The Relationship Between Harmful Alcohol Use and Antiretroviral Non-adherence in People Accessing HIV Treatment in Cape Town, South Africa: An Event-Level Analysis

Alexandra L. Rose (University of Maryland at College Park)
Jennifer M. Belus (Swiss Tropical and Public Health Institute)
Tianzhou Ma (University of Maryland at College Park)
Jasper S. Lee (University of Miami)
Christine Wan (University of Maryland at College Park)
Andres De Los Reyes (University of Maryland at College Park)
John A. Joska (University of Cape Town)
Lena S. Andersen (University of Copenhagen)
Bronwyn Myers (Curtin University)
Jessica F. Magidson (University of Maryland at College Park)

CITATION

Rose, A., Belus, J., Ma, T., Lee, J.S., Wan, C., De Los Reyes, A., Joska, J.A., Andersen, L.S., Myers, B., & Magidson, J.F. (2022). An event-level analysis of the relationship between harmful alcohol use and antiretroviral treatment non-adherence in people accessing HIV treatment in Cape Town, South Africa. *Aids and Behavior*, *26*(6), 2055-2066. https://doi.org/10.1007/s10461-021-03552-x

FUNDING INFORMATION

This study was funded by the National Institute of Drug Abuse (K23DA041901, PI: Magidson). ALR's time on this manuscript was supported by the National Institute of Mental Health (F31MH123020, PI: Rose). ADLR's time on this manuscript was supported by the Institute of Education Sciences (R324A180032, PI: De Los Reyes, National Center for Special Education Research).

Abstract

Harmful alcohol consumption can significantly compromise adherence to antiretroviral therapy (ART). Prior research has identified aggregate relationships between alcohol use and ART non-adherence, largely relying on concurrent assessment of these domains. There is relatively limited evidence on more nuanced day-level associations between alcohol use and ART non-adherence, despite potentially important clinical implications. We recruited adults with HIV treatment adherence challenges and harmful alcohol use (n=53) and examined relationships between alcohol use and *same* and *next day* ART adherence, accounting for the role of weekends/holidays and participant demographics, including gender. Results demonstrated that weekends/holidays were significantly associated with worse same day ART adherence. Next day adherence was significantly worse in the context of weekend alcohol use and among men. These results suggest the importance of tailoring intervention strategies to support ART adherence during weekend drinking and for men engaged in heavy episodic drinking.

Key words: HIV; alcohol; antiretroviral therapy; South Africa; treatment adherence

Introduction

With the largest number of people living with HIV (PLWH) globally, adherence to antiretroviral therapy (ART) is a key public health priority to achieve viral suppression and reduce ongoing transmission in South Africa (1,2). Alcohol use is a well-established risk factor for non-adherence to ART among PLWH (3,4,5). In a meta-analysis of 40 studies, people who drank alcohol at harmful or hazardous levels, defined as a quantity or pattern of alcohol consumption likely to put patients at risk for adverse events (6), were half as likely to be categorized as sufficiently adherent to ART compared with those who drink at lower levels and non-drinkers (7). Harmful or hazardous alcohol use is prevalent among PWLH in South Africa, where 25-32% of patients accessing HIV treatment at public clinics drink in this manner (8,9). With studies showing that hazardous/harmful alcohol use is associated with poor ART adherence (10) and viral non-suppression (11) among PLWH in South Africa, reducing alcohol use among PLWH represents a key intervention target for improving HIV treatment outcomes in South Africa.

The design of interventions aiming to improve ART adherence among PLWH using alcohol are limited by a lack of nuanced information on the relationship between alcohol use and daily adherence. Studies typically measure both alcohol use and adherence in aggregate and retrospectively at discrete time-points (12,13) using time scales that range from one month to one year (14). Such an approach allows for a good understanding of the aggregate relationship between alcohol use and ART non-adherence and has led to the development of interventions that help individuals reduce overall alcohol use and remember to take ART while actively drinking (15). However, aggregate data do not allow for an understanding of how patterns of alcohol use and non-adherence map onto each other, which may have implications for the timing

and content of intervention sessions. There is evidence that alcohol consumption has next day effects on mood and memory (16,17), constructs that are important for medication adherence (18,19). There is also prior evidence from the United States that substance use has a negative effect on next day pre-exposure prophylaxis (PrEP) adherence (20). Additionally, patterns of drinking and adherence are known to differ on weekends or holidays as compared to weekdays across many contexts, including South Africa (21-25). Prior research in the United States has found that overall higher average alcohol use is associated with worse average ART adherence on the weekends (26). Understanding whether drinking has effects on ART adherence that extend beyond the immediate drinking occasion to the next day (and the alcohol quantities at which these effects begin to occur and for whom) and whether weekends or holidays are times at which some PLWH are especially vulnerable to non-adherence while drinking could help facilitate more adaptive and individualized intervention strategies in the longer term (27).

Event-level analysis, an approach commonly used to understand the relationship between substance use and instances of risky sexual behavior (28,29), has helped start to better describe the relationship between alcohol use and HIV medication adherence (30,31). However, only one study on the event-level study on the relationship between alcohol use and adherence has been conducted in South Africa (31), and no studies that we are aware of have been conducted using an objective measure of adherence. Relying on self-report adherence data in these studies may limit the accuracy of prior estimates (32,33). Moreover, no prior event-level studies have examined whether there is a difference in the relationship between alcohol use and adherence on weekends or holidays, despite potential implications for interventions.

