Title

Cardiovascular Disease Risk Factor Control in People With and Without HIV.

Journal

Clinical Infectious Diseases, 78(5)

Authors

Silverberg, Michael
Levine, Tory
Lea, Alexandra
et al.

Publication Date

2024-05-15

DOI

10.1093/cid/ciad728

Peer reviewed

Clinical Infectious Diseases

MAJOR ARTICLE

Cardiovascular Disease Risk Factor Control in People With and Without HIV

Michael J. Silverberg,[1,©] Tory M. Levine,[1] Alexandra N. Lea,[1] Andrew E. Williams,[2] Stacey E. Alexeeff,[1] Kendall Bryant,[3] Matthias Cavassini,[4] Jason A. Flamm,[5] C. Bradley Hare,[6] Suzanne M. Ingle,[7] Amy C. Justice,[8] Jennifer O. Lam,[1] Stacy A. Sterling,[1] Michael A. Horberg,[9] and Derek D. Satre[1,10]

[1]Division of Research, Kaiser Permanente Northern California, Oakland, California, USA; [2]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts, USA; [3]National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland, USA; [4]Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; [5]Kaiser Permanente Sacramento Medical Center, Sacramento, California, USA; [6]Kaiser Permanente SanFrancisco Medical Center, San Francisco, California, USA; [7]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom; [8]VA Connecticut Healthcare System, Yale University Schools of Medicine and Public Health, New Haven, Connecticut, USA; [9]Kaiser Permanente Mid-Atlantic Permanente Research Institute, Rockville, Maryland, USA; and [10]Department of Psychiatry, Weill Institute for Neurosciences, University of California, SanFrancisco, California, USA

Background. Management of hypertension, dyslipidemia, diabetes and other modifiable factors may mitigate the cardiovascular disease (CVD) risk in people with human immunodeficiency virus (HIV, PWH) compared with people without HIV (PWoH).

Methods. This was a retrospective cohort study of 8285 PWH and 170 517 PWoH from an integrated health system. Risk factor control was measured using a novel disease management index (DMI) accounting for amount/duration above treatment goals (0% to 100% [perfect control]), including 2 DMIs for hypertension (diastolic and systolic blood pressure), 3 for dyslipidemia (low-density lipoprotein, total cholesterol, triglycerides), and 1 for diabetes (HbA1c). CVD risk by HIV status was evaluated overall and in subgroups defined by DMIs, smoking, alcohol use, and overweight/obesity in adjusted Cox proportional hazards models.

Results. PWH and PWoH had similar DMIs (80%–100%) except for triglycerides (worse for PWH) and HbA1c (better for PWH). In adjusted models, PWH had an elevated risk of CVD compared with PWoH (hazard ratio [HR], 1.18; 95% confidence interval [CI], 1.07–1.31). This association was attenuated in subgroups with controlled dyslipidemia and diabetes but remained elevated for PWH with controlled hypertension or higher total cholesterol. The strongest HIV status association with CVD was seen in the subgroup with frequent unhealthy alcohol use (HR, 2.13; 95% CI, 1.04–4.34).

Conclusions. Control of dyslipidemia and diabetes, but not hypertension, attenuated the HIV status association with CVD. The strong association of HIV and CVD with frequent unhealthy alcohol use suggests enhanced screening and treatment of alcohol problems in PWH is warranted.

Keywords. HIV; cardiovascular disease; hypertension; dyslipidemia; diabetes.

Despite therapeutic advances and better prevention, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in the United States [1]. People with human immunodeficiency virus (HIV, PWH) have consistently higher risks of acute myocardial infarction [2–4], stroke [5, 6], and heart failure [7–9] compared with people without HIV (PWoH). The etiology of CVD in PWH likely includes traditional CVD risk factors [10], HIV-specific inflammation and immunodeficiency [4, 11–13], and adverse effects of certain antiretroviral therapy (ART) medications [14–16].

This excess risk of CVD in PWH has existed for decades despite extensive research on prevalence, risk factors, and intervention strategies [10]. One possibility is that primary prevention of CVD, including control of lipids, hypertension, and diabetes, is more challenging in PWH. HIV providers may have less experience managing these conditions or have more competing priorities than primary care physicians [17]. It is also possible that current targets for hypertension, dyslipidemia, and diabetes may not have the same impact on outcomes among PWH. Finally, key CVD modifiable risk factors (eg, smoking, alcohol, obesity) might be more harmful for PWH than for PWoH.

Here, our overall study goal was to investigate reasons for the sustained higher risk of CVD among PWH. We address key knowledge gaps, including whether there are differences by HIV status in control of hypertension, dyslipidemia, and diabetes using a novel disease management index (DMI) [18] that incorporates how far and for how long someone is above clinical guideline targets and whether the CVD risk disparity for PWH vs PWoH is similar across subgroups defined by well-established modifiable CVD risk factors [19].

Received 02 November 2023; editorial decision 13 November 2023; published online 16 January 2024

Correspondence: M. J. Silverberg, Division of Research, Kaiser Permanente Northern California (KPNC), 4460 Hacienda Dr, Pleasanton, CA 94588 (Michael.J.Silverberg@kp.org); D. D. Satre, Department of Psychiatry and Behavioral Sciences, Weill Institute for Neurosciences, University of California, San Francisco, 675 18th Street, San Francisco, CA 94107 (derek.satre@ucsf.edu).

