Published in final edited form as:

Drug Alcohol Depend. 2016 February 1; 159: 174–180. doi:10.1016/j.drugalcdep.2015.12.013.

Binge Drinking is Associated with Differences in Weekday and Weekend Adherence in HIV-Infected Individuals

Raquel B. De Boni^{a,b,*}, Lu Zheng^a, Susan L. Rosenkranz^a, Xin Sun^a, Jeffrey Lavenberg^a, Sandra W. Cardoso^b, Beatriz Grinsztejn^b, Alberto La Rosa^c, Samuel Pierre^d, Patrice Severe^d, Susan E. Cohn^e, Ann C. Collier^f, and Robert Gross^g

Raquel B. De Boni: raqueldeboni@gmail.com

^aCenter for Biostatistics in AIDS Research (CBAR), Harvard School of Public Health, Boston, MA, USA

^bInstituto Nacional de Infectologia Evandro Chagas, FIOCRUZ, Rio de Janeiro, Brazil

^cAsociacion Civil Impacta Salud y Educacion, Lima, Peru

^dInstitut National de Laboratoire et de Recherches, Centres Gheskio, Port au Prince, Haiti

^eNorthwestern University Feinberg School of Medicine, Chicago, IL, USA

^fHarborview Medical Center, University of Washington, Seattle, WA, USA

^gDepartment of Medicine (Infectious Diseases) and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Abstract

Background—Understanding patterns of antiretroviral adherence and its predictors is important for designing tailored interventions. Alcohol use is associated with non-adherence. This study aimed to evaluate: 1) if there was a difference in weekday compared with weekend adherence in HIV-infected individuals from low and middle income countries (LMIC), and 2) whether binge drinking was associated with this difference.

Methods—Data from a randomized trial conducted at 9 sites in 8 LMIC were analyzed. Microelectronic monitors were used to measure adherence. Differences between weekday and

*Corresponding author at: Instituto Nacional de Infectologia Evandro Chagas-FIOCRUZ, LAPCLIN DST/AIDS, Av. Brasil 4365. Rio de Janeiro, Brazil. Zip code: 21040-360. Tel.: 55-21-3865-9122.

Presented at IAPAC, 10th International Conference on HIV Treatment and Prevention Adherence, Miami, June 28–30, 2015.

Trial Registration: ClinicalTrials.gov NCT00608569

Conflict of Interest: None

Contributors

RBDB, LZ, and RG conceptualized the study. RBDB analyzed data and wrote the manuscript first draft. LZ, RG supervised data analysis, interpretation and manuscript writing. SLR, XS, JL worked on data analysis and interpretation and revised the manuscript for important intellectual content; SWC, BG, ALR, SP, PS acquired and interpreted data and revised the manuscript for important intellectual content; SEC, ACC interpreted data and revised the manuscript for important intellectual content. All authors approved the manuscript final version.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

weekend adherence in each quarter (successive 12-week periods) were compared using Wilcoxon signed rank tests and predictors of adherence, including baseline binge drinking, were evaluated using Generalized Estimating Equations.

Results—Data from 255 participants were analyzed: 49.8% were male, median age was 37 years and 28.6% enrolled in Haiti. At study entry, only 2.7% reported illicit substance use, but 22.3% reported binge drinking at least once in the 30 days prior to enrollment. Adherence was higher on weekdays than weekends (median percent doses taken: 96.0% vs 94.4%; 93.7% vs 91.7%; 92.6% vs 89.7% and 93.7% vs 89.7% in quarters 1–4 respectively, all $p < 0.001$). Binge drinking at baseline and time on study were both associated with greater differences between weekday and weekend adherence.

Conclusions—Adherence was worse on weekends compared to weekdays: difference was small at treatment initiation, increased over time and was associated with binge drinking. Screening and new interventions to address binge drinking, a potentially modifiable behavior, may improve adherence in HIV-infected individuals in LMIC.

Keywords

alcohol; binge drinking; HIV/AIDS; adherence; microelectronic monitors; low and middle income countries

1. INTRODUCTION

Combined Antiretroviral Therapy (cART) has changed the course of the HIV/AIDS epidemic, reducing morbidity and mortality (Lima et al., 2007), as well as preventing new infections (Cohen et al., 2011; Montaner et al., 2010). In order for cART to be effective, people living with HIV must maintain high levels of adherence to achieve viral suppression (Bangsberg et al., 2001) and to prevent the development of resistant strains (Gardner et al., 2009). Although progress has been made with simpler and more tolerable medication regimens, sustaining high levels of adherence remains a challenge for many individuals.

It has become clear that patterns of adherence vary over time and patterns may differ in their effect on virologic and clinical outcomes (Gras et al., 2012; Gross et al., 2001; Parienti et al., 2008). Self-report, the most commonly used method for measuring adherence, is not able to capture detailed patterns and suffers from a well-described “ceiling effect” (Ortego et al., 2011; Thirumurthy et al., 2012). In contrast, microelectronic monitors (e.g., MEMS) record the time of each medication bottle opening, making it a useful tool for evaluating adherence patterns (Knafl et al., 2011). For example, Genberg et al. (2012) used data generated by microelectronic monitors to show that consecutive interruptions may have a greater impact on viral load than the same number of sporadically missed doses.

