ORIGINAL RESEARCH

Adjudicated Heart Failure in HIV-Infected and Uninfected Men and Women

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***Background*—**HIV is associated with elevated risk of heart failure (HF). Despite poor agreement between automated, administrative code–based HF definitions and physician-adjudicated HF, no studies have evaluated incident adjudicated HF for people living with HIV (PLWH).

***Methods and Results*—**We analyzed PLWH and uninfected controls receiving care in an urban medical system from January 1, 2000, to July 12, 2016. Physicians reviewed data from medical records to adjudicate HF diagnoses. We used multivariable-adjusted Cox models to analyze incident HF for PLWH versus controls and HIV-related factors associated with incident HF. We also analyzed the performance of automated versus physician-adjudicated HF definitions. Incident adjudicated HF occurred in 97 of 4640 PLWH (2.1%; mean: 6.8 years to HF) and 55 of 4250 controls (1.3%; mean: 6.7 years to HF; multivariable-adjusted hazard ratio: 2.10; 95% confidence interval, 1.38–3.21). Among PLWH, higher HIV viral load (hazard ratio per $\log_{10}$ higher time-updated viral load: 1.22; 95% confidence interval, 1.11–1.33) was associated with greater HF risk and higher CD4+ T cell count was associated with lower HF risk (hazard ratio per 100 cells/mm^3 higher time-updated CD4 count: 0.80; 95% confidence interval, 0.69–0.92). In exploratory analyses, the most accurate automated HF definitions had sensitivities of 67% to 75% and positive predictive values of 54% to 60%.

***Conclusions*—**In a cohort with rigorous HF adjudication, PLWH had greater risks of HF than uninfected people after adjustment for demographics and cardiovascular risk factors. Higher HIV viral load and lower CD4+ T cell count were associated with higher HF risk among PLWH. Automated methods of HF ascertainment exhibited poor accuracy for PLWH and uninfected people. **(*J Am Heart Assoc*. 2018;7:e009985. DOI: 10.1161/JAHA.118.009985)**

Key Words: heart failure • HIV • immunology • inflammation

Modern combination antiretroviral therapy (ART) has transitioned HIV from a fatal progressive disease to a chronic manageable infection marked by noncommunicable disease complications.[1] People living with HIV (PLWH) are increasingly at risk for cardiovascular diseases, which may present differently (eg, at an earlier age) and with different underlying risk factors than in the general population.[1–3] Compared with uninfected people, PLWH also have greater risks for myocardial infarction, arrhythmias, pulmonary hypertension, and subclinical myocardial dysfunction (systolic and diastolic), even after adjustment for traditional cardiovascular risk factors.[4–12]

Clinically overt heart failure (HF) also appears to be common among PLWH, though data are limited. Seminal

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Clinical Perspective

What Is New?

- This study is the first to compare incidence of physician-adjudicated heart failure (HF) for people living with HIV (PLWH) and uninfected controls.
- The hazard ratio for HF (adjusted hazard ratio for PLWH versus uninfected controls: 2.10; 95% confidence interval, 1.38–3.21) was substantially higher than results from recent studies that used administrative (rather than physician-adjudicated HF) data to ascertain HF; automated definitions of HF may undercapture HF events in HIV.
- Higher HIV viremia and lower CD4+ T cell count were associated with significantly elevated hazards of adjudicated HF.

What Are the Clinical Implications?

- PLWH had significantly higher risk of HF than uninfected people, even in the modern era with most HIV-infected individuals on HIV therapy; prevention, diagnosis, and treatment of HF are high priorities for PLWH.
- Effective HIV therapy should remain first line for PLWH, as those with poorly controlled HIV had the highest risks of HF.

analyses of a large cohort of US veterans used administrative codes to find significantly higher rates of HF among veterans with HIV compared with uninfected veterans.[13,14] These studies have been essential to informing knowledge of HF incidence among PLWH in the current era of effective ART but are limited by the predominantly male (>97%) sample and lack of physician-adjudicated HF end points. Because HF is a complex clinical syndrome requiring combinations of subjective and objective criteria for diagnosis, high rates of disagreement (≥30%) exist between HF administrative codes and physician-adjudicated HF end points.[15,16] Accordingly, the American College of Cardiology and American Heart Association Task Force on Clinical Data Standards has noted the importance of standardized, adjudicated definitions of HF, given low "concurrence between initial and adjudicated assessment of HF" and "challenges investigators face in classifying HF events."[17]

No studies to our knowledge have compared HF in PLWH and uninfected controls using physician-adjudicated HF end points. In a previous cross-sectional analysis of PLWH receiving care at a large urban medical center with adjudicated HF end points, we found that HIV-related immunosuppression and viremia were associated with prevalent HF after adjustment for demographics, traditional cardiovascular risk factors, and ART use.[18] In the present study, we had the opportunity to evaluate risks for incident adjudicated HF among PLWH and uninfected controls receiving inpatient and/or outpatient care at a large urban medical center. Our central hypotheses were that PLWH would have significantly higher rates of adjudicated HF than uninfected controls and that, among PLWH, low CD4+ T cell count and high HIV viral load would be associated with elevated HF risk.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure because of an institutional permissible data use policy. However, the authors are open to sharing their analytic methods (including adjudication methods) with any interested investigators, who are encouraged to contact the corresponding author.

