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ORIGINAL RESEARCH

Evaluating the Cardiovascular Risk in an Aging Population of People With HIV: The Impact of Hepatitis C Virus Coinfection

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BACKGROUND: People with HIV (PWH) are at an increased risk of cardiovascular disease (CVD) with an unknown added impact of hepatitis C virus (HCV) coinfection. We aimed to identify whether HCV coinfection increases the risk of type 1 myocardial infarction (T1MI) and if the risk differs by age.

METHODS AND RESULTS: We used data from NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) from January 1, 2000, to December 31, 2017, PWH (aged 40–79 years) who had initiated antiretroviral therapy. The primary outcome was an adjudicated T1MI event. Those who started direct-acting HCV antivirals were censored at the time of initiation. Crude incidence rates per 1000 person-years were calculated for T1MI by calendar time. Discrete time-to-event analyses with complementary log–log models were used to estimate adjusted hazard ratios and 95% CIs for T1MI among those with and without HCV. Among 23 361 PWH, 4677 (20%) had HCV. There were 89 (1.9%) T1MIs among PWH with HCV and 314 (1.7%) among PWH without HCV. HCV was not associated with increased T1MI risk in PWH (adjusted hazard ratio, 0.98 [95% CI, 0.74–1.30]). However, the risk of T1MI increased with age and was amplified in those with HCV (adjusted hazard ratio per 10-year increase in age, 1.85 [95% CI, 1.38–2.48]) compared with those without HCV (adjusted hazard ratio per 10-year increase in age,1.30 [95% CI, 1.13–1.50]; *P*<0.001, test of interaction).

CONCLUSIONS: HCV coinfection was not significantly associated with increased T1MI risk; however, the risk of T1MI with increasing age was greater in those with HCV compared with those without, and HCV status should be considered when assessing CVD risk in aging PWH.

Key Words: cardiovascular disease ■ coinfection ■ hepatitis C virus ■ HIV ■ myocardial infarction

Despite significant advancements in HIV therapeutics, people with HIV (PWH) experience higher rates of cardiovascular disease (CVD).[1] Studies in different regions have documented ≈50% to 75% increased risk of CVD compared with people without HIV.[2–5] The risk of CVD among people with hepatitis C virus (HCV) infection alone is not as consistent, with some studies demonstrating increased risk[6–10] and others showing no association.[11,12] Because of shared transmission routes, HIV/HCV coinfection is common (10%–30%) globally.[13] Less is known about CVD risk among PWH with HCV, particularly within an aging population on contemporary antiretroviral therapy (ART).[14,15]

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CLINICAL PERSPECTIVE

What Is New?

- People with HIV (PWH) are at an increased risk of cardiovascular disease; however, the added impact of hepatitis C virus (HCV) coinfection was largely unknown.
- HCV coinfection among PWH was not associated with increased type 1 myocardial infarction (T1MI) risk among PWH aged 40 to 79 years from North America who had initiated antiretroviral therapy; however, the risk of T1MI with increasing age was greater in those with HCV compared with those without HCV.
- Traditional CVD risk factors were associated with T1MI among PWH, but HIV-associated risk factors also contribute, including low CD4 count, history of AIDS-defining illness, and protease inhibitor use.

What Are the Clinical Implications?

- Aging PWH with HCV are at greater risk of T1MI relative to PWH without HCV; therefore, HCV status should be considered when assessing T1MI risk in aging PWH.
- As PWH within North America are an aging population, identifying factors that increase their risk of comorbidities associated with aging such as T1MI is of importance to provide clinicians the tools to accurately counsel patients on their risks, promote CVD risk reduction behaviors, and highlight the importance of appropriate therapy for both HIV and HCV.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
DAA	direct-acting HCV antiviral
HBV	hepatitis B virus
HCV	hepatitis C virus
IR	incidence rate
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
PI	protease inhibitor
PWH	people with HIV
T1MI	type 1 myocardial infarction
T2MI	type 2 myocardial infarction
TC	total cholesterol

Because of shared unfavorable social determinants of health and differences in behavioral and sociodemographic factors, traditional risk factors for CVD (eg, smoking, hypertension, and diabetes) are more prevalent among HIV/HCV coinfected individuals.[16,17] Cumulative exposure to chronic inflammation is also believed to contribute to an increased risk of CVD.[18–20] Both HIV and HCV are immune system modulating chronic viral infections associated with inflammatory pathways that are overlapping yet discrete.[21,22] It is hypothesized that the inflammatory nature of these infections combined could contribute synergistically to the risk of CVD.[1,23] Liver disease progression and HCV viremia have been associated with elevations of multiple inflammatory biomarkers that are also associated with the pathogenesis of HIV-associated CVD.[24–26] In a study of HIV/HCV coinfected men, HCV viremia was linked to markers of subclinical atherosclerosis.[27] However, chronic HCV has also been associated with decreased plasma lipid levels, fueling theories of a potential protective effect on CVD among PWH.[28–31]

Increasing age is an independent risk factor for CVD in both PWH and in people with HCV.[6,32] The population of PWH is aging; in 2018 more than half of PWH living in the United States were aged ≥50 years.[33] PWH often experience accelerated aging, with reports demonstrating earlier onset of CVD compared with people without HIV.[32,34] Data on the association of HCV coinfection on CVD risk among the aging population of PWH is lacking. As PWH continue to age, accurate risk prediction for CVD by age among those with and without HCV is needed.

Our objective was to quantify the risk for predominantly atheroembolic, type 1 myocardial infarction (T1MI) in PWH with and without chronic HCV in the United States and Canada between 2000 and 2017. We also aimed to identify risk factors associated with CVD among PWH with HCV and evaluate the effect of age on T1MI risk by HCV status among PWH.

METHODS

Study Population

NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) is a collaboration of 29 clinical and interval cohorts from the United States and Canada, and the North American region of the International epidemiology Databases to Evaluate AIDS.[35] Enrollment criteria for the NA-ACCORD collaboration includes ≥2 HIV clinical care visits within initial 12 months of cohort entry among participants of clinical cohorts. Each collaborating cohort submits data annually to the Data Management core at the University of Washington (Seattle, WA). Data are harmonized and transmitted to the Epidemiology and Biostatistics Core at Johns Hopkins University. Each participating cohort has been granted approval by their local institutional review board, and the NA-ACCORD collaboration has been approved by the institutional review board at the

Johns Hopkins School of Medicine. Written consent or waivers of individual consent are obtained through each site's respective local institutional review board. Complete data for this study cannot be publicly shared because of legal and ethical restrictions; please refer to the NA-ACCORD data availability statement for full details on data requests.

