Association of Alcohol Consumption and HIV Surrogate Markers in Participants of the Swiss HIV Cohort Study

Anna Conen, MD, Qing Wang, PhD,† Tracy R. Glass, PhD,† Christoph A. Fux, MD,* Maria C. Thurnheer, MD,‡ Christina Orasch, MD,§ Alexandra Calmy, MD, PhD,‖ Enos Bernasconi, MD,¶ Pietro Vernazza, MD,# Rainer Weber, MD,** Heiner C. Bucher, MD, MPH,††† Manuel Battegay, MD,†† and Jan Fehr, MD***

Background: Alcohol consumption may affect the course of HIV infection and/or antiretroviral therapy (ART). The authors investigated the association between self-reported alcohol consumption and HIV surrogate markers in both treated and untreated individuals.

Design: Prospective cohort study.

Methods: Over a 7-year period, the authors analyzed 2 groups of individuals in the Swiss HIV Cohort Study: (1) ART-naïve individuals remaining off ART and (2) individuals initiating first ART. For individuals initiating first ART, time-dependent Cox proportional hazards models were used to assess the association between alcohol consumption, virological failure, and ART interruption. For both groups, trajectories of log-transformed CD4 cell counts were analyzed using linear mixed models with repeated measures.

Results: The authors included 2982 individuals initiating first ART and 2085 ART naives. In individuals initiating first ART, 241 (8%) experienced virological failure. Alcohol consumption was not associated with virological failure. ART interruption was noted in 449 (15%) individuals and was more prevalent in severe compared with none/light health risk drinkers [hazard ratio: 2.24, 95% confidence interval: 1.42 to 3.52]. The association remained significant even after adjusting for nonadherence. The authors did not find an association between alcohol consumption and change in CD4 cell count over time in either group.

Conclusions: No effect of alcohol consumption on either virological failure or CD4 cell count in both groups of ART-initiating and ART-naive individuals was found. However, severe drinkers were more likely to interrupt ART. Efforts on ART continuation should be especially implemented in individuals reporting high alcohol consumption.

Key Words: alcohol, HIV infection, virological failure, CD4 cell count, antiretroviral therapy

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INTRODUCTION

Alcohol consumption is an important cause of morbidity and mortality in developed countries and likewise affects HIV-infected individuals.[1] The World Health Organization

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From the *Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital Aarau, Aarau, Switzerland; †Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland; ‡Clinic for Infectious Diseases, University Hospital Berne, University of Berne, Berne, Switzerland; §Division of Infectious Diseases and Hospital Epidemiology, University Hospital Lausanne, University of Lausanne, Lausanne, Switzerland; ‖Division of Infectious Diseases and Hospital Epidemiology, University Hospital Geneva, University of Geneva, Geneva, Switzerland; ¶Division of Infectious Diseases, Regional Hospital Lugano, Lugano, Switzerland; #Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; **Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zürich, University of Zürich, Zürich, Switzerland; and ††Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland.

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A.C. and J.F. were the main authors involved in conception and performing the study, in data interpretation and manuscript writing. Q.W., T.G., and H.C.B. were involved in the conception of the study and were responsible for the analysis of data. M.B. was involved in planning the study, data interpretation and reviewing the article. All authors were involved in data interpretation and revised the article critically. All centers collected data for the Swiss HIV Cohort Study.

Correspondence to: Jan Fehr, MD, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zürich, Rämistrasse 100, CH-8091 Zürich (e-mail: jan.fehr@usz.ch).

categorizes daily alcohol consumption into drinking with light (<20 g for women and <40 g for men), moderate (20–40 g for women and 40–60 g for men), and severe (>40 g for women and >60 g for men) health risks.[2] The reported prevalence of alcohol drinking in HIV-infected individuals varies widely: 40%–82% for any and 8%–35% for severe alcohol consumption.[3–10] In the Swiss HIV Cohort Study (SHCS), alcohol consumption was reported by up to 52% of individuals and 2.8% reported severe health risk drinking.[11]

