Title

Tobacco smoking and binge alcohol use are associated with incident venous thromboembolism in an HIV cohort.

Journal

HIV medicine, 23(10)

ISSN

1464-2662

Authors

Luu, Brandon
Ruderman, Stephanie
Nance, Robin
et al.

Publication Date

2022-11-01

DOI

10.1111/hiv.13309

Peer reviewed

Associations of alcohol and cigarette use with type 1 and 2 myocardial infarction (MI) among people with HIV (PWH)

Running Head: Cigarette and alcohol use and MI by type in PWH

Lydia N. Drumright, PhD, MPH[1,2]: Robin M Nance, MS[1]; Stephanie A Ruderman, MPH[1]; Jimmy Ma, MD, MS[1]; Bridget M Whitney, PhD, MPH[1]; Andrew Hahn, MD[1]; Rob J Fredericksen, PhD, MPH[1]; Brandon Luu, HBSc[4]; William B Lober, MD, MS[1]; Richard D Moore, MD[5]; Matthew J Budoff, MD[5]; Jeanne C Keruly, MS, CRNP[5]; Katerina Christopoulos, MD, MPH[6]; Sarah Puryear, MD, MPH[6]; Amanda Willig, PhD, RD[7]; Karen Cropsey, PsyD[7]; William C Mathews, MD[9]; Edward Cachay, MD[8]; Laura Bamford, MD[8]: Joseph J Eron, MD[8]; Sonia Napravnik, PhD[8]; Kenneth M Mayer, MD[10]; Conall O'Cleirigh, PhD[10]; Mary E McCaul, PhD[5]; Geetanjali Chander, MD, MPH[5]; Matthew J Feinstein, MD[11]; Michael S Saag, MD[7]; Mari M Kitahata, MD, MPH[1]; Susan R Heckbert, MD, PhD[1]; Heidi M Crane, MD, MPH[1]; Joseph AC Delaney, PhD, MA, MSc[3]

[1]University of Washington, Seattle, United States; [2]University of Cambridge, Cambridge, United Kingdom; [3]University of Manitoba, Winnipeg, Canada; [4]Northern Ontario School of Medicine, Thunder Bay, Canada; [5]Johns Hopkins University, Baltimore, United States; [6]University of California, San Francisco, United States; [7]University of Alabama, Birmingham, United States; [8]University of California, San Diego, United States; [9]University of North Carolina, Chapel Hill, United States; [10]Harvard University, Cambridge, United States; [11]Northwestern University, Evanston, United States.

Corresponding Author:

Lydia N Drumright, PhD, MPH
University of Washington
School of Medicine Division of Allergy and Infectious Diseases
Harborview Medical Center
Box 359931 325 9th Ave
Seattle, WA 98104
lnd23@uw.edu

Summary: Among 13,506 people with HIV (PWH) over 4 years median follow-up, we observed a 1.6-fold increased risk of type-1 (T2MI) and type-2 (T2MI) myocardial infarction for current versus never smoking. Women had higher risk of T2MI than men and vice-versa.

Keywords: type 1 myocardial infarction, type 2 myocardial infarction, smoking, alcohol use, HIV, people with HIV

Word counts

Running head (40): current 10

Summary (40): current 40

Abstract (250): current 246

Body (3000): current 2992

References (40): current 40

Abstract

Introduction

People with HIV (PWH) have a higher risk of myocardial infarction (MI) than the general population, with a greater proportion of type 2 MI (T2MI), due to oxygen demand-supply mismatch, compared to type 1 (T1MI) resulting from atherothrombotic plaque disruption. PWH report greater prevalence of smoking and alcohol use than the general population. While smoking has been associated with increased risk, and alcohol consumption with decreased risk, of MI in the general population, alcohol use and smoking as risk factors for MI by type are not well studied among PWH.

Methods

Using longitudinal data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, we conducted time-updated Cox proportional hazards models to determine the impact of smoking and alcohol consumption on adjudicated T1MI and T2MI.

Results

Among 13,506 PWH, median 4 years follow-up, we observed 177 T1MI and 141 T2MI. Current smoking was associated with a 60% increase in risk of both T1MI and T2MI. In addition, every cigarette smoked/day was associated with a 4% increase in risk of T1MI, with suggestive, but not significant, increases for T2MI. Cigarette use had a greater impact on T1MI for men and T2MI for women. Increasing alcohol use

was associated with a lower risk of T1MI, but not T2MI. Frequency of heavy-episodic alcohol use was not associated with MI.