The present study uses an event-level approach and objective real-time adherence monitoring assessment, Wisepill, to understand nuanced relationships between the timing of

alcohol use and ART non-adherence. Specifically, we test the hypotheses that consuming a greater quantity of alcohol on a particular day reduces the odds of ART adherence on 1) that *same day* and 2) the *next day*, after accounting for whether it is a weekend or holiday and key demographic characteristics associated with alcohol use, namely age and gender.

Methods

This study uses data from a randomized controlled trial (RCT) conducted in a primary care clinic with integrated HIV services in Cape Town, South Africa focused on reducing substance use and improving ART adherence (15). Participants in the parent RCT (N=61) were recruited via clinic records and staff referrals based on the following criteria: (1) HIV positive and on antiretroviral therapy (ART); (2) 18-65 years old; (3) at least moderate alcohol or drug use severity on the WHO Alcohol, Smoking, and Substance Involvement Screening Test (WHO-ASSIST (34) as well as ART non-adherence in recent months. Complete inclusion and exclusion criteria are available in [redacted for peer review] (15). For this analysis, we include participants (n=53) from the parent study who reported moderate or high-risk alcohol use at the time of screening and for whom day-level alcohol use data were available at baseline. There were no significant differences in age, WHO-ASSIST, or average adherence between the current sample and the parent sample. The proportion of women in the current sample was significantly lower than in the parent study. However, we controlled for gender in our models.

Procedures

All data for the current study were collected before participants were randomized and received any intervention in the parent RCT. At the end of the baseline visit, participants provided demographic data and were given a real-time electronic adherence monitoring device to monitor daily use of ART for two weeks. Participants were provided instructions on how to use the device

and instructed to store ART in the device throughout the course of the study. Two weeks after the baseline visit, participants returned for randomization visits, at which they provided alcohol use data for the prior fourteen days.

Measures

WHO-ASSIST. The WHO-ASSIST is a self-report assessment of lifetime and past three-month alcohol and drug-related problems (34). The WHO-ASSIST has defined risk categories for alcohol use (≥27 high risk, 11-26 moderate, 0-10 low). Past three-month WHO-ASSIST score was used for inclusion into this study from the parent study.

ART adherence. Wisepill, a real-time electronic adherence monitoring device, was used to measure daily ART adherence (35). The Wisepill electronically records each time it is opened and once daily whether the device is functional, data that it transmits in real time to a server via cellular signal. Days were defined as 24-hour periods from midnight (i.e., 00:00am) to 23:59 pm the following day. Participants were considered adherent *to a dose* within a day if their Wisepill was opened two hours before or after a pre-specified target dosing time. Participants were considered adherent *on a day* if they adhered to all doses within a day (e.g. taking one of two doses on a day would be coded as non-adherent). We examined possible differences in alcohol use, adherence, and demographics between participants with one (n=40) and two (n=13) dosing times (i.e., on first- or second-line treatment) using chi-square or t-tests and a Bonferroni correction for multiple comparisons (36). We found no significant differences so participants with one and two dosing times were combined in analyses.

Number of standard drinks consumed daily. Quantity of alcohol use consumed each day was retrospectively measured using the Timeline Follow-Back (TLFB) method (37), which has been widely used in South Africa (38). A research assistant showed the participant a printed

calendar and asked them to recall their drinking days, as well as quantity and brand or type of alcohol they consumed during each drinking day. Local bottles of alcohol were displayed to help aid participant recall for quantities and brands. Percent alcohol by volume for each type of alcohol was then extracted from publicly available sources. Using the following formula, we standardized the data (quantity consumed of alcohol A X alcohol by volume of Alcohol A). Standardized drinks were summed across types of alcohol to calculate total standard drinks for each drinking day. From these standardized data, mean number of drinks consumed during the study period were calculated for each participant.

Demographic characteristics. Participant age, gender, and race were recorded at the time of screening. Women were coded as 0 and men were coded as 1.

Analytic Sample and Data Analysis

Temporal relationships between alcohol and adherence variables within this sample are visualized with example data in Figure I. Extracted data totaled 685 days, an average of 11.9 days per participant. Participants' baseline or randomization visit days were excluded due to the possible impact that study visits may have on alcohol use and adherence. Twenty-three days (3.4% of total days) on which the Wisepill had failed were then excluded, resulting in 662 usable days within the analytic sample. Using a standard twelve-month calendar and a list of South African holidays, each date was coded as a weekend/holiday or as a weekday/non-holiday. Fridays were coded as weekends as most target dosing times in this sample were in the evening.

All analyses were conducted using R version 3.5.1. Descriptive statistics were calculated to characterize the sample and variables of interest, including number of drinks consumed on a day and the weekend/holiday construct, were examined for collinearity, with none correlated above $r = .30$. We then conducted event-level analyses. For model 1 (relationship between

alcohol use and *same day* adherence), number of drinks consumed on a given day was the primary predictor of interest. To disentangle within and between person effects, number of drinks was person mean centered with positive values indicating consumption of more drinks than a participant's own average (i.e., the within person effect). Mean quantity of alcohol use across the period was included to account for between person effects, as were a priori covariates of grand mean centered age, gender, and whether a given day was a weekend or holiday (vs. weekday). A random intercept was used. Predictors and covariates were treated as fixed effects, as has been done previously in event-level analyses of the relationship between alcohol use and healthy behaviors (31,39). After running models without interactions, we added interactions between number of drinks and gender, age, and weekend/holiday (21,40,41). All interactions were modeled simultaneously because prior research suggests that gender, age, alcohol consumption, and weekend/holiday behavior are all interrelated (42,43,44). To probe significant interactions, we conducted post-hoc comparisons of the probability of adherence at specified numbers of drinks with the additional grouping factor (e.g., gender) using the lsmeans package and a Tukey correction for multiple comparisons (45). To examine interactions, drinks were categorized into 0, 5, 10, 15, and 20 drinks, which aligns with alcohol consumption terminology that defines a binge as five or more drinks on one occasion (46). In the case of multiple significant interactions, we also examined relevant three-way interactions.

