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The detrimental effect of alcohol on HIV treatment adherence

A systematic review and meta-analysis

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Abstract

Introduction: The fight against HIV is addressed in both the Sustainable Development Goals and in the 90-90-90-goals set by the United Nations. Emerging evidence is suggesting a “neglected interface” between alcohol consumption and HIV. Earlier studies has sought out to quantify this relationship, but there are still uncertainties regarding the generalizability of the results and if this also applies to different types of drinking intensities.

Methods: This study applied a systematic search for articles published between 1990-2017 in Pubmed/Medline. 46 studies was included in the final analysis.

Results: Alcohol was found to have a significant detrimental effect on treatment adherence on all drinking intensities. All but one analysis showed a significant amount of heterogeneity.

Conclusion: The findings of this study goes in line with previous research but adds insight on the harm of moderate drinking. The result of this and earlier findings give a clear point of direction of alcohol consumption guidelines in people living with HIV. If global targets of viral suppression should be achieved, a more holistic approach where the prevention of non-communicable diseases and infectious diseases go hand in hand might actually be the only way forward.

Conflict of interest:

The author has no conflict of interest to declare.

List of acronyms

ART: antiretroviral therapy

ASI: Addiction Severity Index

AUDIT: Alcohol Use Disorder Identification Test

AUD: Alcohol Use Disorder

CAGE: abbreviation for four questions targeted to identify alcohol use disorder

CASI: Computerized Alcohol Screening Intervention

MEMS: Medication Event Monitoring Systems

NIAAA: National Institute on Alcohol Abuse and Alcoholism

PLWH: People Living With HIV

SDG: Sustainable Development Goals

SE: Standard Error

VAS: Visual Analogue Scale

WHO: The World Health Organization

Introduction

HIV is one of the most frequently addressed pathogens and has been targeted in the Millennium Development Goals as well as the new Sustainable Development Goals (SDGs) [1]. In the end of 2013 there were an estimated 35 million people living with HIV (PLWH), with 240 000 children newly infected. In parallel with the SDGs, UNAIDS has set the 90-90-90 goal to 2020 [2]. This means that by 2020 90% of all PLWH will know their HIV status, 90% of all people diagnosed with HIV will receive sustained antiretroviral therapy (ART) and 90% of all people receiving ART will have viral suppression.

Even though HIV/AIDS could be said to be a multifactorial disease, where several factors will affect the success of achieving the 90-90-90 goal, alcohol use's interaction with HIV is rising as a "neglected interface" [3]. Ecological relationships have been pointing in this direction for several years where southern Africa and eastern Europe have both massive health burdens of HIV and alcohol but where appropriate policies seem to be lacking [4].

The mechanisms and interactions between alcohol and HIV is several but can conceptually be described as behavioral and biological. Alcohol is a drug that exerts harmful effects on the body and is an important puzzle piece in the global burden of disease [5], which includes detrimental effects on the immune system [6]. The connection between alcohol use and tuberculosis (TB) is well established; it is estimated that 10% of global TB cases can be attributed to alcohol [7]. A systematic review investigating possible interactions with alcohol and HIV found that alcohol was a risk factor affecting several steps of the treatment cascade of HIV. Studies have linked alcohol to decreased viral suppression, diagnosis, linkage to care, retention in care, ART initiation and ART adherence [8]. There is also strict biological indications of the harmful effect of alcohol on infectious diseases as there seem to be synergistic effects on the permeability of the blood-brain-barrier [9], on CD4⁺ cell count and viral levels [10] which could be crucial factors for treatment outcome.

The behavioral aspects of alcohol on HIV is several and multifaceted. There is evidence that suggest that alcohol could influence the risk-seeking behavior [11,12] but this could vary greatly between countries, context and personalities making it uncertain what is cause and correlation. Other behavioral effects could be that PLWH actively wait or skip their medications when they are in or prepare for drinking situations [13,14] because of the belief of the detrimental effects of mixing alcohol and HIV medications. This could be one important factor in the relationship between alcohol and non-adherence that has been seen previously [8,15]. A meta-analysis investigating subjective barriers to medication adherence found that alcohol was the fourth most common reason for adults to skip their HIV medication [16]. The most common reasons was

“forgetting”, “being away from home” and “change of daily routine” and alcohol could potentially have a role to play in these barriers as well.

Systematic reviews has been conducted on this topic, either narratively [8] or quantitatively [15]. These studies state the presence of negative interactions of alcohol in the treatment cascade of HIV and conclude that hazardous alcohol use and disorders should be targeted to achieve viral suppression and decrease HIV transmission. Hendershot et al [15] conclude that alcohol use in general seem to be detrimental for treatment adherence, with a greater effect seen when adjusting for drinking intensity. Moderate drinking was found to have a detrimental effect as well, but was not significantly difference from other drinking intensities. They also report a significant amount of heterogeneity in their analysis which is likely due to differences in methodology which would explain the heterogeneity and inconsistent results seen across studies.

With this previous findings at hand, this analysis will try to answer the following questions: 1) Is it possible to replicate earlier findings when adding recently published literature? 2) Is it possible to reduce the amount of heterogeneity when analyzing studies with different methodology and thus making conclusions with a higher external validity? 3) Is it possible to quantify the effect of light/moderate/social drinking on treatment adherence?

Methods

Systematic review

The electronic database Pubmed/Medline was searched for original human research published between 1990-2017 in the field of HIV medication adherence and alcohol use using a combination of the following conceptual categories: (1) alcohol (search terms: alcohol drinking, alcohol disorder, alcohol abuse, alcohol use, alcoholism), (2) seropositivity for HIV-1 (search terms: human immunodeficiency virus, HIV-1, HIV, HIV/AIDS), (3) adherence to HIV treatment (search terms: treatment, therapy, adherence, ART, antiretroviral therapy). Relevant articles also had their references screened for potential articles. See figure 1 for flow chart representation of the selection process.

The following inclusion criteria were applied: (1) measurement of patient’s alcohol use or abuse (2) patients living with HIV/AIDS (PLWH) (3) reference to treatment outcome for HIV. Studies were excluded if measurement of adherence levels or alcohol use were not possible to use, irrelevant for the data analysis or if the measurement of outcome or risk factors was considered insufficient.