Conclusions

Our findings reinforce prioritizing smoking reduction, even without cessation, and cessation among PWH for MI prevention and highlight different impacts on MI type by gender.

Background

People with HIV (PWH) have a higher risk of cardiovascular disease (CVD), including myocardial infarction (MI), compared to those without HIV.[1-3] The Universal Definition of MI lists five types based on underlying mechanisms of myocardial ischemia.[4] Type I MI (T1MI) is attributable to disruption of atherothrombotic plaques.[4] Type 2 MI (T2MI) results from an acute imbalance in myocardial oxygen (i.e., increased demand or decreased supply), as with hypotension or vasospasm.[4] Type 3 are defined by MI-related death without cardiac biomarkers, and type 4 and 5 occur in coronary revascularization. In the general population, T1MI is 5-10 times more common than T2MI.[5,6] In contrast, we demonstrated that the incidence of T2MI is almost as frequent as T1MI among PWH.[7]

Associations between MI and both tobacco cigarette smoking and alcohol consumption have been widely studied in the general population, but to a lesser extent among PWH, and more importantly not by MI type. Cigarette smoking is considered one of the leading risk factors for CVD.[8] In large cohort studies of the general population, people who smoke tend to have ≥2 times the risk of MI than those who never smoked,[9-11] with hazard ratios consistently higher for women than men.[10,11] Conversely, alcohol consumption has been reported to be protective

against MI in the general population,[12-14] including increased alcohol intake,[14-17] above recommended limits,[12,14] showing a greater protective effect than no or light consumption. PWH report a greater prevalence of smoking[18] than the general population and meta-analysis suggests 24% prevalence of alcohol use disorder compared with 5-15% in the general population.[19] In addition, both smoking and alcohol use have been associated with lower likelihood of HIV viral suppression in large diverse samples.[20-22]

Given different epidemiological presentation of MI among PWH and the high prevalence of smoking and alcohol use, it is important to assess risk factors for MI by type among PWH to determine if the dynamics of MI are the same as in the general population. Using a large, well-characterized cohort of PWH with comprehensive clinical data, including alcohol use, smoking, and clinical MI adjudication by type, we examined the associations of alcohol use and smoking with T1MI and T2MI.

Methods

Population, Setting and Data Sources

Data from Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, comprising >37,000 PWH in care at eight United States (US) clinical sites (http://www.uab.edu/cnics/), was included.[23] CNICS sites received Institutional Review Board approval for use of data collected on participants. The CNICS data repository integrates comprehensive longitudinal data from outpatient and inpatient encounters including demographic, clinical, medication, and laboratory data from

electronic health records and other sources,[23] as well as patient-reported outcomes and measures (PRO).

We included data from six sites where sufficient MI adjudication was completed. Last adjudication date varied by site (~2018/2019) with on-going assessments. PWH who completed at least one PRO were included in the analyses. Baseline date was defined as the initial CNICS visit date plus 6 months or first completed PRO, whichever was later and within the MI adjudication period for that site. Participants who had a potential MI event before baseline (n=295) were excluded, as were those with incomplete data (n=139). Cohort exit occurred on the earliest of the following: (a) date of first MI, (b) nine months after last CNICS visit or lab test, (c) death, or (d) end of the site-specific MI adjudication period.

Predictors and Covariates

Data on cigarette smoking and alcohol consumption were collected via PRO at routine care appointments every ~4-6 months. Participants were asked if they have ever smoked or currently smoke tobacco cigarettes, including the current number of cigarettes smoked per day. Current alcohol consumption was assessed using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C),[24] and modelled as (1) continuous AUDIT-C scores (0-12)[24],(2) AUDIT-C derived categories, (3) AUDIT-C use frequency, and (4) heavy-episodic use, defined as ≥6 drinks in one sitting. We categorized AUDIT-C scores into no current use, no current use with a prior alcohol use disorder (AUD), non-hazardous alcohol use, and hazardous alcohol use defined as ≥5 drinks for men and ≥4 for women per day. Prior AUD was defined by either clinical diagnoses of alcohol abuse/dependency in the participants' medical records or ever reporting treatment for AUD by PRO. Both alcohol use and smoking were

time updated for every PRO completed and carried forward until the next measurement.