Clinical Infectious Diseases® 2024;78(5):1264–71

https://doi.org/10.1093/cid/ciad728

METHODS

Study Population and Design

The study setting was Kaiser Permanente Northern California (KPNC), a private, nonprofit integrated health system with more than 4.5 million members, with membership demographics similar to the Northern California population [20]. The source population consisted of an existing retrospective cohort study [21] of PWH and demographically matched PWoH designed to assess the health impacts of alcohol use and smoking in PWH. During rooming procedures for primary care visits, all adult KPNC members are routinely asked about current smoking and daily and weekly alcohol use based on National Institute on Alcohol Abuse and Alcoholism screening recommendations [22]. The source cohort study included 11 380 PWH (aged ≥18 years) who were KPNC members between 1 July 2013 (roll-out of routine alcohol use screening at KPNC) and 31 December 2017. The comparison group included 227 600 PWoH frequency-matched 20:1 to PWH by age, sex, race/ethnicity, and baseline year. The final study population excluded those from the source cohort study with no alcohol use screening results (n = 2276 PWH, n = 42 228 PWoH) and those with a prior history of coronary heart disease or ischemic stroke (n = 674 PWH, n = 14 575 PWoH), resulting in 8285 PWH and 170 517 PWoH. Baseline was defined as the first of the month following the earliest date on which participants met eligibility, including date of first alcohol screen, HIV date (for PWH only), start of KPNC enrollment, and eighteenth birthday. PWH were followed from baseline until CVD or censored due to death, loss to follow-up, or administrative end of study.

Data Sources and Measurements

The primary data sources were the KPNC HIV registry and electronic health record (EHR). The KPNC HIV registry maintains a database of all HIV patients, with HIV status confirmed by manual chart review. EHR databases capture diagnoses, laboratory tests, and pharmacy fills. Primary outcomes were inpatient or outpatient CVD diagnoses, including coronary heart disease and ischemic stroke. Comorbidities evaluated were hypertension (≥2 outpatient diagnoses or 1 outpatient diagnosis and hypertension medications filled), dyslipidemia (elevated low-density lipoprotein [LDL] >130 mg/dL or total cholesterol >240 mg/dL), or diabetes mellitus (inclusion in the KPNC Diabetes Registry [23]).

We computed 6 DMIs [18], including 2 for those with hypertension (diastolic blood pressure [DBP] and systolic blood pressure [SBP]), 3 for those with dyslipidemia (LDL, total cholesterol, and triglycerides), and 1 for those with diabetes (HbA1c). The DMI measures how effectively a condition is managed over time, similar to the concept of cigarette pack-years, with details regarding its calculation provided in the Supplementary Appendix. Briefly, among those with a history of the condition, the DMI simultaneously quantifies both the duration and the extent of a patient's deviation from a guideline-based threshold. We chose clinical targets in use during the study period as follows: DBP <90 mmHg and SBP <140 mmHg [24]; <200 mg/dL, <130 mg/dL, and <150 mg/dL for total cholesterol, LDL cholesterol, and triglycerides [25]; and <48 mmol/mol (ie, 6.5%) for HbA1c [26]. All DMIs were computed for 6-month intervals, with carry forward for 1 year for blood pressure and HbA1c and 2 years for lipids. The DMI is computed as 1 minus the ratio of the amount and duration out of control divided by the total days during the defined interval of interest, with a range from 0% (no control) to 100% (complete control).

Additional CVD risk factors of interest were unhealthy alcohol use, smoking (current or noncurrent), and overweight/obesity (ie, body mass index ≥25 kg/m^2). Unhealthy alcohol use was defined as reporting either any heavy drinking days (4+/5+ drinks for females and males aged >65 years and males aged ≤65 years) or reporting an average 8+/15+ drinks in a week in the last 90 days [22]. We categorized alcohol use as none, moderate (any use not meeting unhealthy definition), infrequent heavy alcohol use (<5 days in last 90 days with 4+/5+ drinks), and frequent heavy alcohol use (5 or more days in last 90 days with 4+/5+ drinks) [21]. Other baseline covariates included age, sex, race/ethnicity, alcohol use disorder diagnosis (ever prior), depression diagnoses (ever prior), neighborhood deprivation index (NDI) score (based on recent address) [27], number of outpatient visits (in prior year), HIV transmission risk factor, CD4+ T-cell count (most recent in prior year), HIV RNA levels (most recent in prior year), and prior clinical AIDS (ever prior).

Statistical Analyses

Our first objective was to evaluate differences by HIV status in control of hypertension, dyslipidemia, and diabetes. As detailed in the Supplementary Appendix, among those with a history of hypertension, dyslipidemia, and diabetes, we measured DMIs over 6-month intervals (participants could contribute up to 9 observations throughout follow-up). First, we analyzed DMI as a continuous outcome. To account for multiple observations contributed per participant, we used generalized estimating equation regression models with the identity link and a working covariance structure to estimate differences in mean DMI by HIV status. Models adjusted for age, sex, race/ethnicity, NDI, insurance status, depression, overweight/obesity, alcohol use disorder, unhealthy alcohol use, and smoking. Next, we analyzed DMIs as a dichotomous outcome using a DMI cutoff of ≤80% (ie, above guideline cutoffs for 20% or more of days during interval was considered out of control). We computed adjusted prevalence ratios (PRs) by fitting modified Poisson regression models with a log link and robust standard errors [28], with adjustment for the same covariates as above.