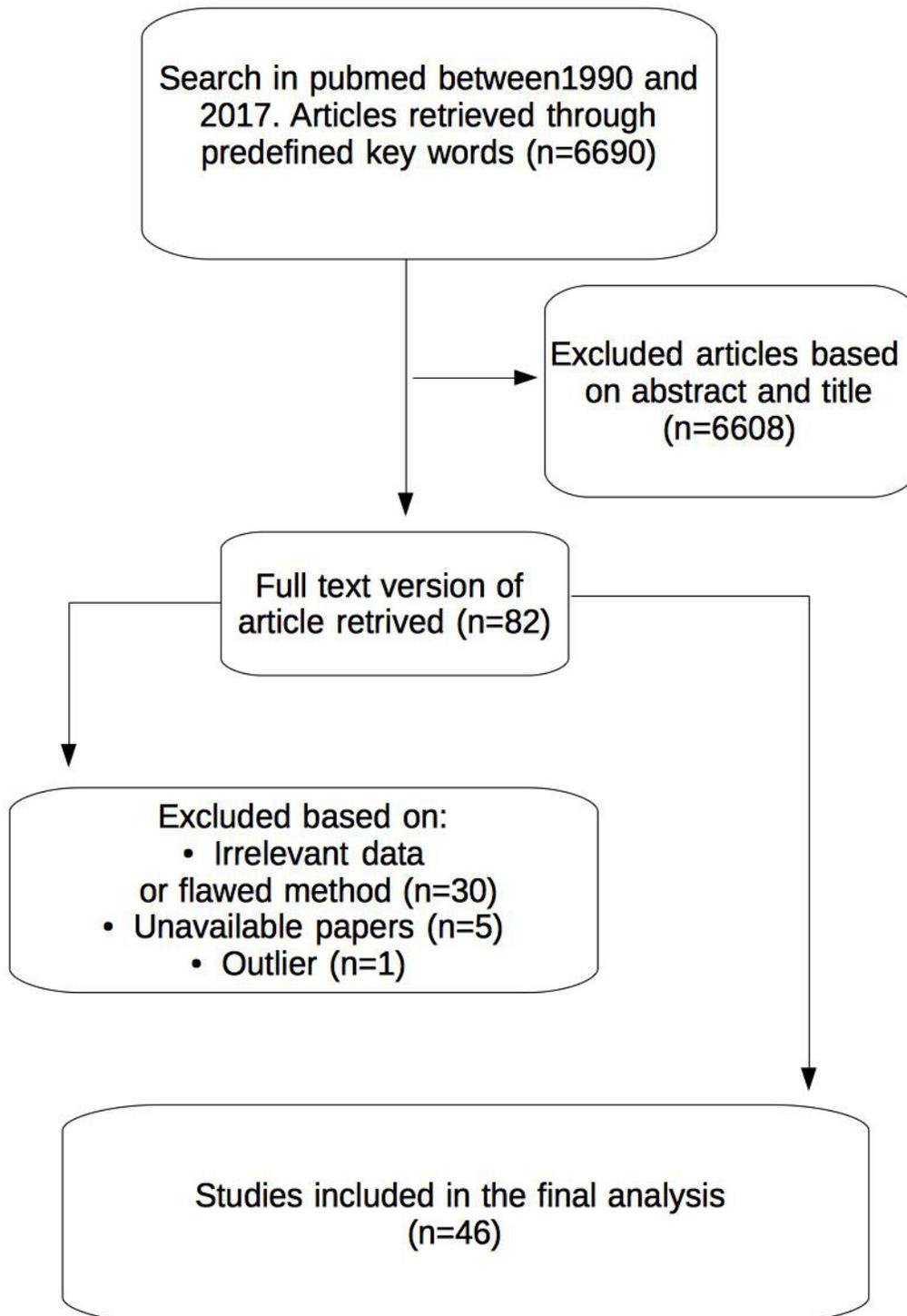


Figure 1. Flow chart over the systematic selection process.

Measurement and data coding

Alcohol consumption

Alcohol consumption was measured in several different ways:

- AUDIT questionnaire
- CAGE questionnaire
- ASI composite score
- CASI test
- Self report on binge drinking, drinking days and alcohol consumption

AUDIT

The AUDIT (Alcohol-Use-Disorder-Identification-Test) is a test created by the WHO (The World Health Organization) for identifying problematic alcohol use, using a 10 question-questionnaire that measures three domains in alcohol consumption: addiction, consumption and alcohol related harm. Participants can receive a score between 0 and 40 where 0 represents abstaining and a score of eight or above is considered as hazardous consumption. The questionnaire takes 10 minutes to accomplish and doesn't need trained personnel for its administration[18].

CAGE

The CAGE test consists of four questions targeted to identify problematic alcohol use:

1. Have you ever felt you needed to **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticizing your drinking?
3. Have you ever felt **G**uilty about drinking?
4. Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?

The CAGE test was created by John Ewing in 1984 [19] and is supposed to be a questionnaire to screen and identify alcohol problems. The questionnaire is not an in depth screening tool but rather a quick way to assess potential alcohol related problems and use. Participants that answer at least two out of four questions in a way that favor the concept are considered as hazardous users.

ASI

The ASI (Addiction-Severity-Index) was developed in 1980 and is an in depth questionnaire to assess harm and impairment caused by drug abuse. It has been commonly used as an assessment of drug abuse in mental health setting, prisons and addiction clinics [20,21].

CASI

The CASI test (Computerized-Alcohol-Screening-Intervention) is developed by The Center for Trauma & Injury Prevention Research at UC Irvine School of Medicine and helps to identify dependent and at risk drinkers using parts from the AUDIT [22].

Other types screening tools

Common practice for a the majority of the included studies was different kinds of self reporting questions where drinking was assessed by asking participants about their alcohol use. It could include include questions like “Have you used any alcohol past month – yes or no” to questions about number of drinking days or typical amount of alcohol consumed in a drinking session. For details of each study see table 1.

Since there were different measurement and classifications of alcohol consumption among the different studies, in order to detect differences between different types of consumption, alcohol use was classified into three different groups:

- Abstainers
- Low or moderate alcohol consumption
- Hazardous or problematic alcohol use

Groups classifications followed the definitions made by each study, for a detailed presentation of each study included in the analysis, see table 1.

Abstainers

Abstainers was defined as no use of alcohol for a given period of time, i.e. use preceding month or year. The period of abstention varied between one to 12 months for the studies included.

Low, moderate or “social” alcohol consumption

In relation to AUDIT scores, low or moderate consumption was defined as having a score lower than 8, this was consistent between all studies that used this identification tool. For a detailed view of all studies see table 1.

Hazardous or problematic alcohol use

Hazardous or harmful alcohol use was defined in several ways. When AUDIT was used it was defined as a score of above 8 which is common practice for the AUDIT tool in measuring harmful alcohol use. When CAGE questions was applied two out of four questions needs to be answered in favor of the concept measured. Several studies used the NIAAA (National Institute on Alcohol Abuse and Alcoholism) definition of drinking that have a high risk of developing alcohol use disorder (AUD) which is defined as[23]:

- Drinking more than seven drinks per week and more than three drinks per session for women and

- Drinking more than 14 drinks per week and more than four drinks per session for men

Even though different definitions was applied across all studies they all have in common frequent drinking and/or bingeing elements; for a detailed view of all studies see table 1.

Adherence to medication

Adherence level to HIV medication was fundamentally measured in four different ways:

- Self report on number of missing doses via questionnaire
- Trained interviewer asking on missed doses
- Electronic monitoring system, i.e. MEMS
- Behavioral assessments with Lickert scale-like questions, i.e. “how often do you take your prescribed medications”

Data analysis

The studies included in this analysis had a wide range of different measurement and control groups; subgroups were therefore created in order to decrease heterogeneity between studies where effect sizes were compared. These groups were (with number of unique samples within each group):

- Abstainers vs hazardous alcohol consumption (n=9) [24-31]
- Abstainers vs low or moderate alcohol consumption (n=11) [24-33]
- Abstainers vs any alcohol consumption (n=21) [24-26,31,32,34-48]
- Low or moderate alcohol consumption vs hazardous consumption (n=19) [24-26,28,31,32,39,46,49-58]

One group collected all studies (n=12) [45,59-69] with effect sizes that used continuous measurement of either alcohol consumption or adherence to treatment.

The main outcome for the majority of the studies (n=34) was odds ratios (OR), due to the studies case-control design, some however used correlational data. These data where converted to odds ratio via following equation [70] :

$$d = \frac{2r}{\sqrt{1 - r^2}}$$

d represents *Cohen's d* or the standardized mean difference and r is correlational data. Cohen's d was then converted to the Log Odds Ratio via this equation [70]:

$$d = \text{LogOddsRatio} * \frac{\sqrt{3}}{\pi}$$

Since raw data on cases and controls among exposed and non-exposed was only available in half of the studies, variances was fabricated for data where only ORs was available. Since the standard error (SE) for ORs is calculated by following equation:

$$SE = \sqrt{\frac{1}{n_{11}} + \frac{1}{n_{10}} + \frac{1}{n_{01}} + \frac{1}{n_{00}}}$$

Where n_{xx} represents cases and control among exposed and non-exposed. Since sample size was available for all studies, the sample size of studies without a SE was distributed among these four groups. If groups are equally divided, the SE will tend to be lower than if groups are asymmetrical. Therefore, in order not to underestimate the SE, groups were created asymmetrically where group n_{11} included 50 %, group n_{10} included 25 % and group n_{01} and n_{00} contained 12,5 % each of the participants.