For our nested study, the source population was composed of NA-ACCORD clinical cohorts with validated MI data on individuals aged ≥18 years at enrollment and with data regarding smoking on >50% of cohort participants. Participants were required to have measurements of at least 1 HIV viral load or CD4 count, and an ascertainable HCV status while under observation in the NA-ACCORD (7 participating cohorts in North America). Additional individual-level inclusion criteria were having initiated ART and having at least 3 months of observation in the NA-ACCORD. Participants must have also been within the age range for which the American College of Cardiology/American Heart Association Pooled Cohort Equations have been validated (among those aged 40–79 years at study entry).

Myocardial Infarction Ascertainment

The protocol for ascertainment, validation, and classification of myocardial infarction (MI) within NA-ACCORD has been previously described.[36] Using a standard protocol based on MI diagnoses and cardiac biomarkers, potential MI events were ascertained. Contributing sites each obtained medical records including clinician notes, ECGs, echocardiograms, laboratory investigations, and cardiac catheterization results from electronic health records to further characterize each event. Each potential event was adjudicated by at least 2 experienced physician reviewers. Potential events were classified according to the universal definition of MIs as type 1 (T1MI) or type 2 (T2MI).[37] For this study, all validated MIs (including all incident MIs [T1MIs] and those who had a cardiac intervention consistent with severe underlying coronary artery disease to avert a T1MI [coronary artery bypass graft or percutaneous coronary intervention with stent placement]) were included in the outcome of an incident T1MI event. T2MIs were not evaluated in this study because of their heterogenous etiology, and our objective was to identify whether HCV coinfection increases the risk for predominantly atheroembolic MI (T1MI) and not supply–demand mismatch MI (T2MI) that may be associated with drug use or infection. PWH with T2MI were excluded from the study population following T2MI event.

HCV Coinfection Ascertainment

HCV infection was defined as a positive HCV antibody test, detectable HCV RNA, or the presence of an HCV genotype result measured at any time while under observation in the NA-ACCORD. HCV infection was measured as a time-fixed variable as either ever or never infected because HCV is known to be more transmissible than HIV and the 2 viruses share transmission routes,[38] making it plausible that infection occurred at or before HIV infection in most individuals.

Covariates

Time-fixed variables assessed at study entry included sex, race or ethnicity, HIV transmission risk, hepatitis B virus (HBV) infection, cigarette smoking, alcohol abuse or dependence, and class of ART exposure. Sex (male, female), race or ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and Other/Unknown), and HIV transmission risk (men who have sex with men, heterosexual contact, injection drug use (IDU) history, and other) were self-reported at entry into NA-ACCORD. Injection drug use history was prioritized when >1 HIV transmission risk was reported. HBV infection was defined as ever having a positive HBV surface antigen, HBV e-antigen, or HBV DNA test result. Cigarette smoking and alcohol abuse or dependence was defined as ever, via self-report/substance survey or a diagnosis in the medical record, respectively. Antiretroviral drug classes were categorized as non-nucleoside reverse transcriptase inhibitors, protease inhibitors (PIs), and integrase strand transfer inhibitors used in addition to the nucleoside reverse transcriptase inhibitor.

Variables that were assessed at or before study entry (closest measurement to study entry within 21 months before entry to 3 months after entry) included age, systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol (TC), low-density lipoprotein, high-density lipoprotein, statin use, and anemia (ever having a hemoglobin <13 g/dL for men or <12 g/dL for women). The 10-year composite CVD risk score at study entry was calculated using the American College of Cardiology/American Heart Association Pooled Cohort Equations.[39]

Time-varying covariates included treated hypertension, type 2 diabetes, chronic kidney disease (CKD), and history of AIDS-defining illness (defined as ever previously reported), as well as CD4 count and HIV viral load. Treated hypertension was defined as a clinical diagnosis of hypertension in addition to a prescribed antihypertensive medication. Diabetes was defined as hemoglobin A_{1C} >6.5%, a record of prescribed diabetes medications, or a diabetes diagnosis and diabetes medications. CKD diagnosis was established by a documented estimated glomerular filtration rate <60 mL/min per 1.73m^2 for at least 3 months. Missing values for smoking (n=3256), CD4 count at ART initiation (n=2951), systolic blood pressure (2674), diastolic blood pressure (n=2676), TC (5264), high-density lipoprotein (n=7483), low-density lipoprotein (n=8028), and body mass index (4301) were imputed using multiple imputation by the fully conditional specification method.

Statistical Analysis

Observation windows[40] specific to each cohort were used to minimize the risk of falsely assuming complete event ascertainment for the diagnosis of assessed comorbidities that were obtained from electronic health records. An observation window defines the period for an individual contributing cohort that ascertainment of the event of interest is reasonably complete. We defined the start of follow-up as the latest of the following dates: cohort open date; patient enrollment date; at age 40 years; initiation of ART; observation window open date for T1MI, HCV, HBV, anemia, hypertension, diabetes, CKD, statin prescription, body mass index, or lipid measurements; or January 1, 2000. Participants who started direct-acting HCV antiviral (DAA) therapy during the follow-up period were censored at the time of DAA initiation so that our estimates would be potentially more generalizable to the risk of MI before HCV cure. Follow-up continued until the earliest of the following: cohort close date, observation window close date for all variables listed as part of the study entry criteria, loss to follow-up, death, DAA initiation, or 10 years following study entry. Individuals were considered lost to follow-up after 2 years elapsed without a CD4 or HIV viral load test result. Participants with prevalent MI at or before study entry were excluded.

Crude incidence rates (IRs) per 1000 person-years and 95% CI for T1MI and death were calculated, with the primary comparison between the rates in PWH with HCV versus without HCV collapsed into 3 calendar periods: 2000 to 2006, 2007 to 2013, and 2014 to 2017; and 3 age categories; <50 years, 50 to 59 years, and ≥60 years. A discrete time-to-event approach with person-month periods was used. Complementary log–log models were used to estimate unadjusted and adjusted hazard ratios (aHRs) with 95% CIs for T1MI. The discrete-time hazard was visualized in each calendar period to ensure that the proportional hazard assumption was valid.

