Research Article

The Impact of Alcohol use during Seemingly Suppressive Antiretroviral Therapy: Risk of Blips and Rebounds

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Abstract

Background: After achieving “clinically undetectable levels”, many HIV positive individuals remain in a phase called residual viremia. Some of these patients have viral blips, while others have viral rebounds, but little is known about their causes. Our objective was to identify the rate and determinants of viral load dynamics, particularly the effect of hazardous alcohol use.

Methods: We evaluated 400 cohort participants starting ART and comprehensively assessed alcohol intakes using validated instruments. Viral load (VL) was measured at four time points (baseline, 6, 12 and 18 months), along with potential covariates, such as demographics, CD4, CD8, platelets, alcohol use profiles, and medication adherence. VL suppression was assessed at 6 months and then based on prior published work, viral trajectories were censored according to the following categories: reference Group 1 (very low viremia<50), viral blips Group 2 (50-399), and the viral rebound Group 3 (400-1000 copies/mL). Factors associated with VLV, blips, and rebounds were identified using logistic regression models.

Results: Among the 320 subjects who achieved undetectable viral loads, during the subsequent 12 months of therapy, 20% exhibited viral blips, and 43% had viral rebounds. Despite similar medication adherence (95% vs. 85%), hazardous alcohol users were twice more likely to have a viral rebound, compared with non-users (95% CI, 1.8-2.5; p=0. 000). Alcohol users were also more likely to have blips. After adjustment for potential confounders, regression analyses indicated that CD4 counts at the time of therapy initiation, alcohol use, and age were independently associated with blips and rebounds.

Conclusions: In this cohort, hazardous alcohol use was associated with an increased risk of viral blips, and thus will likely play an important role in the development of effective strategies to eliminate HIV, and prevent transmission and disease progression. These findings have implications for clinicians, researchers and policy makers, as they highlight the detrimental effects of alcohol use while on ART therapy.

Introduction

The development of a combination therapy to treat HIV infection has changed the history of one of the most devastating epidemics [1]. Through a complex multi-phase process, one of the main goals of antiretroviral therapy (ART) has been to suppress HIV-1 below the limit of detection of a standard RT–PCR assay [1]. The first phase consists of an exponential decrease in circulating viral loads, which takes advantage of the short half-lives of free viruses. The second, much slower phase represents the turnover of chronically infected cells [2]. After achieving clinical undetectable levels, patients may undergo a phase of sub-clinical viremia, in which the virus replicates below 50 copies per ml (cp/ml). The currently accepted concept is that this very low level of viremia (VLLV) represents the latently infected cell reservoir [3].

Unfortunately, in a sizable proportion of individuals receiving therapy (20 to 60%) transient bursts of viral replication between 50 and 400 cp/ml, known as ‘blips’ occur. This residual viral replication probably represents new cycles of viral replication that forces the need of continuous therapy [4,5]. Clinicians are concerned with this up burst as it may increase the risks of: 1) chronic immune activation, 2) high rates of viral mutations, and 3) increased risk of HIV onward transmission [4]. Accordingly, the identification of the potential causes is an active area of research. So far, low CD4 cell counts, suboptimal potency of the prescribed ART regimen, immune stimulation associated with other opportunistic infections, and polymorphisms in chemokine receptor genes have been identified as possible causes. Changes in adherence have been proposed and debated [6-10].

Another possibility, which has been overlooked, is hazardous alcohol use. The intersection of HIV and HAU is a critical issue given the social acceptability of alcohol use, and alcohol's widespread use in PLWH (29-60%) [11-15]. Exploring the plausible role of HAU is also justified by in-vitro studies showing a direct effect of alcohol on viral control. Unfortunately, for the most part cohort studies analyzing VLLV and blips have failed to include alcohol in their analyses. Therefore, additional research is needed in the HIV/alcohol field to determine the role of HAU on viral control. Such information is highly relevant given that many of our participants continue to engage in hazardous alcohol use because they foresee no harm in such behavior. Establishing if alcohol may or may not impact viral loads is highly valuable for clinicians due to this belief. In addition, every nation across the globe will struggle to find the resources needed to pay for lifelong ART. If alcohol use is impacting the outcome of treatments, then alcohol intervention efforts should be prioritized. This information is also critical for public health authorities, as uncontrolled viral loads can increase the rates of HIV infection. Therefore, the overall aim of this

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cohort study is to describe viral load dynamics in a closely monitored group of PLWH with and without hazardous alcohol use, who entered the study when starting antiretroviral therapy.