For some studies, several effect sizes were available with regards to type of exposure, i.e. several types of problem drinking (binging, heavy drinking, hazard drinking). If the raw data was available groups were added in order to create the exposure “any problem drinking”. If only effect sizes where available then the drinking intensity deemed most severe was chosen as comparison. There could also be several effect sizes with regards to measurement of treatment adherence, i.e. adherence over three days, 30 days or 6 months. Since long term effects on adherence probably are more important than short term effects, adherence measurement was chosen according to the length of time span where longer time measurements were included in the final analysis. When it was impossible to conclude appropriate effect size on the basis of the mentioned criteria, groups were chosen with regards to the largest sample sizes in order to secure statistical power.

In cases where raw data on cases and controls were available as well as adjusted effect sizes, then the adjusted effect size was chosen but with the SE calculated from the raw data. This choice of method was made under the belief that when given the option to include adjusted or unadjusted data in the final model, adjusted data would to larger extent reflect reality and the true effect of alcohol use rather than the unadjusted effect sizes. With the same mode of reasoning, calculated SE was chosen over fabricated ones and thus included in the final model.

Moderators

There were three factors that was coded as potential moderators in this analysis:

- Sex of included participants
- Adjustment of effect size
- Definition of cases and controls
- Type of protocol for identifying alcohol use

Sex of included participants

All studies were coded as one of three different categories: “males”, “females” or “mixed”. All studies that didn’t exclusively include either males or females were defined as mixed.

Adjustment of effect size

All studies were coded as one of two categories: “adjusted” or “unadjusted”. Adjusted factors differed between studies but usually included age, sex, illicit drug use, time between interviews (in cohort designs) and ethnicity.

Definition of cases and controls

All studies were coded as one of two categories: “95%” or “100%”. The definition of being an adherent participant differed between studies but were usually divided between perfect and optimal treatment adherence. Perfect treatment adherence means not missing or skipping any doses while optimal adherence was defined as taking at least 95% of prescribed HIV medication. Adherence levels in the category “95%” varied between 80-95%. Adherence could also be measured with Lickert scale-like questions, such as: “How often do you take you medications?” where a definition of cases that included more than the answer that was the most favorable to the concept was coded as “95%”. The exception of this coding was in the group containing continuous data.

Type of protocol for identifying alcohol use

The AUDIT protocol is known to be the “gold standard” for identifying problematic alcohol use, and there could be important differences in precision and validity between the different types of screening tools and protocols among the studies included. Studies were therefore coded as one of the two categories “Audit” or “Non-audit”, where the label “Audit” included all studies that used the AUDIT protocol to measure participants alcohol use. This choice was made to isolate any potential effect of differences between different types of protocols. The dichotomous character was chosen in order to create more statistical certainty; coding with all different types protocols would likely fail to identify any potential difference. Secondly, even though some protocols, like the CAGE test, is better to assess alcohol use than just self reported alcohol use, compared to the AUDIT protocol, they are likely more comparable in precision and validity.

Statistical analysis

Based on the groups and dataset presented a meta-analysis with random effects modeling was performed. A mixed effects model was performed when coded moderators had a significant effect on the result. All analyses was made in the statistical software R 3.3.1. and with the free, open-source, software package “metafor”, designed for conducting meta-analyses in R [75].

Results

46 studies were included in the final analysis, where one study contributed with two different data sets, divided between males and females [31]. All models showed a statistical significant effect of alcohol consumption on treatment adherence. An odds ratio above 1 is indicative of a detrimental effect of alcohol on HIV treatment adherence levels.

Abstainers vs any alcohol consumption (analysis 1)

The odds ratio comparing no alcohol consumption to any alcohol consumption was 1,98 (95% CI: 1,57-2,50), indicating an association between alcohol consumption and decreased adherence, see figure 2. No significant difference was found when controlling for moderators.

Abstainers vs low or moderate alcohol consumption (analysis 2)

The odds ratio comparing no alcohol consumption to low or moderate alcohol consumption was 1,72 (95% CI: 1,24-2,38), see figure 3. No significant difference was found when controlling for moderators.

Abstainers vs hazardous alcohol consumption (analysis 3)

The odds ratio comparing no alcohol consumption to hazardous alcohol consumption was 3,1 (95% CI: 1,92-5,01). When controlling for moderators, a significant effect was found on adherence cut off-level. A definition of adherence set to 100% yielded an odds ratio of 2,04 (95% CI: 1,52-2,73) and a definition set to 95% yielded an odds ratio of 7,53 (95% CI: 4,90-11,58). This difference can be observed in figure 4 but with the result unadjusted for moderators excluded.

Low or moderate alcohol consumption vs hazardous consumption (analysis 4)

The odds ratio comparing low or moderate alcohol consumption to hazardous alcohol consumption was 1,94 (95% CI: 1,64-2,29), see figure 5. No significant difference was found when controlling for moderators.

The analysis based on continuous data (analysis 5) showed an odds ratio of 1,65 (95% CI: 1,42-1,92), see figure 6. No significant difference was found when controlling for moderators.

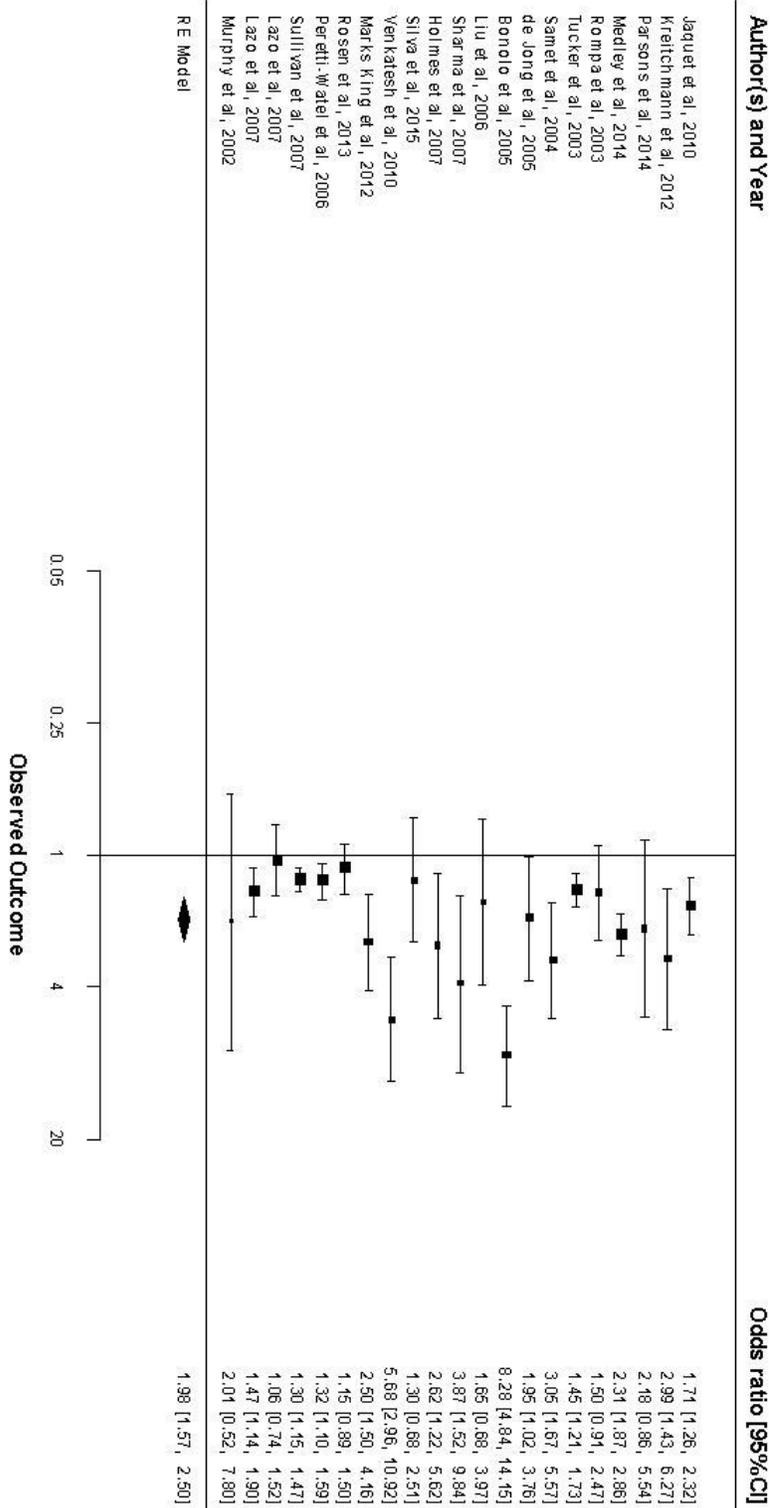


Figure 2. The effect of any alcohol consumption compared with no alcohol consumption on treatment adherence. ORs >1 should be interpreted as a detrimental effect of alcohol on treatment adherence.