To investigate whether HCV modified the known association of increasing T1MI risk with increasing age, a nested model approach was used. The null model was adjusted for age, sex, race, hypertension, diabetes, smoking, alcohol abuse or dependence, injection drug use history, statin prescription, CKD, HCV infection, HBV infection, viral load, CD4 count, and PI use. A history of clinical AIDS diagnosis was not included in adjusted models because of multicollinearity with other covariates. In the extended model, an interaction term was included to evaluate whether the association of HCV infection on T1MI risk was modified by age (ie, HCV × age). All *P* values were 2-tailed tests with a statistical significance level of 0.05. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Study Population

Among PWH meeting inclusion criteria (N=23 361; Figure 1), 4677 (20%) had HCV (Table 1). A total of 108 499 person-years were observed with slightly longer median follow-up in those with HCV compared with those without HCV (4.09 years versus 3.89 years, respectively). HCV coinfected PWH were more likely to be women (23% versus 16%), non-Hispanic Black (47% versus 30%), and people who inject drugs (53% versus 7%) and have a history of AIDS-defining illness (29% versus 26%), PI use (65% versus 56%), and unsuppressed HIV viral replication (≥200 copies/mL) at study entry (35% versus 24%) (*P* values for all <0.001). The proportion of person-time spent with a CD4 count >500 cells/mm^3 was 39% for PWH with HCV and 53% for PWH without HCV. The proportion of person-time spent with an undetectable viral load (<200 copies/mL) was 75% for PWH with HCV and 85% for PWH without HCV. PWH with HCV were more likely to be smokers (76% versus 57%; *P*<0.001) and have alcohol abuse or dependence (36% versus 16%; *P*<0.001), diabetes (8% versus 7%; *P*=0.006), CKD (6% versus 4%; *P*<0.001), and anemia (60% versus 45%; *P*<0.001). Individuals with HCV had lower median TC levels (163 mg/dL versus 183 mg/dL) and lower low-density lipoprotein levels (88 mg/dL versus 105 mg/dL) at study entry (*P*<0.001).

There were 403 incident T1MIs observed during the study period, with 89 occurring among PWH with HCV and 314 among those without HCV (Table S1). Those who experienced T1MIs were more likely to be men (87% versus 83%; *P*=0.023), have reported ever smoking (76% versus 60%; *P*<0.001) and were of older median age at study entry (49 versus 45 years; *P*<0.001). PWH who had a T1MI were also more likely to have a diagnosis of an AIDS-defining illness (34% versus 26%; *P*=0.001), HBV (9% versus 6%; *P*=0.020), hypertension (50% versus 26%; *P*<0.001), diabetes (15% versus 7%; *P*<0.001), CKD (11% versus 5%; *P*<0.001), and anemia (56% versus 48%; *P*<0.001). Median TC levels were higher among those who experienced a T1MI (185 mg/dL [interquartile range, 156–220 mg/dL]) compared with those who did not (170 mg/dL [interquartile range, 153–209 mg/dL]; *P*-value 0.003). PWH with T1MI had lower CD4 counts at ART initiation (239 cells/mm^3 versus 289 cells/mm^3; *P*<0.001), were less likely to be virologically suppressed at study entry (69% versus

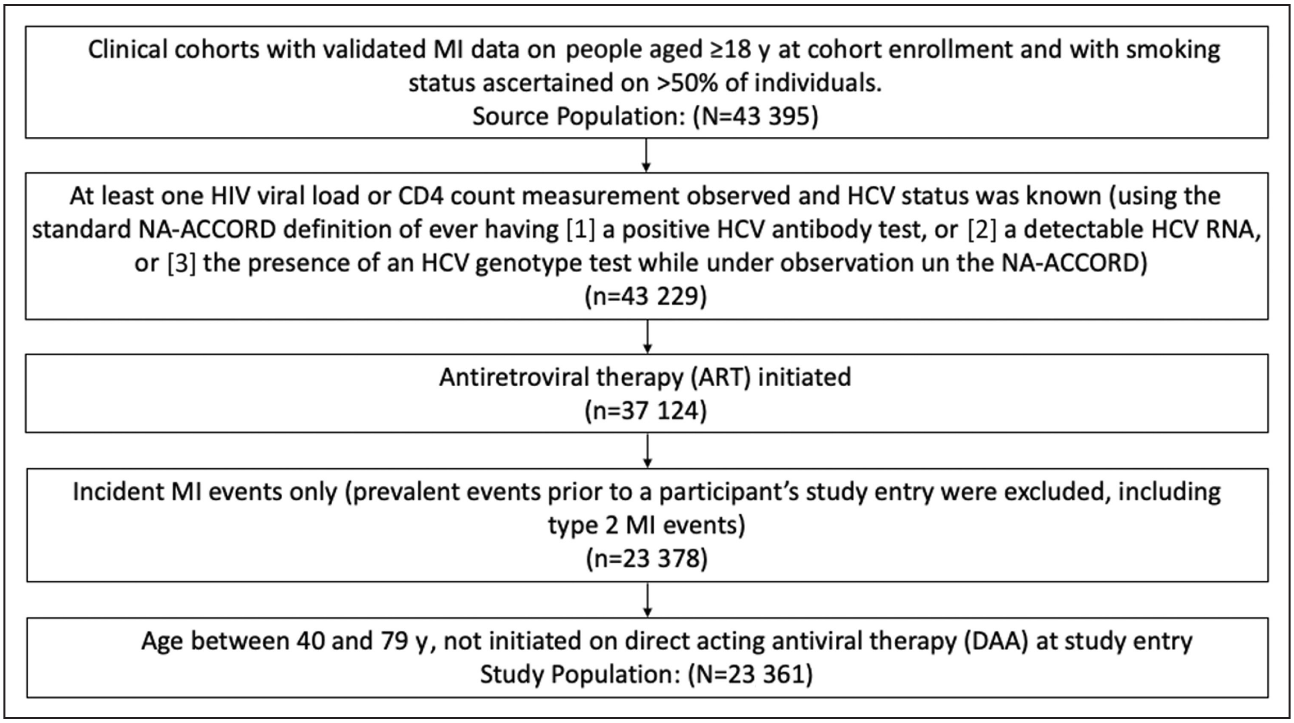


Figure 1. Flowchart of study population selection, N=23 361.
ART indicates antiretroviral therapy; DAA, direct-acting HCV antiviral; HCV, hepatitis C virus; MI, myocardial infarction; and NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

74%; *P*=0.013), and had greater exposure to PI (71% versus 58%; *P*<0.001).