CNICS has standard operational definitions for other key covariates at baseline. Diabetes was defined as a prior hemoglobin A_{1c} level of ≥6.5, or use of a diabetes-specific or diabetes-associated medication in the setting of also having a diabetes diagnosis. Hypertension was defined as a recorded diagnosis of hypertension and receiving an antihypertensive medication prescription. Dyslipidemia was identified by receipt of lipid-lowering medications. Estimated glomerular filtration rate (eGFR) was calculated based on serum creatinine, age, sex and race/ethnicity, with an eGFR<30 defined as severe kidney disease. HIV viral load (VL) and CD4 counts assessed as part of clinical care were time updated for each new result from baseline until cohort exit.

Outcomes

MI events were adjudicated as previously described.[7,25] Ascertainment for potential MIs includes MI diagnoses, elevated cardiac biomarkers (e.g., troponin I or T), or documentation of coronary interventions (e.g., coronary artery bypass). For each potential event, sites assemble packets including medical notes, laboratory tests, imaging results, and electrocardiograms, which are reviewed independently by two expert physicians, who categorize potential events as no, probable, or definite MI, with further differentiation into MI types. Discordance between reviewers' results in a third physician review. All events adjudicated as definite or probable MI were included.

Statistical Analyses

Unadjusted summary statistics, including comparisons of central tendency and frequencies, were applied to baseline measures to describe the cohort by MI type. Rare MI types (e.g., <10 type 4 or 5 MIs to date, type 3) are not discussed further.

Associations between cigarette smoking or alcohol consumption and MI by type, adjusted for known MI risk factors, were assessed using time-updated Cox proportional hazards models in which smoking status, alcohol consumption, VL and CD4 count were time updated. Alcohol use was based on the four models described above and shown in Table 1. Smoking status (never, former, current) and number of cigarettes smoked per day among current smokers, centered on the median number of cigarettes, was modelled the same way in all models. Given potentially differential associations by age and sex by type of MI, we graphed type-specific MI-free survival by current smoking, age and cigarettes per day (pack equivalent) among males and females in models that excluded alcohol. All models were adjusted for age, birth sex, race/ethnicity, hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, dyslipidemia, hypertension, diabetes, VL, and CD4 count. The assumption of proportional hazards was assessed by Schoenfeld residuals. Analyses were conducted using STATA v17.0 (College Station, TX).

Results

13,506 PWH were included, with a median follow up time of 4.04 years (IQR: 1.8-12.3 years), median of 8.1 PROs/person (IQR: 3.6-24.6), and a mean age 44 years at baseline; 18% of participants were female (n=2491); 56% reported non-White race/ethnicity (Table 1). T1MI occurred in 177 participants and 141 had a T2MI during the

study period. In univariate analyses, participants who had either T1MI or T2MI were significantly older and were more likely to report current smoking and smoking more cigarettes per day at baseline than those without an MI during the study period (Table 1). Current alcohol use, frequency of use, heavy-episodic use, frequency of heavy-episodic consumption, and AUDIT-C scores were lower among those who experienced a T1MI compared to those with no MI; those who had a T1MI or T2MI were also more likely to report not consuming alcohol than those who did not have MI. Female participants were significantly less likely than males to have a T1MI, but more likely to have a T2MI.

Adjusting for potential confounders, those reporting current cigarette use, compared to never smoking, had a consistently increased risk of T1MI regardless of how alcohol was modelled (Hazard ratio (HR) range 1.61-1.67) (Table 2). Furthermore, the risk of T1MI increased by 4% for every cigarette currently smoked/ day in all models. Current cigarette use was associated with a similar significant increase in risk for T2MI across all four models (HR range 1.57-1.64 (Table 2)). A similar pattern to that of T1MI was observed for cigarettes smoked/day, including similar stability in the point estimate and confidence intervals, but did not achieve significance in T2MI models. Those reporting former smoking did not have an increased risk of either MI type compared to those who had never smoked.