Study Population

We analyzed a nested cohort of HIVE-4CVD (HIV Electronic Comprehensive Cohort of CVD Complications), which has been described previously[18,19] and consists of PLWH receiving care at Northwestern Medicine and uninfected controls who were frequency matched on age, sex, race/ethnicity, ZIP code of residence, and outpatient clinic location. All clinical data obtained in the course of clinical care at Northwestern Medicine from January 1, 2000, to July 12, 2016, were stored in the Northwestern Medicine Enterprise Data Warehouse and available for analysis of the study participants. Because of variable timing and frequency of covariate data collection in this clinical (not interval) cohort, there were not uniform baseline dates or follow-up times. We determined the baseline for PLWH as the first clinical encounter during which criteria for HIV diagnosis were met (ascertained as described below using validated criteria based on administrative codes and laboratory data[18,20]). Baseline for uninfected controls was defined as the earliest date of an in-person clinical encounter. All HIVE-4CVD participants who were ≥18 years old at baseline were eligible for analysis. The HIVE-4CVD cohort creation and research protocol was approved by the institutional review board at Northwestern University (Chicago, IL); a waiver of informed consent was granted.

Exposures

The primary exposure was a diagnosis of HIV, which was defined using validated criteria for each patient as (1) positive HIV-1 antibody, antigen, or serology; (2) positive (>0) HIV viral load; and/or (3) concurrent orders of HIV viral load and CD4+ T cell count on at least 2 separate dates.[18,20] For analyses of HIV-specific covariates and incident HF (in PLWH only), the primary exposures were time-updated CD4+ T cell count

(cells/mm^3) and HIV viral load (copies/mL) from baseline to the date of censoring or most recent follow-up. Patients without CD4+ T cell count or HIV viral load measurements anytime from HIV diagnosis date through at least 30 days before HF diagnosis or censoring date were excluded from analyses of HIV-specific covariates and HF.

Covariates

We evaluated baseline age, sex, and race/ethnicity, as well as several clinical covariates. Baseline body mass index (BMI; kg/m^2) was determined by the concurrent height and weight measurement closest to the baseline date for each participant. People without baseline BMI data or whose first BMI measurements were within 30 days of incident HF were excluded from multivariable-adjusted analyses; we excluded the latter group to limit the potential for reverse causality (HF leading to changes in BMI). Relevant covariates related to clinical diagnoses were defined using criteria we published previously.[18] Diabetes mellitus was defined based on administrative codes and confirmatory laboratory evidence of hyperglycemia and/or use of antidiabetic medications. Hypertension was defined using administrative codes, given the heterogeneity of clinical visits (eg, inpatient versus outpatient, routine versus emergent) from which data in this cohort are drawn and the resulting potential for systematic differences in blood pressure values obtained. Infection with hepatitis C virus was determined based on laboratory criteria (any positive hepatitis C virus antibody and/or viral RNA). Diagnosis of coronary heart disease (CHD; which includes myocardial infarction, angina, and other ischemic heart disease) was determined by administrative codes that have been used previously and demonstrated high levels of agreement with expert chart review.[21–23] Substance use (smoking, alcohol intake, and illicit drug use) was not consistently or systematically assessed in HIVE-4CVD and, therefore, was not included as a covariate. For PLWH, we assessed (1) baseline ART use (documented ART use on the day of HIV determination or any date before then) and (2) ART use at any point up until censoring or 30 days before HF. We applied a strict definition of baseline ART use (eg, on the precise day of HIV diagnosis or before) given the complexity and potential instability of incorporating ART use as a time-dependent covariate into Cox models.