One factor associated with non-adherence has been alcohol use (Azar et al., 2010; Chibanda et al., 2014; Hendershot et al., 2009), although this association is susceptible to misclassification due to different methods of measuring both alcohol use and adherence. An important gap in the current literature is understanding how different patterns of alcohol use predict patterns of adherence. Among problem alcohol use patterns (US Preventive Services Task Force, 2014), binge drinking (defined as ingestion of five or more drinks in a single

occasion for men and four or more drinks in a single occasion for women (NIAAA, 2004)) or heavy episodic drinking (6 or more drinks in a single occasion, as defined by World Health Organization- WHO (WHO, 2014)), is important to screen for because it is highly prevalent in many high and low/middle countries (WHO, 2014; CDC, 2012). Binge drinking has been associated with poor health outcomes, including alcohol dependence and mortality (Graff-Iversen et al., 2013; Plunk et al., 2014); in a multicenter US HIV clinical trial, binge drinking increased the odds of non-adherence by 1.53 fold (95% CI 1.21 – 1.95; Cohn et al., 2011). A 2010 US study showed that adherence to antiretrovirals was consistently lower during weekends compared to weekdays (Bachhuber et al., 2011). Alcohol use, including binge drinking, is reported to be more frequent during weekends (Heeb et al., 2008; Padrão et al., 2011; Sieri et al., 2002). Understanding the different patterns of antiretroviral adherence, as well as its predictors, is important for designing tailored interventions before non-adherence, treatment failure, and resistance ensue. This study aimed to evaluate: 1) if there was a difference in weekday compared with weekend adherence in HIV-infected individuals from low and middle income countries (LMIC), and 2) whether binge drinking was associated with this difference.

2. METHODS

2.1 Study design

We conducted a secondary analysis of the AIDS Clinical Trial Group (ACTG) A5234 clinical trial. Details of the study design and its main results are published elsewhere (Gross et al., 2015). In brief, A5234 was a randomized open-label clinical trial that evaluated partner-based modified directly observed therapy (mDOT) as a strategy to increase adherence among individuals after first-line treatment failure. It was conducted in eight LMIC (Brazil, Botswana, Haiti, Peru, South Africa, Uganda, Zambia, and Zimbabwe). At study entry, all participants started on a single cART regimen: emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) 200/300 mg once daily (QD) and lopinavir (LPV)/ritonavir (RTV) 400/100 mg twice a day (BID), as second line cART. They were randomized to mDOT or site standard of care (SOC) adherence measures and followed for 52 weeks, with scheduled visits at 4, 8, 12, 24, 36, 48 and 52 weeks after enrollment. There were no clinically or statistically significant effects of the intervention on virologic outcome or adherence. All A5234 participants who had electronically monitored medication adherence data available were included in this analysis.

2.2 Measures and Definitions

2.2.1 Primary Outcome: Difference between Weekday and Weekend

Adherence—The main outcome evaluated was the within-participant difference (weekday-weekend) in the percentage of doses taken during weekdays and the percentage of doses taken during weekends over the 4 quarters of the year-long study. Each quarter was considered a successive 12-week period (weeks 0–12, 12–24, 24–36, and 36–48).

There is no universal definition of weekends versus weekdays. Considering that in many settings, Friday evening is viewed as the start of a weekend, we defined “Weekend” as Friday, Saturday and Sunday, and the remaining days as “Weekdays”.

Adherence was measured using the Microelectronic Event Monitoring System (MEMS, MWV Healthcare) on the lopinavir/ritonavir bottle. The electronic monitor captured the date and time the bottle was opened and participants were expected to open their bottles twice/day in two different time-intervals (herein called “dose- intervals”). Dose-intervals were considered the time between 03:01am–03:00pm and between 03:01pm–03:00am. To calculate adherence, the denominator was the number of dose-intervals for each participant in each quarter. The only discounted time periods removed from denominators were those when the participant was hospitalized. The numerator was the number of dose-intervals with electronic monitor openings for each participant. The percent of doses taken for each participant in each quarter was calculated separately for weekdays and weekends as the percent of dose-intervals where there was at least one dose-interval with an opening registered.

2.2.2 Primary Exposure Variable: Alcohol Use—*Binge drinking*, defined as ingestion of five or more drinks in a single occasion was evaluated at baseline through the face-to-face question “During the past 30 days, how often have you had 5 or more drinks of alcohol in a row within a couple of hours?.” Possible responses were daily, nearly every day, 3–4 times/week, once-twice/week, 2–3 times/month, once a month and never. Responses were dichotomized as never vs. once or more. For the purpose of the present analysis, we chose to evaluate binge drinking and other covariates only at the baseline interview because we wanted to identify drinking patterns that could be intervened upon before they resulted in clinically important non-adherence, which in turn leads to resistance and loss of the regimen.