Liver disease in HIV-infected individuals, caused mainly by coinfection with the hepatitis C virus (HCV), is aggravated by alcohol-induced toxicity. Due to the success of combined antiretroviral therapy (ART), survival of HIV-infected individuals has markedly improved and therefore made the development of end-stage liver disease a greater concern.[12–17] Furthermore, in vitro studies using human cell cultures and animal studies indicate that alcohol may have cytotoxic and immunosuppressive effects. In simian immunodeficiency virus–infected macaques, a deterioration of immunological and virological parameters (eg, lower CD4 cell count and higher viral loads) were observed after alcohol exposure.[18–23] However, studies investigating the association of alcohol exposure and immune function or compromised immune restoration under ART in HIV-infected individuals show conflicting results.[4,6,7,9–11,24–33]

We assessed the association between self-reported alcohol consumption and HIV surrogate parameters in 2 groups of individuals in the SHCS. The first group included all the individuals initiating their first ART. This group was selected to analyze specifically the impact of alcohol under the influence of ART. We assessed the association between alcohol consumption and the risk of virological failure and discontinuation of ART. The second group included all the ART-naive individuals remaining off ART during the study period. In both groups, we investigated the impact of alcohol on immunological parameters by comparing the CD4 cell count trajectories across different categories of alcohol consumption.

METHODS

Study Population and Assessment of Self-Reported Alcohol Consumption

The SHCS is a multicenter observational study for interdisciplinary HIV research in Switzerland. Since 1988, HIV-positive adults, aged 16 years or older, have prospectively and continuously been enrolled at 7 cohort centers, affiliated hospitals, and private practices collaborating with the centers. Over 17,000 HIV-infected individuals have been included since 1988, corresponding to approximately 70% of all HIV-infected individuals in Switzerland (for more details consult http://www.shcs.ch).[34] At a semiannual follow-up in outpatient clinics and associated private practices, structured clinical and laboratory data are obtained. Clinicians or study nurses collect data on sociodemographic and clinical characteristics, antiretroviral treatment, comorbidities including injecting and noninjecting drug use, and comedications based on a predefined questionnaire. Predefined laboratory tests, including HIV viral load and CD4 cell count, are performed at routine follow-up visits every 6 months but also in between cohort visits. Written informed consent was given by all participants and ethical approval by all local ethical committees.

In August 2005, a questionnaire on self-reported alcohol consumption was introduced. The following questions are asked by clinicians or study nurses every 6 months: (1) Did you drink alcohol at least once a week during the last 6 months? (yes, no, refuse to answer), and (2) If "yes," how much did you drink on a daily basis? Average daily alcohol consumption is estimated with the help of a predefined list of different alcoholic beverages with their alcohol content in grams. Daily alcohol intake was translated into health risk categories developed by the World Health Organization [2]: light (<20 g for women and <40 g for men), moderate (20–40 g for women and 40–60 g for men), and severe health risk (>40 g for women and >60 g for men). For simplicity, individuals were referred to as "nondrinkers," if they did not consume at least 1 alcoholic beverage a week in the previous 6 months.

For this study, 2 groups were analyzed: (1) individuals who initiated their first ART between August 1, 2005, and October 1, 2012, and answered at least 1 alcohol questionnaire within the first 12 months of therapy; and (2) ART-naive individuals with a known date of first positive HIV test between August 1, 2005, and October 1, 2012, and answered at least 1 alcohol questionnaire within 12 months of diagnosis.

Outcome Variables

"Virological failure" was defined, based on the US Department of Health and Human Services guidelines for the use of antiretroviral agents, as either failure to achieve virological suppression (the first of 2 consecutive viral load measurements >400 copies per milliliter after 24 weeks or >50 copies per milliliter after 48 weeks) or a viral rebound after viral suppression (the first of 2 consecutive detectable viral load measurements after 2 consecutive undetectable viral load measurements, ie, ≤50 copies per milliliter). "ART interruption" was defined as discontinuation of ART for >7 days without medical indication. Longitudinal "changes in CD4 cell count" were modeled as continuous measures.