HF Ascertainment

The primary outcome was incident HF. First, we identified all eligible HIVE-4CVD participants with possible HF, using an intentionally sensitive protocol that screens for the presence of any of the following: (1) any single inpatient or outpatient administrative code of HF or cardiomyopathy (*International Classification of Diseases, Ninth Revision [ICD-9]* codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425, 428, 429; and/or *ICD-10* codes I42, I43, I50); (2) B-type natriuretic peptide (BNP) >100 pg/mL; and/or (3) use of intravenous loop diuretics.[18,24–26] Next, 2 physician adjudicators independently used a validated protocol that we described previously to determine whether participants had HF.[18] Disagreements were infrequent (>96% agreement rate; κ=0.91) and resolved by consensus or a third physician adjudicator if no consensus was reached. This protocol, adapted from MESA (Multi-Ethnic Study of Atherosclerosis),[27,28] required symptoms, a physician diagnosis, and HF medication for probable HF and additional objective clinical criteria (primarily imaging-based) for definite HF. We combined probable and definite HF into a single HF end point for these analyses.

Follow-up

Follow-up time was defined as the time from baseline date until the earliest of the following: (1) incident HF; (2) death, determined using the Northwestern Medicine health record and linked to the Social Security administration death master file; or (3) for people without incident HF or death during follow-up, the most recent clinical encounter (inpatient or outpatient) through July 12, 2016.

Statistical Analyses

Baseline characteristics for PLWH and uninfected controls were reported as mean±SD or as absolute values and percentages, as appropriate. Survival free of HF was estimated by the Kaplan-Meier method, and multivariable Cox survival analyses were used to determine associations of exposures and covariates with incident HF. We first analyzed the association of HIV status with incident HF, adjusted for age, sex, and race (model 1). We then sequentially added the following covariates for adjustment: baseline BMI, hepatitis C virus, hypertension, and diabetes mellitus (model 2); baseline year (model 3: 2000–2005, 2006–2010, or 2011–2016); and CHD (model 4). The only covariate with missing data was baseline BMI (missing for 912 PLWH and 584 uninfected people); people with missing baseline BMI data were excluded from analyses adjusted for baseline BMI. Likewise, people with missing data for covariates included in sequentially adjusted multivariable analyses were excluded from analyses involving the missing covariate. We adjusted for CHD given the potential for different prevalence of CHD among PLWH and controls and the potential for different associations of CHD and myocardial infarction with HF depending on myocardial infarction presentation and treatment for PLWH versus controls. Sensitivity analyses adjusting for duration of clinical diagnoses were also performed.

Next, we analyzed associations of time-updated CD4+ T cell count and HIV viral load with incident HF among PLWH. For these analyses, we adjusted sequentially for age, sex, and race (model 1); baseline BMI, hypertension, and diabetes mellitus (model 2); baseline year (model 3: 2000–2005, 2006–2010, or 2011–2016); and baseline ART use. The purpose of adjusting for baseline year was to account for potential changing associations between HIV and incident HF as the epidemiology and management of HIV evolved over time. Time-updated HIV viral load and CD4+ T cell count were modeled as continuous variables (log-transformed in the case of HIV viral load, given its distribution) to optimize power for the primary analyses. People with missing data on HIV viral load (n=60; 1.3% of PLWH) and CD4+ T cell count (n=474; 10.3% of PLWH) from baseline through 30 days before censoring or last follow-up date were excluded from these multivariable analyses. Sensitivity analyses evaluating clinically relevant baseline CD4+ T cell count categories (<200, 200–500, and >500 cells/mm^3) were also performed.

In a separate set of analyses, we evaluated the performance of automated HF ascertainment protocols incorporating *ICD* codes and/or HF biomarkers. We included PLWH and controls with HF at baseline for these analyses, which were exploratory in nature, because the purpose was to evaluate automated HF ascertainment versus physician adjudication of HF rather than to analyze factors associated with incident HF. We determined the sensitivity and positive predictive value (PPV; with adjudicated HF as the gold standard), separately for PLWH and controls, for the following simple automated definitions of HF: (1) any *ICD* code for HF; (2) any BNP >100 pg/mL; (3) any *ICD* code for HF or any BNP >100 pg/mL; and (4) any *ICD* code for HF and any BNP >100 pg/mL. Physician-adjudicated HF was used as the gold standard for HF based on current data standards.[17] Calculation of sensitivity relies on the assumption that no true HF diagnoses were missed by our (intentionally oversensitive) screening and ascertainment protocol; to justify this assumption, we reviewed charts for 95 randomly selected HIVE-4CVD participants who screened negative for HF from our highly sensitive screen and found that none had adjudicated HF. After evaluating the performance of these different automated HF definitions, we performed exploratory analyses comparing the odds of HF for PLWH versus uninfected controls using each of the 4 automated definitions of HF as well as our adjudicated HF definition. These exploratory analyses used odds rather than hazard ratios (HRs) because these analyses were not time-to-event and included people with HF at baseline.

