al., 2013; Kowalski, et al., 2012)

This relationship between ART non-adherence and alcohol-antiretroviral interactive toxicity beliefs has also been observed on a daily level. Kalichman et al. (2013) used daily interactive text message surveys to assess alcohol use for 10-consecutive days, six times during a 12-month prospective study of alcohol users. The authors also collected 3-day retrospective self-report adherence assessments that coincided with these daily assessments. They found that participants who held alcohol-ART interactive toxicity beliefs were more likely to stop or skip taking their medication while drinking. Additionally, individuals who stated that they skip or stop taking their medications when drinking had significantly more days with concurrent drinking alcohol and missing their medications (Kalichman et al., 2013).

The previous day-level analysis of this relationship, however, has some limitations. The authors utilized self-report measures (3-day recall) to assess adherence to HIV medication. Using a more objective measure of daily ART adherence would provide additional support for this phenomenon. For the daily analyses, Kalichman et al. (2013) also used reported behavior about skipping or stopping ART when drinking rather than the belief that alcohol and HIV medications interact in toxic ways to predict adherence. By testing beliefs rather than reported actions we can gather a more robust picture of how these views may influence both daily adherence behaviors and daily drinking behaviors. Finally, previous studies have not teased apart whether it is specifically alcohol-ART interactive toxicity beliefs that influences non-adherence or if it is due to more general concerns about these HIV medications. The current study aims to address all of these issues by using the Wisepill device for a more objective measure of adherence, by testing the relationship between beliefs and daily non-adherence and by including a general measure of medication concerns.

Methods

This study utilized data available from an observational cohort that included 45-days of daily text message surveys and daily electronic medication monitoring. Participants also completed an audio computer-assisted self interview (ACASI) and provided chart-abstracted CD4 T-cell count and HIV RNA viral loads. Participants were compensated for all completed study activities and the University Institutional Review Board approved the study protocol.

Population and Screening

Study participants consisted of men and women living with HIV/AIDS in and around Atlanta, GA, an area with a substantial HIV epidemic (Georgia Department of Public Health, 2012). Because these data come from a previous study of daily food insecurity, alcohol use, and adherence (Pellowski et al., *under review*), participants included in this study had to meet several criteria for eligibility. Eligibility criteria included (a) being 18 or older, (b) name-matching proof of positive HIV status and photo identification, (c) currently taking antiretroviral medications (ARVs), (d) self-reported missing at least one dose of medication in the past month, (e) self-reported food insecurity within the past month, (f) self-reported consumption of at least one alcoholic beverage within the past month, and (g) willingness to use a Wisepill device for 45-days of medication management.

Time-varying variables

Participants were provided with a study cell phone to complete daily interactive text message assessments.

Daily alcohol use—Participants received the same text message survey for 45 consecutive days and the questions referred to the previous day. To assess alcohol use, participants were asked “How many alcohol drinks did you have yesterday? If you did not drink say 0.” These responses indicated quantity of alcohol when drinking and were recoded to create a second dichotomous variable to indicate whether or not they drank alcohol that day, *0 = did not drink or 1 = drank alcohol*.

Medication adherence—Participants were also asked to use a Wisepill device during the course of the 45 days in order to track daily medication adherence. The Wisepill device functions as a medication pillbox that when opened sends an electronic signal to a central server that can then be accessed in real time by study staff via a secure, internet-based interface (Bachman DeSilva, et al., 2013; Haberer, et al., 2010; Pellowski et al., 2014). These data were downloaded from the website and were compared to each participant’s dosing schedule to determine when doses of medication were missed. Wisepill signal lapses of 48 hours or greater were investigated by a phone call to the participant to determine whether the lapse was due to a technical failure (battery failure, loss of cellular signal) or if it was due to a behavioral cause (pocket dose, missed dose; Bachman DeSilva, et al., 2013) and daily adherences were adjusted accordingly (Haberer et al., 2010). Prior to analysis, these data were restructured so that the alcohol data and the medication adherence data corresponded to the same days.

Time-invariant variables

Following the 45-day text message survey period, participants completed an audio-computer assisted self-interview (ACASI) regarding a number of behavioral, psychosocial and cognitive factors associated with medication non-adherence using the past 45 days as the time frame for reflection.

Alcohol-antiretroviral interactive toxicity beliefs—Three items were used to assess the extent to which participants believed that drinking alcohol while taking HIV medications was problematic (Kalichman, et al., 2009, 2015). The exact wording of these three items appears in the Results section. These items were developed by Kalichman et al. (2009) based on previous qualitative research on beliefs about alcohol among people living with HIV and how these beliefs influence ART adherence (Sankar, Wunderlich, Neufeld, & Luborsky, 2007).