Our second objective was to assess differences in risk of CVD by HIV status. We report hazard ratios (HRs) from a series of 3 Cox proportional hazards models, using time from baseline as the time scale. Our first set of analyses estimated the HR for overall association of HIV status on risk of coronary heart disease, ischemic stroke, or the composite outcome of CVD (first occurrence of each outcome analyzed separately). Adjusted models included HIV status, age, sex, race/ethnicity, NDI, insurance status, depression, overweight/obesity, alcohol use disorder, alcohol use, smoking, hypertension, dyslipidemia, and diabetes. We performed a sensitivity analysis for the overall association of HIV status on CVD risk that consisted of complete case analyses excluding those with missing baseline data. In our second set of analyses, we estimated the HR for HIV status on risk of CVD within subgroups defined by level of control of hypertension, dyslipidemia, and diabetes. As detailed in the Supplementary Appendix, we estimated the associations of HIV status with CVD among those without the condition, among those with the condition but in control (ie, DMI >80%), and among those with the condition but out of control (ie, DMI ≤80%). Finally, the third set of Cox models estimated the HR for the association of HIV status on CVD risk within subgroups defined by alcohol use, smoking, and overweight/obesity.

Analyses were performed with SAS (Version 9.4; Cary, NC). The study was approved by the KPNC Institutional Review Board, including waivers of written informed consent.

RESULTS

As shown in Table 1, there were 8285 PWH and 170 517 PWoH. These groups were similar with respect to age (mean, 47 years for PWH and 48 years for PWoH), sex (91% males among PWH and 90% among PWoH), and race/ethnicity (45% race/ethnicities other than White non-Hispanic among PWH and 46% among PWoH), which were matching variables in the source cohort study. Other notable baseline differences included a greater number of outpatient visits and higher prevalence of depression, alcohol use disorders, and current smoking among PWH and greater prevalence of overweight/obesity in PWoH. PWH were generally well treated, with 79% on ART at baseline and 74% with undetectable HIV RNA levels, with a mean 651 CD4 T cells/μL.

Table 1. Baseline Characteristics

Characteristic	People With Human Immunodeficiency Virus (n = 8285)	People Without Human Immunodeficiency Virus (n = 170 517)
Mean age, (SD), y	47.2 (12.0)	48.0 (13.0)
Males, N (%)	7549 (91.1)	153 482 (90.0)
Race/ethnicity, N (%)[a]		
Black, non-Hispanic	1243 (15.6)	28 356 (16.9)
Hispanic	1504 (18.9)	31 206 (18.6)
White, non-Hispanic	4400 (55.2)	90 910 (54.3)
Other, non-Hispanic	822 (10.3)	17 022 (10.2)
N missing	316	3023
Neighborhood deprivation index quartile, N (%)[a]		
1 (least deprived)	2413 (29.2)	39 904 (23.5)
2	1655 (20.1)	41 440 (24.4)
3	1863 (22.6)	42 858 (25.2)
4 (most deprived)	2322 (28.1)	45 842 (27.0)
N missing	32	473
Insurance, N (%)		
Commercial	6589 (79.5)	146 340 (85.8)
Medicare	1380 (16.7)	19 013 (11.2)
Medicaid	213 (2.6)	3570 (2.1)
Other	103 (1.2)	1594 (0.9)
Depression, N (%)	2608 (31.5)	20 986 (12.3)
Overweight/Obese, N (%)[a]	4842 (59.4)	130 151 (78.0)
N missing	127	3725
Mean outpatient visits (SD)	14.2 (17.9)	7.3 (10.6)
Alcohol use disorder, %	871 (10.5)	11 821 (6.9)
Alcohol use, %		
Abstained	4705 (56.8)	85 177 (50.0)
Moderate	2719 (32.8)	62 611 (36.7)
Unhealthy (infrequent)	594 (7.2)	15 178 (8.9)
Unhealthy (frequent)	267 (3.2)	7551 (4.4)
Current smoker, N (%)	898 (10.8)	14 788 (8.7)
Hypertension, dyslipidemia, or diabetes history, N (%)	4139 (50.0)	88 568 (51.9)
Hypertension	1606 (19.4)	39 505 (23.2)
Dyslipidemia	3415 (41.2)	70 551 (41.4)
Diabetes	641 (7.7)	16 700 (9.8)

All comparisons are statistically significant ($P < .05$) except dyslipidemia.

Abbreviation: SD, standard deviation.

[a]Percentages based on those with nonmissing values.

Control of Hypertension, Dyslipidemia, and Diabetes

Blood pressure, cholesterol, and HbA1c raw results were similar by HIV status (Figure 1), and average adjusted DMIs indicated a high level of control, with most DMIs >80%. Adjusted DMIs were generally similar by HIV status, except for reduced control of triglycerides for PWH and better control of HbA1c. Similar to continuous DMI results, the largest differences with dichotomous measures were noted for triglycerides and HbA1c, with a higher percentage with inadequate control among PWH for triglycerides (33% vs 23%; adjusted PR, 1.52; 95% CI, 1.45–1.59) but lower for HbA1c (42% vs 54%; adjusted PR, 0.80; 95% CI, .75–.86; Table 2).

Association of HIV Status With Risk of CVD Overall

PWH experienced 450 CVD events (215, coronary heart disease; 246, ischemic stroke) with an 8.0% 4-year cumulative risk; PWoH experienced 7648 CVD events (3754, coronary heart disease and 4058, ischemic stroke) with a 6.8% cumulative risk. The adjusted HR for CVD comparing PWH and PWoH (reference) was 1.18 (95% CI, 1.07–1.31). HRs were similar in magnitude for coronary heart disease with an adjusted HR of 1.19 (95% CI, 1.08–1.32) and ischemic stroke with an HR of