IRs of T1MI and Death by HCV Status

The overall average IR of T1MI was 3.71 [95% CI, 3.35–4.08] per 1000 person-years. The IR was 3.99 [95% CI, 3.16–4.82] for those with HCV and 3.64 [95% CI, 3.24–4.05] for those without HCV. Over calendar time, the IR of T1MI trended down among PWH without HCV (*P* for trend<0.001); however, the IR of T1MI did not significantly change in those coinfected with HCV (*P* for trend=0.761) (Figure 2). The incidence of T1MI in PWH increased with advancing age in both those with HCV coinfection (40–49 years: IR, 2.16 [95% CI, 1.29–3.02]; 50–59 years: IR, 4.79 [95% CI, 3.36–6.22]; ≥60 years: IR, 10.11 [95% CI, 5.89–14.34]), and in those without HCV (40–49 years: IR, 2.54 [95% CI, 2.09–3.00]; 50–59 years: IR, 4.16 [95% CI, 3.42–4.90]; ≥60 years: IR, 7.04 [95% CI, 5.43–8.64]).

The IR (per 1000 person-years) of death from all causes among all participants between 2000 and 2017 was 18.76 [95% CI, 17.94–19.57], which was higher among PWH with HCV (IR, 33.42 [95% CI, 31.02–5.82]) than those without HCV (IR, 14.96 [95% CI, 14.15–15.78]). In both coinfected and HIV monoinfected populations, the IR of death declined significantly across time (*P* for trend<0.001); however, in all 3 time periods, the IR of death remained significantly higher in those with HCV (*P*<0.05; Figure 2).

Risk of T1MI Among People Coinfected With HIV/HCV and People Who Are HIV Monoinfected

In unadjusted analyses, HCV coinfection had no association with the risk of T1MI (crude hazard ratio,1.09 [95% CI, 0.86–1.38]) (Table 2). T1MI risk increased by 71% with each 10-year increase in age and was 28% lower among women. Risk for T1MI was 2.6-fold higher among individuals with diabetes or CKD (versus without diabetes or CKD), 4.6-fold higher among those with hypertension (versus without) and 2.1-fold higher among individuals prescribed a statin (compared with those without a prescription). CVD risk score was a strong predictor of T1MI as each 1-point increase resulted in a 5% increased risk of T1MI. A history of AIDS-defining illness, low CD4 count, and use of PI all increased the risk of T1MI by >30%.

In the adjusted analyses, HCV coinfection was not associated with the risk of T1MI when adjusted for age, sex, race or ethnicity, HBV, diabetes, hypertension, CKD, alcohol abuse or dependence, smoking status, statin usage, viral load, CD4 count, and PI use (aHR, 0.98 [95% CI, 0.74–1.30]). There was a 38% increase in the risk of T1MI with each decade of age. There was a

Table 1. Characteristics at Study Entry Among People With HIV in NA-ACCORD by Hepatitis C Virus Infection Status

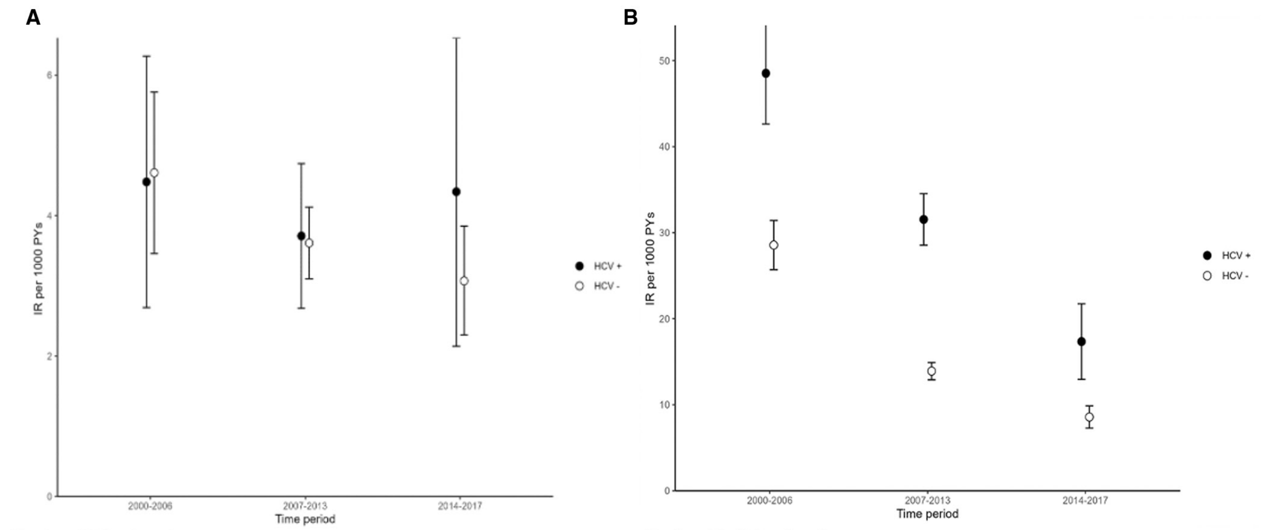
Characteristic	Total participants, n=23 361	HIV monoinfected, N=18 684*	HIV/HCV coinfected, N=4677*	*P* value†
Myocardial infarction	403 (1.7)	314 (1.7)	89 (1.9)	0.300
Female	4070 (17.4)	3014 (16.1)	1056 (22.6)	<0.001
Age	45 (41–51)	45 (40–51)	46 (42–52)	<0.001
Age, y				
40–49	15 983 (68.4)	12 924 (69.2)	3059 (65.4)	<0.001
50–59	5859 (25.1)	4466 (23.9)	1393 (29.8)	
60–69	1332 (5.7)	1121 (6.0)	211 (4.5)	
70–79	187 (0.8)	173 (0.9)	14 (0.3)	
HIV transmission risk				
Heterosexual	5960 (25.5)	5156 (27.6)	804 (17.2)	<0.001
Men who have sex with men	12 397 (53.1)	11 197 (59.9)	1200 (25.7)	
Injection drug use	3713 (15.9)	1250 (6.7)	2463 (52.7)	
Other/unknown	1291 (5.5)	1081 (5.8)	210 (4.5)	
Race or ethnicity				
Non-Hispanic White	11 521 (49.3)	9591 (51.3)	1930 (41.3)	<0.001
Non-Hispanic Black	7792 (33.4)	5591 (29.9)	2201 (47.1)	
Hispanic	2625 (11.2)	2279 (12.2)	346 (7.4)	
Other‡/unknown	1423 (6.1)	1223 (6.5)	200 (4.3)	
History of an AIDS-defining illness	6120 (26.2)	4758 (25.5)	1362 (29.1)	<0.001
Hepatitis B infection	1488 (6.4)	1132 (6.1)	356 (7.6)	<0.001
Reported ever smoking				
No	6014 (25.7)	5475 (29.3)	539 (11.5)	<0.001
Yes	14 091 (60.3)	10 552 (56.5)	3539 (75.7)	
Not assessed	3256 (13.9)	2657 (14.2)	599 (12.8)	
Alcohol abuse or dependence	4722 (20.2)	3030 (16.2)	1692 (36.2)	<0.001
Hypertension	6195 (26.5)	4881 (26.1)	1314 (28.1)	0.006
Diabetes	1685 (7.2)	1304 (7.0)	381 (8.1)	0.006
Chronic kidney disease	1068 (4.6)	790 (4.2)	278 (5.9)	<0.001
Statin prescription	2963 (12.7)	2687 (14.4)	276 (5.9)	<0.001
Treated hypertension	6337 (27.1)	5068 (27.1)	1269 (27.1)	>0.900
Anemia	11 229 (48.1)	8416 (45.0)	2813 (60.1)	<0.001
Systolic BP	125 (117–135)	125 (118–135)	124 (115–135)	0.018
Diastolic BP	80 (72–84)	80 (72–84)	80 (72–85)	0.120
CD4 at ART initiation, cells/mm^3	288 (130–489)	296 (134–502)	255 (116–434)	<0.001
Viral load at ART initiation, copies/mL	19 305	18 284	23 898	<0.001
Virally suppressed at study entry	16 708 (74.2)	13 781 (76.4)	2927 (65.3)	<0.001
Follow-up time, y, median (IQR)	3.94 (2.06–7.26)	3.89 (2.05–7.26)	4.09 (2.10–7.50)	0.002
BMI	25.6 (23.0–28.9)	25.7 (23.1–29.0)	25.0 (22.3–28.2)	<0.001
Total cholesterol, mg/dL	179 (153–209	183 (157–212)	163 (138–192)	<0.001
HDL, mg/dL	41 (33–51	41 (33–51)	42 (33–53)	0.056
LDL, mg/dL	103 (80–127)	105 (84–129)	88 (66–113)	<0.001
Ever PI use at study entry	13 489 (57.7)	10 448 (55.9)	3041 (65.0)	<0.001
Ever NNRTI use at study entry	13 270 (56.8)	10 838 (58.0)	2432 (52.0)	<0.001
Ever INSTI use at study entry	3319 (14.2)	2800 (15.0)	519 (11.1)	<0.001