P<0.05 indicated statistical significance. Analyses were completed using SAS software v9.4 (SAS Institute).

Results

Baseline Characteristics

After excluding people in HIVE-4CVD with adjudicated HF before or within 30 days after baseline, 4640 PLWH and 4250 uninfected controls were eligible for analysis. Baseline

Table 1. Baseline Characteristics by HIV Status

	HIV+ (n=4640)	Controls (n=4250)
Age, y, mean±SD*	40.8±10.7	40.4±11.8
Male sex	3840 (82.8)	3410 (80.2)
Race†		
White	1794 (38.8)	1998 (47.3)
Black	1441 (31.1)	1312 (31.1)
Hispanic	60 (1.3)	32 (0.8)
Asian	58 (1.3)	74 (1.7)
American Indian or Alaskan Native	4 (0.1)	1 (0.02)
Native Hawaiian or Other Pacific Islander	2 (0.04)	1 (0.02)
Declined	409 (8.8)	377 (8.9)
Other	687 (14.8)	348 (8.2)
Baseline year, n (%)		
1996–2005	1669 (36.0)	1825 (42.9)
2006–2010	1584 (34.1)	1696 (39.9)
2011–2016	1387 (29.9	729 (17.1)
BMI, kg/m^2	26.3±6.0	28.9±7.0
Hepatitis C virus	260 (5.6)	45 (1.1)
Hypertension	743 (16.0)	795 (18.7)
Diabetes mellitus	207 (4.5)	261 (6.1)
Coronary heart disease	234 (5.0)	228 (5.4)
HIV viral load <500 copies/mL or undetectable‡	2448 (53.5)	
CD4+ T cell count‡	397±272	
Baseline antiretroviral therapy use	1563 (33.7)	
Antiretroviral use ever during follow-up	4047 (87.2)	
Protease inhibitor use ever during follow-up	2240 (48.3)	

Data are shown as n (%) except as noted. BMI indicates body mass index; PLWH, people living with HIV.

*Variables for which standard deviation is shown were normally distributed.

†Baseline BMI data were incomplete or missing for 912 (19.7%) PLWH and 584 (13.7%) controls; therefore, baseline BMI measurements in Table 1 are for 3728 PLWH and 3666 uninfected controls.

‡HIV viral load and CD4+ T cell count measurements are based on the first recorded value for each following HIV diagnosis date, up to 30 days before HF or most recent follow-up. Overall, 60 PLWH (1.3%) had missing HIV viral load data and 79 (1.7%) had missing CD4+ T cell count data. Therefore, baseline HIV viral load data from Table 1 are for 4580 PLWH, and baseline CD4+ T cell count data are for 4561 PLWH.

characteristics are shown in Table 1. For PLWH and uninfected controls, baseline age and sex were similar, as was the proportion of black participants, as expected in a cohort frequency-matched on these characteristics. Whereas PLWH tended to have lower baseline BMI than controls and, not surprisingly, were more likely to have hepatitis C virus, the prevalence of hypertension, diabetes mellitus, and CHD was generally similar for PLWH and controls. At baseline, 33.7% of PLWH were taking ART, suggesting that some were either in care or initiated on ART immediately on diagnosis. The vast majority (87.2%) of PLWH used ART during follow-up, and 48.3% used a protease inhibitor (PI) during follow-up. The first measured viral load was undetectable or <500 copies/mL (the cutoff for undetectable on earlier HIV viral detection assays included in these analyses) for 53.5% of PLWH.

HF Adjudication and Incidence by HIV Serostatus

Results from the HF screening and physician adjudication process are shown in Figure 1. Of 4759 PLWH (mean follow-up: 5.6 years), 886 screened as having possible HF (based on our objective screening criteria including diagnosis codes,