2.2.3 Other Variables—Demographics (sex, age and site location) and clinical characteristics (the number of years on cART before entry in the study, CD4 count (cells/mm³) and plasma viral load (log₁₀ copies/ml)) were assessed at baseline interview. As the largest group of participants was enrolled at the Haitian site, the site variable was dichotomized as Haitian versus non-Haitian site. Treatment arm (mDOT vs. SOC) was considered a possible confounder in the analysis because the original study was an intervention designed to increase adherence. Illicit substance use was evaluated at baseline interview through a series of yes/no questions “In the past 30 days have you used any of the following substances (marijuana, cocaine-powder, crack, freebase injections, heroin, amphetamines, sniffing organic solvents/glues/thinners, and other).” Self-perception of health was evaluated at baseline interview with the question “In general, would you say your health is...(Excellent, very good, good, fair, poor)?.” Answers were dichotomized as Excellent, Very Good, Good compared to Fair, Poor.

2.3 Statistical Analysis

The characteristics of binge drinkers and non-binge drinkers at baseline interview were compared using chi-squared test and Fisher’s exact test, for categorical variables; T-test, for symmetrical continuous variables; and Wilcoxon rank sum test, for asymmetrical continuous variables. The differences between the percent of doses taken on weekdays and weekends in each quarter were compared using Wilcoxon signed rank tests.

The association of binge drinking, as well as the other variables measured at baseline interview, and the outcome (difference between the percent of doses taken on weekdays and weekends) was evaluated using Generalized Estimating Equations (GEE) with exchangeable correlation structure. GEE was selected to account for repeated outcome measures over up to four quarters per participant. In the univariable analysis, demographics, treatment arm, clinical characteristics, binge drinking, substance use, self-perception of health, and quarter on study were analyzed separately and those associated with differences in weekday and weekend adherence with a p -value <0.1 were further evaluated in multivariable models using backward selection. The most parsimonious model, e.g., including only variables significantly associated with the outcome at $p<0.05$, was selected, with sex, age and treatment arm included in the final model regardless of statistical significance. Collinearity among variables included in the final model was assessed by examining the parameter estimate changes between the univariable models and multivariable model.

3. RESULTS

The A5234 trial enrolled 257 eligible participants and microelectronic adherence data were available for 255 (99%) participants who were included in this analysis. Baseline characteristics of the participants, overall and stratified by baseline binge drinking, are presented in Table 1. The study population was evenly divided between the sexes and Haiti was the largest enrolling site. At study entry, seven (2.7%) reported any illicit substance use in the 30 days before enrollment: 2 individuals reported using marijuana, 2 reported cocaine use, 1 reported marijuana and cocaine and 2 reported drugs different than marijuana, cocaine-powder, crack, freebase injections, heroin, amphetamines, and sniffing organic solvents/glues/thinners. During the month prior to enrollment, 198 participants (77.6%) reported no binge drinking, 38 (14.9%) reported 1 episode, 6 (2.35%) reported 2–3 episodes and 13 (5.1%) reported one or more episodes of binge drinking per week. Binge drinking was more common among men than women and among illicit substance users than non-users (Table 1).

Figure 1 displays the medians (interquartile range [IQR]) of the percent of doses taken during weekdays and weekends for each quarter. The first quarter had the highest adherence percent with a median of 96.0% (IQR 81.4%–98.9%) of doses taken during weekdays and 94.4% (IQR 76.9%–100%) during weekends. The third quarter had the lowest adherence with 92.6% (IQR 63.4%–98.9%) of doses taken during weekdays and 89.7% (IQR 62.2%–98.6%) of doses taken during weekends. Adherence was consistently lower on weekends and the differences were statistically significant in all four quarters (all p -values <0.001).

In the univariate analysis, being male ($p=0.04$), binge drinking in the past 30 days ($p<0.01$), self-perception of excellent/very good/good health ($p<0.01$) and later quarter on study ($p<0.01$) were associated with a larger difference in the percent of doses taken during weekdays and weekends (Table 2). In Table 2, positive numbers represent an average increase in the difference between weekday and weekend adherence for the indicated covariate comparison.

Variables included in the initial multivariable model were sex, age, treatment arm, site, years on cART before entry, binge drinking, self-perception of health and quarter on the study. Only years on cART was not associated with the outcome at $p < 0.05$ in adjusted analyses and was excluded from the final model. In the final multivariable model adjusting for sex, age and treatment arm, the following factors were associated with a larger difference between weekday and weekend adherence (Figure 2): binge drinking ($p < 0.01$), self-perception of excellent/very good/good health ($p < 0.01$), non-Haiti site ($p = 0.02$), and later quarter ($p < 0.01$).