ART indicates antiretroviral therapy; BMI, body mass index; BP, blood pressure; HCV, hepatitis C virus; HDL, high-density lipoprotein; INSTI, integrase strand transfer inhibitors; LDL, low-density lipoprotein; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; and NNRTI, nonnucleoside reverse transcriptase inhibitors.

*n (%); median [IQR].

†Pearson's chi-squared test; Wilcoxon rank-sum test.

‡Other race or ethnicity categories include Asian, Indigenous, Multiracial, and "other" (no further specification).



A

Number of MI/number of person-years			
HIV	62/13445	191/52923	61/19837
HIV/HCV	24/5358	50/13476	15/3460
IR (95% CI)			
HIV	4.61 (3.46-5.76)	3.61 (3.10-4.12)	3.07 (2.30-3.85)
HIV/HCV	4.48 (2.69-6.27)	3.71 (2.68-4.74)	4.34 (2.14-6.53)

B

Number of deaths/number of person-years			
HIV	384/13445	736/52923	170/19837
HIV/HCV	260/5358	425/13476	60/3460
IR (95% CI)			
HIV	28.56 (25.70-31.42)	13.91 (12.90-14.91)	8.57 (7.28-9.86)
HIV/HCV	48.53 (42.63-54.43)	31.54 (28.54-34.53)	17.34 (12.95-21.73)

Figure 2. Rates and 95% CIs (per 1000 person-years) of (A) myocardial infarction and (B) death, by time period and hepatitis C virus coinfection.

HCV indicates hepatitis C virus; IR, incidence rate; MI, myocardial infarction; and PY, person-years.

49% increase in the risk of T1MI with (versus without) diabetes, a 36% increase among those with (versus without) CKD, a 33% increase among those prescribed statins (compared with those without a prescription), and a 3.8-fold increase among those with (versus without) hypertension. PWH with low CD4 counts (≤200 cells/mm^3) had a 39% increased risk of T1MI and those with prior PI use had a 45% increased risk.

HCV Amplified the Effect of Age and T1MI Risk in PWH

The test of interaction (*P*=0.03) indicated that the increasing risk of T1MI with age among PWH differed by HCV coinfection status. Individuals with HCV had an 85% [95% CI, 1.38–2.48] higher risk of T1MI per each 10-year increase in age, whereas those without HCV had a 30% [95% CI, 1.13–1.50] increased risk of T1MI per 10-year increase in age (Figure 3A). A sensitivity analysis to adjust for the competing risk of death found that this interaction remained significant with PWH with HCV having an 84% [95% CI, 1.39–2.43] increased risk of T1MI per 10-year increase in age and PWH without HCV having a 32% [95% CI, 1.14–1.52] increased risk of T1MI per 10-year increase in age (Figure 3B).

To evaluate the interaction of age and HCV on T1MI risk, we performed a stratified analysis comparing individuals aged <50 years, 50 to 59 years, and ≥60 years (Table 3). The risk of T1MI in those with HCV increased with advancing age. In adjusted analyses, the T1MI estimated risk was 17% higher in those aged 50 to 59 years with HCV and 77% higher in those aged ≥60 years with HCV compared with those without HCV, although neither association was statistically significant, likely attributable to a smaller number of participants contributing to older age categories. The risk of T1MI was significantly higher among PWH aged 40 to 49 years with diabetes, hypertension, CKD, and PI use and smokers. Among PWH aged 50–59 years, TIMI risk was significantly greater among those with hypertension and PI use and smokers. Hypertension and low CD4 count were associated with a significantly increased T1MI risk among PWH aged ≥60 years.