Alcohol use—To assess each participant's level of alcohol use, the Alcohol Use Disorders Identification Test (AUDIT) was used (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). The AUDIT assesses alcohol consumption and alcohol-related problems. A score of 8 or above indicates potentially hazardous drinking levels (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). This scale demonstrated acceptable reliability in this sample (Cronbach's $\alpha = 0.80$).

Psychosocial factors—A shortened version of the Centers for Epidemiological Studies Depression scale (CES-D) was used to assess emotional distress (Radloff, 1977). This version excluded somatic symptoms that correlate highly with HIV symptoms in order to avoid inflating depression scores (Kalichman, Rompa, & Cage, 2000). Twelve items focused on how often a participant had specific thoughts, feelings and behaviors in the last seven days. Responses were *0 = 0 days, 1 = 1–2 days, 2 = 3–4 days, 3 = 5–7 days*. (Cronbach's $\alpha = 0.89$). Level of social support was assessed through a 10-item scale of tangible, emotional, and informational support (adapted from Brock, Sarason, Sarason, & Pierce, 1996). Responses were *1 = completely true, 2 mostly true, 3 = mostly false and 4 = completely false*. Possible scores ranged from 10–40 and responses were scored so that higher scores indicated more social support. Sample items are “There are several people that I trust to help me solve problems” and “If I needed a place to stay for a week because of an emergency, I could easily find someone who would put me up.” (Cronbach's $\alpha = 0.90$).

Horne's medication necessity-concerns beliefs—It is plausible that previous findings that show alcohol-ART interactive toxicity beliefs leads to non-adherence is due to more general concerns about these medications. Participants' general beliefs about their medications were assessed using the Beliefs About Medicines Questionnaire (Horne et al., 2004, Horne, Cooper, Gellaitry, Date, & Fisher, 2007). The medication necessity subscale consists of five items including “My health, at present, depends on my HIV medications.” The medication concerns subscale consists of five items including “I sometimes worry about long-term effects of my HIV medications.” All items are responded to on a 5-point scale, *1 = Strongly Agree, 5 = Strongly Disagree*. Scales were coded such that higher scores indicated higher levels of necessity and higher levels of concerns, respectively. Both scales were

internally consistent (medication necessity scale Cronbach's $\alpha = 0.87$, medication concerns scale Cronbach's $\alpha = 0.78$). Medication concerns was correlated with the alcohol-ART interactive toxicity beliefs in this sample, although not significantly ($r = .233$, $p = 0.10$).

Chart Abstracted HIV RNA Viral Load and CD4 T Cell Count

During the study, participants were asked to obtain a copy of their latest HIV RNA viral load and CD4 T cell counts from their health care provider. These records could be no older than three months. These records had to be marked with a clinic stamp to verify its authenticity. For consistency across viral load chart values, we defined undetectable viral load as <50 copies/mL.

Statistical Analyses

To characterize the sample, means and rates were calculated. Chi-squares and t-tests were performed to determine if there were significant differences between those with low and high toxicity beliefs. Bivariate regressions were conducted to determine the relationship between alcohol-ART interactive toxicity beliefs and daily missed doses of medications. These bivariate regressions were conducted twice, once with days during which participants were drinking and once with the days during which they did not drink.

Bivariate regressions were also conducted to determine the relationships between common correlates of non-adherence and daily missed doses of medication. Bivariate regressions that were $p < 0.10$ were included in a multivariate regression to determine the driving predictors of daily missed doses of medication. The multivariate regression was conducted using multilevel modeling using event records as a statistical unit of analysis (or "level 1 unit"), nested within participants (or "level 2 unit"). Fixed and random effects were used such that the intercepts and slopes of the models were modeled first as random effects in logistic regressions. If the residual variances for the slopes are determined to not vary across level 2 units, they were converted to fixed effects (Snijders & Bosker, 1999). B estimates and standard errors are reported for model estimates.

All of these analyses were conducted using R version 3.1.3. (R Core Team, 2015) and the library "lme4: Linear mixed-effects models using Eigen and S4" (version 1.7; Bates et al., 2015). Missing data days were included in these analyses and were handled using multiple imputation by chained equations using all variables in the dataset to estimate missing data using the R package "mice: Multivariate Imputation by Chained Equations" version 2.22 (van Buuren, & Groothuis-Oudshoorn, 2015). Predictive mean matching, a semi-parametric imputation method, was used in order to preserve any non-linear relationships present in the data (van Buuren, & Groothuis-Oudshoorn, 2011).