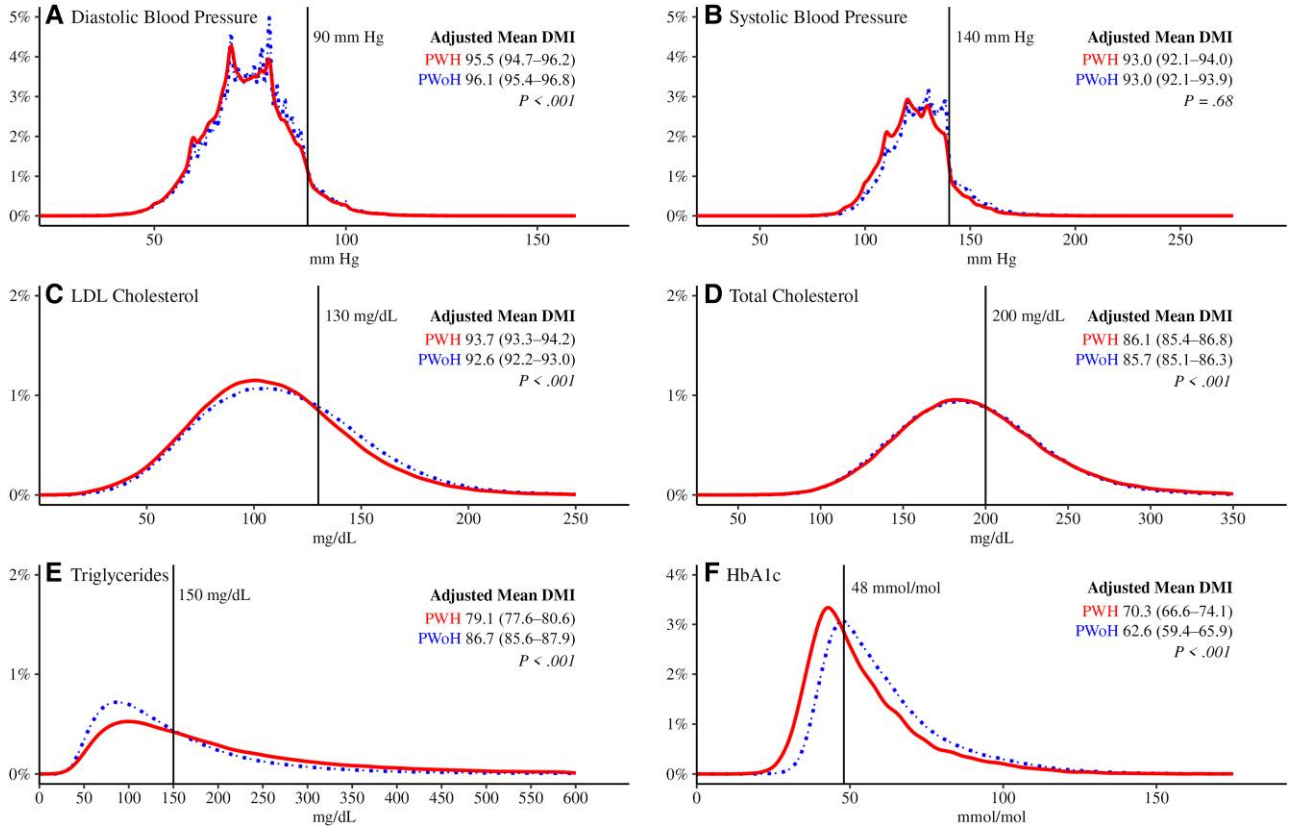

Figure 1. Cardiovascular disease management indices by human immunodeficiency virus (HIV) status. Plots depict crude results of 6 clinical measures by HIV status including diastolic blood pressure (*A*), systolic blood pressure (*B*), LDL cholesterol (*C*), total cholesterol (*D*), triglycerides (*E*), and HbA1c *(F).* Solid line plots are results for PWH, and dotted plots are results for PWoH. For each measure, we also present the adjusted mean DMIs and 95% confidence intervals by HIV status, which were obtained from generalized estimating equation models with adjustment for age, sex, race/ethnicity, neighborhood deprivation index, insurance status, depression, overweight/obesity, alcohol use disorder, unhealthy alcohol use, and smoking. *P* values indicate differences in DMIs by HIV status. Abbreviations: DMI, disease management index; HbA1c, hemoglobin A1C; LDL, low-density lipoprotein; PWH, people with human immunodeficiency virus; PWoH, people without human immunodeficiency virus.

1.22 (95% CI, 1.11–1.34). Thus, subsequent analyses only evaluated overall CVD. A complete-case sensitivity analysis excluding those with missing baseline data had minimal effect, with a corresponding adjusted HR of 1.18 (95% CI, 1.07–1.30) for association of HIV status with CVD.

Association of HIV Status With Risk of CVD by Level of Control of Hypertension, Dyslipidemia, and Diabetes

The association of HIV status and CVD remained among those with no history of the condition, ranging from 1.19 (95% CI, 1.04–1.37; Figure 2*A*) for those without hypertension to 1.25 (95% CI, 1.07–1.46; Figure 2*E*) for those without dyslipidemia. Among those with hypertension, the elevated risk of CVD remained for those with 100% control for SBP (HR, 1.24; 95% CI, 1.08–1.43; Figure 2*A*) and 100% control for DBP (HR, 1.19; 95% CI, 1.04–1.37; Figure 2*B*). In contrast, the associations with HIV status were attenuated and nonsignificant for those with 100% control of LDL (Figure 2*C*), total cholesterol (Figure 2*D*), triglycerides (Figure 2*E*), and HbA1c (Figure 2*F*). For most conditions, there was no association between HIV status and CVD for those with inadequate control (ie, DMI, 80%). One exception was for total cholesterol with 80% control (HR, 1.22; 95% CI, 1.03–1.44; Figure 2*D*), with similar magnitude (although not significant) for those with 80% LDL control (HR, 1.25; 95% CI, .92–1.69; Figure 2*C*).