DISCUSSION

Among PWH on ART in North America, HCV coinfection was not associated with a significantly increased T1MI risk. Several prior studies have shown an increased risk of MI with HCV coinfection,[14,15] a possible explanation for our differing results is that we assessed only T1MI, whereas others have included T2MI, which can be driven by underlying factors such as infection or drug use that may confound the effect. One prior study isolating the association of HCV on T1MI among PWH also identified no increased risk.[14] We identified that the risk of T1MI with increasing age was greater

Table 2. Crude and Adjusted Hazard Ratios of Risk Factors Associated With Myocardial Infarction Among People With HIV in NA-ACCORD (N=23 361)

Characteristic	cHR		aHR with no interaction term		aHR with interaction term between age and HCV	
	cHR	95% CI	*aHR	95% CI	†aHR	95% CI
Age (per 10-y increase)	1.71	1.52–1.92	1.38	1.21–1.57	…	…
Per 10-y increase in age among HCV negative	…	…	…	…	1.30	1.13–1.50
Per 10-y increase in age among HCV positive	…	…	…	…	1.85	1.38–2.48
Hepatitis C infection	1.09	0.86–1.38	0.98	0.74–1.30	…	…
Sex						
Male	Ref		Ref		Ref	
Female	0.72	0.54–0.96	0.68	0.50–0.92	0.68	0.50–0.93
Race or ethnicity						
Non-Hispanic White	Ref		Ref		Ref	
Non-Hispanic Black	0.93	0.75–1.16	0.77	0.61–0.98	0.76	0.60–0.96
Hispanic	0.78	0.55–1.10	0.95	0.67–1.35	0.94	0.66–1.34
Other‡/Unknown	0.65	0.39–1.08	0.82	0.48–1.39	0.82	0.49–1.39
Hepatitis B infection	1.36	0.97–1.91	1.21	0.85–1.72	1.22	0.86–1.74
Cardiovascular Risk Score (per 1-point increase)	1.05	1.04–1.06	…	…	…	…
Diabetes	2.63	2.09–3.31	1.49	1.16–1.90	1.46	1.17–1.92
Chronic kidney disease	2.57	2.01–3.28	1.36	1.05–1.77	1.36	1.06–1.79
Statin prescription	2.14	1.70–2.68	1.33	1.04–1.71	1.34	1.05–1.71
Hypertension	4.64	3.72–5.79	3.76	2.94–4.73	3.70	2.92–4.70
Treated hypertension	2.52	2.07–3.07	…	…	…	…
Anemia	1.23	1.01–1.49	…	…	…	…
History of an AIDS-defining illness	1.32	1.08–1.62	…	…	…	…
Smoking	1.98	1.51–2.59	1.89	1.44–2.50	1.90	1.44–2.50
Injection drug use	1.05	0.80–1.36	0.94	0.68–1.29	0.94	0.69–1.29
Alcohol abuse or dependence	1.25	1.00–1.56	1.08	0.85–1.37	1.09	0.86–1.37
Detectable viral load, >200 copies/mL	1.16	0.90–1.49	1.19	0.90–1.56	1.20	0.91–1.58
Low CD4 count, ≤200 cells/mm^3	1.39	1.06–1.83	1.39	1.04–1.86	1.40	1.04–1.87
PI use	1.50	1.21–1.86	1.45	1.16–1.81	1.45	1.16–1.81

The proportional hazards assumption was assessed using log–log-survival plots.

aHR indicates adjusted hazard ratio; cHR, crude hazard ratio; HCV hepatitis C virus; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; and PI, protease inhibitor.

*Hazard ratios were estimated using discrete time to event with complementary log–log regression models and adjusted for all variables in the table.

†Hazard ratios were estimated using discrete time to event with complementary log–log regression models and adjusted for all variables in the table including an interaction term tested by a likelihood ratio test to compare models with and without an interaction between age and HCV status.

‡Other race or ethnicity categories include Asian, Indigenous, Multiracial, and "other" (no further specification).

in those with HCV compared with those without HCV, with an 85% increased risk per 10-year age increase for those with HCV versus a 30% increased risk for those without HCV.

Age is a significant independent risk factor for CVD, which is also compounded by additional factors such as frailty and comorbidities.[32] PWH are at greater risk of experiencing premature onset of age-associated comorbidities, which have become the most frequent causes of hospitalization and death in PWH living in Western countries.[41–43] While other studies have evaluated the risk of T1MI among PWH with HCV coinfection,[1,14–16] to our knowledge none have evaluated whether HCV coinfection impacts the effect of age on T1MI risk. We found that HCV coinfection among PWH modifies the association of age on risk of T1MI. As PWH age as a population, reducing their risk for CVD is a primary therapeutic goal. Aging PWH with HCV remain at greater risk of CVD relative to PWH without HCV, highlighting the importance of maintaining ART, promoting CVD risk-reduction strategies, and initiating treatment of their HCV to reduce the chronic inflammation believed to contribute to this risk.

The incidence rates of T1MI declined over time between 2007 and 2017 among PWH, among those with HCV incidence rates also appeared to be declining