PWH who had a higher AUDIT-C score by continuous measure were significantly less likely to experience T1MI (HR: 0.91, 95% CI: 0.84-0.98), but not T2MI (Table 2). Additionally, in models where alcohol use was categorized into current non-use without AUD, non-use with AUD, non-hazardous drinking, and hazardous drinking, the risk of T1MI was reduced among those reporting alcohol consumption, regardless of category. In contrast, the risk of T2MI was reduced for those reporting

non-hazardous alcohol consumption, but not hazardous consumption. Neither frequency of alcohol use nor heavy-episodic consumption in the past 30 days was associated with either MI type.

Using survival cures to examine the impact of aging and smoking on type of MI, for every decade of age (from 30-60 years), current smoking increased our participants' risk of T1MI by approximately one age decade. However, for T2MI the increased risk from smoking was greater than a single decade of age. Similarly, when we plotted amount smoked by sex, we saw different patterns for the types of MI (Figure 2). The impact of increased number of cigarettes per day (assessed by intervals of half packs) on T1MI was greater for men than women. However, the reverse pattern was seen for T2MI.

Discussion

PWH who completed detailed, longitudinal assessments on cigarette/alcohol use over a median follow-up of 4 years had 60% higher risk of either T1MI or T2MI if they currently smoked compared to those who never smoked. Furthermore, current smoking increased the risk of MI by the equivalent of one or more decade of age, and smoking appeared to have a greater association with T1MI risk in men and T2MI risk in women. These findings taken together with the observed per cigarette smoked daily risk for T1MI suggests that both smoking cessation ***and*** reduction among PWH are important for mitigating their already increased risk of MI. Alcohol use was associated with lower MI risk , as observed in the general population.. However, this association was only observed for AUDIT-C score and hazardous/non-hazardous drinking for T1MI and non-hazardous alcohol consumption for T2MI. Our

study is one of the few to examine T1MI and T2MI separately regardless of population.

We found that current, but not former, smoking among PWH was associated with increased MI risk with a similar effect size to most general population studies[9-11,26]. In contrast to our study, most prior studies did not differentiate between T1MI and T2M. We also collected smoking status more frequently than other studies, and these were time-updated in our models. We adjusted for a number of factors known to be associated with both MI and smoking, including HCV infection, diabetes and hypertension, while prior studies rarely adjusted for these[26].

Greater numbers of cigarettes smoked/ day was associated with increased MI risk in our study, which was similar to general population studies.[10,11,17] While general population studies tended to categorize cigarettes used/day, we examined this association continuously, demonstrating a 4% increase in T1MI risk per cigarette/day. While this association did not reach significance in our T2MI analyses, Figure 2 demonstrates the impact that each half pack (i.e., 10 cigarettes/day) has on increasing risk of T1MI and T2MI. This could be explained by reduced power for T2MI, due to fewer events, or differences in mechanism of how cigarette smoking results in T1MI and T2MI. Non-nicotine components of cigarettes have been shown to result in platelet activation, which has been associated with atherosclerotic plaque formation,[27] increasing the risk for T1MI, which would be consistent with a dose-response dynamic. A proposed mechanism for smoking-induced T2MIsuggests that an oxygen supply versus demand imbalance is created when high blood carboxyhemoglobin is present, reducing oxygen levels in the blood, while nicotine stimulates the sympathetic nervous system resulting in elevated heart rate and blood pressure and coronary vasoconstriction.[8] This could be dose-response related

(i.e., the longer one smokes at any one time the higher the risk), but not necessarily over the long-term.

Interestingly, our data demonstrated differential risk for men and women by MI type with respect to smoking, suggesting that both smoking cessation ***and reduction*** are critically important for reducing MI risk in both men and women with HIV. In addition to assessing and preventing atherosclerosis for both men and women with HIV who smoke, careful attention to factors associated with T2MI, such as infection, low CD4 cell count, higher viral loads, and stimulant use, is also important for preventing and managing MI in PWH, particularly among women with HIV who smoke.