Association of HIV Status With Risk of CVD by Alcohol Use, Smoking, and Obesity

Several CVD-related health factors appeared to modify the association of HIV status with CVD risk (Table 3). We noted an HIV status association in subgroups that reported no alcohol use (adjusted HR, 1.22; 95% CI, 1.09–1.38) and for those who reported frequent unhealthy alcohol use (adjusted HR, 2.13; 95% CI, 1.04–4.34), but no difference by HIV status for moderate use or infrequent unhealthy alcohol use. We found an increased CVD risk for PWH among nonsmokers (adjusted HR, 1.21; 95% CI, 1.09–1.34) but not among smokers. Finally, we noted an increased CVD risk for PWH among those who were not overweight/obese (adjusted HR, 1.32; 95% CI, 1.14–1.53) but not among those who were overweight/obese.

Table 2. Cardiovascular Disease Risk Factor Control by Human Immunodeficiency Virus Status

Clinical Measure	% Inadequate Control[a]	Adjusted Prevalence Ratio (95% Confidence Interval)[b]
Diastolic blood pressure		
PWH	3.8	1.38 (1.20–1.58)
PWoH (reference)	3.3	1
Systolic blood pressure		
PWH	6.9	0.98 (.89–1.09)
PWoH (reference)	7.5	1
Low-density lipoprotein cholesterol		
PWH	4.6	0.70 (.62–.78)
PWoH (reference)	7.4	1
Total cholesterol		
PWH	15.3	0.94 (.88–1.00)
PWoH (reference)	17.9	1
Triglycerides		
PWH	33.0	1.52 (1.45–1.59)
PWoH (reference)	22.7	1
Hemoglobin A1C		
PWH	41.9	0.80 (.75–.86)
PWoH (reference)	54.2	1

Abbreviations: PWH, people with human immunodeficiency virus; PWoH, people without human immunodeficiency virus.

[a]Disease management index ≤80% during 6-month intervals.

[b]Adjusted prevalence ratio from Poisson regression models with robust standard errors, with adjustment for age, sex, race/ethnicity, neighborhood deprivation index, insurance status, depression, overweight/obesity, alcohol use disorder, unhealthy alcohol use, and smoking.

DISCUSSION

In this large, diverse cohort of PWH and PWoH identified from the same health system, we noted generally excellent and similar levels of control of dyslipidemia, hypertension, and diabetes by HIV status. Overall, we found a 20% increased risk of CVD for PWH compared with PWoH that were independent of clinical and behavioral CVD risk factors. However, the CVD disparity varied across key risk groups. First, the HIV status association with CVD was attenuated among those with successful control of dyslipidemia and diabetes but not hypertension. The HIV status association with CVD also remained among those with inadequately controlled dyslipidemia. Notably, the higher risk of CVD for PWH compared with PWoH was sustained in subgroups without a history of unhealthy alcohol use, smoking, or overweight/obesity. Finally, we found that PWH who reported frequent heavy alcohol use endured a 218% higher risk of CVD compared with PWoH.

Others have compared cardiovascular risk scores (eg, Framingham or American College of Cardiology/American Heart Association [ACC/AHA] CVD risk scores) by HIV status, which incorporate cholesterol and blood pressure, including a Swiss HIV cohort study and a prior KPNC study that indicated better scores for PWH compared with the general population [29, 30]. Similar to our study, an analysis in the Veterans Administration (VA) noted better control of diabetes in PWH compared with PWoH [31]. Differences in risk factor control by HIV status may be explained by use and adherence of CVD medications. Regarding statins, a clinic-based study noted greater use for PWH [32], while a large outpatient survey found reduced statin use for PWH compared with PWoH with a statin indication [33]. A large outpatient survey also noted no differences by HIV status in use of hypertensive medications [33].

Similar to prior studies, we noted an increased risk of CVD in PWH compared with PWoH that was independent of behavioral and clinical risk factors [2–9]. However, the key contribution here is the evaluation of the variability of the HIV status disparity across key subgroups. First, we noted an attenuation of the HIV status association among those with a history of dyslipidemia or diabetes with 100% control. However, the higher CVD risk for PWH remained for those with 100% control of SBP or DBP. PWH with cholesterol that was inadequately controlled also had a higher CVD risk compared with PWoH. These findings together suggest that more aggressive clinical targets for dyslipidemia and hypertension may be needed for PWH. Regarding lipids, the landmark Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) [34] confirmed that statin use among PWH with low to moderate CVD risk significantly reduced the risk of major adverse cardiovascular events compared with placebo. In light of our findings, similar studies are warranted for hypertension.

Another important finding was that higher risk of CVD in PWH compared with PWoH was sustained among those without a history of hypertension, dyslipidemia, diabetes, smoking, and alcohol use. A VA study similarly found a higher risk of CVD for PWH compared with PWoH only in the subset with no reported alcohol use, smoking, and depression [35]. The higher rate of CVD for PWH compared with PWoH in those without these risk factors may indicate the importance of HIV-specific risk factors in the etiology of CVD in PWH, including adverse impacts of immunosuppression and/or HIV-induced inflammation, as supported by findings from our prior research [4, 6] and others [11–13].