Methods

Study population

The study took place in South Florida, where HIV rates are among the highest in the United States. Recruitment and follow-up procedures of the 400 individuals enrolled in PADS have been previously described [10]. The main focus of this cohort study was to assess the potential effects of alcohol in PLWH and under regular care. Our choice of PLWH in an open-access public health system with standard treatment protocols was purposefully designed to minimize social, medical, and treatment inequalities.

Non-ambulatory patients, and those presenting major medical comorbidities, were excluded. Participants were ineligible if they had any serious conditions that could compromise participation or outcomes, such as: central nervous system diseases (i.e., opportunistic infection, head injury with or without loss of consciousness, tumor, major psychiatric disease, a developmental disorder, past or current bipolar disorder), chronic diseases (i.e., kidney, thyroid, cardiovascular, liver or immune-based diseases), or severe malnutrition. To reduce the confounding effects of illicit drug use, the DSM-IV-TR questionnaire was administered, and those participants who were dependent on drugs or injecting illicit psychoactive substances were excluded. To control the confounding effect of viral hepatitis, subjects with liver enzymes two standard deviations above normal values or with records indicating active viral hepatitis were excluded. Those participants who were binge drinkers [18]. Alcohol groups were matched demographically.

Lymphocyte profiling

Blood samples were collected and processed within 6 hours. Isolated peripheral blood mononuclear cells were prepared for four-color direct immunofluorescence procedures (Becton Dickinson, San Jose, CA). Flow cytometry quantified the percentage and absolute numbers of T lymphocyte sub populations CD3+/CD4+ and CD3+/CD8. A good immunological response was defined as having more than 500 CD4+ cells, or as a gain of CD4+ cells ≥ 50 cells/mm² from week 0 to week 24. Alcohol groups were matched at baseline based on CD4 cell counts (above or below 200 cells).

Antiretroviral therapy and adherence

Following national protocols the usual ART regimen combines three or more different drugs such as two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or other such combinations.

An AIDS Clinical Trial Group (ACTG), self-reported adherence questionnaire [19] was used at each visit. Based on the missed doses per week and during the weekend, the percentage of adherence was calculated at baseline and at follow-up visit. Since self-report measures often over-estimate adherence, we triangulated the information with both pharmacy and medical records. If discordant, we endorsed medical/pharmacy reports.

Covariates

Upon entry into the study, data were collected at baseline and after 24 weeks by using standardized questionnaires; sociodemographic (age, gender, income, and race/ethnicity) and medical history information, along with the following covariates were obtained (i.e., AIDS-defining conditions yes/no, and US Centers for Disease Control and Prevention CDC clinical staging).

Statistical Analyses

The data were analyzed using SAS version 8 and SPSS version 21. The data set was checked for logical inconsistencies and abnormal distributions before beginning analysis. We analyzed viral load over time, both in absolute and relative terms (counts per ml.), and stratified into mutually exclusive categories based on prior published work.
Viral load was also log10 transformed. We used a mixed linear model to calculate VL change, over time, incorporating random effects to account for multiple updated measures. Using Univariate analyses we identified individual factors that impacted on VL decline and groups, by building a model with an interaction between time and that factor. Results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). When the interaction was plausible and statistically significant (at \( \alpha=0.05 \)) we included it in the final multivariable analysis. Similar to prior studies we used a Generalized linear mixed effects models to account for repeated observations on the same subject. Models were stratified based on ART status, a factor previously shown to modify the effect of alcohol consumption level on HIV progression. Based on our research and a literature review, we controlled for the following potential confounders in the multivariate model: gender, age, body mass index, viral hepatitis. Although the nadir CD4 count has been recommended as a preferable measure of disease severity, data were not available for most participants, and therefore the baseline CD4 counts were used.

**Results**

**Sample characteristics**

Demographics data, indices of HIV disease status, and general health for HAULWH and non-HAULWH are provided in Table 1. Nutritional status, determined by level of serum albumin, was within the normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group. The normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group. The normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group. The normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group. The normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group. The normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group. The normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group. The normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin<3.5 g/dL) was observed in only 1% of the group.