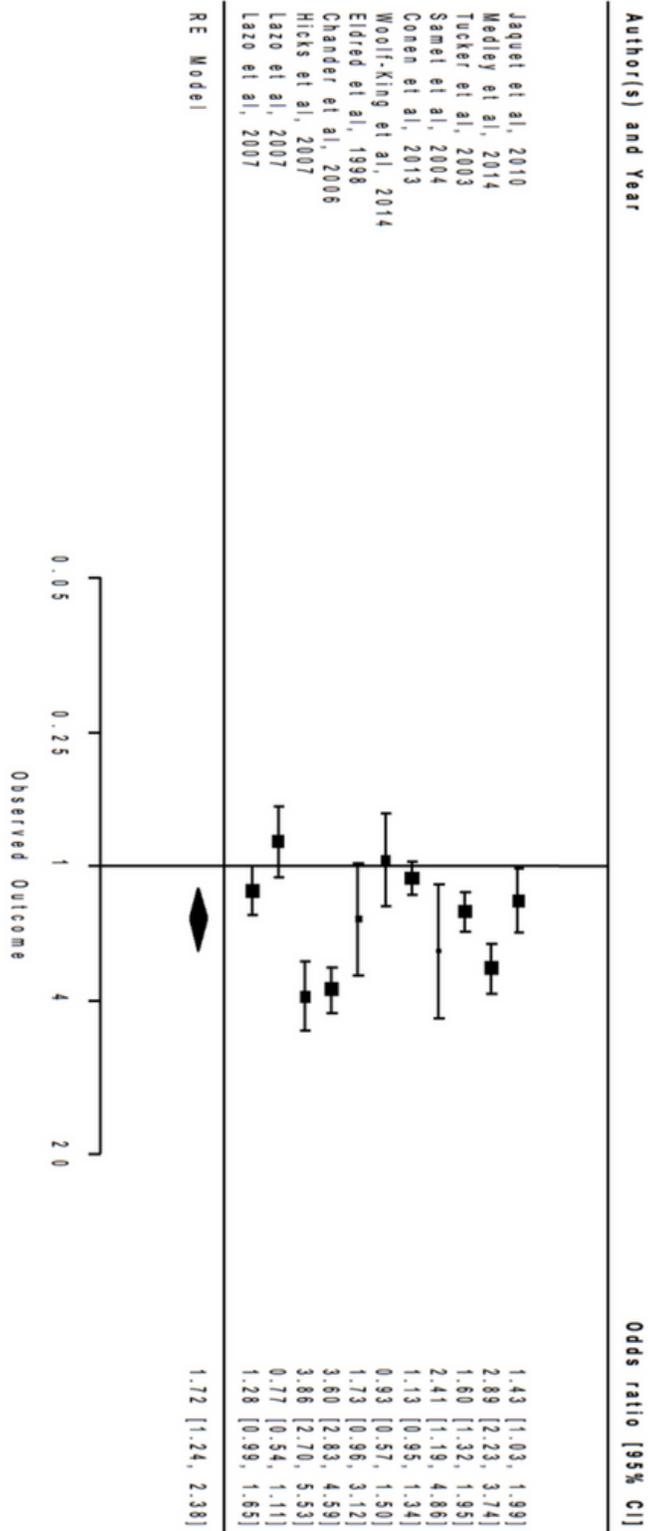


Figure 3. The effect of low alcohol consumption compared with no alcohol consumption on treatment adherence. ORs >1 should be interpreted as a detrimental effect of alcohol on treatment adherence.

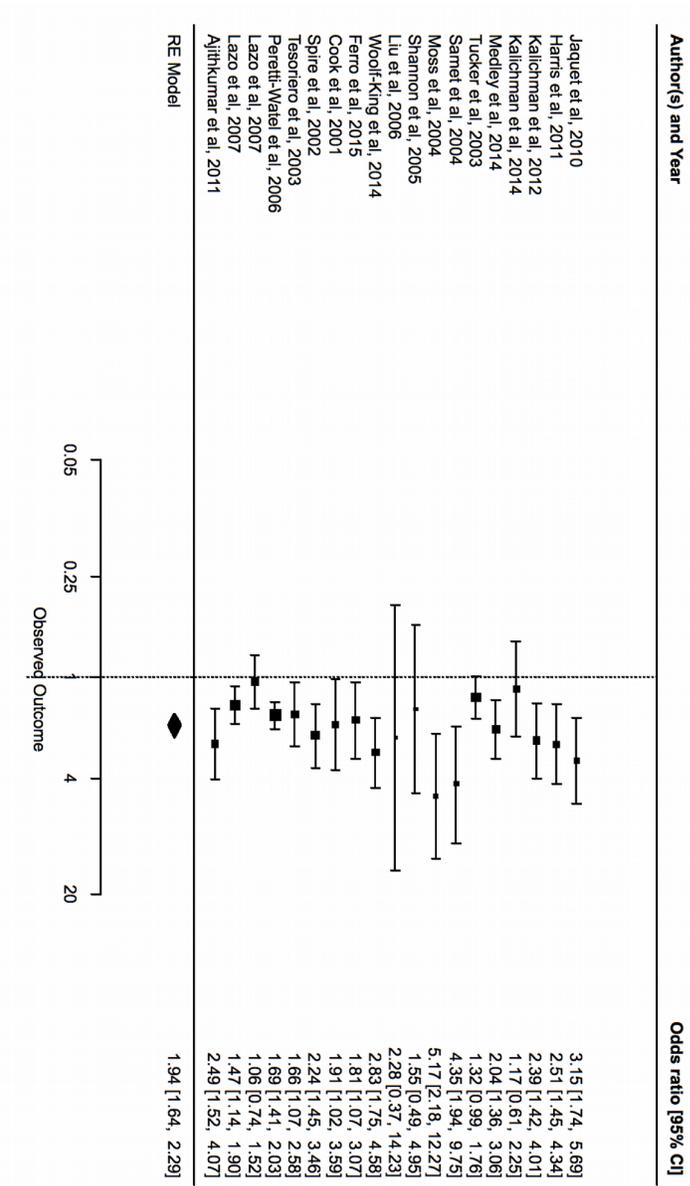


Figure 5. The effect of hazardous alcohol consumption compared with low alcohol consumption on treatment adherence. ORs >1 should be interpreted as a detrimental effect of alcohol on treatment adherence.