4. DISCUSSION

The present study shows that adherence was higher on weekdays than weekends and binge drinking was associated with a greater difference between these weekly time periods.

During all four quarters of the initial year on a second-line regimen, adherence to cART was worse on weekends compared to weekdays. This finding is consistent with the study by Bachhuber et al. (2011) who reported a small but significant difference in the percent of doses taken during weekdays and weekends (95.3% vs. 93.2%; respectively; $p = 0.012$) in an observational cohort in the US. Our results also show that the difference between weekday and weekend adherence increases over time, which may have important repercussions when considering lifelong treatment. In 2007, with data from two US cohorts, Lazo et al. (2007), showed that average adherence is a “dynamic behavior”. It decreased (from 100% to 80%) among men and was stable among women (around 70%) during the 1998–2003 timeframe. Although it is hard to compare this result with the one presented here - given the methodological and geographical differences, as well as the effect of more than a decade of improvement in tolerability, number of tablets, and frequency of cART regimens - it is possible that the difference we observed could increase even more during a longer follow-up. The reasons for declining adherence over time remain unclear and should be investigated in future longitudinal studies. Wilson et al. (2013), modeling pooled data from 11 US studies using electronic monitors, suggest that difference in clinical and organizational practices should be investigated; and from individual's perspective, the 'Necessity-Concerns Framework' (Horne et al., 2013) could be useful for understanding longitudinal differences on adherence patterns.

Binge drinking was the strongest predictor of the difference between weekday and weekend cART adherence. Our results show that, after controlling for other variables, the difference between percent of doses taken on weekdays and weekends among binge drinkers was on average 3.7 percentage points larger than in non-binge drinkers. A meta-analysis (Hendershot et al., 2009) showed that alcohol drinkers had lower antiretroviral adherence overall than non-drinkers [odds ratio (OR) = 0.548, CI 95% 0.490 – 0.612], and a subsequent review also reported lower overall adherence among individuals with alcohol use disorders (Azar et al., 2010). However, a limitation of both studies was the inclusion of few participants from low and middle income countries. This was partially addressed by Chibanda et al., 2014 who reviewed and described the association of alcohol use disorders and adherence also in LMIC. None of these reviews specifically addressed binge drinking, but some studies have associated this alcohol use pattern with decreased average adherence

among persons living with HIV (Cohn et al., 2011; Lazo et al., 2007). A possible explanation for the association of binge drinking and the difference of weekday-weekend adherence may be the phenomenon of “weekending” as described in a small exploratory study (n=43) in which cART was intentionally skipped on weekends because of a planned increase in alcohol use (Kenya et al., 2013). It may be that individuals fear drug-alcohol interactions based on having been told that it is dangerous to “mix alcohol and medication” (Kalichman et al., 2013). It is not possible in our study to say how many participants decreased their cART on weekends because they planned to drink, but our results suggest that it is an important topic to discuss with participants. Future longitudinal research should also assess how different binge drinking patterns (i.e., such as bingeing on the weekends versus weekdays) are associated with adherence.

Regarding clinical relevance, alcohol use disorders are under-recognized/diagnosed in both primary and secondary care (Mitchell et al., 2012). This problem is compounded by the fact that different alcohol use patterns and disorders may require different interventions (Babor et al., 2001; Jonas et al., 2012). For instance, risky/harmful alcohol use is often addressed through brief counseling interventions, while alcohol dependence may require a pharmacological intervention (Bradley and Kivlahan, 2014; Jonas et al., 2014). Specifically in the context of HIV care, the time tradeoff of screening for binge drinking is mitigated by the simplicity of asking a single question that takes less than one minute to answer. In the context of the original A5234 trial, partners were trained to report excessive alcohol or drug use to the study team, so participants could be referred to substance use treatment. However, considering the results from the present study, a positive answer for binge drinking in the last 30 days might also indicate the need of additional adherence counseling, perhaps focused on weekend adherence and its relation with alcohol drinking. In addition, it is noteworthy that adherence in our study did not fall below 89.7%. Although 90% adherence is relatively high, many studies have found a gradient between 80–90%, 90–95%, and >90%. Furthermore, some evidence from LMIC suggest that very high rates of adherence are necessary for success, although the amount of data in this area is limited (Bisson et al., 2008). Adherence tends to wane over time, as we have also shown. Therefore, the missed doses that we have observed may increase further and thus be a harbinger of later treatment failure.

Finally, enrollment at the Haitian site and report of fair/poor health status were related to smaller differences in weekday and weekend adherence. We observed in that average adherence was lower in Haiti compared to other sites in all four quarters (data not shown). It is plausible that differences between weekdays and weekends are less relevant when overall adherence is lower, and further studies are necessary to investigate this issue and reasons for the differences. We could not find previous reports associating perception of fair/poor health status with adherence patterns, but a recent cross-sectional study showed that individuals who report fair/poor health had more frequent treatment interruptions (Samji et al., 2014).