Covariates and Definitions

We adjusted for potential confounding risk factors.[35] Time-independent variables measured at baseline were gender, ethnicity, age, and time since HIV diagnosis. Time-updated variables were current intravenous drug use (IDU) or being in a drug maintenance program, psychiatric comorbidities (defined as either diagnosed/treated by a psychiatrist or taking antidepressant drugs), AIDS-defining disease, chronic infection with hepatitis B virus (HBV) (positive HBs antigen test or detection of HBV DNA) or HCV (detection of HCV RNA or being on treatment for HCV), CD4 cell count, HIV viral load and drug class of current regimen [nonnucleoside reverse transcriptase inhibitor, boosted or unboosted protease inhibitor (PI), triple nucleoside reverse transcriptase inhibitor]. We also considered self-reported nonadherence to ART (at least 1 missed dose in the previous 4 weeks)—a time-dependent confounder which is likely to lie on a causal pathway.

Statistical Methods

For individuals initiating first ART, time-dependent Cox proportional hazards models were used to assess the effect of alcohol consumption on time to virological failure. Individuals were followed from the date of initiating ART and were censored when they stopped ART for >7 days, were lost to follow-up (>9 months since last cohort visit), or at the closing date of the study (October 1, 2012), whichever came first. Likewise, we estimated the association between alcohol consumption and ART interruption. Alcohol consumption was time updated, and covariates listed above were adjusted in all models. We fitted separate models with and without adjusting for nonadherence to assess the overall and cause-specific effect of alcohol consumption on each outcome. Results were presented as hazards ratios (HRs) and 95% confidence intervals (CI).

For both groups of individuals, the trajectories of CD4 cell counts were fitted using linear mixed models with a random effect on the intercept to allow for the fitted curve to vary between individuals. Log-transformed CD4 cell counts were used to ensure that the assumption of linearity was met. A square root transformation was also performed in a sensitivity analysis; although it was considered a better fit, the estimates could not be easily back transformed to the original scale.[36] Individuals initiating first ART contributed to the models until they stopped ART for >7 days, were lost to follow-up, or at the closing date of the study, whichever came first. However, we followed ART-naive individuals from the first CD4 cell count measurement after HIV diagnosis until the last measurement strictly before initiating ART, loss to follow-up, or at the closing date of the study, whichever came first. In all models, follow-up time was modeled as a cubic spline with 5 knots at percentiles 5, 27.5, 50, 72.5, and 95. Results were presented as changes in the ratio of geometric means of CD4 cell counts with 95% CIs.

In all analyses, we considered the combined categories of none and light health risk drinkers as the reference category. Given the small number of visits where individuals refused to answer the alcohol questions, these entries were considered as missing. We also carried out a series of sensitivity analyses: (1) we combined moderate and severe health risk drinkers into a single category termed "at-risk drinkers" due to the small numbers in each category; (2) we expanded the definition of drug use to include noninjecting drug use, which was only collected since April 2007; (3) we only included ART-naive individuals who had at least 6 months of follow-up, given that CD4 cell count does not change very rapidly; (4) we did not censor individuals initiating first ART at ART interruption to get an overall estimate of the effect of alcohol consumption on virological failure and CD4 cell count; (5) we adjusted for misclassification due to underreport by assuming all individuals to underreport their alcohol consumption equally by 40%.[37] All analyses were done using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Participants' Characteristics

During the study period, 3464 individuals initiated their first ART. Of which, 482 were excluded due to incomplete alcohol consumption questionnaire or missing data on CD4 cell count and viral load within 12 months of initiating ART. The 2982 (86%) included individuals had a median follow-up of 30 [interquartile range (IQR): 14–51] months. A total of 2607 ART-naive individuals had a known date of first positive HIV test. Of which, 522 were excluded due to incomplete alcohol consumption questionnaire or missing data on CD4 cell count and viral load within 12 months of diagnosis. The 2085 (80%) included individuals were followed for a total of 1614 person-years. During this time, 7809 CD4 cell count measurements were made, with a median time between measurements of 2.6 (IQR: 0.9–3.9) months. Their median follow-up time was 2 (IQR: 1–14) months: 1744 (84%) started ART with a median follow-up of 1 (IQR: 0.4–10) month, and 341 (16%) remained off ART with a median follow-up of 12 (IQR: 1–36) months.

Missing data in excluded individuals was largely due to early censoring. Among individuals initiating first ART, 324 (67%) excluded individuals had a follow-up of at least 12 months and were on average younger (mean age was 37 years for excluded vs. 40 years for included individuals), more likely to be female (31% vs. 25%), non-Caucasian (37% vs. 24%), or IDUs (15% vs. 8%). Among ART-naive individuals, 273 (52%) excluded individuals had a follow-up of at least 12 months and were more likely to be IDUs (9% vs. 4%).