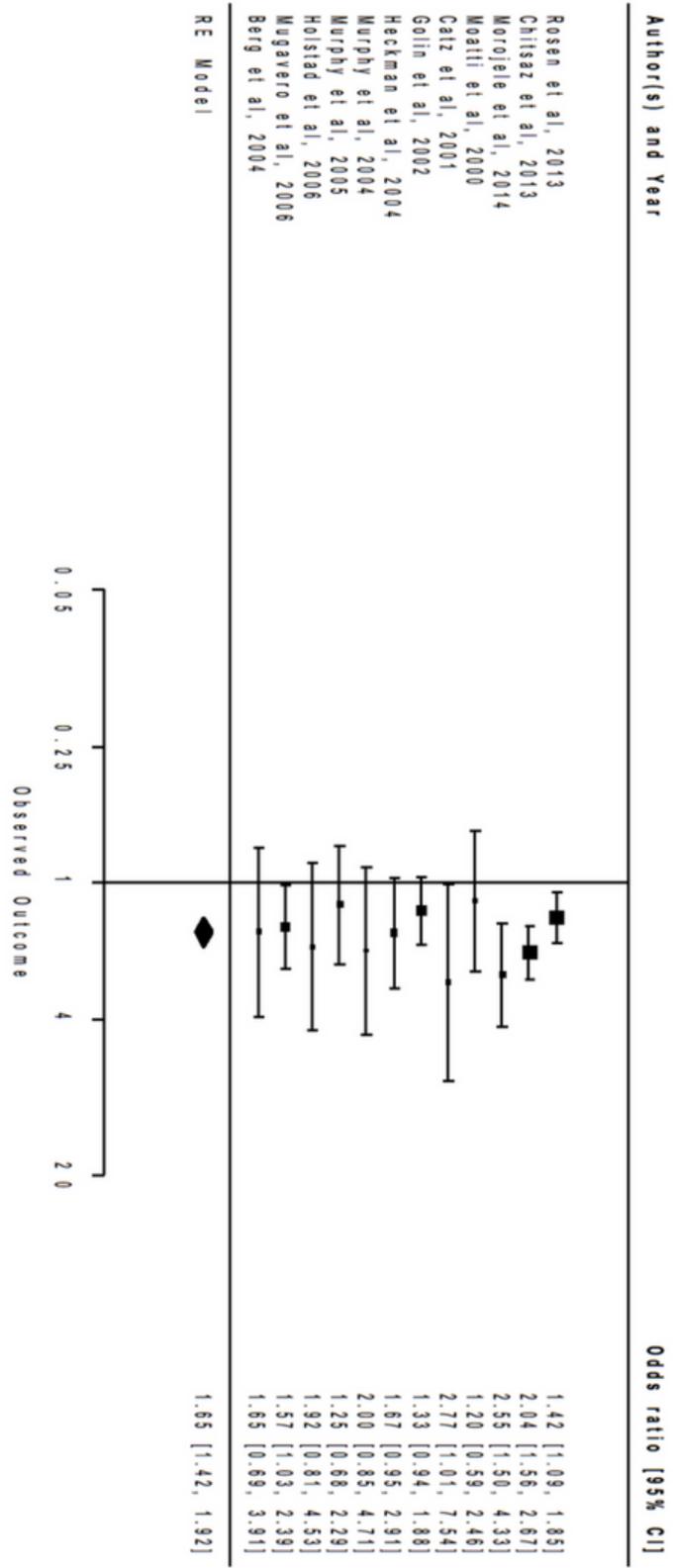


Figure 6. The effect of alcohol consumption on treatment adherence based on continuous data. Continuous data were transformed into OR before analyzing. ORs >1 should be interpreted as a detrimental effect of alcohol on treatment adherence.

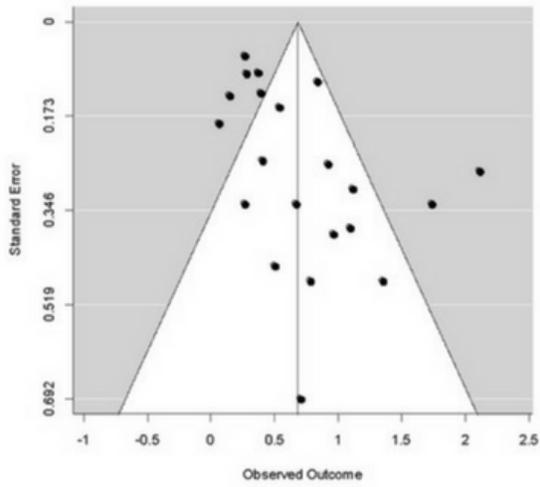
All analyses except for analysis 5 showed a significant amount of heterogeneity presented in the data, see table 2. The majority of the heterogeneity in analysis 3 can be explained by the effect of how adherent participants was defined.

Table 2. Table over heterogeneity in each analysis.

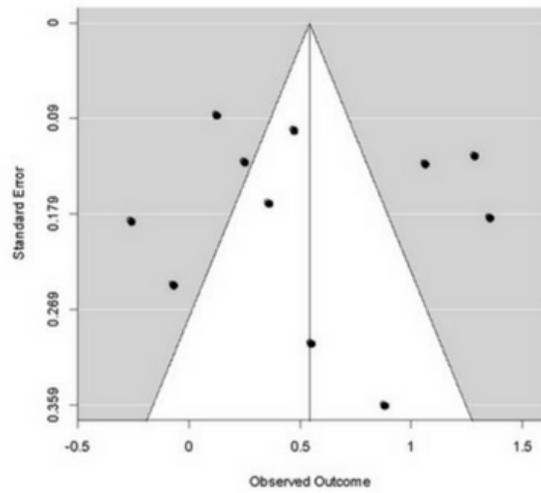
Comparison	I², %	H²	R², %	P-value
No alcohol vs any alcohol	88,86	8,98	-	<0,0001
Low/moderate vs hazardous consumption	59,62	2,48	-	0,002
No alcohol vs hazardous consumption	81,67	5,46	79,09	0,0001
No alcohol vs low/moderate consumption	92,55	13,42	-	<0,0001
Continuous data	16,82	1,2	-	0,47

H^2 can be defined as a measurement of the heterogeneity, or more precisely, the total variability divided by the sampling variability. The I^2 is the proportion of the variance that is unexplained, which is calculated as $H^2 - 1/H^2$. The R^2 statistics shows the proportion of the total variance that can be explained by its covariates, thus is this only applied in the multivariate analysis.

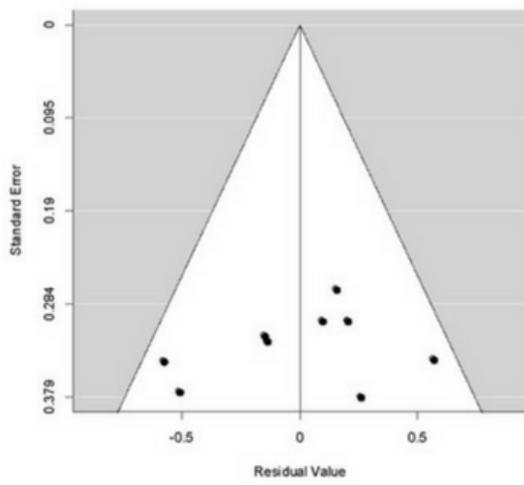
Funnel plots were performed on all analyses to inspect a potential selection or publication bias, see figure 7. All analyses, except analysis 1, show a symmetrical distribution of studies with comparable effect size and SE. In analysis 1 we see an overrepresentation of studies with a small SE presenting a negative result (unfavorable to the concept of alcohol and adherence) and two studies with “medium” SE showing a positive result (favorable to the concept of alcohol and adherence).