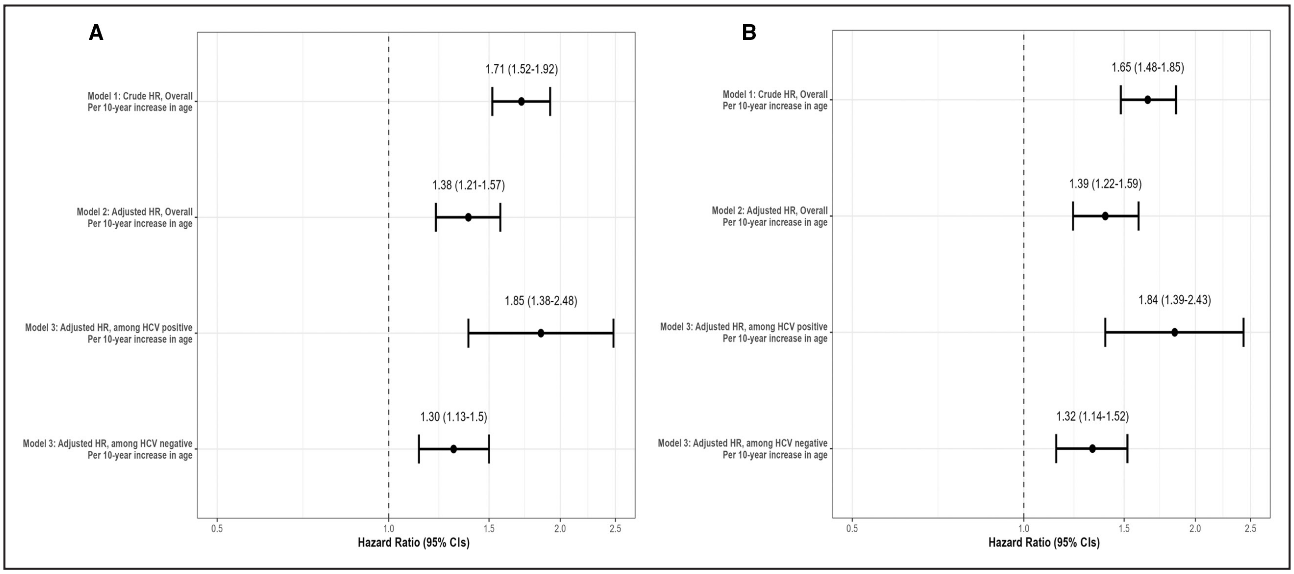


Figure 3. Forest plot of the association between myocardial infarction among people with HIV in NA-ACCORD (N=23361) (A) comparing crude HR for 10-year increase in age, adjusted HR per 10-year increase in age and the interaction of HCV status; and (B) accounting for the competing risk of death of the association between myocardial infarction among people with HIV in NA-ACCORD comparing crude HR for 10-year increase in age, adjusted HR per 10-year increase in age and the interaction of HCV status.

HCV indicates hepatitis C virus; HR, hazard ratio; and NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

before the most recent period. In the most recent time period (2014–2017), variation in incidence rates may be attributable to the reduced number of PWH included, particularly within the HCV coinfected group, or may be attributable to differential receipt of cardiovascular preventative care. Advancements in HIV care and highly effective ART have led to significant improvements in survival rates among PWH and likely also contribute to the reduction of T1MI rates.[44] While the incidence rate of all-cause mortality decreased over time among both PWH with and without HCV, rates remained significantly higher in those with HCV for each time period, a finding that has been observed in other settings.[45] These mortality differences could reflect differences in comorbidities or engagement in care by HCV status.

In PWH, established CVD risk algorithms are thought to incompletely reflect the unique mechanistic factors that drive CVD in this population.[39,46,47] Several studies have shown that the Framingham 10-year risk score for CVD underestimates risk of MI,[48] stroke,[49] and coronary heart disease[50] among PWH; in more recent studies, the Pooled Cohorts Equations have also underestimated risk in PWH.[51–54] In HCV infection, despite lower lipid indices, inflammatory biomarkers are elevated, suggesting that calculated risk scores for CVD may also underestimate risk. While our study did not show an independent association of HCV infection with T1MI risk among all PWH, it did demonstrate a clinically relevant interaction with age, suggesting the possibility of a synergistic effect between HCV and age on T1MI risk and further underscoring the importance of tailored risk stratification approaches. We showed that HCV coinfection might impact secondary complications such as MI risk differently according to age strata. Progress has been made in access to HCV treatment for all PWH, but medical providers must know the additional risk associated with HCV, HIV, and aging. Future work to understand CVD risk in PWH with HCV is needed, as the accuracy of current algorithms for this group is unknown.[50]

Several studies have identified that HCV clearance is associated with reduced risk of cardiovascular events[55–59]; however, there are few data of this effect among PWH with HCV.[60,61] One study demonstrated that HCV clearance reduces systemic inflammation and may reduce CVD risk among PWH with HCV.[60] A subsequent prospective analysis failed to demonstrate any beneficial effect of eradicating HCV in PWH when assessing arterial stiffness, intimal thickening, proinflammatory cytokines, and biomarkers of endothelial dysfunction.[61] Consistent with several previous studies, there were lower median TC and lower median low-density lipoprotein levels among PWH with HCV.[28–31] Further work is needed to characterize the MI risk among PWH following HCV eradication, using differences in CVD risk factors or MI events themselves.

As previously identified in both the general population and PWH, we found risk factors for T1MI included

Table 3. Adjusted Hazard Ratios of Risk Factors Associated With Myocardial Infarction Among People With HIV in NA-ACCORD Stratified by Age (N=23 361)

	40–49 y		50–59 y		≥60 y	
	n=15 975 events=211		n=5853 events=135		n=1517 events=57	
Characteristic	aHR	95% CI	aHR	95% CI	aHR	95% CI
Hepatitis C infection	0.73	0.51–1.04	1.17	0.78–1.76	1.77	0.87–3.63
Sex						
Male	Ref		Ref		Ref	
Female	0.73	0.50–1.08	0.60	0.34–1.04	0.59	0.23–1.51
Race or ethnicity						
Non-Hispanic White	Ref		Ref		Ref	
Non-Hispanic Black	0.90	0.66–1.23	0.81	0.54–1.22	0.39	0.18–0.82
Hispanic	0.75	0.45–1.25	1.16	0.66–2.07	1.07	0.44–2.57
Other*/unknown	1.00	0.52–1.91	0.39	0.12–1.24	1.20	0.36–3.96
Diabetes	1.86	1.32–2.62	1.38	0.91–2.08	1.26	0.68–2.32
Hypertension	3.83	2.79–5.24	3.50	2.31–5.29	2.81	1.41–5.62
Chronic kidney disease	2.73	1.94–3.85	0.76	0.46–1.26	0.88	0.49–1.59
Statin use	1.20	0.82–1.74	1.30	0.86–1.95	1.61	0.93–2.80
Alcohol abuse or dependence	1.26	0.93–1.71	0.74	0.48–1.14	1.36	0.73–2.53
Smoking	2.19	1.48–3.24	1.76	1.12–2.75	1.56	0.80–3.02
Low CD4 count, ≤200 cells/mm^3	1.32	0.91, 1.93	1.29	0.77, 2.14	2.73	1.34–5.54
PI use	1.42	1.04–1.94	1.52	1.05–2.20	1.14	0.66–1.98

Hazard ratios were estimated using discrete time to event with complementary log–log regression models and adjusted for all variables in the table.
aHR indicates, adjusted hazard ratio; n, participants included in each stratified analysis event, number of myocardial infarction events occurring among participants included in each stratified analysis; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.
*Other race or ethnicity categories include Asian, Indigenous, Multiracial, and "other" (no further specification).

male sex and having diabetes, hypertension, CKD, and a greater CVD risk score.[39] A history of AIDS-defining illness, prior PI use, and a CD4 count ≤200 cells/mm^3 were associated with a higher risk for T1MI among PWH. Prior AIDS-defining illness and a low CD4 count is representative of advanced HIV disease or poorly controlled HIV infection resulting in immune dysfunction and inflammation likely contributing to this increased T1MI risk.[32]

The strengths of this work include the use of the largest and most diverse cohort of PWH in North America. A major strength lies in the comprehensive ascertainment method for T1MIs that was used. By incorporating both cardiac biomarker data as a screening tool and an expert physician panel to validate and adjudicate events, we believe we were able to accurately identify and classify T1MI events.