We observed an inverse association between continuous AUDIT-C score and any use compared to no alcohol use with T1MI and non-hazardous use compared to no alcohol use with T2MI. These associations were not observed for frequency of alcohol or heavy-episodic use over a 30-day period. Most general population studies demonstrated more consistent inverse associations with measures of alcohol use, however, they used different categories of alcohol consumption than we did, such as moderate and heavy,[12,13] sometimes and regularly,[28] any consumption in the past 12 months,[29] timing of consumption prior to MI (e.g., hours, weeks, days),[30,31] and grams/day or week,[14,15], which might explain why we saw an inverse association with MI on some measures and not others. Our study was consistent with results regarding no association between heavy episodic/binge alcohol consumption and MI.[13] It is also important to note that the inverse association between alcohol use on MI is not observed in all populations,[29] and our sample is racially/ethnically diverse. Furthermore, epidemiological studies suggest that the mechanisms by which alcohol may lower the risk of MI include lowering blood lipids,[28] increasing HDL

cholesterol,[15] and improving insulin sensitivity.[15] Experimental studies demonstrate that feeding participants ≥30 g of alcohol/day increased HDL cholesterol[32] and insulin sensitivity.[33] However, HIV infection results in increased dyslipidemia and insulin resistance,[33] which may attenuate the positive effects of moderate alcohol consumption observed in the general population, and might explain the inconsistent association between alcohol consumption and MI in our study.

The findings of a moderate inverse or protective effect of alcohol on MI should be tempered with regard to health more generally. Studies examining the effects of alcohol on all types of CVD demonstrate heterogeneous effects,[12,14] where the risk of stroke and other cardiovascular events are increased by alcohol consumption, even though alcohol consumption appears protective for MI. While alcohol consumption may be associated with reduced risk of MI, it has also been associated with increased risk of renal damage,[34] cirrhosis,[35] cancer,,[13] and all-cause mortality.[36] Furthermore, alcohol consumption is the seventh leading cause of death worldwide.[37] While complete alcohol cessation has been recommended for PWH, this study suggests that smoking cessation and/or reduction might be a more important priority for long-term health outcomes over cessation of light/moderate alcohol use among PWH who do not have HCV infection or liver disease.

Our study had several limitations with respect to measurement of primary exposures and follow-up. While we collected robust measures on smoking behavior, passive exposure to cigarette smoke, which has been associated with increased risk for MI,[10] was not measured. If non-smoking participants had significant exposure to second-hand cigarette smoke, this could reduce the strength of the association between smoking and MI observed in our study. Additionally, while we used AUDIT-C as a robust measure of alcohol consumption, we did not measure whether alcohol

was paired with food, which has been shown to support insulin sensitivity,[38] a mechanism by which alcohol is thought to be protective against MI.[15] Additionally, we measured alcohol consumption over discrete time-periods rather than by daily journaling. While this has advantages for understanding overall impact, we could not examine the effect of alcohol consumption on the day of, or just before, an MI. Previous studies have shown increased risk of MI within a few hours after alcohol consumption.[29,30] Additionally, we did not examine modifications in associations between smoking and MI with respect to illicit substance use, as illicit substance use was not measured on the entire cohort. While there is significant interest regarding the impact of illicit substance use on MI by type, the focus of this study was to determine if the effects of alcohol and smoking on MI among PWH differed from the general population, where illicit substance use is not normally studied. While we had a sufficiently long median follow-up of 4 years, events and longitudinal follow-up continues to accrue, allowing greater opportunity to examine changes in alcohol use and smoking patterns in the future, as well as effects of illicit substance use.

Our study has several strengths. CNICS has a large demographically, clinically, and geographically diverse population. CNICS collects consistent, robust repeated measures on alcohol use, smoking, clinical laboratory assessments, and other health measures, which allowed for time varying assessment of important factors. The assessment of MI through our clinical adjudication process reduces the risk of misclassification of the outcome and allows for examination of risk by MI type. Our data collection and assessment processes also enhance completeness of data on all participants.

Among 13,506 PWH with repeated measures on smoking/alcohol consumption over ~4 years follow-up, we demonstrate that current cigarette smoking is associated

with a 1.6-fold increased risk of both T1MI and T2MI compared with non-smoking. Furthermore, 4% of this risk could be decreased for every cigarette/ day reduction; this had a greater impact on T1MI in men and T2MI in women. This study highlights the potential benefits of not only cessation, but also reducing number of cigarettes/ day even without achieving cessation, on CVD health among PWH, with potentially different impact on MI type between men and women.