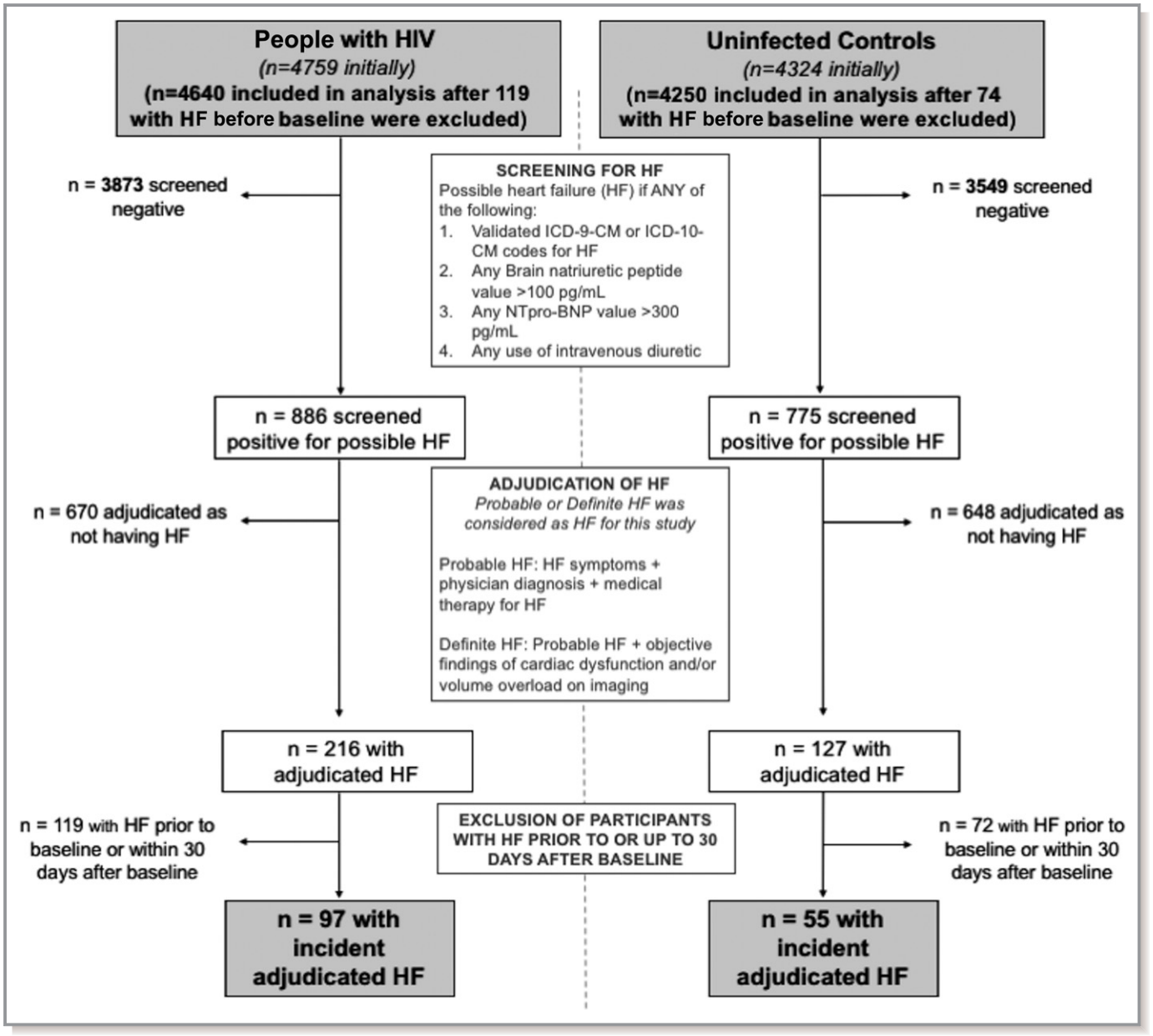

Figure 1. Heart failure screening and adjudication in HIVE-4CVD (HIV Electronic Comprehensive Cohort of CVD Complications). HF indicates heart failure; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; *ICD-10-CM*, *International Classification of Diseases, 10th Revision, Clinical Modification*; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

laboratory evidence, and/or use of intravenous diuretic); 216 of these 886 PLWH were determined to have HF by physician adjudication. Of the 216 PLWH with adjudicated HF, 119 had HF before or within 30 days after baseline and therefore were excluded from analyses because they were not at risk for incident HF. This left 97 PLWH with incident adjudicated HF (2.1% of 4640 PLWH without HF at or within 30 days of baseline; mean time to HF: 6.8 years). Of 4324 uninfected controls (mean follow-up: 5.8 years), 775 screened as having possible HF, and 127 of these 775 people had adjudicated HF. Of these 127 people, 72 had HF before or within 30 days after baseline and were excluded from analysis. There were thus 55 uninfected controls with incident adjudicated HF (1.3% of 4250 controls without HF at or within 30 days of baseline; mean time to HF: 6.7 years). The Kaplan–Meier estimates of survival free from HF for PLWH versus uninfected controls are shown in Figure 2. On multivariable-adjusted analysis (Table 2), PLWH had significantly greater hazards of incident HF than uninfected controls, even after adjustment for age, sex, race/ethnicity, baseline BMI, hypertension, diabetes mellitus, year of study entry, and CHD (HR: 2.10; 95% confidence interval [CI], 1.38–3.21). Results were similar when we adjusted for duration of clinical diagnoses (Table S1). There were no significant interactions by race and sex, and when black and white people were analyzed separately, results were highly similar (data not shown). Similar proportions of PLWH and uninfected people with incident HF had CHD diagnoses at least 30 days before HF diagnosis (10/55 uninfected people [18.2%] and 17/97 PLWH [17.5%]).