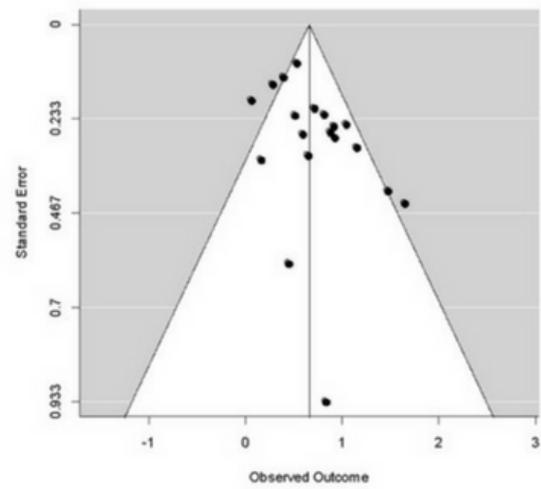
Analysis 1



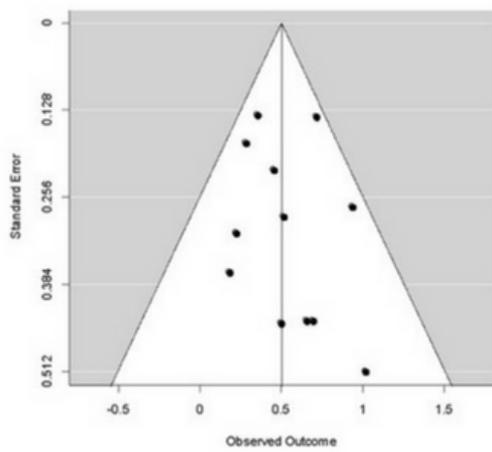
Analysis 2



Analysis 3



Analysis 4



Analysis 5

Figure 7. Funnel plots for all five analyses.

Discussion

This study found a significant effect of alcohol use on HIV medication adherence. The results goes in line with similar studies made [8,15] where alcohol was found to have a negative effect on medication adherence.

The result in this study was split into five separate analyses, where all five showed a significant relationship between alcohol consumption and treatment non-adherence. When comparing abstainers to any alcohol consumption, abstainers were almost twice as likely to be defined as adherent (OR = 1,98, 95% CI: 1,57-2,50). Similar effect sizes was found across all analyses except for analysis 3 where abstainers where seven times as likely to be adherent (OR = 7,53, 95% CI: 4,90-11,58) compared to hazardous alcohol users when optimal ($\geq 95\%$) adherence was applied. When perfect adherence (=100%) was applied the effect size was similar to that of the other analyses (OR = 2,04, 95% CI: 1,52-2,73), see figure 3.

How should a finding like this be interpreted? When we use a rigorous definition of how controls are defined, using perfect adherence as our mean for definition of such, we are shifting a part of the unexposed (abstainers) to the case group (non-adherent). If we instead use a definition of optimal adherence, the consequence will be that more abstainers will be classified as adherent, thus shifting the effect size to favor abstention rather than alcohol use. Which interpretation of these results serves our research questions? Should the results be discussed from a perspective of optimal or perfect adherence treatment levels? It is not hard to argue that perfect adherence always is preferred in a treatment setting, although, when it comes to viral suppression in PLWH optimal adherence is likely enough to satisfy the need of the treatment. There is no simple answer to this question of interpretation; hazardous alcohol use is indeed detrimental for adherence, but how much? A careful interpretation would interpret these results with perfect adherence in mind, in order to give perfect adherence the benefit of the doubt, if reality were to show that perfection is not the enemy of the good. On the other hand, it might be careless to draw conclusions that places the damage of hazardous alcohol on the same levels as moderate alcohol use, thus *not* giving heavy alcohol user the benefit of the doubt when it comes to communicating the health gains made by switching to a drug free lifestyle. Future studies should seek out to investigate the implications of different definitions of adherence in relation to different risk factors.

Unlike earlier findings, this study was able to show a significant effect of light alcohol use on treatment adherence, when comparing abstainers to moderate drinkers. This was shown in analysis 2 where abstainers were almost twice as likely to be adherent (OR = 1,72, 95% CI: 1,24-2,38) compared to moderate drinkers.

Despite being the largest meta-analysis up to date that investigates the effect of alcohol consumption on treatment adherence levels, there are several limitations to this study. Even though this is a systematic review, only one database was searched for articles in the collection process (Pubmed/Medline). The rationale for this choice was due to practical limitations and time management and it can't be excluded that a search process that included more databases could have yielded a different result. Although due to the systematic process, the risk of publication or selection bias can be considered low, which is supported by the result of the funnel plots from the analysis, as seen in figure 4. There is some skewness in the variation of the effect sizes in analysis 1, which shows an overrepresentation of large trials that show a negative result and two medium size studies that potentially could be due to publication bias. It should be kept in mind when interpreting figure 7 that a large part of the SE was fabricated in order to be handle quantitatively. Errors were fabricated in order to underestimate the results, thus creating larger SE. In reality a large part of the data points would likely be shifted towards zero. Since the results of the funnel plot show a comparable amount of studies with both positive and negative result, this would probably not pose a threat to the authority of this study. The risk for publication bias can still be considered low.

Another factor that could affect the outcome of this study is the coding of the moderators. As seen in figure 3, the effect of alcohol on treatment adherence was moderated by how an adherent patient was defined, where fairly surprisingly, a greater effect was seen if adherence was defined in a less strict manner. Since the categories "95 %" and "100 %" was set in order to separate differences in optimal and perfect adherence respectively, this could have been coded differently. Since adherence measurement varied in the group defined as "95 %", with adherence levels varying between 80-95 % this could have been coded continuously instead of dichotomously. Although, any other outcome moderated by changing the cut-off in adherence level can be ruled out in analysis 3 since the studies included in the analysis didn't include any other cut off values than what they where coded as in the analysis.

The fact that variances was fabricated in a portion of the studies could also have affected the result, but since variances was fabricated to replicate a greater skewness among groups, it is not likely that the results seen in these analyses are overestimates of the true effect of alcohol use on treatment adherence.

The generalizability of this study can be questioned due to the effect on real clinical outcomes; does increased adherence lead to lower virus levels or higher CD4⁺ cell count in PLWH? Even though several studies have shown a consistent relationship between good medication adherence and lower virus levels [53,66,77,78], future studies should aim to analyze data with clinical outcomes, such as virus levels or CD4⁺ cell count, in order to establish the detrimental effect of alcohol use in PLWH on biological variables, since this relationship seem less consistent. In the article by Conen et al. [27] included in the analysis, alcohol was not associated with virologic failure, though heavy

alcohol use was associated with discontinuation of ART-therapy. The opposite has also been shown, as indicated by Deiss et al [79] as well Baum et al. [10], where alcohol use was associated with virologic failure, higher viral loads and a lower CD4⁺ cell count respectively. A recent randomized controlled behavioral intervention aimed to decrease alcohol consumption and increase adherence managed to increase adherence and biological markers for HIV disease progression but with no apparent change in alcohol use [80], which shows that behavioral changes can occur independently of alcohol consumption. Although, no effects in adherence or biological markers were sustained after six months, which could suggest that more holistic approach to lifestyle changes are needed to motivate a behavioral change.

The question of generalizability to the clinical reality could also be made due to the fact that PLWH might change their alcohol consumption habits after they get their diagnosis, thus making alcohol habits less of a concern in ART experienced participants. Healthy lifestyle changes seems to be common among cancer patients [71] but there are also indications that sustainable behavioral changes could be hard to achieve [72]. There was not enough studies in this analysis comparing ART-naïve and ART-experienced PLWH but according to Conen et al. [27] there was no difference in alcohol consumption between these two groups. This is indicating that the results of the present study are still valid despite the data included a mix of PLWH with different experience of ART.

Even though no difference was found between sexes, this should be interpreted with caution. There were few studies including exclusively males or females which didn't give us enough statistical power to rule out that there is a difference between males and females in their alcohol habits and the interaction with HIV medication. There are indications that alcohol use and behavior are highly affected by social norms [73] and thus still an important area of research. It should also be noted that in the studies included in this analysis that were coded as "mixed sex" the vast majority of subjects were predominately males and thus not "mixed" in an intuitive sense.