To analyze model 2, which examined the relationship between alcohol use and *next day* adherence, the last observation was removed because next day adherence would have occurred on the day of the randomization visit, resulting in sub-sample of 612 participant days. Number of standard drinks on the day prior to the adherence measurement was the primary predictor of interest and was person mean centered. We included mean quantity of alcohol use across the

period, grand mean centered age, gender, and whether adherence was measured on a weekend or a holiday. In addition, we controlled for alcohol use on the same day adherence was measured to isolate the effects of prior day use on adherence. We included a random intercept, with other predictors and covariates treated as fixed effects. We then included interactions using the same methods as for model 1.

We used an autoregressive correlation structure to be able to account for inclusion of both alcohol use on the day before *and* the day on which adherence was measured in model 2. We used the glmmPQL function in specifying our models, which allows for binary outcomes and autoregressive correlations (47,48). Models 1 and 2 used the same approach to allow for model comparisons. To ensure this approach was appropriate for model 1, we also conducted model 1 analyses using the glmer function. No differences between functions were observed for model 1.

Results

Across participants, the mean age was 37.4 years (*SD*=9.3). Participants were predominantly (98.1%) Black African and 47.2% female. At screening, the mean WHO-ASSIST score for alcohol was 25.8 (*SD*=6.7), indicating an average of moderate to high alcohol risk in the sample. Across study days, including both weekdays and weekends, participants drank an average of 1.72 drinks per day (*SD*=4.03); women drank an average of 1.52 drinks per day (*SD*=1.50) and men drank an average of 1.91 drinks per day (*SD*=2.31). Participants drank on an average of 2.8 days per week (*SD*=2.6). Average number of drinks consumed on drinking days was 7.41 (*SD*=3.63). Average number of drinks consumed on weekends (Fri-Sun) or holidays was higher than on weekdays (Mon-Thurs) or non-holidays, with an average of 2.84 (*SD*=5.0) on weekends or holidays and an average of 0.70 (*SD*=2.5) on weekdays or non-holidays. Average percentage of adherent days across the sample was 47%. Adherence was on average lower on

weekends, with average percent of adherent days on weekends or holidays of 37.6%, and an average percent of adherent days on weekdays or non-holidays of 52.7%. Please see Table I for detailed characteristics of the sample.

Table II presents the results of model 1, without and then with interaction terms included. In the main model, number of drinks consumed (above one's own average) was not related to *same day* ART adherence (β=-0.04, aOR=0.96, 95% CI: 0.92-1.01, p=0.14). However, when a day was a weekend or holiday, the odds of ART adherence was less than half than that of a weekday (β=-0.87, aOR= 0.42; 95% CI: .29-.61; p<0.001). No other covariates were statistically significant. In the model with the interaction terms included, results were almost identical. Number of drinks consumed (above one's own average) was not related to *same day* ART adherence (β=-0.07, p=0.44). However, when a day was a weekend or holiday, the odds of ART adherence was reduced (β=-0.88, p<0.001). No other covariates or interaction terms were statistically significant.

Table III presents the results of model 2, examining the relationship between alcohol use and *next day* ART adherence, without and then with interaction terms included. In the main model, each drink (above one's own average) reduced the likelihood of next day adherence by 5% (β = -0.05, aOR= 0.95; 95% CI 0.90- 1.00; p=0.04). Weekends/holidays also reduced the likelihood of next day adherence by almost half (β = -0.46, aOR= 0.63; 95% CI 0.43- 0.93; p=0.02). Each drink above one's own average also reduced the likelihood of same day adherence by 9% in this model (β = -0.10, aOR= 0.91; 95% CI 0.86- 0.96; p<0.001). No other covariates were statistically significant. When including interaction terms in the model, there was almost no change to the effect of weekend/holiday on next day adherence or of drinks above one's own average on same day adherence. After including interaction terms, the effect of each drink above

one's own average appeared to increase the likelihood of next day adherence (β = 0.25, p=0.001).

However, there were two significant interactions related to next day adherence in model 2, between 1) number of drinks consumed and weekend/holiday; and 2) number of drinks consumed and gender. Figure II depicts the interaction in which weekend/holiday moderates the relationship between alcohol use and next day adherence. For 5 (t= 2.04, p_{adj}= 0.003), 10 (t= 3.44, p_{adj}= 0.005), 15 (t= 4.83, p_{adj}= 0.008), and 20 drinks (t= 6.23, p_{adj}= 0.01) consumed above own's average, next day adherence was significantly lower if the next day was a weekend/holiday relative to a weekday/non-holiday. There was no significant difference in next day adherence between weekends/holidays (vs. weekdays/non-holidays) if a participant did not drink 5+ drinks more than their average. The second interaction, in which gender moderated the relationship between alcohol use and adherence, is depicted graphically in Figure III. At fifteen drinks above own's average there was a significant difference in next day adherence between male and female participants (t= 4.54, p_{adj}=0.04), such that next day adherence was worse for men. A similar pattern was noted for twenty drinks above one's own average (t= 5.80, p_{adj}= 0.03). In both figures, graphed lines depict relative probabilities of next day adherence and do not indicate that next day adherence was increasing along with alcohol use for either women or weekdays/non-holidays, only that the probability of next day adherence was higher for women than men and higher for weekdays/non-holidays than weekends/holidays at the specified number of drinks. A three-way interaction between drinks, gender, and weekend/holiday was not statistically significant.