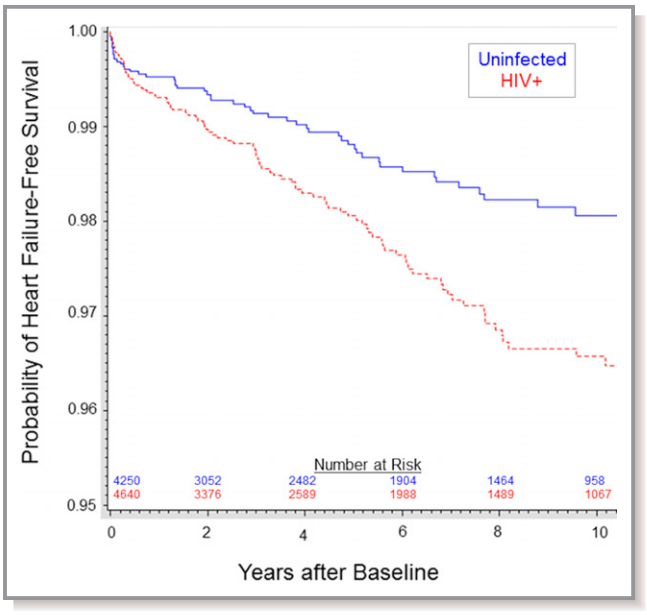

Figure 2. Survival free of heart failure by HIV serostatus.

HIV-Related Factors Associated With Incident HF

We then restricted our analyses to PLWH and evaluated associations of HIV-related immunosuppression (time-updated CD4+ T cell count) and viremia (time-updated measured HIV viral load) with incident HF. In multivariable analyses adjusted for age, sex, race, baseline BMI, hypertension, diabetes mellitus, year of study entry, and ART use, higher HIV viral load was associated with a significantly greater incidence of HF (Table 3; HR per $\log_{10}$ greater HIV viral load: 1.22; 95% CI, 1.11–1.33). Higher CD4+ T cell count (reflecting less immunosuppression) was associated with a significantly lower incidence of HF after adjustment for the same demographic and clinical covariates (Table 4; HR per 100 cells/mm^3 greater CD4+ T cell count: 0.80; 95% CI, 0.69–0.92). When HIV viral load and CD4+ T cell count were included in the same model adjusted for demographics, clinical characteristics, and baseline year, each was associated with a statistically significant difference in HF risk (Table 3; HR per $\log_{10}$ higher HIV viral load: 1.19; 95% CI, 1.09–1.30; HR per 100 cells/mm^3 higher CD4+ T cell count: 0.85; 95% CI, 0.74–0.95). In exploratory analyses evaluating clinically relevant categories of CD4+ T cell count, PLWH with baseline CD4+ T cell count <200 cells/mm^3 had a borderline greater hazard of HF (HR: 1.84; 95% CI, 0.97–3.50) than those with baseline CD4+ T cell count >500 cells/mm^3 (Table S2).

Automated Versus Physician-Adjudicated HF Definitions

The sensitivity and PPV of different automated HF definitions, with adjudicated HF as the gold standard, in the expanded cohort (including people in HIVE-4CVD with HF at baseline; n=4759 PLWH and n=4324 controls) are shown in Figure 3. The most sensitive automated HF definitions—(1) any *ICD* code for HF and (2) any *ICD* code for HF or any BNP >100 pg/mL—had low PPVs ranging from 20.3% to 30.2%. The other automated HF definitions had somewhat higher PPVs, with a trade-off being lower sensitivities. An automated definition based only on BNP >100 pg/mL had sensitivities of 75.0% and 67.7% and PPVs of 46.2% and 45.5% for PLWH and uninfected controls, respectively. Meanwhile, a more selective definition based on BNP >100 pg/mL and any *ICD* code for HF had sensitivities of 74.1% and 67.7% for PLWH and uninfected controls, respectively, with PPVs of 59.5% and 54.8%, respectively. Therefore, the most accurate automated definition of HF still lacked adequate sensitivity (missing >25% of HF diagnoses for PLWH and uninfected controls) and had excessive false positives (with PPV <60% for PLWH and uninfected controls) when considered relative to the gold standard of adjudicated HF. The relative excess in HF odds for PLWH versus uninfected people differed depending on the HF