Strengths of this study include the use of accurate methods for adherence measurement (microelectronic monitors) in a diverse population from LMIC across the globe, suggesting that these results may be applicable in many countries. Although microelectronic monitors may overestimate (individuals may open the bottle and not take the medication) or

underestimate (individuals may remove more than one dose when they open the bottle) adherence (Bova et al., 2005), they have been shown to be more accurate than self-reported measures in both high and low income countries (Arnsten et al., 2001; Deschamps et al., 2004; Hugen et al., 2002; Lyimo et al., 2011; Vriesendorp et al., 2007). There are limitations to our study. Data are from a clinical trial and generalizability to other HIV-infected populations (external validity) may be limited. However, our findings were consistent with those from a prior observational study (Bachhuber et al., 2011), suggesting this pattern may be common in different settings. Additionally, the definition of binge drinking was not adjusted for sex since all participants answered the same question and its prevalence may have been underestimated for women since binge drinking in women are classified as drinking only four drinks at one occasion. However, the proportion of men and women who reported binge drinking (3:1) was similar to the proportion found in the general population from many countries (WHO, 2014; CDC, 2012; Laranjeira et al., 2010). Further research is necessary to evaluate how the different adherence patterns, as well as alcohol patterns, may be associated to virologic failure and other HIV-related outcomes. Finally, very few individuals reported illicit substance use (n=7) and the lack of association with adherence pattern may be related to the small sample size. Other studies should address the possible additive effects of illicit substance use.

In conclusion, in this second line cART study in LMIC, adherence was worse on weekends compared to weekdays: the difference was small at treatment initiation, increased over time and was associated with baseline binge drinking. Screening and new interventions to address binge drinking, a potentially modifiable behavior, may improve adherence to cART in HIV-infected individuals in LMIC.

Acknowledgments

Author Disclosures

Role of Funding Source: funding sources had no role in study design; collection, analysis and interpretation of data; writing the report; or in the decision to submit the article for publication.

The authors wish to thank to the AIDS Clinical Trials Group (ACTG) and SDMC. We would like to acknowledge the following individual sites' grant support, study team members, and site personnel: Les Centres GHESKIO CRS (Site 30022) ACTG CTU Grant; Joint Clinical Research Centre CRS (Site 12401) ACTG CTU Grant U01-A1069501; Parirenyatwa CRS (Site 30313) ACTG CTU Grant UM 1AI069436; Wits HIV CRS (Site 11101) ACTG CTU Grant AI069463; Barranco CRS (Site 11301) ACTG CTU Grant 2UM1AI069438-08; San Miguel CRS (Site 11302) ACTG CTU Grant AI069438; Kalingalinga Clinic CRS (Site 12801) ACTG CTU Grant 7UMIAI069455; Gaborone Prevention/Treatment Trials CRS (Site 12701) ACTG CTU Grant 2UMIAI069456-08; CFDA Grant 93.865; Instituto de Pesquisa Clinica Evandro Chagas (IPEC) CRS (Site 12101) ACTG CTU Grant AI069476 and Northwestern ACTG Grant 1U01AI069471. We also would like to thank to AbbVie Inc. and Gilead Pharmaceuticals, which provided the medications for the trial.

References

- Arnsten JH, Demas PA, Farzadegan H, Grant RW, Gourevitch N, Chang C, Buono D, Eckholdt H, Howard A, Schoenbaum EE. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-reported and electronic monitoring. *Clin Infect Dis*. 2001; 33:1417–1423. [PubMed: 11550118]
- Azar MM, Springer SA, Meyer JP, Altice FL. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. *Drug Alcohol Depend*. 2010; 112:178–193. [PubMed: 20705402]