Funding

This study was funded by the National Heart, Lung, and Blood Institute (NHLBI) R01 HL126538; the National Institute of Alcohol Abuse and Alcoholism (NIAAA) [U24AA020801, U01AA020793 and U01AA020802], the National Institute of Allergy and Infectious Diseases (NIAID) [CNICS R24 AI067039; UW CFAR NIAID Grant P30 AI027757; UAB CFAR grant P30 AI027767; UNC CFAR grant P30 AI050410; and JHU CFAR grant P30 AI094189], the National Institute on Drug Abuse (NIDA) [R01DA047045 and R01DA044112], and the National Institute on Aging (NIA) [R33AG067069].

Acknowledgements

We would like to thank our participants for their generosity in sharing their de-identified information to support research that can lead to better health outcomes for all people living with HIV. We would also like to thank all care providers, staff and researchers across CNICS for time and effort in supporting all CNICS activities, making this research possible.

References

1. Drozd DR, Kitahata MM, Althoff KN, et al. Increased risk of myocardial infarction in HIV-infected individuals in North America compared to the general population. *Journal of acquired immune deficiency syndromes (1999).* 2017;75(5):568.
2. Eyawo O, Brockman G, Goldsmith CH, et al. Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis. *BMJ open.* 2019;9(9):e025874.
3. Rosenson RS, Hubbard D, Monda KL, et al. Excess risk for atherosclerotic cardiovascular outcomes among US adults with HIV in the current era. *Journal of the American Heart Association.* 2020;9(1):e013744.
4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *European heart journal.* 2019;40(3):237-269.
5. Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. *Cardiovascular diagnosis and therapy.* 2017;7(4):348.
6. McCarthy CP, Kolte D, Kennedy KF, Vaduganathan M, Wasfy JH, Januzzi Jr JL. Patient characteristics and clinical outcomes of type 1 versus type 2 myocardial infarction. *Journal of the American College of Cardiology.* 2021;77(7):848-857.
7. Crane HM, Paramsothy P, Drozd DR, et al. Types of Myocardial Infarction Among Human Immunodeficiency Virus–Infected Individuals in the United States. *JAMA cardiology.* 2017;2(3):260-267.
8. Services UDoHaH. *The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA, USA2010.
9. Banks E, Joshy G, Korda RJ, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. *BMC medicine.* 2019;17(1):1-18.
10. Iversen B, Jacobsen BK, Løchen M-L. Active and passive smoking and the risk of myocardial infarction in 24,968 men and women during 11 year of follow-up: the Tromsø Study. *European journal of epidemiology.* 2013;28(8):659-667.
11. Jonsdottir LS, Sigfússon N, Gunason V, Sigvaldason H, Thorgeirsson G. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. *Journal of cardiovascular risk.* 2002;9(2):67-76.
12. Bell S, Daskalopoulou M, Rapsomaniki E, et al. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *bmj.* 2017;356.