Discussion

Our findings underscore the importance of more nuanced examinations of the relationships between alcohol use and ART nonadherence. Findings pont to the potential value in examining not only same day but also next day effects of alcohol use on ART non-adherence in addition to aggregate effects, as well as distinguishing between weekend and weekday use. Our findings suggest that both the day on which drinking takes place and the gender of an individual affect the event-level relationship between alcohol use and ART non-adherence. We found that weekends and holidays may be particular times of risk for both same day and next day ART non-adherence while consuming alcohol. We also found that a greater number of drinks consumed was associated with lower odds of next day ART adherence, but only among male participants consuming large quantities of alcohol. These findings support and extend previous work that has documented patterns of higher average alcohol use and worse adherence on weekends (21-26) by linking specific instances of alcohol use and ART non-adherence on weekends. Findings also add greater nuance to prior self-report event-level research in South Africa that found alcohol use can affect next day ART adherence (31), by highlighting differences among men and women. These findings could provide preliminary work for future studies aiming to tailor existing alcohol use and adherence interventions to directly address weekend risk of non-adherence while drinking and adherence among men using alcohol.

Overall, findings suggest a strong relationship between alcohol use during weekends/holidays and ART non-adherence. Though participants in this sample on average drank more and had lower adherence on weekends (compared to weekdays), a finding consistent with the literature in both South Africa and other contexts (20,49), the number of drinks consumed on a day and the weekend/holiday constructs were not highly correlated in this sample. Moreover, the weekend/holiday construct controlled for alcohol consumption in our

models. This suggests that weekends/holidays impact adherence through mechanisms other than just increased alcohol use on weekends or holidays. There are several possible explanations for how weekends/holidays may negatively impact adherence unrelated to alcohol use. Several known barriers to ART adherence that may be unrelated to alcohol use, such as traveling away from home or routine changes, are more likely to occur on weekends or holidays (50,51). Participants may have also intentionally not taken ART during the weekends, a practice known as "weekending" and for which we did not have a measure (26). In addition to the fact that individuals may not adhere for reasons other than alcohol use on a weekend or holiday, behavior may also differ while drinking the night before a weekend or a holiday as compared to the night before a weekday or non-holiday. It is possible that participants were proactive about plans to take ART the next day when they knew they would be drinking large quantities of alcohol during the week, due to existing responsibilities or other external weekday reminders to cue them (52,53). Instead of drinking individually or with one other person, participants may also have been more likely to be drinking in groups, a social context that may undermine individual adherence plans, on days preceding weekends or holidays, though context for drinking was not something which was systematically recorded or for which we accounted. Testing these potential mechanisms will be important to explore in future research. Notably our findings are from Cape Town in the Western Cape and results may differ from those in rural areas or from other cities in South Africa, as epidemiological studies have reported regional differences in alcohol use within South Africa (54).

It is well documented that men across South Africa are at higher risk than women for ART non-adherence (55–57). Our findings suggest that, when drinking large quantities of alcohol (e.g., 15-20 drinks above one's own average), men may be at greater risk of non-

adherence the next day. Prior work in South Africa (31), though finding a significant event-level relationship between alcohol use and next day adherence, did not find a significant relationship between gender and adherence outcomes. However, these authors note that they had an uneven proportion of men and women in their sample and used self-reported adherence, which may have influenced findings. In our study, it is important to note that drinks on a given day were measured relative to each person's own average and men reported higher average drinking than women in this study overall. This may help explain why men had worse adherence outcomes than women after consuming similar amounts of alcohol relative to their average, as they may still be consuming greater quantities of alcohol overall on a given day if their average is higher. Prior research has also identified that in general men are less likely to be engaged in HIV care then are women (58), which may further contribute to worse ART adherence in the context of alcohol use. Lastly, we hypothesize that gender roles may have influenced this relationship. The lower ART adherence among men drinking large quantities of alcohol in our sample may reflect other research demonstrating that men are more likely than women to drink in groups, which may be social contexts that undermine individual adherence plans (59). Specifically, prior qualitative research in South Africa identified that drinking in a group fulfills a psychosocial need for men and that binge-drinking together with other men is seen as "respectable" in the Western Cape of South Africa (59). In contrast, women may be less likely to drink heavily in this group social context, and thus women may experience fewer disruptions to adherence. Understanding the degree to which differences in risk for non-adherence while drinking among men and women may generalize outside of Cape Town and the Western Cape is necessary. Differences in household responsibilities for men and women could also impact adherence, with domestic and childcare duties that are more typically held by women in South African

communities helping provide structure for female adherence even following binge drinking (24, 60). Although the three-way interaction we tested between gender, the weekend/holiday construct, and number of drinks consumed was not significant, likely due to the size of our sample, this will be important to test in future work with a larger sample.

Our findings have potentially important clinical implications. For example, it may be appropriate to design studies that shift intervention delivery to on or before the weekend for participants who struggle with weekend adherence to assess if this better supports adherence outcomes. Notably, PLWH have expressed an interest in adherence-related interventions being offered on the weekend in prior studies (61,62). Our findings also support the potential relevance of behavioral activation as a clinical intervention for people with adherence challenges related to alcohol, as weekend patterns of drinking and adherence could be targeted through activity monitoring and scheduling (63,64). The additional value of other intervention components, for instance text message reminders to take ART, among men who engage in heavy episodic drinking could also be explored (65). In general, interventions aiming to improve ART adherence and reduce heavy episodic drinking among men represent an important future area of research. This future work may build on existing masculinity-focused interventions in South Africa that improve alcohol outcomes but have not yet incorporated HIV outcomes (66). In tailoring these interventions to incorporate HIV outcomes, attending to issues of masculinity and cultural norms and how identity and culture influence the relationship between alcohol use and non-adherence will be important.