- Babor, T.; Higgins-Biddle, J.; Saunders, J.; Monteiro, M. Guidelines For Use In Primary Care. WHO; Geneva: 2001. AUDIT-The Alcohol Use Disorders Identification Test.
- Bachhuber M, Bilker WB, Wang H, Chapman J, Gross R. Is antiretroviral therapy adherence substantially worse on weekends than weekdays? *J Acquir Immune Defic Syndr*. 2011; 54:109–110. [PubMed: 20418726]
- Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, Moss A. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*. 2001; 15:1181–1183. [PubMed: 11416722]
- Bisson GP, Rowh A, Weinstein R, Gaolathe T, Frank I, Gross R. Antiretroviral failure despite high levels of adherence: discordant adherence-response relationship in Botswana. *J Acquir Immune Defic Syndr*. 2008; 49:107–110. [PubMed: 18667926]
- Bova CA, Fennie KP, Knafl GJ, Dieckhaus KD, Watrous E, Williams AB. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. *AIDS Behav*. 2005; 9:103–110. [PubMed: 15812617]
- Bradley KA, Kivlahan DR. Bringing patient-centered care to patients with alcohol use disorders. *JAMA*. 2014; 311:1861–1862. [PubMed: 24825640]
- CDC. Vital signs: binge drinking prevalence, frequency, and intensity among adults - United States, 2010. *MMWR*. 2012; 61:14–19. [PubMed: 22237031]
- Chibanda D, Benjamin L, Weiss HA, Abas M. Mental, neurological, and substance use disorders in people living with HIV / AIDS in low- and middle-income countries. *J Acquir Immune Defic Syndr*. 2014; 67:s54–67. [PubMed: 25117961]
- Cohen M, Chen Y, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-manning E, Wang L, Ph D, Makhema J, Mills LA, De Bruyn G, Ch B, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaudo H, Elharrar V, Burns D, Taha TE, Nielsen-saines K, Celentano D, Sc D, Essex M, Fleming TR, Study H. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med*. 2011; 365:493– 505. [PubMed: 21767103]
- Cohn SE, Jiang H, McCutchan J, Koletar S, Murphy R, Robertson K, deStMaurice A, Currier J, Williams P. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: results from ACTG 362. *AIDS Care*. 2011; 23:775–785. [PubMed: 21293986]
- Deschamps AE, Graeve VDE, van Wijngaerden E, De Saar V, Vandamme AM, van Vaerenbergh K, Ceunen H, Bobbaers H, Peetermans WE, de Vleeschouwer PJ, de Geest S. Prevalence and correlates of nonadherence to antiretroviral therapy in a population of HIV patients using Medication Event Monitoring System. *AIDS Patient Care STDS*. 2004; 18:644–657. [PubMed: 15633262]
- Gardner EM, Burman WJ, Steiner JF, Anderson PL, Bangsberg DR. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS*. 2009; 23:1035–1046. [PubMed: 19381075]
- Genberg BL, Wilson IB, Bangsberg DR, Arnsten J, Goggin K, Remien RH, Simoni J, Gross R, Reynolds N, Rosen M, Liu H. Patterns of antiretroviral therapy adherence and impact on HIV RNA among patients in North America. *AIDS*. 2012; 26:1415–1423. [PubMed: 22767342]
- Graff-Iversen S, Jansen MD, Hoff Da, Hoiseth G, Knudsen GP, Magnus P, Morland J, Normann PT, Naess OE, Tambs K. Divergent associations of drinking frequency and binge consumption of alcohol with mortality within the same cohort. *J Epidemiol Community Health*. 2013; 67:350–357. [PubMed: 23235547]
- Gras G, Schneider MP, Cavassini M, Lucht F, Loilier M, Verdon R, Bernard L, Parienti JJ. Patterns of adherence to raltegravir-based regimens and the risk of virological failure among HIV-infected patients: the RALTECAPS cohort study. *J Acquir Immune Defic Syndr*. 2012; 61:265–269. [PubMed: 22895438]
- Gross R, Bilker WB, Friedman HM, Strom BL. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS*. 2001; 15:2109–2117. [PubMed: 11684930]
- Gross R, Zheng L, La Rosa A, Sun X, Rosenkranz SL, Cardoso SW, Sali F, Camp R, Godfrey C, Cohn SE, Robbins GK, Chisada A, Wallis CL, Reynolds NR, Lu D, Safren SA, Hosey L, Severe P,