Participants had open access to antiretroviral medications, and mostly were receiving Truvada (44%), Atripla (22%) alone or in combination with Norvir (32%) or Kaletra (13%). None of the antiretroviral regimens were changed during pre, blip, or post periods. Based in prior studies raising concerns regarding the plausible impact of alcohol on adherence and liver toxicity we assessed these relationships. Adherence, as measured by the ACTG questionnaire, was similar between the groups, and was high during the week (93%), and more limited during weekends (83%). Liver enzymes were similar between the groups at baseline and during the follow-up visits suggesting not apparent risks of liver toxicity among alcohol drinkers.

**Viral load response after six months of therapy**

Over half of the group (58%) achieved undetectable viral loads (defined as <50 copies of HIV-1 RNA /ml cp/ml). An additional 20% reached 400 cp/ml. The others failed to achieve the 400 threshold, because their baseline loads were extremely high. Yet, findings are similar to those from MACS and WHI studies. Mean (SD) adherence during the first 6 months of therapy was slightly higher in those who attained very low levels of viremia 95%, as compared to the other two groups (91% and 90% respectively). As depicted in Table 2, differences in adherence became larger during the weekends. Although there were within-group differences in adherence during this initial period, (P=0.07), there was no significant differences in adherence during subsequent 2 time periods (P=0.27).

**Viral trajectories after achieving undetectable viral loads and alcohol use**

To achieve this goal, the study population was divided into: Group 1 (VLLV<50 cp), Group 2 (Blips viremia between 50 - 400 cp with returns to undetectable levels), and Group 3 (Rebounds>400 cp that persist). Among those who attained undetectable viral loads at the 6-month visit, only 58% of them remained undetectable. Near a quarter (22%) became detectable 6 months later, and 20% experienced viral load blips.

As depicted in Table 1 Groups 1 and 2 had age emerge as a plausible cofactor in the first six months of therapy, but not during the follow-ups. A similar pattern was observed for adherence. In the first six months, adherence was significantly different among the groups, yet when undetectable levels are reached, levels of adherence were no longer significant.

After adjusting for demographics and adherence, HAU subjects were twice more likely than non-HAU subjects to have detectable viral loads at the 12 month visit (OR=2.1 95% CI 1.8-2.5, p=0.000).

**Role of CD4 and CD8 in the maintenance of VLL during ART**

Since the extent of CD4+ T cell reconstitution can also impact viral control and studies suggest that it can impact the size of the latent reservoir, we examined the relationship between CD4 and viral trajectories. Individuals who under ART maintained undetectable viral loads exhibited significantly higher CD4+ T cell counts. On the contrary, those who became detectable had low CD4 cell counts since the time of ART initiation.

Even though monitoring of lymphocyte subsets other than CD4 such as CD8 is not routinely recommended we monitored both CD4 and CD8 lymphocytes and was proven clinically useful. As summarized in Table 3 individuals who remained undetectable had lower CD8 percentages, and higher CD4 cell counts. Indeed a high percentage of CD8 cells (>50%) was associated with increased odds of experiencing HIV rebounds (OR=1.8 95% CI 1.1-2.8, p=0.004).

**Final analyses**

| Variable                     | HAUN= | Non-HAUN= | P value |
|------------------------------|-------|-----------|---------|
| Age                          | 42.4 ± 6.5 | 42.8 ± 6.37 | 0.08 |
| Men                          | 67%   | 60%       | 0.1    |
| Women                        | 33%   | 40%       |        |
| African American             | 70%   | 66%       | 0.4    |
| Black Caribbean              | 2%    | 4%        |        |
| Hispanic                     | 22%   | 23%       |        |
| White                        | 6%    | 4%        |        |
| Annual Income: Less than $10,999 | 88%   | 88%       | 0.7    |
| $11,000-$19,999              | 9%    | 10%       |        |
| $20,000-$49,999              | 2%    | 2%        |        |
| >$50,000                     | 2%    | 2%        |        |
| Education (years of school)  | 11.3 ± 2.1 | 11.4 ± 2.6 | 0.1    |
| Albumin mg/dl                | 4.2 ± 0.43 | 4.2 ± 0.5 | 0.9    |
| AST IU/L                     | 39.8 ± 21.0 | 33.6 ± 21.0 | 0.2    |
| ALT IU/L                     | 36.6 ± 22.2 | 34.8 ± 32.9 | 0.8    |
| CD4 cell counts              | 404.2 ± 260.9 | 456.9 ± 323 | 0.06   |
| Adherence weekdays           | 2.7 ± 1.3 | 2.6 ± 1.3  | 0.4    |

**Table 1:** Sociodemographic and clinical characteristics by alcohol groups.

**Note:** Demographic characteristics were expressed as percentages by BMI group. Biological measures were presented as means and standard deviations.