In contrast, the higher risk of CVD for PWH compared with PWoH was attenuated in subgroups with specific risk factors, including those who reported smoking; those who were overweight/obese; and those with inadequate control of hypertension, triglycerides, and diabetes. One possible explanation of these findings is that there is a higher overall risk of CVD in those subgroups; thus, HIV-specific risk factors (ie, immunosuppression and inflammation) may only have marginal effects. However, a notable exception to this pattern was the >200% higher risk of CVD for PWH compared with PWoH with frequent unhealthy alcohol use. Similarly, a VA study found that alcohol was more strongly associated with prevalent CVD in PWH compared with PWoH [36]. The Multicenter AIDS Cohort Study also noted that heavy alcohol use was associated

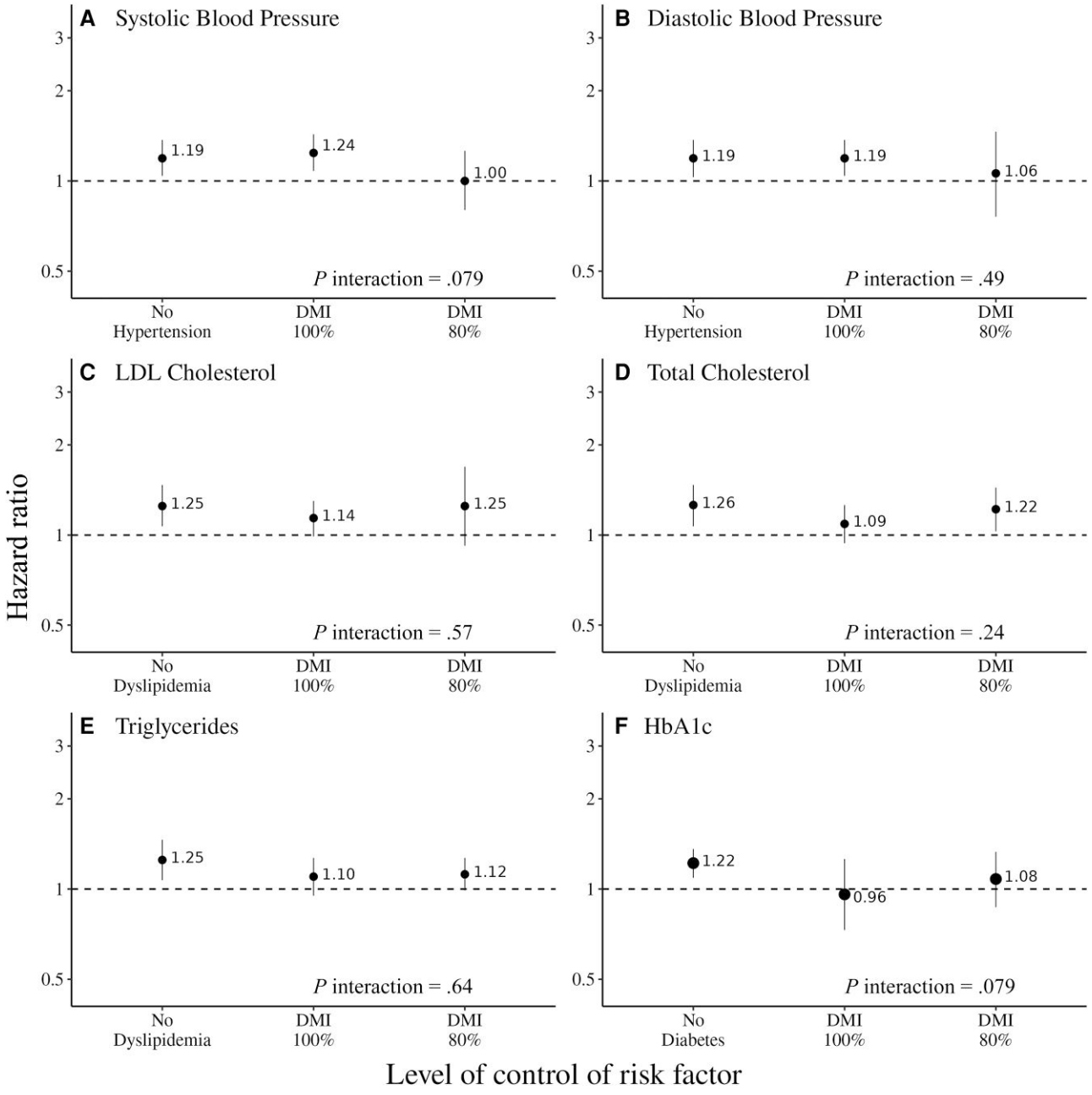

Figure 2. Association of human immunodeficiency virus (HIV) status and cardiovascular disease (CVD) by control of hypertension, dyslipidemia, and diabetes. Hazard ratios (HRs) and 95% confidence intervals (depicted by vertical lines) for association of HIV status (people without human immunodeficiency virus as reference) with CVD for those without a condition of interest (ie, hypertension, dyslipidemia, and diabetes), and among those with the condition by level of control (ie, DMI 100% and DMI 80%). Six separate models were constructed corresponding with management of systolic blood pressure (SBP) (*A*), diastolic blood pressure (*B*), LDL cholesterol (*C*), total cholesterol (*D*), triglycerides (*E*), and HbA1c (*F*). HRs were from Cox proportional hazards models with terms for HIV status, age, sex, race/ethnicity, neighborhood deprivation index, insurance status, depression, overweight/obesity, alcohol use disorder, alcohol use, smoking, and indicators for hypertension, dyslipidemia, and diabetes. In addition, for each of 6 the models, we included the following terms (using systolic blood pressure as an example): a term for the corresponding DMIs (eg, systolic blood pressure DMI); interaction term for HIV status × diseases of interest (eg, hypertension); and interaction term for HIV status*DMI (eg, HIV status*systolic blood pressure DMI). Each panel depicts 3 HRs for association of HIV status with CVD in 3 groups (eg, no hypertension history; 100% DMI for SBP; 80% DMI for SBP). Abbreviations: DMI, disease management index; HbA1c, hemoglobin A1C; LDL, low-density lipoprotein.

with coronary artery plaque among PWH only, while low to moderate alcohol use was protective in PWoH only [37]. These findings suggest that alcohol use may be particularly harmful for PWH.