- Collier AC. Partner-focused adherence intervention for second-line antiretroviral therapy: a multinational randomized trial (ACTG A5234). *Lancet HIV*. 2015; 2:e12–e19.
- Heeb JL, Gmel G, Rehm J, Mohler-Kuo M. Exploring daily variations of drinking in the Swiss general population. A growth curve analysis. *Int J Methods Psychiatr Res*. 2008; 17:1–11. [PubMed: 18286462]
- Hendershot CS, Ph D, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence;review and meta-analysis. *J Acquir Immune Defic Syndr*. 2009; 52:1–26. [PubMed: 19584740]
- Horne R, Chapman SCE, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. *PLoS One*. 2013; 8:e80633. [PubMed: 24312488]
- Hugen PWH, Langebeek N, Burger DM, Zomer B, van Leusen R, Schuurman R, Koopmans PP, Hekster YA. Assessment of adherence to HIV protease inhibitors: comparison and combination of various methods, including MEMS (electronic monitoring), patient and nurse report, and therapeutic drug monitoring. *J Acquir Immune Defic Syndr*. 2002; 30:324–334. [PubMed: 12131570]
- Jonas D, Garbutt J, Amick H, Brown J, Brownley K, Council C, Viera A, Wilkins T, Schwartz O, Richmond E, Yeatts J, Evans T, Wood S, Harris R. Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the US Preventive Services Task Force. *Ann Intern Med*. 2012; 157:645–654. [PubMed: 23007881]
- Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*. 2014; 311:1889–1900. [PubMed: 24825644]
- Kalichman SC, Grebler T, Amaral CM, McNerey M, White D, Kalichman MO, Cherry C, Eaton L. Intentional non-adherence to medications among HIV positive alcohol drinkers: prospective study of interactive toxicity beliefs. *J Gen Intern Med*. 2013; 28:399–405. [PubMed: 23065532]
- 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; 17:61–67. [PubMed: 22961583]
- Knafl G, Bova C, Fennie K, O'Malley J, Dieckhaus K, Williams A. An analysis of electronically monitored adherence to antiretroviral medications. *AIDS Behav*. 2011; 14:755–768. [PubMed: 19107587]
- Laranjeira R, Pinsky I, Sanches M, Zaleski M, Caetano R. Alcohol use patterns among Brazilian adults. *Rev Bras Psiquiatr*. 2010; 32:231–241. [PubMed: 19918673]
- Lazo M, Gange SJ, Wilson TE, Anastos K, Ostrow DG, Witt MD, Jacobson LP. Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women. *Clin Infect Dis*. 2007; 45:1377–1385. [PubMed: 17968839]
- Lima VD, Hogg RS, Harrigan PR, Moore D, Yip B, Wood E, Montaner JSG. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS*. 2007; 21:685–692. [PubMed: 17413689]
- Lyimo, Ra; van den Boogaard, J.; Msoka, E.; Hospers, HJ.; van der Ven, A.; Mushi, D.; de Bruin, M. Measuring adherence to antiretroviral therapy in northern Tanzania: feasibility and acceptability of the Medication Event Monitoring System. *BMC Public Health*. 2011; 11:92. [PubMed: 21306643]
- Mitchell AJ, Meader N, Bird V, Rizzo M. Clinical recognition and recording of alcohol disorders by clinicians in primary and secondary care: meta-analysis. *Br J Psychiatry*. 2012; 201:93–100. [PubMed: 22859576]
- Montaner JSG, Lima VD, Barrios R, Yip B, Wood E, Kerr T, Shannon K, Harrigan PR, Hogg RS, Daly P, Kendall P. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet*. 2010; 376:532–539. [PubMed: 20638713]
- NIAAA. NIAAA News. NIAAA; Bethesda, MD: 2004. NIAAA council approves definition of binge drinking.
- Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodríguez E, Warren MR, Vejo J. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. *AIDS Behav*. 2011; 15:1381–1396. [PubMed: 21468660]

- Padrão P, Damasceno A, Silva-Matos C, Laszczy ska O, Prista A, Gouveia L, Lunet N. Alcohol consumption in Mozambique: regular consumption, weekly pattern and binge drinking. *Drug Alcohol Depend.* 2011; 115:87–93. [PubMed: 21123009]
- Parienti JJ, Das-Douglas M, Massari V, Guzman D, Deeks SG, Verdon R, Bangsberg DR. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS One.* 2008; 3:e2783. [PubMed: 18665246]
- Plunk AD, Syed-Mohammed H, Cavazos-Rehg P, Bierut LJ, Grucza Ra. Alcohol consumption, heavy drinking, and mortality: rethinking the j-shaped curve. *Alcohol Clin Exp Res.* 2014; 38:471–478. [PubMed: 24033586]
- Samji H, Chen Y, Salters K, Montaner JSG, Hogg RS. Correlates of unstructured antiretroviral treatment interruption in a cohort of HIV-positive individuals in British Columbia. *AIDS Behav.* 2014; 18:2240–2248. [PubMed: 24781638]
- Sieri S, Agudo a, Kesse E, Klipstein-Grobusch K, San-José B, Welch aa, Krogh V, Luben R, Allen N, Overvad K, Tjønneland a, Clavel-Chapelon F, Thiébaud a, Miller aB, Boeing H, Kolyva M, Saieva C, Celentano E, Ocké MC, Peeters PHM, Brustad M, Kumle M, Dorronsoro M, Fernandez Feito a, Mattisson I, Weinehall L, Riboli E, Slimani N. Patterns of alcohol consumption in 10 European countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) project. *Public Health Nutr.* 2002; 5:1287–1296. [PubMed: 12639233]
- Thirumurthy H, Siripong N, Vreeman RC, Pop-Eleches C, Habyarimana JP, Sidle JE, Siika AM, Bangsberg DR. Differences between self-reported and electronically monitored adherence among patients receiving antiretroviral therapy in a resource-limited setting. *AIDS.* 2012; 26:2399–2403. [PubMed: 22948266]
- US Preventive Services Task Force. Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: recommendation statement. *Am Fam Physician.* 2014; 89:970A–D.
- Vriesendorp R, Cohen A, Kristanto P, Vrijens B, Rakesh P, Anand B, Iwebor HU, Stiekema J. Adherence to HAART therapy measured by electronic monitoring in newly diagnosed HIV patients in Botswana. *Eur J Clin Pharmacol.* 2007; 63:1115–1121. [PubMed: 17882408]
- WHO. Global Status Report On Alcohol And Health. WHO; Geneva: 2014. Available at: www.who.int
- Wilson IB, Bangsberg DR, Shen J, Simoni JM, Reynolds NR, Goggin K, Gross R, Arnsten JH, Remien RH, Erlen JA, Liu H. Heterogeneity among studies in rates of decline of antiretroviral therapy adherence over time: results from the multisite adherence collaboration on HIV 14 study. *J Acquir Immune Defic Syndr.* 2013; 64:448–454. [PubMed: 24225904]

Highlights

- Participants of clinical trial conducted in low/middle income countries were evaluated
- Adherence to antiretrovirals was higher on weekdays than weekends
- Binge drinking was associated with greater difference on weekday-weekend adherence

Figure 1. Median and inter-quartile range of the percentage of doses taken on weekdays and weekends within quarters. The difference between weekday and weekend adherence in each quarter was compared using Wilcoxon signed rank tests. $p < 0.001$ in all quarters.