Results

Responses on the alcohol-ART interactive toxicity beliefs scale ranged from 4 to 15 ($M = 10.4$, $SD = 3.2$; median = 11). This variable demonstrated acceptable internal consistency (Cronbach's $\alpha = 0.76$) and was normally distributed (skewness = -0.19 , kurtosis = -0.97). A median split was performed to compare demographic and behavioral variables between those with low and high toxicity beliefs; subsequent analyses use the full scale

scores. Participants who had low toxicity beliefs were fairly similar to those who had high toxicity beliefs (Table 1). The majority of sample was male, African-American/Black and living in extreme poverty. There was a small sample of participants who abstained from using alcohol during the course of the study but this did not differ based on toxicity beliefs. The majority of participants had undetectable HIV RNA viral loads and CD4 T-cell counts above 200, however, 5 participants could not obtain their HIV RNA viral load or CD4 T-cell count from their doctor by the end of the study and an additional participant was only able to obtain their HIV RNA viral load.

Behaviorally, those with high toxicity beliefs were significantly more likely to miss doses of medication during the course of the 45 day study; those with high toxicity beliefs, on average, had 10.7 days that they missed a dose of medication compared to only 6.3 days, on average, for those who had low toxicity beliefs ($t = -2.01$, $p < 0.05$). Participants with low toxicity beliefs had more days of the study when they drank, but this was not statistically significant. The two groups also did not significantly differ in their scores on the AUDIT.

For psychosocial measures, those with low toxicity beliefs and those with high toxicity did not significantly differ in depression scores (CES-D) and level of social support that they had. There were also no differences on the medication necessity beliefs scale or on the medication concerns scale.

Alcohol-ART Interactive Toxicity Belief Items

Table 2 shows bivariate regressions of the alcohol-ART interactive toxicity belief items predicting missed doses of medication on days when participants were and were not drinking. On days when participants were drinking, all interactive toxicity belief items predicted missing doses of medication. In comparing Z-scores, the item “Alcohol breaks down HIV medications so they will not work right” was the strongest individual predictor of missing medication on days when participants were drinking ($Z = 4.56$, $p < 0.001$).

In addition, most of the interactive toxicity belief items also predicted missing doses even on days when participants were not drinking except for one. “Alcohol and HIV medication should never be mixed” did not predict missing medications on days when participants were not drinking ($z = 0.45$, $p = 0.65$).

Bivariate Regressions Predicting Missed Doses

Analyses were conducted to determine the bivariate relationships between key variables and daily missed doses of medication (Table 3). For variables that occurred on a daily level, day in the study was a significant predictor of missing a dose of medication, such that the longer that participants were in the study the more likely they were to miss a dose of medication ($B = 0.017$, $SE = 0.007$, $p < 0.05$). Whether or not a participant drank on a given day was not a significant predictor of missing a dose of medication on that day. Consuming more alcohol on a given day was associated with a greater likelihood of missing a dose of medication ($B = 0.101$, $SE = 0.061$, $p = 0.09$).

For variables that occurred on the level of the individual, the Alcohol-ART Interactive Toxicity Belief Scale predicted missing a dose of medication, such that greater endorsement

of toxicity beliefs predicted a greater likelihood of missing a dose of medication on any given day ($B = 0.122$, $SE = 0.018$, $p < 0.001$). Score on the AUDIT also predicted missing a dose of medication; higher AUDIT scores predicted a greater likelihood of missing a dose of medication ($B = 0.033$, $SE = 0.009$, $p < 0.001$). Higher depression scores also predicted a greater likelihood of missing a dose of medication on a given day ($B = 0.019$, $SE = 0.007$, $p < 0.01$). The levels of perceived social support that they had did not predict daily missed doses of medication. For medication beliefs, Medication Necessity Beliefs did not predict missed doses of medications, however, Medication Concerns did ($B = 0.034$, $SE = 0.012$, $p < 0.01$).

Multivariate Regression Predicting Missed Doses

The variables that predicted daily missed doses of medications in bivariate regressions ($p < 0.10$), were included in a multilevel multivariate regression (Table 4). When controlling for other variables, day in the study still significantly predicted daily missed doses of medications ($B = 0.016$, $SE = 0.006$, $p < 0.01$). Quantity of alcohol consumed on a given day no longer predicted missing a dose of medication on that day. Alcohol-ART Interactive Toxicity Beliefs remained a significant predictor of missed doses ($B = 0.405$, $SE = 0.200$, $p < 0.05$). The AUDIT, depression scores and concerns about medications were not significant predictors of daily missed doses of medication when controlling for day and quantity of alcohol consumed.