Table 2. Association Between HIV Status and Hazards of HF

	HR (95% CI)			
Characteristic	Model 1 (n=8851)	Model 2 (n=7371)	Model 3 (n=7371)	Model 4 (n=7371)
HIV+	1.63 (1.17–2.28)	2.03 (1.33–3.08)	2.10 (1.38–3.21)	2.10 (1.38–3.21)
Baseline age, y	1.05 (1.03–1.06)	1.03 (1.01–1.05)	1.03 (1.01–1.05)	1.02 (1.01–1.04)
Sex (female)	1.02 (0.67–1.53)	1.17 (0.71–1.92)	1.17 (0.71–1.92)	1.22 (0.74–2.01)
White race	Referent	Referent	Referent	Referent
Black race	2.72 (1.90–3.91)	1.99 (1.27–3.12)	2.02 (1.29–3.17)	1.96 (1.25–3.08)
Other race	0.82 (0.49–1.38)	0.60 (0.31–1.17)	0.62 (0.32–1.20)	0.60 (0.31–1.16)
Baseline BMI (kg/m^2)		1.02 (1.00–1.05)	1.02 (1.00–1.05)	1.02 (0.99–1.05)
Hypertension		1.46 (0.93–2.31)	1.48 (0.94–2.34)	1.30 (0.81–2.08)
Diabetes mellitus		2.30 (1.31–4.04)	2.29 (1.30–4.04)	2.13 (1.20–3.75)
Hepatitis C virus		0.71 (0.26–1.95)	0.69 (0.25–1.92)	0.70 (0.25–1.94)
Baseline year 1996–2005 (vs 2011–2016)			1.66 (0.86–3.19)	1.60 (0.83–3.08)
Baseline year 2006–2010 (vs 2011–2016)			1.36 (0.70–2.64)	1.28 (0.66–2.50)
Coronary heart disease				2.38 (1.38–4.11)

BMI indicates body mass index; CI, confidence interval; HF, heart failure; HR, hazard ratio.

definition used, with effect sizes most muted for definitions incorporating *ICD* codes that did not require elevated BNP. Odds ratios were 1.22 (95% CI, 1.09–1.38) for any *ICD* code; 1.32 (95% CI, 1.17–1.47) for any *ICD* code or BNP >100 pg/mL; 1.79 (95% CI, 1.47–2.19) for any *ICD* code and BNP >100 pg/mL; 1.97 (95% CI, 1.64–2.36) for BNP >100 pg/mL; and 1.77 (95% CI, 1.42–2.21) for physician-adjudicated HF.

Discussion

In this study of a clinical cohort of PLWH and uninfected controls with adjudicated HF end points, PLWH had an approximately 2-fold greater risk of HF than uninfected controls. This association remained after adjustment for demographics, cardiovascular risk factors, CHD, and secular trends. Among PLWH, higher HIV viremia and lower CD4+ T cell count were both statistically significantly associated with greater risk of HF. Automated definitions of HF based on combinations of administrative codes and BNP values had relatively low accuracy compared with adjudicated HF end points, with the most accurate automated definition tested having sensitivity <75% and PPV <60%. Furthermore, HF definitions based on administrative codes alone estimated a substantially lower effect size for HF among PLWH versus uninfected controls compared with (1) HF definitions incorporating BNP and (2) physician-adjudicated HF.

This study is the first, to our knowledge, to evaluate incident HF in HIV using adjudicated HF end points. Previous studies that either performed imaging of subclinical myocardial dysfunction or assessed HF based on diagnosis codes only (without physician adjudication) have suggested that HIV is associated with HF. Indeed, we observed a significantly elevated HF risk among PLWH (multivariable-adjusted HR of 2.10 for PLWH versus controls; P=0.0005). This association is similar to but stronger than that observed in previous studies relying on diagnosis codes that did not have adjudicated HF events.[13,14]

A reason for the large effect size we observed may relate to the relatively young nature of our cohort, with a mean baseline age of approximately 40 years. The incidence of HF for PLWH versus controls in the VACS (Veterans Aging Cohort Study) was greatest at younger age (incidence rate ratio for PLWH versus controls <40 years old was 2.02 versus 1.15–1.35 for age groups ≥40 years, in which 94% of HF events occurred in the VACS).[13,14] Furthermore, because our study included a substantially greater proportion of women (>17% of PLWH, versus <3% in the VACS study), our findings may reflect particularly high HIV-associated HF risks for women relative to men. Although our study was not powered to perform sex-specific analyses, future studies of HIV-associated myocardial dysfunction and HF by sex are of interest; inflammation, immune activation, and perhaps autonomic dysfunction are implicated in HIV-related cardiovascular diseases,[29] and it is possible that the effects they exert differ by sex. It is also possible that our lack of valid substance use–related data may have contributed to the large effect size we observed; although smoking is more common among PLWH, it is unclear whether smoking would be independently associated with HF after adjustment for demographics,