Key strengths of the study include examination of a large cohort of PWH and demographically similar PWoH from the same health system, comprehensive and highly accurate ascertainment of HIV status and CVD, and use of the novel

Table 3. Association of Human Immunodeficiency Virus Status and Cardiovascular Disease by Alcohol, Smoking, and Body Mass Index Subgroups

	Unadjusted		Adjusted	
Subgroup	HR[a] (95% CI)	*P* Interaction	HR[a] (95% CI)	*P* Interaction
Alcohol use subgroups	…	.12	…	.18
Abstain	1.27 (1.14–1.43)	…	1.22 (1.09–1.38)	…
Moderate	1.01 (.84–1.23)	…	1.03 (.85–1.26)	…
Unhealthy (infrequent)	0.98 (.60–1.59)	…	1.26 (.77–2.04)	…
Unhealthy (frequent)	1.77 (.87–3.62)	…	2.13 (1.04–4.34)	…
Smoking subgroups	…	.83	…	.12
No current	1.23 (1.11–1.35)	…	1.21 (1.09–1.34)	…
Current	1.18 (.84–1.65)	…	0.92 (.65–1.29)	…
Body mass index subgroups	…	.24	…	.18
Not overweight/obese	1.34 (1.16–1.56)	…	1.32 (1.14–1.53)	…
Overweight/obese	1.14 (1.00–1.29)	…	1.10 (.97–1.25)	…

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Hazard ratios from Cox proportional hazards models for association of human immunodeficiency virus (HIV) status (people without HIV reference) and cardiovascular disease. Adjusted models include terms for age, sex, race/ethnicity, neighborhood deprivation index, insurance status, depression, overweight/obesity, alcohol use disorder, alcohol use, smoking, prior hypertension, dyslipidemia, and diabetes, and interaction terms for HIV status and each of the 3 health factors (alcohol use, smoking, body mass index).

index for measuring risk factor control. There are several study limitations. First, there is likely unmeasured confounding for factors not routinely collected in the her, such as diet, exercise, and family history of CVD, and residual confounding for measured factors, such as smoking, which was measured as current or noncurrent. However, any misclassification is likely nondifferential by HIV status. There may be limited generalizability to some PWH including the uninsured, women, and transgender people for whom sex-based alcohol screening methods may be inadequate [38]. Nevertheless, the closed system of KPNC ensured internal validity, and the source of insurance was diverse with >20% public sources (ie, Medicare, Medicaid) [39].

In summary, we found that PWH engaged in care had excellent control of hypertension, dyslipidemia, and diabetes. Yet, PWH had a sustained higher risk of CVD compared with PWoH, including among those without a history of established CVD risk factors. Results also indicated that while effective control of dyslipidemia and diabetes may help reduce the CVD disparity in PWH, elevated CVD risks are concerning despite well-controlled hypertension. PWH with elevated cholesterol were also at greater CVD risk. Future research is needed to assess benefits and harms of more aggressive hypertension targets (eg, 130/80 mm Hg per recent ACC/AHA guidelines [40]) for PWH. The REPREIVE trial [34] has also confirmed PWH as a high-risk group who benefit from statin therapy at lower thresholds. Finally, a striking finding was the 218% higher risk of CVD among PWH reporting frequent unhealthy alcohol use. This warrants additional research on enhanced alcohol screening and interventions for PWH with frequent unhealthy alcohol use who have rarely been studied in order to prevent CVD and other adverse alcohol consequences.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. Study conception and design: M. J. S., D. D. S.; secured funding: M. J. S., D. D. S.; biostatistical guidance: S. E. A.; data collection: T. M. L.; data analysis: T. M. L.; drafting of the manuscript: M. J. S. All authors contributed to review and interpretation of results, critical revisions of the draft manuscript, and approval of the final version of the manuscript.

Financial support. This work was supported by grants from the National Institute on Alcohol Abuse and Alcoholism (U01 AA026230 to D. D. S. and M. J. S.; U01-AA026209 to S. M. I.; U01-AA026224 to A. C. J.; and K24AA025703 to D. D. S.) and the National Institute of Allergy and Infectious Diseases (K01 AI157849 to J. O. L.).

Potential conflicts of interest. M. C. reports research grants from Gilead, MSD, and ViiV (paid to institution); payment for expert testimony from Gilead, MSD, and ViiV Healthcare (paid to institution); and support for attending meetings and/or travel from Gilead (paid to institution). C. B. H. reports grants or contracts from Gilead (payments to institution for unrelated research). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. Circulation **2022**; 145:e153–639.
2. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med **2013**; 173:614–22.
3. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab **2007**; 92:2506–12.
4. Silverberg MJ, Leyden WA, Xu L, et al. Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. J Acquir Immune Defic Syndr **2014**; 65:160–6.
5. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. J Acquir Immune Defic Syndr **2012**; 60:351–8.