Discussion

This study supports other findings in the literature in a unique population of resource-constrained individuals who are living with HIV and drink alcohol. This study shows that alcohol-ART interactive toxicity beliefs predict daily adherence over and above common predictors of adherence, including variables that are more proximal in time to the actual missed dose. In particular, these beliefs predicted adherence over and above quantity of alcohol consumed on that day, which has been shown to be a robust predictor of daily adherence (Parsons, Rosof, & Mustanski, 2008). Those with high toxicity beliefs also had a similar number of days during which they were drinking compared to those with low toxicity beliefs. This supports the notion that alcohol-ART interactive toxicity beliefs are not simply a proxy for quantity or frequency of alcohol consumption.

Results showed that endorsing the item alcohol and HIV medications should never be mixed was associated with ART non-adherence on drinking days but not on days that the participant did not drink. However, endorsing beliefs that alcohol breaks down HIV medications and that a person should stop taking ART when drinking predicted missing ART whether or not the individual is drinking on that day. Thus, not only do these beliefs impact adherence on days when alcohol is consumed but there is also a halo effect for days when individuals are not drinking alcohol. There are several plausible explanations for this. It is possible that participants planned on drinking so they did not take their medications but did not end up drinking that day. Another reasonable explanation is that participants may endorse toxicity beliefs in order to justify missing doses of medication, regardless of whether or not they were drinking. A third explanation is that alcohol-antiretroviral toxicity

beliefs may be indicators of something more general, such as lack of knowledge or misunderstandings about their HIV medications. This overall confusion about when and how to take their medications and how these medications work would impact missed doses on drinking and non-drinking days. Future research should tease apart these potential explanations.

This study also extends previous research by including a measure of ART medication concerns. Alcohol-ART interactive toxicity beliefs predicted daily missed doses of medication over and above the more general measure of concerns about HIV medications and these measures were not highly correlated. This rules out the possibility that toxicity beliefs are actually tapping into more basic medication concerns rather than specific concerns about alcohol use. This may also indicate that interventions to address medication adherence should focus on alcohol-ART interactive toxicity beliefs in addition to general concerns about medications.

This study is not without limitations. Alcohol-ART interactive toxicity beliefs were only collected at one time point after the daily data was collected. Although we assume that these beliefs remain stable, it is possible that there are fluctuations over time. If the toxicity beliefs were assessed on a daily level along with alcohol use and adherence we may have seen different trends in the data particularly on the days when participants were not drinking but missed doses of medication. Additionally, if alcohol-ART interactive toxicity beliefs were also measured before starting the daily data collection part of the study, we might be able to get a sense if reporting on these beliefs serves as a justification of missed doses after the fact by looking at a change in the beliefs before and after the daily observation period.

Sample characteristics may also limit the generalizability of this study. This study was conducted in one large city in the southeastern United States and had a largely African-American sample. This study is also limited because these analyses used data collected for a study focused on food insecurity and thus, participants were recruited specifically based on their experience of food insecurity in the past month in addition to alcohol use. There may be something specific about these individuals that may have influenced their beliefs and/or behaviors, however, given that the results from this study fall in line with other studies from the literature that use more general populations (Kalichman et al., 2009; 2013), we are not overly concerned about how these results may generalize to food secure samples.

The current findings have implications for improving ART adherence among people living with HIV who drink alcohol. Health care providers should directly address interactive toxicity beliefs by acknowledging that some medications should not be mixed with alcohol, but that is not true for all medications. Adhering to ART should take precedence even when drinking. The broader harms of drinking alcohol, particularly its unintended impact on adherence, should be emphasized. People with HIV who face multiple challenges to maintaining adherence, such as the participants in this study, risk failed treatment because they intentionally miss their medications. Thus, removing the sources of intentional non-adherence due to misinformation and false beliefs should be a priority in adherence interventions.