The baseline characteristics are shown in Table 1. Individuals initiating first ART and ART-naive individuals reported to be nondrinkers in 46.4% and 42.4%, light health risk drinkers in 45.9% and 51.3%, moderate health risk drinkers in 4.7% and 3.9%, and severe health risk drinkers in 2.2% and 2.2%, respectively. Only 0.8% and 0.2% refused to answer the alcohol questionnaire, respectively.

Treatment Outcome and Association With Alcohol Use

In individuals initiating first ART, 241 (8%) experienced virological failure, of which 91 (38%) failed to achieve suppression and 150 (62%) experienced viral rebound. There was no significant effect of alcohol consumption on the risk of virological failure (Table 2). ART interruption without medical indication was noted in 449 (15%) individuals initiating first ART with a median time to interruption of 12 (IQR: 5–22) months. Severe health risk drinkers were more likely to stop treatment compared with none/light health risk drinkers (HR: 2.24, 95% CI: 1.42 to 3.52). This association remained significant when nonadherence was included in the model (HR: 2.20, 95% CI: 1.40 to 3.46). Estimates from other covariates confirmed known associations from a previous study from the SHCS concerning ART interruption and virological failure.[38] In a sensitivity analysis where individuals were not censored at ART interruption, severe health risk drinkers were more likely to experience virological failure (HR: 1.66, 95% CI: 1.00 to 2.77).

In both groups of individuals initiating first ART and ART-naive individuals, we found no association between alcohol consumption and CD4 cell count change over time (Table 3). In individuals initiating first ART, lower CD4 cell count was found in those who were older, non-Caucasian,

TABLE 1. Baseline Characteristics for Individuals Initiating First ART and ART-Naive Individuals in the SHCS (n = 5067)

Baseline Characteristics	Initiating First ART Group* (n = 2982)	ART-Naive Group*† (n = 2085)
Self-reported alcohol consumption‡		
Nondrinkers, %	46.4	42.4
Light risk, %	45.9	51.3
Moderate risk, %	4.7	3.9
Severe risk, %	2.2	2.2
Refused to answer, %	0.8	0.2
Median age (IQR), yrs	39 (32–46)	37 (30–45)
Male gender, %	75	79
Caucasian ethnicity, %	76	75
Median time since HIV diagnosis (IQR), yrs	1.0 (0.1–3.7)	0.0 (0.0–0.1)
Education <9 yrs, %	22	19
Transmission risk category, %		
Homosexual	51	56
Heterosexual	38	36
IDU	7	4
Other	4	4
IDU or in drug maintenance programme, %	8	4
Psychiatric comorbidities, %	14	4
Coinfection, %		
Hepatitis B virus	4	2
Hepatitis C virus	10	5
AIDS, %	13	7
Median CD4 cell count (IQR), cells per μL	269 (171–367)	355 (193–526)
Median HIV viral load (IQR), $\log_{10}$ copies per mL	4.7 (4.2–5.2)	4.7 (4.1–5.3)
First ART regimen, %		
NNRTI based	43	—
PI based	52	—
Triple NRTI or other	5	—
Self-reported adherence, % (at least one missed dose of ART within 4 weeks)	6	—

* Between August 1, 2005, and October 1, 2012.

† Baseline for the ART-naive group is the first CD4 cell count measurement after diagnosis of HIV.

‡ Average daily alcohol consumption is estimated in grams and is translated into health risk categories developed by the World Health Organization: light risk (<20 g for women and <40 g for men), moderate risk (20–40 g for women and 40–60 g for men), severe risk (>40 g for women and >60 g for men).

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; IDU, intravenous drug use; ART, antiretroviral therapy; PI, protease inhibitor.

diagnosed with HIV for longer, coinfected with HBV or HCV, had lower baseline CD4 cell count, higher baseline viral load, and initiated nonnucleoside reverse transcriptase inhibitor–based regimens. In ART-naive individuals, lower CD4 cell count was found in females, individuals with psychiatric comorbidities, AIDS, lower baseline CD4 cell count, and higher baseline viral load. All sensitivity analyses gave similar results, which led to the same conclusion (data not shown).