One question of concern is the potential for confounders. How do we know that result seen is not due other factors affecting adherence like age, drug use or income? We can't exclude the possibility that there might be confounders affecting the results that we see; but adjusting of the original data was coded as a moderator in the analysis and no analyses showed a difference of adjusting the results compared with the unadjusted data. Which factors that were adjusted for were different for each study but usually included age, sex, illicit drug use and ethnicity.

The difference between this study and earlier meta analyses is the grouping of data which allowed analyses between different types of exposure. Even though illicit drug use and hazardous drinking have been associated with lower adherence, there was still some uncertainty if this also applied to light or moderate drinkers. In a previous meta analysis [15], Hendershot et al. analyzed all studies included together with drinking intensity added as a moderator which allowed them to have more

data analyzed even though control groups differed. In this analysis however, data was grouped in order to compare abstainers with any type of drinking, moderate drinkers with hazardous drinkers etc. The grouping of the data allowed us to make conclusions on other drinking intensities as well. As seen in the results; hazardous drinking was unfavorable to the concept of adherence compared to abstainer, but it was also more unfavorable compared to moderate drinking. Moderate or light drinking was shown to be clearly unfavorable compared to no drinking as well. These results suggests that the effects of alcohol should be understood as a product of total consumption rather than the often used categories “harmful” and “non harmful” drinking. This concept of understanding the harm of alcohol is common knowledge in other areas of alcohol prevention [74].

The limitation of the approach of grouping data used in this study is that it provides less statistical power but probably less heterogeneity and a more solid basis on making generalized assumptions. There was still, in varying degree, a significant amount of heterogeneity in four of the analyses, as seen in table 2. The coding for moderators was also a strategy for limiting heterogeneity, as in analysis 3 where the majority of the heterogeneity was explained by how adherence was defined.

The dataset with continuous data was the only analysis that didn't show a significant effect of heterogeneity. This might suggest that at an approach comparing cause and effect with data on a continuous basis reflect reality to a greater sense than categories of being a specific type of alcohol consumer.

Even if heterogeneity always is an unpleasant finding it wasn't unexpected. In the meta-analysis by Hendershot et al. [15] This means that differences observed between studies could depend on differences in methodology or outcome measurement rather than the actual effect of the treatment.

Another limitation of this analysis was that there was no division or grouping of alcohol intake based on external objective measurement; the definitions of alcohol intensity or type made by the authors of each study was applied in the analysis even when definitions between studies were different. This did not apply to all analyses since the definitions “abstainer” and “any alcohol consumption” is inherently the same across contexts. Definitions like “moderate”, “social” and “light” and “harmful”, “hazardous” and “risk” could contain several over-arching definitions, which could also explain some of the heterogeneity. This methodology was flawed but it did not disqualify any of the result; a majority of the studies used the definitions based on best available practices (i.e. AUDIT, CAGE, ASI and the NIAAA's guidelines), which still gives this study high validity for measuring and defining alcohol use.

Future studies that seek out to measure alcohol use and HIV treatment adherence should try to assess relevant variables with objective measurements. Several of the included studies had no formal protocol for assessing alcohol use and used question similar to: “Did you did drink alcohol

at least once a week the past 6 months?”. This is probably not important when distinguishing the effect of alcohol between abstinence and any alcohol use, but could pose a problem when trying to understand the effect of other types of drinking intensities.

A minority of the studies seemed to have used objective or semi-objective measurements of treatment adherence. This means using electronic bottle caps (i.e. MEMS) that record how many times a pill bottle is opened or subjective data paired with pill counting or cross checking with pharmacy staff. This is most likely a favorable choice of method, but might not increase precision extensively, since electronic recordings also have several drawbacks and that self report can be comparable to electronic systems [76].

Conclusion

Earlier findings have indicated the importance of alcohol in the fight against HIV. Despite this fact there is no indication of this relationship in the new SDGs. This study further acknowledges the detrimental effects of alcohol use in one of the most important steps in the HIV treatment cascade.

Despite the significant and clear relationship of alcohol use and adherence there are still some uncertainties of the generalizability of the results due to high amount of heterogeneity present in these analyses. Future studies that investigate this relationship should try to use objective and standardized measurement of alcohol use and medication adherence since this could reduce heterogeneity in future analyses. Although, with this new information presented in this analysis together with earlier findings we have a clear point of direction when it comes to recommendations of alcohol use in PLWH. If the 90-90-90 goals and SDGs set by UNAIDS and the rest of the world should be achieved, a more holistic approach where the prevention of non-communicable diseases and infectious diseases go hand in hand might actually be the only way forward.

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Table 1. Overview of studies included in analyses. MEMS=Medication-Event-Monitoring-Systems, ASI=Addiction-Severity-Index, AUDIT=Alcohol-Use-Disorder-Identification-Test, VAS=Visual-Analogue-Scale, AUD=Alcohol-Use-Disorder.

Main author and year of publication	Sample size and sex	Measurement of adherence	Definition of being adherent	Measurement of alcohol use	Definition of exposure (alcohol use)
Ajithkumar, 2011	n=350, 60% male	Self report of adherence with cross checking in pharmacy and counseling	Not missing >3 doses of medication per month	Self report	Presence of alcoholism
Berg, 2004	n=113, 57% male	MEMS	Continuous	Self report	Problematic use was defined as drinking 5 drinks on one occasion or drinking frequently (=every day or several days per week)
Bonolo, 2005	N=306, 65% male	Self report, adherence last 3 days	Taking more than 95% of prescribed medications	Self report, past month	Use or no use of alcohol
Catz, 2001	N=81, 75% male	Self report, adherence last 7 days	No skipped doses	Self report, past 2 months	How many days past two month had participants used alcohol (continuous measurement)
Chander, 2006	N=1433, 64% male	Self report, adherence past 2 weeks	Missing <2 doses	Self report	Hazardous alcohol use was defined as >7 drinks/week or >3 drinks/session for women and >14 drinks/week or >4 drinks per session for men. All other consumption was defined as moderate consumption
Chitsaz, 2013	N=1166, 72%	Self report	Taking \geq 95%	ASI composite	Continuous

	male		of prescribed doses	score	
Conen, 2013	N=2982, 75%	Self report	Non-adherence was defined as discontinuation of ART for >7 days without medical indication	Self report. Question: "Did you drink alcohol at least once a week during the last 6 months. If yes, how much did you drink on a daily basis". Drinking was categorized into three categories, light, moderate and severe	Non-drinker defined as <1 drink/week last 6 months. Light drinking was defined as <20g alcohol for women, <40g for men, moderate drinking 20-40g for women, 40-60g for men and severe drinking was defined as >40g for women, >60g for men
Cook, 2001	N=212, 72% men	Self report	If participants took their medications on schedule previous week "all the time" or "most of the time".	AUDIT questionnaire	Problem drinking was defined as drinking at least 5 drinks (women) or 6 drinks (men) in one sitting at least monthly; consuming more than 12 (women) or 16 (men) drinks per week during the previous month or if persons scored at least 8 of 40 possible points on the AUDIT
de Jong, 2015	N=168, 75% male	Self report, adherence last 7 days	Not missed a single dose	Self report	Alcohol use past month, yes vs no
Eldred, 1998	N=244, 63% male	Self report	Taking $\geq 80\%$ of prescribed doses past week and taking medication $\geq 80\%$ of days past two weeks	Self report	Moderate alcohol intake was defined as 3-4 beverages of intake 3-4 times a week
Ferro, 2015	N=302, 100%	Self report	Perfect	AUDIT	AUD was