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Table 1
Demographic characteristics for participants who have low and high alcohol-HIV interactive toxicity beliefs

Variables	Low Toxicity Beliefs N=26		High Toxicity Beliefs N=31		X ²
	N	%	N	%	
Gender					
Female	6	23.1	5	16.1	1.93
Male	16	61.5	24	77.4	
Transgender	4	15.4	2	6.5	
Race/Ethnicity					
White	0	0	1	3.2	1.74
African-American/Black	26	100	29	93.5	
Hispanic/Latino	0	0	1	3.2	
Income					
\$0 – \$10,000	18	69.2	23	74.2	3.27
\$11,000 – \$20,000	7	26.9	6	19.4	
\$21,000– \$30,000	0	0	2	6.5	
Over \$30,000	1	3.8	0	0	
Abstained from using alcohol during study					
Yes	3	11.5	7	22.6	1.19
No	23	88.5	24	77.4	
HIV RNA Viral Load ^a					
Undetectable	21	87.5	22	78.6	0.72
Detectable	3	12.5	6	21.4	
CD4 T-cell Count ^a					
Less than 200	3	13	2	7.1	0.50
Greater than or equal to 200	20	87	26	92.9	
Days missed doses	M	SD	M	SD	<i>t</i>
	6.3	6.3	10.7	10.3	-2.01*

Variables	Low Toxicity Beliefs N=26		High Toxicity Beliefs N=31		χ^2
	N	%	N	%	
Days when drinking	12.8	13.6	6.9	10.0	1.87 ^a
Average number of drinks	2.7	1.4	2.7	1.3	0.05
AUDIT	6.1	5	4.8	6.1	0.89
CES-D	11	8.7	11.4	7.4	-0.18
Social Support	30.4	6.3	31	7.8	-0.33
Medication Necessity Beliefs	7.8	3.2	7.3	3.1	0.47
Medication Concerns	12.1	4.3	14.3	4.9	-1.62

^a p<0.10,

* p<0.05

^aNote: 5 participants could not obtain their HIV RNA viral load or CD4 T-cell count from their doctor by the end of this 45 day study. An additional participant was able to obtain their viral load but not their CD4 T-cell count by the end of the study.

Table 2

Bivariate regressions of alcohol-ART interactive toxicity belief items predicting daily missed doses of medication on days when participants were drinking and were not drinking

Item	Predicting missed doses on days when drinking				Predicting missed doses on days when Not drinking			
	B	SE	Z	p-value	B	SE	Z	p-value
Alcohol and HIV medication should never be mixed	0.270	0.084	3.216	**	0.022	0.049	0.450	0.65
Alcohol breaks down HIV medications so they will not work right	0.436	0.095	4.561	***	0.178	0.056	3.198	**
A person should stop taking their HIV medications if they are going to be drinking	0.259	0.064	4.025	***	0.339	0.046	7.355	***

* p<0.05,

** p<0.01,

*** p<0.001

Scale Cronbach's alpha = 0.76, Skewness = -0.19, Kurtosis = -0.97

Table 3

Bivariate regressions predicting daily missed doses of medications

Variables	B	SE	Z	p-value
Day-Level				
Day	0.017	0.007	2.523	*
Drank that day (Yes/No)	0.293	0.266	1.099	0.27
Quantity of alcohol consumed that day	0.101	0.061	1.657	0.09
Individual-Level				
Alcohol-ART Interactive Toxicity Belief Scale	0.122	0.018	6.835	***
AUDIT	0.033	0.009	3.707	***
CES-D	0.019	0.007	2.749	**
Social Support	-0.004	0.008	-0.538	0.59
Medication Necessity Beliefs	0.001	0.018	0.052	0.96
Medication Concerns	0.034	0.012	2.762	**

*
p<0.05,

**
p<0.01,

p<0.001

Note: Day-level bivariate regressions controlled for within participant variance.

Table 4
Fixed effects and random effects estimates for multilevel model predicting daily missed doses of medication

Fixed Effects				
Parameter	B	SE	Z	p-value
Intercept	-2.341	0.269	-8.713	***
Level 1 (Daily Level Data)				
Day	0.016	0.006	2.606	**
Quantity of alcohol consumed	0.145	0.106	1.378	0.170
Level 2 (Individual Level Data)				
Alcohol-ART Interactive Toxicity Belief Scale	0.405	0.200	2.022	*
AUDIT	0.199	0.205	0.969	0.330
CES-D	0.100	0.257	0.039	0.970
Medication Concerns	0.180	0.261	0.688	0.490
Random Effects				
	Variance	SD		
Intercept	2.010	1.418		
Level 1 (Daily Level Data)				
Day	0.000	0.010		
Quantity of alcohol consumed	0.100	0.316		
Day * Quantity	0.000	0.005		

* p<0.05,
** p<0.01,
*** p<0.001