Limitations

Findings must be interpreted in the context of study limitations. Even with an objective measure of ART adherence such as Wisepill, which is a strength of this study, Wisepill non-use

can be conflated with non-adherence, thus may be an underestimate of ART adherence. However, participants were given clear instructions on how to use the device at the time of enrollment and data examined in this study date from a two-week window after enrollment in the study, likely minimizing device non-use. A second limitation is that alcohol use was assessed retrospectively using self-report data. More objective biomarkers of alcohol consumption could potentially be considered for further studies of the event-level relationship between alcohol use and ART adherence; however, their feasibility in a community-based sample would have to be explored (67). Alcohol data was also collected at the day-level, meaning we could not differentiate between the impacts of drinking at 2 am versus at 8 pm on dosing on a given day, which may explain why the same day effects of alcohol use on ART adherence were non-significant or weak in our sample. An ecological momentary assessment design offers one potential future option to examine the impact of timing of drinking on adherence (68). Additional limitations include the relatively small sample size and relatively short number of days between baseline and randomization in the parent trial. However, a 14-day study period has often been used in prior event level research and the use of repeated timepoints with a relatively small sample increases power (28,29). Additionally, this study only aimed to examine the relationship between alcohol use and ART adherence, not viral suppression. This decision was in part due to the short time frame of this study, as changes in viral load would not be observable based on daily adherence fluctuations and are only observable after a much longer time period (69,70). However, examining more nuanced relationships between alcohol use and viral suppression over time is an important next step of this research.

Conclusions

Improving ART adherence among PLWH using alcohol is an important public health goal in South Africa. Further understanding nuances in the relationship between alcohol use and non-adherence could generate findings critical to refining alcohol and ART adherence-focused interventions. Current findings particularly highlight weekends and holidays as potential high-risk periods for non-adherence, likely both due to alcohol use and otherwise, as well as a risk for non-adherence among men following instances of binge drinking. Findings suggest that testing tailored intervention strategies to support ART adherence during weekend drinking and for men engaged in heavy episodic drinking would be important areas of future intervention work.

References

1. UNAIDS. South Africa [Internet]. 2018 [cited 2019 Nov 19]. Available from: https://www.unaids.org/en/regionscountries/countries/southafrica

2. South African National AIDS Council. South Africa's National Strategic Plan for HIV, TB, and STIs: 2017-2022. Pretoria, South Africa; 2017.

3. Gonzalez A, Barinas J, O'Cleirigh C. Substance Use: Impact on adherence and HIV medical treatment. Curr HIV/AIDS Rep. 2011;8:233.

4. Kader R, Govender R, Seedat S, Koch JR, Parry C. Understanding the impact of hazardous and harmful use of alcohol and/or other drugs on ARV adherence and disease progression. PLOS ONE. 2015 May 1;10(5):e0125088.

5. Braithwaite RS, McGinnis KA, Conigliaro J, et al. A temporal and dose-response association between alcohol consumption and medication adherence among veterans in care. Alcohol Clin Exp Res. 2005 Jul;29(7):1190-7. doi: 10.1097/01.alc.0000171937.87731.28. PMID: 16046874.

6. Reid MC, Fiellin DA, O'Connor PG. Hazardous and harmful alcohol consumption in primary care. Archives of Internal Medicine. 1999 Aug 9;159(15):1681–9.

7. Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: Review and meta-analysis. J Acquir Immune Defic Syndr. 2009 Oct 1;52(2):180.

8. Huis in t' Veld D, Pengpid S, Colebunders R, Skaal L, Peltzer K. High-risk alcohol use and associated socio-demographic, health and psychosocial factors in patients with HIV infection

in three primary health care clinics in South Africa. Int J STD AIDS. 2016 Jul 21;28(7):651–9.

9. Magidson JF, Fatch R, Orrell C, et al. Biomarker-measured unhealthy alcohol use in relation to CD4 count among individuals starting ART in Sub-Saharan Africa. AIDS and Behavior [Internet]. 2018 Dec 17; Available from: https://doi.org/10.1007/s10461-018-2364-2.

10. Parry CD, Londani M, Shuper PA, et al. Characteristics and drinking behaviour of patients on antiretroviral therapy who drink and attend HIV clinics in Tshwane, South Africa: Implications for intervention. S Afr Med J. 2019 Sep 30;109(10):784–91.

11. Myers, B., Lombard, C., Joska, J.A., et al. Associations Between Patterns of Alcohol Use and Viral Load Suppression Amongst Women Living with HIV in South Africa. *AIDS Behav* (2021). https://doi.org/10.1007/s10461-021-03263-3.

12. Santos G-M, Strathdee SA, El-Bassel N, et al. Psychometric properties of measures of substance use: a systematic review and meta-analysis of reliability, validity and diagnostic test accuracy. BMC Medical Research Methodology. 2020 May 7;20(1):106.

13. Mboup A, Béhanzin L, Guédou F, et al. Comparison of adherence measurement tools used in a pre-exposure prophylaxis demonstration study among female sex workers in Benin. Medicine (Baltimore). 2020 May 22;99(21):e20063.

14. Velloza J, Kemp CG, Aunon FM, Ramaiya MK, Creegan E, Simoni JM. Alcohol use and antiretroviral therapy non-adherence among adults living with HIV/AIDS in Sub-Saharan Africa: A systematic review and meta-analysis. AIDS Behav. 2020 Jun 1;24(6):1727–42.

15. [redacted for peer review].