	male	using VAS	adherence (=100%) was defined as being adherent	questionnaire	defined as an AUDIT score of ≥ 8
Golin, 2002	N=117, 80% male	MEMS, adherence over 48 weeks	Continuous	Self report, past 30 days	None vs any use
Harris, 2011	N=300, 45% male	Self report, VAS, adherence past 30 days	Taking $\geq 95\%$ of prescribed medication	Self report	Heavy use vs non-heavy use. Heavy use defined as ≥ 2 drinks/day or ≥ 5 drinks/episode (women), ≥ 3 drinks/day or ≥ 6 drinks/episode (men)
Heckman, 2004	N=272, 72% male	Self report, six point Likert scale, adherence past 7 days	Perfect (=100%) adherence was applied	Self report, number of drinking days past 2 months	Unclear definition of exposure
Hicks, 2007	N=659, 70% male	Self report, interview, adherence past 2 weeks	Optimal adherence ($\geq 95\%$) was applied	Self report. Alcohol use was assessed from questions asking: (1) how many days in the past 4 weeks the respondent drank alcohol, (2) how many drinks the respondent consumed on a typical day when drinking and (3) number of days the respondent consumed ≥ 5 drinks	Problem drinking was defined as $\geq 14/\geq 7$ drinks/week (men/women) or ≥ 5 drinks/session. All other drinking was defined as moderate. No drinking was also included as a category.
Holmes, 2007	N=116, 81% male	MEMS, adherence past 3 months	Taking $\geq 95\%$ of prescribed doses	Self report, past 12 months	Any use vs no use
Holstad, 2006	N=115, 65% male	Self report, adherence past 4 weeks	Continuous, past 4 weeks	Self report	Current use vs no current use

Jaquet, 2010	N=2065, 29% male	Self report, questionnaire, adherence past 4 days	Taking $\geq 95\%$ of prescribed medications	AUDIT questionnaire	Current used was defined as any use past year, an AUDIT score of ≥ 8 was defined as hazardous drinking. No drinking was also included as a category.
Kalichman & Rompa, 2003	N=255, 70% male	Self report, adherence past week	Adherent was defined as no missed doses of prescribed medications	Self report, past 3 months	Use vs no use
Kalichman, 2012	N=333, 77% male	Self report, VAS	Adherence was defined as taking $>85\%$ of prescribed doses	AUDIT	AUDIT score of ≥ 8
Kalichman, 2014	N=183, 77% male	Self reported pill count, phone interview together with pharmacy info	Adherence was defined as taking $>85\%$ of prescribed doses	AUDIT	AUDIT score of ≥ 8
Kreitchmann, 2012	N=393, 0% male	Self report, interview, adherence past 3 days	Perfect (=100%) adherence was applied	Self report	Current use vs no current use
Lazo, 2007	N=640 males, N=1304 females,	Self report, questionnaire, adherence past 3 or 4 days (females and males resp)	Perfect (=100%) adherence was applied	Self report, past 6 months	Low alc consumption was defined as drinking ≤ 2 drinks/day among men and ≤ 1 drink/day for women; moderate-to-heavy consumption was defined as drinking 3–4 drinks ≥ 3 times/month or >5 drinks at a time but less frequently than once a month; binge drinking was defined as drinking >5

					and >4 drinks at least once per month for men and women, respectively.
Liu, 2006	N=148, 0% males	Self report, questionnaire, adherence past 2 weeks	Perfect (=100%) adherence was chosen for the analysis.	Self report, past 4 weeks and AUDIT	Current alcohol use (yes vs no). Problem drinking was defined as AUDIT score ≥ 8
Marks King, 2012	N=326, 72% male	Self report, questionnaire, past 4 days	Perfect (=100%) adherence was applied	AUDIT questionnaire, past 30 days	Any use of alcohol
Medley, 2014	N=3538, 42% male	Self report, past 30 days	No missed doses of prescribed medication	AUDIT	Harmful drinking was defined as an AUDIT score of ≥ 8 . Non-harmful drinking was defined as an AUDIT score of 1-7.
Moatti, 2000	N=164, 68% male	Self report (interview), past week	Taking $\geq 80\%$ of prescribed doses	Self report, interview	Continuous
Morojele, 2014	N=303, 32% male	Self report, questionnaire (CASE adherence index)	Continuous	AUDIT, interview	Continuous
Moss, 2004	N=102, 86% male	Self report	Continuing of therapy vs discontinuation	Self report	Consuming ≥ 5 drinks/day at baseline (yes vs no)
Mugavero, 2006	N=474, 71% male	Self report, past 7 days	Not missing any dose of prescribed medication	ASI score, past 30 days	Continuous
Murphy, 2004	N=115, 85% male	Questionnaire (5-point scale), past 30 days	Participants were coded adherent if they reported taking their medication “ <i>all of the time</i> ” or “ <i>most of the time</i> ”	Questionnaire measuring frequency of use (5-point scale)	Unclear
Murphy, 2005	N=231, 27%	Questionnaire	Participants	CAGE	Intensity of

	male	(5-point scale), past 30 days	were coded adherent if they reported taking their medication “ <i>all of the time</i> ” or “ <i>most of the time</i> ”		alcohol use, but otherwise unclear
Murphy, 2002	N=46, 0% male	Pill count	Taking $\geq 95\%$ of prescribed medications	Questionnaire, past 3 months	Any alcohol used
Parsons, 2014	N=193, 63% male	Self report: “How many days in the last 30 days have you missed taking any of you doses of HIV medication?”	Adherent was defined as taking $>90\%$ of prescribed medication	Self report	Any use of alcohol (group mean was alcohol use in 7,5/30 days)
Peretti-Watel, 2006	N=2484, 74% male	Self report (interview), past 7 days	Perfect adherence (=100%) was applied	CAGE	Answering favorable to the concept on 2/4 CAGE questions
Rosen, 2013	N=1216, 68% male	MEMS, past 4 weeks	Continuous	Self report, frequency of use last 7-90 days	Continuous
Samet, 2004	N=205, 81% male	Self report, past 3 days	Perfect adherence (=100%) was applied	ASI score	High risk: >14 drinks/week (or >4 drinks/day) for men, and >7 drinks/ week (or >3 drinks/day) for women. Alcohol consumption below these levels was considered as moderate use
Shannon, 2005	N=184, 66% male	Reported refill compliance	Optimal adherence (= $\geq 95\%$) was applied	Self report, questionnaire	Frequent use (=daily or most days) vs no frequent use
Sharma, 2006	N=226, 98% male	Self report	Never missed a dose of prescribed	Self report, past 4 weeks	Any use vs no use

			medication		
Silva, 2015	N=216, 65% male	Pharmacy dispensation records, past 6 months	Success at collecting drugs at pharmacy 5-6 out of 6 was considered adherent	Self report	Use of alcoholic beverage, yes vs no
Spire, 2002	N=445, 78% male	Self report, past 4 days	Perfect adherence (=100%) was applied	Self report, questionnaire	Increasing consumption to >1 unit/day vs same or decreased consumption to ≤1 unit/day
Sullivan, 2007	N=5887, 74% male	Self report, past 48 hours	Optimal adherence (≥95%) was applied	Self report	Any use past year, yes vs no
Tesoriero, 2003	N=435, 61% male	Self report (interview), past 3 days	Perfect adherence (=100%) was applied	Self report (interview): Have you been drinking >3 drinks/day past 3 months?	Answered “yes” at both baseline and follow up 3 months later compared to answering “no” at both interviews
Tucker, 2003	N=1910, 78% male	Self report (interview), past week	Perfect adherence (=100%) was applied	Self report (interview), past 4 weeks	No drinking compared to non-heavy (always <5 drinks/day) or frequent heavy (≥5 drinks on ≥5 occasions)
Venkatesh, 2010	N=198, 69% male	Self report (questionnaire) VAS, past 30 days	Optimal adherence (≥95%) was applied	Self report, past 30 days	Use vs no use
Wolf-King, 2014	N=365, 100% male	Self report (questionnaire) VAS, past 30 days	Perfect adherence (=100%) was applied	AUDIT questionnaire	Harmful drinking was defined as an AUDIT score of ≥8. Non-harmful drinking was defined as an AUDIT score of 1-7. No drinking (AUDIT score=0) was

					also included.
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