DISCUSSION

The influence of alcohol on HIV surrogate markers is controversially discussed. Our study uses one of the largest dataset of self-reported alcohol consumption in HIV-infected individuals to assess the putative association with immunological and virological parameters among individuals initiating first ART and ART-naïve individuals. We found no association between CD4 cell count change over time and the different alcohol drinking categories, neither in ART-initiating nor in ART-naïve individuals. However, we found a higher rate of ART interruption in ART-initiating individuals with severe health risk drinking but no increased risk of virological failure.

The prevalence of severe health risk drinking in the SHCS was lower (2.2%) compared with other studies (10%–30%).[4,30,31] This probably is due to the fact that most of the comparator studies recruited from their study populations, such as homeless people or individuals with known harmful substance consumption, or due to a higher rate of underreport of the real alcohol consumption in our study.

Our findings challenge the hypothesis generated by studies from cell cultures and animals indicating an association between higher alcohol intake, lower CD4 cell count and higher simian immunodeficiency virus viral loads.[18,19,21,22] Previous studies on HIV-infected individuals with and without ART also suggested an association between alcohol consumption and unfavorable virological and/or immunological outcomes.[26,27,29,39] Due to the high heterogeneity of study designs and populations, these findings are difficult to interpret. Many of them were cross-sectional and were performed in the pre-ART era with both selected and small samples.

In line with our results, the following studies on treated and untreated HIV-infected individuals found no effect of alcohol on CD4 cell counts.[4,10,24,25,30,31] In a large study of 1107 individuals initiating ART, Kowalski et al[31] concluded that the positive effects of ART on viral suppression and immunological function predominated the potential immunotoxic effects of alcohol. But unlike our study, untreated individuals were not included to analyze the effect of alcohol in the absence of ART. Samet et al[4] conducted a longitudinal study in 595 individuals over 7 years and found no effect of alcohol on CD4 cell count in ART-treated individuals but an impact in untreated individuals. This provides more evidence for the hypothesis of the counterbalancing effect of ART. Notably, only individuals with current or previous alcohol problems were included, limiting generalizability. Wu et al showed in 325 individuals that neither in ART-treated nor untreated individuals, there was an association between alcohol consumption and CD4 cell count.[30] However, daily alcohol consumers had a 4-fold increase in detectable HIV viral load, and this remained significant when results were adjusted for adherence. Smaller earlier studies, even from the pre-ART era, found neither an effect of alcohol on CD4 cell count nor on AIDS-defining events.[10,24,25]

Nonadherence to ART in heavy alcohol drinkers is a frequent problem and nonadherence rates are 3–3.6 times higher in moderate and severe drinkers compared with nondrinkers.[9,33] In our previous publication, we found similar results with a dose-dependent relationship between alcohol

TABLE 2. Association Between Alcohol Consumption, Virological Failure, and Interruption of ART in Individuals Initiating First ART (n = 2982)

	Virological Failure*		ART Interruption†	
	Multivariate HR (95% CI)	***P***	**Multivariate HR (95% CI)**	***P***
Alcohol consumption‡				
Nondrinkers/light risk	Reference	—	Reference	—
Moderate risk	0.52 (0.21 to 1.27)	0.15	1.13 (0.72 to 1.76)	0.60
Severe risk	1.42 (0.65 to 3.07)	0.38	2.24 (1.42 to 3.52)	<0.01
Age per 10-yr increase	0.98 (0.86 to 1.12)	0.80	0.89 (0.81 to 0.99)	0.03
Male gender	0.90 (0.65 to 1.25)	0.53	0.77 (0.62 to 0.96)	0.02
Caucasian ethnicity	0.75 (0.53 to 1.05)	0.09	0.70 (0.55 to 0.89)	<0.01
Time since HIV diagnosis per 10-yr increase	1.01 (0.76 to 1.35)	0.94	1.10 (0.90 to 1.34)	0.34
IDU or in drug maintenance programme	1.45 (0.76 to 2.77)	0.26	1.40 (0.93 to 2.11)	0.11
Psychiatric comorbidities	0.92 (0.63 to 1.35)	0.67	1.05 (0.81 to 1.36)	0.70
Hepatitis coinfection (B or C)	0.85 (0.54 to 1.33)	0.47	1.11 (0.83 to 1.49)	0.49
AIDS	1.11 (0.80 to 1.55)	0.52	0.96 (0.73 to 1.25)	0.74
Baseline CD4 cell count per 100 cells per μL increase	0.91 (0.83 to 1.00)	0.05	1.20 (1.14 to 1.26)	<0.01
Baseline viral load per $\log_{10}$ copies per mL increase	1.56 (1.34 to 1.83)	<0.01	0.97 (0.89 to 1.07)	0.58
ART regimen				
NNRTI based	Reference	—	Reference	—
PI based	1.93 (1.45 to 2.58)	<0.01	1.85 (1.50 to 2.28)	<0.01
Triple NRTI or other	2.75 (1.72 to 4.38)	<0.01	1.94 (1.32 to 2.86)	0.01