16. McKinney A, Coyle K. Next day effects of a normal night's drinking on memory and psychomotor performance. Alcohol Alcohol. 2004 Nov 1;39(6):509–13.

17. McKinney A, Coyle K. Alcohol hangover effects on measures of affect the morning after a normal night's drinking. Alcohol Alcohol. 2006 Jan 1;41(1):54–60.

18. Andersen LS, Magidson JF, O'Cleirigh C, et al. A pilot study of a nurse-delivered cognitive behavioral therapy intervention (Ziphamandla) for adherence and depression in HIV. J Health Psychol [Internet]. 2016;1359105316643375. Available from: https://doi.org/10.1177/1359105316643375

19. Woods SP, Dawson MS, Weber E, et al. Timing is everything: antiretroviral nonadherence is associated with impairment in time-based prospective memory. J Int Neuropsychol Soc. 2009 Jan;15(1):42–52.

20. Grov C, Rendina HJ, John SA, Parsons JT. Determining the roles that club drugs, marijuana, and heavy drinking play in PrEP medication adherence among Gay and Bisexual men: Implications for treatment and research. AIDS Behav. 2019 May;23(5):1277–86.

21. Lau-Barraco C, Braitman AL, Linden-Carmichael AN, Stamates AL. Differences in weekday versus weekend drinking among nonstudent emerging adults. Exp Clin Psychopharmacol. 2016 Apr;24(2):100.

22. Dowshen N, Kuhns LM, Gray C, Lee S, Garofalo R. Feasibility of Interactive Text message Response (ITR) as a novel, real-time measure of adherence to antiretroviral therapy for HIV+ youth. AIDS Behav. 2013 Jul 1;17(6):2237–43.

23. Boucquemont J, Pai ALH, Dharnidharka VR, et al. Association between day of the week and medication adherence among adolescent and young adult kidney transplant recipients. Am J Transplant. 2020;20(1):274–81.

24. Myers B, Sorsdahl K, Morojele NK, Kekwaletswe C, Shuper PA, Parry CDH. "In this thing I have everything I need": perceived acceptability of a brief alcohol-focused intervention for people living with HIV. AIDS Care. 2017 Feb 1;29(2):209–13.

25. Sorsdahl K, Morojele N, Parry C, et al. 'What will it take': addressing alcohol use among people living with HIV in South Africa. Int J STD AIDS. 2019 Aug 27;30(11):1049–54.

26. Kenya S, Chida N, Jones J, Alvarez G, Symes S, Kobetz E. Weekending in PLWH: Alcohol use and ART adherence, a pilot study. AIDS Behav. 2013 Jan;17(1):61–7.

27. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A "SMART" design for building individualized treatment sequences. Annu Rev Clin Psychol. 2012 Mar 29;8(1):21–48.

28. Sullivan MC, Cruess DG, Huedo-Medina TB, Kalichman SC. Substance use, HIV serostatus disclosure, and sexual risk behavior in people living with HIV: An event-level analysis. Archives of Sexual Behavior. 2020 Aug 1;49(6):2005–18.

29. Irwin TW, Morgenstern J, Parsons JT, Wainberg M, Labouvie E. Alcohol and sexual HIV risk behavior among problem drinking men who have sex with men: An event level analysis of timeline followback data. AIDS and Behavior. 2006 May 1;10(3):299–307.

30. Parsons JT, Rosof E, Mustanski B. The temporal relationship between alcohol consumption and HIV-medication adherence: a multilevel model of direct and moderating effects. Health Psychol. 2008 Sep;27(5):628–37.

31. Sileo KM, Simbayi LC, Abrams A, Cloete A, Kiene SM. The role of alcohol use in antiretroviral adherence among individuals living with HIV in South Africa: Event-level findings from a daily diary study. Drug and Alcohol Dependence. 2016 Oct 1;167:103–11.

32. Spinelli MA, Haberer JE, Chai PR, Castillo-Mancilla J, Anderson PL, Gandhi M. Approaches to objectively measure antiretroviral medication adherence and drive adherence interventions. Current HIV/AIDS Reports. 2020 Aug 1;17(4):301–14.

33. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med. 2015 Dec;5(4):470–82.

34. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction. 2002 Sep;97(9):1183–94.

35. Haberer JE, Kahane J, Kigozi I, et al. Real-Time Adherence Monitoring for HIV Antiretroviral Therapy. AIDS Behav. 2010 Dec 1;14(6):1340–6.

36. Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt. 2014 Sep 1;34(5):502–8.

37. Sobell LC, Sobell MB. Timeline follow-back. In: Measuring alcohol consumption. Springer; 1992. p. 41–72.

38. Myers B, Carney T, Rooney J, Malatesta S, White LF, Parry CDH, Bouton TC, Ragan EJ, Horsburgh CR Jr., Warren RM, Jacobson KR. (2021). Alcohol and Tobacco Use in a Tuberculosis Treatment Cohort during South Africa's COVID-19 Sales Bans: A Case Series. *International Journal of Environmental Research and Public Health*. 2021; 18(10):5449. https://doi.org/10.3390/ijerph18105449.

39. Pavlacic JM, Dixon LJ, Schulenberg SE, Buchanan EM. Examining daily-level associations between nightly alcohol use and next-day valued behavior in college students. J Am Coll Health. 2020 Jul 15;1–5.

40. Braitman AL, Lau-Barraco C, Stamates AL. Personalized feedback tempers weekend increases in alcohol use among nonstudent emerging adult drinkers. Addictive Behaviors. 2020 Jun 1;105:106332.