13. Smyth A, Teo KK, Rangarajan S, et al. Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study. *The Lancet.* 2015;386(10007):1945-1954.
14. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *The Lancet.* 2018;391(10129):1513-1523.
15. Mukamal KJ, Jensen MK, Grønbæk M, et al. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation.* 2005;112(10):1406-1413.
16. Gémes K, Janszky I, Laugsand L, et al. Alcohol consumption is associated with a lower incidence of acute myocardial infarction: results from a large prospective population-based study in Norway. *Journal of internal medicine.* 2016;279(4):365-375.
17. Tavani A, Bertuzzi M, Negri E, Sorbara L, La Vecchia C. Alcohol, smoking, coffee and risk of non-fatal acute myocardial infarction in Italy. *European journal of epidemiology.* 2001;17(12):1131-1137.
18. Johnston PI, Wright SW, Orr M, et al. Worldwide relative smoking prevalence among people living with and without HIV. *AIDS.* 2021;35(6):957-970.
19. Duko B, Ayalew M, Ayano G. The prevalence of alcohol use disorders among people living with HIV/AIDS: a systematic review and meta-analysis. *Substance abuse treatment, prevention, and policy.* 2019;14(1):1-9.
20. Cropsey KL, Willig JH, Mugavero MJ, et al. Cigarette smokers are less likely to have undetectable viral loads: results from four HIV clinics. *Journal of addiction medicine.* 2016;10(1):13.
21. Vagenas P, Azar MM, Copenhaver MM, Springer SA, Molina PE, Altice FL. The impact of alcohol use and related disorders on the HIV continuum of care: a systematic review. *Current HIV/AIDS Reports.* 2015;12(4):421-436.
22. Williams EC, McGinnis KA, Edelman EJ, et al. Level of alcohol use associated with HIV care continuum targets in a national US sample of persons living with HIV receiving healthcare. *AIDS and Behavior.* 2019;23(1):140-151.
23. Kitahata MM, Rodriguez B, Haubrich R, et al. Cohort profile: the centers for AIDS research network of integrated clinical systems. *International journal of epidemiology.* 2008;37(5):948-955.
24. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Archives of internal medicine.* 1998;158(16):1789-1795.
25. Crane H, Heckbert S, Drozd D, et al. Lessons learned from the design and implementation of myocardial infarction adjudication tailored for HIV clinical cohorts. *American journal of epidemiology.* 2014;179(8):996-1005.
26. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *Bmj.* 1998;316(7137):1043.
27. Armani C, Landini Jr L, Leone A. Molecular and biochemical changes of the cardiovascular system due to smoking exposure. *Current pharmaceutical design.* 2009;15(10):1038-1053.
28. Hange D, Sigurdsson JA, Björkelund C, Sundh V, Bengtsson C. A 32-year longitudinal study of alcohol consumption in Swedish women: Reduced risk of myocardial infarction but increased risk of cancer. *Scandinavian journal of primary health care.* 2015;33(3):153-162.

29. Leong DP, Smyth A, Teo KK, et al. Patterns of alcohol consumption and myocardial infarction risk: observations from 52 countries in the INTERHEART case–control study. *Circulation.* 2014;130(5):390-398.
30. Mostofsky E, Chahal HS, Mukamal KJ, Rimm EB, Mittleman MA. Alcohol and immediate risk of cardiovascular events: a systematic review and dose–response meta-analysis. *Circulation.* 2016;133(10):979-987.
31. Mostofsky E, van der Bom JG, Mukamal KJ, et al. Risk of myocardial infarction immediately after alcohol consumption. *Epidemiology (Cambridge, Mass).* 2015;26(2):143.
32. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *Bmj.* 1999;319(7224):1523-1528.
33. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR. Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. *Jama.* 2002;287(19):2559-2562.
34. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, et al. High alcohol consumption and the risk of renal damage: a systematic review and meta-analysis. *QJM: An International Journal of Medicine.* 2015;108(7):539-548.
35. Jani BD, McQueenie R, Nicholl BI, et al. Association between patterns of alcohol consumption (beverage type, frequency and consumption with food) and risk of adverse health outcomes: a prospective cohort study. *BMC medicine.* 2021;19(1):1-14.
36. Rehm J, Gmel Sr GE, Gmel G, et al. The relationship between different dimensions of alcohol use and the burden of disease—an update. *Addiction.* 2017;112(6):968-1001.
37. Griswold MG, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet.* 2018;392(10152):1015-1035.
38. C ALGSTABCNEV. Alcohol consumption and acute myocardial infraction: a benefit of alcohol consumed with meals? *Epidemiology.* 2004;15(6):767-769.

Figure Legends

Figure 1: A: T1MI and B: T2MI free survival by daily, current cigarette use and age adjusted for number of cigarettes smoked per day for current smokers,

sex, race/ethnicity, HCV infection, HBV infection, dyslipidemia, treated hypertension, diabetes, severe chronic kidney disease and time updated viral load and CD4 count. Panel 1A shows that current smokers have a T1MI risk similar to that of a PWH a decade older, whereas the risk of T2MI is similar to that of someone even more than a decade older.

Figure 2: A: T1MI and B: T2MI free survival by sex and current daily cigarette use adjusted for age, race/ethnicity, HCV infection, HBV infection, dyslipidemia, treated hypertension, diabetes, severe chronic kidney disease and time updated viral load and CD4 count. Panel 2A highlights the impact of sex on T1MI, where male non-smokers had a similar risk to females who smoked more than a pack/ day, however, this observation was reversed for T2MI (panel 2B), where women had a significantly greater risk of T2MI than men.