For nonadherence as a time-dependent confounder, we fit separate models with and without adjusting for them to assess the overall and cause-specific effects of alcohol consumption.

* Events/total person-years at risk = 241/7709.

† Events/total person-years at risk = 449/8246.

‡ Average daily alcohol consumption is estimated in grams and is translated into health risk categories developed by the World Health Organization: light risk (<20 g for women and <40 g for men), moderate risk (20–40 g for women and 40–60 g for men), and severe risk (>40 g for women and >60 g for men). Refused to answer is treated as missing.

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; IDU, intravenous drug use; ART, antiretroviral therapy; PI, protease inhibitor.

use and nonadherence to ART.[11] Here, severe health risk drinkers were more likely to stop ART compared with none/light health risk drinkers. This association still held when nonadherence was adjusted in the model. Intentional nonadherence by skipping or stopping ART intake while drinking alcohol was identified in a prospective cohort study as an important cause of suboptimal ART adherence in individuals consuming relevant amounts of alcohol.[40] Because reporting of reasons for ART interruption is not detailed in the SHCS, we are not able to analyze the direct influence of drinking behavior on ART interruption. Despite the higher rate of ART interruption, severe health risk drinking was not associated with virological failure. An explanation might be that individuals did not interrupt ART in an "on and off" manner but simply stopped at 1 time, thereby minimizing the risk for virological failure. Furthermore, in our study population, PIs were used in >50% of all individuals. The higher resistance barrier of PIs may counterbalance the risk of virological failure in severe health risk drinkers. If individuals were not censored at ART interruption, severe health risk drinkers were more likely to experience virological failure, implying that alcohol consumption was associated with virological failure largely through ART interruption and poor adherence.

Alcohol is a contributing factor for risky sexual behavior and HIV transmission.[41–44] In the SHCS, IDU and moderate or severe alcohol consumption are associated with unprotected sex.[41] If HIV infection is not optimally treated in severe alcohol drinkers with risky sexual behavior, the risk of sexual HIV transmission is high. This is not only a public health concern in Switzerland but is of utmost importance in regions, such as Eastern Europe, where alcohol consumption per capita is high and an uncontrolled HIV epidemic is ongoing. Hence, it is important to treat these individuals at risk appropriately and to provide them with all the needed support to achieve virological suppression. As severe health risk drinkers were not shown to have a higher risk of virological failure, ART should not be withheld because this was sometimes the case for IDUs.[45] In addition to concerns over possible treatment failure, the physician's fear of alcohol-related liver toxicity might be another reason for postponing ART in heavy drinkers. However, this argument can be disproved as liver-related toxicities from alcohol and ART were found to be rare in a recent D.A.D. publication.[46]

Our study has several strengths. Most importantly, we studied not only ART-naive individuals but also individuals initiating first ART, which allowed us to analyze the influence of different alcohol consumption levels both in the absence and presence of ART. The SHCS has excellent follow-up, and data are of high quality with only a small percentage of missing entries. Our study is based on a large sample and includes individuals from a representative population with different HIV transmission risk groups and social classes.