6. Marcus JL, Leyden WA, Chao CR, et al. HIV infection and incidence of ischemic stroke. AIDS **2014**; 28:1911–9.
7. Butt AA, Chang CC, Kuller L, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. Arch Intern Med **2011**; 171:737–43.
8. Freiberg MS, Chang CH, Skanderson M, et al. Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: results from the Veterans Aging Cohort Study. JAMA Cardiol **2017**; 2:536–46.
9. Go AS, Reynolds K, Avula HR, et al. Human immunodeficiency virus infection and variation in heart failure risk by age, sex, and ethnicity: the HIV HEART Study. Mayo Clin Proc **2022**; 97:465–79.
10. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. Circulation **2019**; 140:e98–e124.
11. Lang S, Mary-Krause M, Simon A, et al. HIV replication and immune status are independent predictors of the risk of myocardial infarction in HIV-infected individuals. Clin Infect Dis **2012**; 55:600–7.
12. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. Clin Infect Dis **2010**; 51:435–47.
13. Triant VA, Regan S, Lee H, Sax PE, Meigs JB, Grinspoon SK. Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system. J Acquir Immune Defic Syndr **2010**; 55:615–9.
14. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. J Infect Dis **2010**; 201:318–30.
15. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. HIV Med **2010**; 11:130–6.
16. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med **2007**; 356:1723–35.
17. Fultz SL, Goulet JL, Weissman S, et al. Differences between infectious diseases-certified physicians and general medicine-certified physicians in the level of comfort with providing primary care to patients. Clin Infect Dis **2005**; 41:738–43.
18. Williams A, Vogt T. Using IT to improve the quality of cardiovascular disease (CVD) prevention and management—final report. Prepared by the Kaiser Permanente Center for Health Research, Hawaii under Grant No. R18 HS017016. Available at: https://healthit.ahrq.gov/sites/default/files/docs/publication/r18hs017016-williams-final-report-2010.pdf. Accessed 20 October 2023.
19. Centers for Disease Control and Prevention. Prevent heart disease. Available at: https://www.cdc.gov/heartdisease/prevention.htm. Accessed 13 October 2023.
20. Gordon NP. Similarity of adult Kaiser Permanente members to the adult population in Kaiser Permanente's Northern California service area: comparisons based on the 2017/2018 cycle of the California Health Interview Survey. Available at: https://memberhealthsurvey.kaiser.org/Documents/compare_kp_ncal_chis2017-18.pdf. Accessed 26 December 2020.
21. Silverberg MJ, Levine-Hall T, Hood N, et al. Health system-based unhealthy alcohol use screening and treatment comparing demographically matched participants with and without HIV. Alcohol Clin Exp Res **2020**; 44:2545–54.
22. National Institute on Alcohol Abuse and Alcoholism. The healthcare professional's core resource on alcohol. Knowledge. Impacts. Strategies. Available at: https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol/basics-defining-how-much-alcohol-too-much. Accessed 13 October 2023.
23. Ahmed AT, Karter AJ, Warton EM, Doan JU, Weisner CM. The relationship between alcohol consumption and glycemic control among patients with diabetes: the Kaiser Permanente Northern California Diabetes Registry. J Gen Intern Med **2008**; 23:275–82.
24. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension **2003**; 42:1206–52.
25. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation **2002**; 106:3143–421.
26. Qaseem A, Wilt TJ, Kansagara D, et al. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. Ann Intern Med **2018**; 168:569–76.
27. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. J Urban Health **2006**; 83:1041–62.
28. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. Stat Methods Med Res **2013**; 22: 661–70.
29. Delabays B, Cavassini M, Damas J, et al. Cardiovascular risk assessment in people living with HIV compared to the general population. Eur J Prev Cardiol **2022**; 29: 689–99.
30. Klein DB, Leyden WA, Xu L, et al. Declining relative risk for myocardial infarction among HIV-positive compared with HIV-negative individuals with access to care. Clin Infect Dis **2015**; 60:1278–80.
31. Herrin M, Tate JP, Akgun KM, et al. Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals. J Acquir Immune Defic Syndr **2016**; 73:228–36.
32. Riestenberg RA, Furman A, Cowen A, et al. Differences in statin utilization and lipid lowering by race, ethnicity, and HIV status in a real-world cohort of persons with human immunodeficiency virus and uninfected persons. Am Heart J **2019**; 209:79–87.
33. Ladapo JA, Richards AK, DeWitt CM, et al. Disparities in the quality of cardiovascular care between HIV-infected versus HIV-uninfected adults in the United States: a cross-sectional study. J Am Heart Assoc **2017**; 6:e007107.
34. Grinspoon SK, Fitch KV, Zanni MV, et al. Pitavastatin to prevent cardiovascular disease in HIV infection. N Engl J Med **2023**; 389:687–99.
35. Chichetto NE, Kundu S, Freiberg MS, et al. Association of syndemic unhealthy alcohol use, smoking, and depressive symptoms on incident cardiovascular disease among veterans with and without HIV-infection. AIDS Behav **2021**; 25: 2852–62.
36. Freiberg MS, McGinnis KA, Kraemer K, et al. The association between alcohol consumption and prevalent cardiovascular diseases among HIV-infected and HIV-uninfected men. J Acquir Immune Defic Syndr **2010**; 53:247–53.
37. Kelly SG, Plankey M, Post WS, et al. Associations between tobacco, alcohol, and drug use with coronary artery plaque among HIV-infected and uninfected men in the multicenter AIDS cohort study. PLoS One **2016**; 11:e0147822.
38. Flentje A, Barger BT, Capriotti MR, et al. Screening gender minority people for harmful alcohol use. PLoS One **2020**; 15:e0231022.
39. Satre DD, Parthasarathy S, Altschuler A, Silverberg MJ, Storholm E, Campbell CI. Demographic, insurance, and health characteristics of newly enrolled HIV-positive patients after implementation of the Affordable Care Act in California. Am J Public Health **2016**; 106:1211–3.
40. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation **2018**; 138: e426–e83.