41. Peltzer K, Davids A, Njuho P. Alcohol use and problem drinking in South Africa: findings from a national population-based survey. Afr J Psychiatry. 2011;14(1):30–7.

42. Chaiyasong, S., Huckle, T., Mackintosh, A., et al. (2018) 'Drinking patterns vary by gender, age and country-level income: Cross-country analysis of the International Alcohol Control Study', *Drug and Alcohol Review*, 37(S2), pp. S53–S62. doi:10.1111/dar.12820.

43. World Health Organization, Department of Mental Health and Substance Abuse (2005) *Alcohol, gender, and drinking problems: perspectives from low and middle income countries*. Geneva, Switzerland: World Health Organization, p. 77.

44. Vellios, N.G. and Van Walbeek, C.P. (2017) 'Self-reported alcohol use and binge drinking in South Africa: Evidence from the National Income Dynamics Study, 2014 - 2015', *South African Medical Journal*, 108(1), p. 33. doi:10.7196/SAMJ.2017.v108i1.12615.

45. Lenth RV. Using the lsmeans Package [Internet]. 2012. Available from: http://www2.uaem.mx/r-mirror/web/packages/lsmeans/vignettes/using-lsmeans.pdf

46. National Institute on Alcohol Abuse and Alcoholism. Drinking Levels Defined [Internet]. [cited 2019 May 3]. Available from: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking

47. Ju K, Lin L, Chu H, Cheng L-L, Xu C. Laplace approximation, penalized quasi-likelihood, and adaptive Gauss–Hermite quadrature for generalized linear mixed models: towards meta-analysis of binary outcome with sparse data. BMC Medical Research Methodology. 2020 Jun 11;20(1):152.

48. glmmPQL function | R Documentation [Internet]. [cited 2021 Jan 14]. Available from: https://www.rdocumentation.org/packages/MASS/versions/7.3-53/topics/glmmPQL

49. Lesch E, Adams AR. Couples living with and around alcohol abuse: A study of a farmworker community in the Cape Winelands, South Africa. Social Science & Medicine. 2016 May 1;156:167–74.

50. Schatz E, Seeley J, Negin J, et al. “For us here, we remind ourselves”: strategies and barriers to ART access and adherence among older Ugandans. BMC Public Health. 2019 Jan 31;19(1):131.

51. Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: A systematic review and meta-analysis. PLoS Med. 2016 Nov 29;13(11):e1002183–e1002183.

52. Gossage JP, Snell CL, Parry CDH, et al. Alcohol use, working conditions, job benefits, and the legacy of the “Dop” system among farm workers in the Western Cape Province, South Africa: hope despite high levels of risky drinking. Int J Environ Res Public Health. 2014 Jul 21;11(7):7406–24.

53. Adeniyi OV, Ajayi AI, Ter Goon D, Owolabi EO, Eboh A, Lambert J. Factors affecting adherence to antiretroviral therapy among pregnant women in the Eastern Cape, South Africa. BMC Infect Dis. 2018 Apr 13;18(1):175.

54. Karl Peltzer & Shandir Ramlagan (2009) Alcohol Use Trends in South Africa. J So Sci. 2009; 18(1): 1-12, DOI: 10.1080/09718923.2009.11892661.

55. Heestermans T, Browne JL, Aitken SC, Vervoort SC, Klipstein-Grobusch K. Determinants of adherence to antiretroviral therapy among HIV-positive adults in sub-Saharan Africa: a systematic review. BMJ Glob Health. 2016 Dec 1;1(4):e000125.

56. Kagee A, Remien RH, Berkman A, Hoffman S, Campos L, Swartz L. Structural barriers to ART adherence in Southern Africa: challenges and potential ways forward. Glob Public Health. 2011 Jan;6(1):83–97.

57. Moosa A, Gengiah TN, Lewis L, Naidoo K. Long-term adherence to antiretroviral therapy in a South African adult patient cohort: a retrospective study. BMC Infect Dis. 2019 Sep 5;19(1):775.

58. Sharma M, Barnabas RV, Celum C (2017) Community-based strategies to strengthen men's engagement in the HIV care cascade in sub-Saharan Africa. PLOS Medicine 14(4): e1002262. https://doi.org/10.1371/journal.pmed.1002262.

59. Lesch E, Casper R. 'Drinking with respect': Drinking constructions of men who live in a Cape Winelands farm community in South Africa. J Health Psychol. 2015 Oct 20;22(4):409–21.

60. Wechsberg WM, El-Bassel N, Carney T, Browne FA, Myers B, Zule WA. Adapting an evidence-based HIV behavioral intervention for South African couples. Subst Abuse Treat Prev Policy. 2015;10.

61. Madiba S, Canti-Sigaqa V. Barriers to participate in support groups for people living with HIV: a qualitative study with men receiving antiretroviral treatment in a HIV clinic in Mthatha, South Africa. Glob J Health Sci. 2012 Sep 18;4(6):119–28.

62. Fuentes LW, Johnson ML, Holtgrave DR. An exploration of weekly patterns in HIV-related behaviors: implications for successful interventions and future research. AIDS Care. 2015 Sep 2;27(9):1118–27.

63. [redacted for peer review].

64. [redacted for peer review].

65. Mayer JE, Fontelo P. Meta-analysis on the effect of text message reminders for HIV-related compliance. AIDS Care. 2017 Apr;29(4):409–17.

66. Wechsberg WM, Zule WA, El-Bassel N, et al. The male factor: Outcomes from a cluster randomized field experiment with a couples-based HIV prevention intervention in a South African township. Drug Alcohol Depend. 2016/02/18 ed. 2016 Apr 1;161:307–15.