Figure 2.

Adjusted estimates for the predictors of the difference between the percentage of doses taken on weekdays and weekends using Generalized Estimating Equations. Factors with $p < 0.1$ in the univariate analysis were evaluated in the multivariable models and most parsimonious model was selected. Sex, age and treatment arm were included a priori. mDOT= modified directly observed therapy.

Table 1

Baseline characteristics of the participants stratified by binge drinking

	Total ¹ (N=255)	Binge Drinking ²		p-value
		Yes (N=57)	No (N=198)	
Sex				
Male	127 (49.8%)	43 (33.9%)	84 (66.1%)	<.001 (<i>a</i>)
Female	128 (50.2%)	14 (10.9%)	114 (89.1%)	
Age				
Mean (s.d.)	38.64 (10.01)	37.54 (8.35)	38.95 (10.44)	0.29 (<i>b</i>)
Site located in Haiti				
Yes	73 (28.6%)	18 (24.7%)	55 (75.3%)	0.58 (<i>a</i>)
No	182 (71.4%)	39 (21.4%)	143 (78.6%)	
Treatment Strategy				
mDOT	127 (49.8%)	31 (24.4%)	96 (75.6%)	0.43 (<i>a</i>)
Standard of Care	128 (50.2%)	26 (20.3%)	102 (79.7%)	
Years on cART before entry				
Median (Q1, Q3)	3.14 (1.98, 4.94)	2.97 (1.89, 4.56)	3.17 (2.04, 5.08)	0.22 (<i>c</i>)
CD4 Count (cells/mm ³)				
Median (Q1, Q3)	175 (91, 271)	213 (112, 320)	169 (89, 263)	0.16 (<i>c</i>)
Viral load(log10(cp/mL))				
Median (Q1, Q3)	4.27 (3.77, 4.91)	4.23 (3.76, 4.84)	4.29 (3.79, 4.92)	0.53 (<i>c</i>)
* Any substance use last 30 days				
Yes	7 (2.7%)	6 (85.7%)	1 (14.3%)	<.001 (<i>d</i>)
No	248 (97.3%)	51 (20.6%)	197 (79.4%)	
Self-perception of health				
Excellent, very good, good	193 (75.7%)	48 (24.9%)	145 (75.1%)	0.09 (<i>a</i>)
Fair, poor	62 (24.3%)	9 (14.5%)	53 (85.5%)	

(a) Chi-Square Test;*(b)* T-Test with Unequal Variance;*(c)* Wilcoxon Rank Sum Test;*(d)* Fisher's Exact Test;¹ Column percent;² Row percent;

* Other than alcohol;

cART=combination antiretroviral therapy; mDOT=modified directly observed therapy; (Q1–Q3)=Interquartile range; s.d.=standard deviation

Unadjusted estimates for the predictors of the difference between the percentage of doses taken on weekdays and weekends using Generalized Estimating Equations.

Table 2

		Estimate	95% CI	p value
Sex	Male vs. female	1.42	0.04 2.80	0.04
Age	Per 10 year increase	-0.58	-1.30 0.15	0.12
Treatment arm	mDOT vs. standard of care	0.98	-0.41 2.37	0.17
Site	Haiti vs. other	-1.14	-2.47 0.20	0.10
Years on cART before entry	Per one year increase	-0.26	-0.54 0.01	0.06
CD4 count (cells/mm³)	Per 100 cell increase	0.36	-0.10 0.83	0.13
Viral load (log 10 copies/ml)	Per 1 log increase	-0.35	-1.18 0.48	0.41
Binge drinking	Yes vs. No	4.23	1.95 6.51	<0.01
*Any substance use last 30 days	Yes vs. No	-2.22	-5.20 0.75	0.14
Self-perception of health	Fair/poor vs. Excellent /Very good/Good	-2.09	-3.29 -0.89	<0.01
Quarter on the study	Per quarter increase	0.44	0.13 0.76	0.01

Positive numbers represent an increase in the difference between weekday and weekend adherence.

* Other than alcohol;

cART=combination antiretroviral therapy; mDOT=modified directly observed therapy; (Q1–Q3)=Interquartile range; s.d.=standard deviation; vs.=versus; Quarter on study= 4 successive 12-week period