TABLE 3. Association Between Alcohol Consumption and CD4 Cell Count Changes Over Time in Individuals Initiating First ART and in ART-Naive Individuals

	Initiating First ART Group (n = 2982)		ART-Naive Group (n = 2085)	
	Multivariate Estimate (95% CI)	*P*	Multivariate Estimate (95% CI)	*P*
Alcohol consumption*				
Nondrinkers/light risk	Reference	—	Reference	—
Moderate risk	1.01 (0.99 to 1.04)	0.30	0.97 (0.93 to 1.01)	0.13
Severe risk	1.02 (0.98 to 1.06)	0.29	0.99 (0.94 to 1.05)	0.80
Age per 10-yr increase	0.96 (0.95 to 0.98)	<0.01	0.99 (0.98 to 1.00)	0.24
Male gender	0.98 (0.95 to 1.01)	0.16	1.04 (1.00 to 1.07)	0.02
Caucasian ethnicity	1.08 (1.05 to 1.12)	<0.01	1.01 (0.98 to 1.04)	0.73
Time since HIV diagnosis per 10-yr increase	0.93 (0.91 to 0.95)	<0.01	—	—
IDU or in drug maintenance programme	0.99 (0.95 to 1.02)	0.46	0.97 (0.92 to 1.02)	0.20
Psychiatric comorbidities	1.01 (1.00 to 1.03)	0.10	0.97 (0.94 to 0.99)	<0.01
Hepatitis coinfection (B or C)	0.95 (0.92 to 0.98)	<0.01	0.98 (0.95 to 1.02)	0.34
AIDS	0.98 (0.95 to 1.02)	0.30	0.87 (0.83 to 0.91)	<0.01
ART regimen				
NNRTI based	Reference	—	—	—
PI based	1.04 (1.02 to 1.05)	<0.01	—	—
Triple NRTI or other	1.02 (0.99 to 1.05)	0.14	—	—

Each estimate is the change in the ratio of geometric means of CD4 cell counts with 95% CIs. Model is also adjusted for baseline CD4 cell count and HIV viral load.

* Average daily alcohol consumption is estimated in grams and is translated into health risk categories developed by the World Health Organization: light risk (<20 g for women and <40 g for men), moderate risk (20–40 g for women and 40–60 g for men), and severe risk (>40 g for women and >60 g for men). Refused to answer is treated as missing.

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; IDU, intravenous drug use; ART, antiretroviral therapy; PI, protease inhibitor.

We acknowledge the following limitations: we had limited power despite the large sample size because of the relatively few individuals in the moderate and severe health risk drinking group. Follow-up was too short to see an immunological change due to alcohol-induced toxicity in ART-naive individuals because they started ART shortly after HIV diagnosis. A social desirability and interviewer bias can lead to underreport of the alcohol consumption, and individuals' reporting behavior might be different in front of physicians or nurses who perform the interview. Data were not missing completely at random as individuals who refused to answer the alcohol questionnaire or missed the follow-up visits were likely to belong to the at-risk population (eg, IDUs). However, the percentage of missing data was low (<1%) and results were based on a large sample from a representative population of HIV-infected individuals, which is a strong argument for our findings being valid and relevant. Finally, there is a lack of data on binge drinking in the SHCS. Binge drinking is known to be a risky drinking behavior and associated with lower adherence to ART, and omitting it can lead to underestimation of the degree of hazardous alcohol consumption.[47,48]

In conclusion, this large representative study of self-reported alcohol consumption in the SHCS showed an association between higher alcohol consumption and ART interruption but not virological failure. Motivational efforts to take ART should be optimized not only to have better virological and immunological outcomes in the individuals themselves but also to avoid sexual HIV transmission through risky sexual behavior due to severe health risk drinking. We could not detect an effect of alcohol on CD4 cell counts neither in ART-naive nor treated individuals. Our data contribute valuable knowledge to the controversy whether alcohol has an influence on HIV surrogates or not.

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Appendix 1. Members of the Swiss HIV Cohort Study (SHCS)

J. Barth, M. Battegay, E. Bernasconi, J. Böni, H. C. Bucher, C. Burton-Jeangros, A. Calmy, M. Cavassini, C. Cellerai, M. Egger, L. Elzi, J. Fehr, J. Fellay, M. Flepp, P. Francioli (President of the SHCS), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. A. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), D. Haerry (Deputy of "Positive Council"), B. Hasse, H. H. Hirsch, B. Hirschel, I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, C. Kind, T. Klimkait, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, K. Metzner, N. Müller, D. Nadal, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, F. Schöni-Affolter, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza, R. Weber, and S. Yerly.