67. Ghosh S, Jain R, Jhanjee S, Rao R, Mishra AK. Alcohol Biomarkers and their Relevance in Detection of Alcohol Consumption in Clinical Settings. Int Arch Subst Abuse Rehabil. 2019; 1(1). doi.org/10.23937/iasar-2017/1710002

68. Wray TB, Merrill JE, Monti PM. Using Ecological Momentary Assessment (EMA) to assess situation-level predictors of alcohol use and alcohol-related consequences. Alcohol Res. 2014;36(1):19–27.

69. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2nd ed. Geneva: World Health Organization; 2016.

70. Safren, S. A., O'Cleirigh, C., Andersen, L. S., et al. Treating depression and improving adherence in HIV care with task-shared cognitive behavioral therapy in Khayelitsha, South Africa: A randomized controlled trial. J Int AIDS Soc. In Press.

Table I: Participant Descriptive Statistics (n=53)

Characteristic	*n*	*%*	*Mean*	*SD*
		Demographics		
Gender				
Woman	25	47.17		
Man	28	52.83		
Age			37.39	9.22
Black African	52	98.11		
		Alcohol Risk and Use		
WHO-ASSIST at screening			25.80	6.66
Number of drinks per day			1.72	4.03
Number drinks per day (women)			1.52	1.50
Number drinks per day (men)			1.91	2.31
Number of drinks per weekday (Mon-Thurs)			0.70	2.52
Number of drinks per weekend day (Fri-Sun)			2.84	4.97
Number of drinking days in period			2.82	2.64
Number of drinks on drinking days			7.41	3.63
		Adherence		
Adherent days in sample	311	47.0%		
Weekdays in sample	355			
Adherent days on weekdays	187	52.7%		
Weekend days in sample	330			
Adherent days on weekend days	124	37.6%		
Treatment target time(s)				
One	40	75.47		
Two	13	24.53		

Table II: Multilevel model examining the relationship between number of drinks above one's own mean and ART adherence on the same day controlling for mean drinks, timepoint, age, gender, and weekend/holiday

	Main effects					**Incorporating interactions**				
	β	Standard error	p-value	Adjusted odds ratio	95% CI	β	Standard error	p-value	Adjusted odds ratio	95% CI
Time-varying factors										
Timepoint	-0.04	0.03	0.28	0.97	0.91-1.03	-0.04	0.03	0.25	0.96	0.90-1.03
Number of drinks	-0.04	0.03	0.14	0.96	0.92-1.01	-0.07	0.07	0.44	-	-
Weekend/holiday	-0.87	0.19	<0.001*	0.42	0.29-0.61	-0.88	0.20	<0.001*	-	-
Time-invariant factors										
Mean drinks (TLFB)	0.02	0.13	0.87	1.02	0.79-1.32	0.02	0.13	0.90	1.02	0.79-1.32
Age	0.03	0.03	0.25	1.03	0.97-1.09	0.03	0.03	0.31	-	-
Gender - Man	-0.60	0.52	0.25	0.55	0.19-1.55	-0.61	0.52	0.25	-	-
Interactions										
Number of drinks X Weekend/Holiday	-	-	-	-	-	-.01	0.07	0.85	-	-
Number of drinks X Age	-	-	-	-	-	-0.001	0.003	0.74	-	-
Number of drinks X Gender	-	-	-	-	-	0.08	0.07	0.21	-	-

Table III: Multilevel model examining the relationship between number of drinks above one's own mean and ART adherence on the following day controlling for next day number of drinks, mean drinks, timepoint, age, gender, and if next day is weekend/holiday

	Main effects					**Incorporating interactions**				
	β	Standard error	p-value	Adjusted odds ratio	95% CI	β	Standard error	p-value	Adjusted odds ratio	95% CI
Time-varying factors										
Timepoint	-0.04	0.04	0.37	0.96	0.89-1.04	-0.04	0.04	0.37	0.96	0.88-1.05
Prior day number of drinks	-0.05	0.03	0.04*	0.95	0.90-1.00	0.25	0.08	0.001*	-	-
Same day number of drinks	-0.10	0.03	<0.001*	0.91	0.86-0.96	-0.11	0.03	<0.001*	0.90	0.85-0.94
Weekend/Holiday	-0.46	0.20	0.02*	0.63	0.43-0.93	-0.64	0.21	0.002*	-	-
Time-invariant factors										
Mean drinks (TLFB)	-0.11	0.15	0.48	0.90	0.67-1.21	-0.08	0.15	0.62	0.93	0.68-1.26
Age	0.03	0.03	0.41	1.03	0.96-1.10	0.02	0.03	0.47	-	-
Gender - Man	-0.67	0.59	0.27	0.51	0.15-1.69	-0.76	0.62	0.23	-	-
Interactions										
Prior day number of drinks X Weekend/Holiday	-	-	-	-	-	-0.28	0.08	<0.001*	-	-
Prior day number of drinks X Age	-	-	-	-	-	0.002	0.003	0.57	-	-
Prior day number of drinks X Gender	-	-	-	-	-	-0.25	0.08	0.001*	-	-

Figure Captions

Figure I: Example Timeline Follow-back showing temporal relationship between standardized alcohol data and adherence data for Model 1 (solid lines) and Model 2 (dashed lines).

Figure II: Relative probability of next day adherence predicted by model for number of drinks consumed above one's average on a weekend/holiday as compared to a weekday/non-holiday, with significant differences between weekends/holidays and weekdays/non-holidays at that number of drinks labeled with an asterisk.

Figure III: Relative probability of next day adherence predicted by model for number of drinks consumed on a day above one's own average for men as compared to women, with significant differences between men and women at that number of drinks labeled with an asterisk.