AST=Aspartate transaminase also called glutamic oxaloacetic transaminase (SGOT) and ALT=Alanine aminotransferase also called glutamic pyruvic transaminase (SGPT).
The list of variables included in the regression model comprised sociodemographics (age, gender, race, socioeconomic status), HIV history (type of transmission, years since seroconversion, CD4 and CD8 percentages at each visit), health behavior factors (current and past alcohol use, adherence, nutritional status, past drug abuse). Two distinctive models were run one for Blips (Table 3) and one for viral rebounds (Table 4). Although both models had comparable predictors, current alcohol use was stronger predictor of rebounds. Similarly, adherence predict rebounds but not blips.

**Discussion**

In this cohort of treated subjects with well-defined treatments and alcohol intakes, analyses provide evidence that alcohol use is playing a role in viral trajectories. Our study is quite unique in focusing in the impact of alcohol once subjects are achieving undetectable viral load levels. Analyses confirmed our initial hypothesis that hazardous alcohol use is reducing the likelihood to maintain viral levels below 50 copies. Specifically, hazardous alcohol use is increasing the likelihood of viral blips and viral rebounds. In contrast to prior reviews of literature indicating that less than 10% of patients with initial LLV progressed to higher degrees of viremia, in our cohort these rates were doubled. These findings are highly relevant for clinical management decisions, as these bursts of viral loads associated with hazardous alcohol use may enhance the risk of viral evolution, immunologic decline, and HIV-1 transmission [20]. Therefore, alcohol use screening and treatment should be prioritized in clinical management. Alcohol users may also be in need of close follow-ups and adjuvant therapy/support. These results could also be valuable for epidemiological modeling, forecasting resource needs, and cost-benefit analysis.
Our analyses also indicated that there are factors important to reach undetectable levels and after attaining this milestone they are no longer significant. In our analyses, alcohol use not only impacts the likelihood of reaching undetectable viral loads but also on keeping the virus under control. Although in the past, studies have been exploring the relationship between alcohol use and achieving undetectable viral loads, these investigations have reached dissimilar conclusions [21-23]. In accord with our findings that alcohol impacts viral burden, several other researchers have demonstrated that alcohol directly impacts viral loads in individuals receiving ART [24,25]. Results have been replicated among veterans, prisoners, and subjects with other comorbidities (i.e. drug users) [26,27]. Results remained significant after adjusting for covariates including adherence. However, others have failed to identify a significant relationship between undetectable viral loads and alcohol use. Discrepancies in the results are probably associated to differences in the study design (i.e., cross-sectional versus longitudinal; primary versus secondary analyses) in the definition of hazardous alcohol use (grams versus standard drinks) in the viral outcome, or timing (before or after the advent of highly active ART). For example, in the Swiss Cohort [28] only 7% of the individuals fulfill the criteria of Moderate to Severe risk, which in our study roughly corresponds to the definition of hazardous alcohol users. Such a small percentage can clearly explain the lack of significant results. On the other hand, our study had a balanced distribution of HAU and non-HAU because it was purposefully designed to assess the impact of alcohol use.

However, our study expanded upon prior research by analyzing what happens once an individual reaches undetectable levels. Statistical models indicated that alcohol use was a significant predictor of blips. Thus our results serve as an additional piece of evidence of the widespread damage that hazardous alcohol use can cause to people living with HIV. From the public health perspective, increased risks of viral blips and rebounds in alcohol drinkers, combined with risky sexual behavior, can maintain the South Florida HIV epidemic.

Based on prior studies raising concerns that alcohol significantly influences adherence and liver toxicity, we assessed these factors. Noteworthy, neither liver damage nor adherence was significantly different among study groups. Similarly, three different studies, one led by Kalichman et al. [28], found that alcohol use was not robustly related to ART adherence [29], so there is no need to withhold ART from hazardous alcohol users. Another study among men who have sex with men (MSM) also failed to find a relationship between HAU and adherence. Although alcohol deleterious effects have been largely attributed to adherence, at least in our population, the issue of adherence and alcohol use deleterious effects are not limited to impacting adherence and are probably related to alcohol's capacity to affect the immune system, including specific cytokines.

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