There are also several limitations to our study. The definition used for HCV diagnosis does not allow differentiation of active HCV infection from HCV that has been cleared either naturally or through treatment. To try to limit the variability in effect of those treated with DAAs, PWH were censored at the time of DAA initiation. Because of the limited amount of observed follow-up time since DAAs have become broadly available, evaluation of the association of DAA therapy on T1MI risk is forthcoming. Despite this being the largest evaluation of risk of T1MI in PWH with HCV, because of small numbers of T1MIs occurring, we were constrained by a small sample size for some analyses. Particularly only 5% of the population of HCV coinfected PWH were aged ≥60 years resulting in wide confidence intervals for the analysis stratified by age. There may be residual confounding impacting the associations we identified, particularly by diet, exercise, primary aspirin prophylaxis, family history of CVD, and advanced liver fibrosis characterization, which were not measured, and data on several variables were incomplete and therefore imputed. Enrollment criteria into the NA-ACCORD includes only individuals successfully linked into care; therefore, we are unable to make inferences about PWH who never successfully link into care.

CONCLUSIONS

Among PWH in care in North America, HCV coinfection was not associated with a significantly increased T1MI risk; however, the risk of T1MI with increasing age was greater in those with HCV compared with those without HCV. Traditional CVD risk factors remain highly associated with T1MI among PWH; however, HIV-associated risk factors also contribute and include low CD4 count, history of AIDS-defining illness, and PI use. Clinicians should be aware that age may be a more significant risk factor for T1MI among PWH with HCV, prompting assessment and mitigation of additional CVD risk factors and promoting HCV treatment. Further understanding of the complex interplay of factors impacting cardiovascular risk as PWH age will improve their long-term care and well-being.

ARTICLE INFORMATION

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Complete data for this study cannot be publicly shared because of legal and ethical restrictions. The NA-ACCORD Principals of Collaboration requires submission and approval of a concept sheet that describes the intended research project for which data are being requested. The NA-ACCORD Executive Committee and the Steering Committee (composed of principle investigators of contributing cohorts) must approve the concept sheet and elect to have their data included for the research project. A signed Data User Agreement is required before data can be released. Guidance for how to obtain NA-ACCORD data are outlined on the NA-ACCORD website (www.naaccord.org/collaboration-policies).

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Disclosures

Dr Althoff is a consultant to the All of Us Research Program and serves on the scientific advisory board for Trio Health. The remaining authors have no disclosures to report.

Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics at study entry among Persons with HIV in NA-ACCORD by MI status.

Characteristic	No MI n = 22,958$^{\alpha}$	MI n = 403*	p-value†
Hepatitis C infection	4,588 (20.0%)	89 (22.1%)	0.300
Female	4,017 (17.5%)	53 (13.2%)	0.023
Age [median, IQR]	45 [41, 51]	49 [44, 56]	<0.001
Age (years)			
40-49	15,772 (68.7%)	211 (52.4%)	<0.001
50-59	5,724 (24.9%)	135 (33.5%)	
60-69	1,284 (5.6%)	48 (11.9%)	
70-79	178 (0.8%)	9 (2.2%)	
HIV transmission risk			
Heterosexual	5,865 (25.5%)	95 (23.6%)	0.051
Men who have sex with men	12,167 (53.0%)	230 (57.1%)	
Injection drug use	3,646 (15.9%)	67 (16.6%)	
Other/unknown	1,280 (5.6%)	11 (2.7%)	
Race/ethnicity			
Non-Hispanic white	11,302 (49.2%)	219 (54.3%)	0.080
Non-Hispanic Black	7,661 (33.4%)	131 (32.5%)	
Hispanic	2,588 (11.3%)	37 (9.2%)	
Other/unknown	1,407 (6.1%)	16 (4.0%)	
History of an AIDS-defining illness	5,983 (26.1%)	137 (34.0%)	<0.001
Hepatitis B infection	1,451 (6.3%)	37 (9.2%)	0.020
Smoking	13,783 (60.0%)	308 (76.4%)	<0.001
Alcohol abuse or dependence	4,616 (20.1%)	106 (26.3%)	0.002
Hypertension	5,995 (26.1%)	200 (49.6%)	<0.001
Diabetes	1,626 (7.1%)	59 (14.6%)	<0.001
Chronic Kidney Disease	1,022 (4.5%)	46 (11.4%)	<0.001

Statin Prescription	2,865 (12.5%)	98 (24.3%)	<0.001
Treated Hypertension	6,150 (26.8%)	187 (46.4%)	<0.001
Anemia	11,004 (47.9%)	225 (55.8%)	0.002
Systolic BP [median, IQR]	125 [117, 135]	129 [120, 140]	<0.001
Diastolic BP [median, IQR]	80 [72, 84]	80 [75, 88]	<0.001
CD4 at ART initiation (cells/mm^3)	289 [131, 490]	239 [96, 402]	<0.001
Viral load at ART initiation (copies/mL)	19,092	29,376	0.006
Proportion virally suppressed at study entry	16,438 (74.3%)	270 (68.7%)	0.013
Follow-up time (years) [median, IQR]	3.95 (2.06, 7.31)	3.09 (1.43, 5.65)	<0.001
BMI [median, IQR]	25.6 [23.0, 28.9]	26.0 [23.1, 29.2]	0.400
Total cholesterol (mg/dL) [median, IQR]	170 [153, 209]	185 [156, 220]	0.003
HDL (mg/dL) [median, IQR]	41 [33, 51]	38 [32, 46]	<0.001
LDL (mg/dL) [median, IQR]	103 [80, 127]	107 [84, 130]	0.085
Ever PI use at study entry	13,202 (57.5%)	287 (71.2%)	<0.001
Ever NNRTI use at study entry	13,067 (56.9%)	203 (50.4%)	0.009
Ever INSTI use at study entry	3,290 (14.3%)	29 (7.2%)	<0.001

*n (%); Median (IQR)

† Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test