Table 3. HF Hazards Among People With HIV by Time-Updated Viral Load

	HR (95% CI)				
Characteristic	Model 1 (n=4568)	Model 2 (n=3687)	Model 3 (n=3687)	Model 4 (n=3372)	Model 5 (n=3361)
Log_{10} of time-updated HIV viral load	1.18 (1.10–1.27)	1.16 (1.06–1.26)	1.17 (1.08–1.28)	1.22 (1.11–1.33)	1.19 (1.09–1.30)
Baseline age, y	1.04 (1.02–1.07)	1.03 (1.00–1.06)	1.03 (1.00–1.06)	1.03 (0.99–1.06)	1.03 (0.99–1.06)
Sex (female)	1.08 (0.56–2.09)	1.41 (0.66–3.02)	1.33 (0.62–2.84)	1.13 (0.49–2.58)	1.05 (0.46–2.42)
White race	Referent	Referent	Referent	Referent	Referent
Black race	3.04 (1.63–5.67)	2.62 (1.26–5.45)	2.78 (1.33–5.84)	2.64 (1.24–5.59)	2.57 (1.20–5.49)
Other race	0.88 (0.37–2.06)	0.76 (0.28–2.03)	0.80 (0.30–2.14)	0.81 (0.30–2.18)	0.80 (0.30–2.17)
Baseline BMI (kg/m^2)		0.99 (0.94–1.05)	0.99 (0.94–1.05)	0.99 (0.93–1.05)	1.00 (0.95–1.06)
Hypertension		0.94 (0.44–2.04)	1.00 (0.46–2.17)	1.08 (0.49–2.37)	1.02 (0.46–2.23)
Diabetes mellitus		2.03 (0.76–6.57)	2.31 (0.78–6.84)	2.45 (0.82–7.32)	2.32 (0.77–6.98)
Baseline year 1996–2005 (vs 2011–2016)				2.09 (0.61–7.11)	2.17 (0.64–7.42)
Baseline year 2006–2010 (vs 2011–2016)				1.12 (0.30–4.13)	1.14 (0.31–4.19)
Baseline ART use (yes)				1.47 (0.76–2.84)	1.48 (0.76–2.88)
Time-updated CD4+ T cell count (per 100 cells/mm^3 greater)					0.85 (0.74–0.98)

ART indicates antiretroviral therapy; BMI, body mass index; CI, confidence interval; HF, heart failure; HR, hazard ratio.

cardiovascular risk factors, CHD, and temporal considerations.[30] If substance use (including but not limited to smoking, cocaine, alcohol, methamphetamine, and intravenous drugs) is more common among PLWH than uninfected people in HIVE-4CVD and is significantly associated with HF in this cohort, this may represent a source of residual confounding.

Another reason for the relatively large effect size we observed for incident HF by HIV serostatus may relate to HF ascertainment protocols. For instance, if providers are systematically less likely to enter diagnosis codes of HF for PLWH than comparable uninfected people (perhaps because of superseding HIV-related diagnoses and comorbidities), then an excess in HF risk among PLWH compared with uninfected people would likely be underestimated. Interestingly, when we evaluated automated definitions of HF for which administrative codes alone were sufficient for diagnosis, the relative difference in HF odds for PLWH was far lower (odds ratio: 1.22 for PLWH versus controls) than for definitions requiring

Table 4. HF Hazards Among People With HIV by Time-Updated CD4+ T Cell Count

	HR (95% CI)			
Characteristic	Model 1 (n=4549)	Model 2 (n=3677)	Model 3 (n=3677)	Model 4 (n=3367)
Time-updated CD4+ T cell count (per 100 cells/mm^3 greater)	0.82 (0.73–0.92)	0.82 (0.71–0.94)	0.81 (0.71–0.93)	0.80 (0.69–0.92)
Baseline age, y	1.03 (1.01–1.06)	1.03 (1.00–1.06)	1.02 (1.00–1.06)	1.02 (0.99–1.05)
Sex (female)	1.05 (0.55–2.03)	1.32 (0.62–2.79)	1.27 (0.60–2.69)	1.03 (0.45–2.34)
White race	Referent	Referent	Referent	Referent
Black race	2.98 (1.64–5.43)	2.54 (1.27–5.08)	2.76 (1.37–5.55)	2.65 (1.30–5.39)
Other race	0.88 (0.39–1.97)	0.76 (0.31–1.90)	0.85 (0.34–2.12)	0.85 (0.34–2.13)
Baseline BMI (kg/m^2)		0.99 (0.94–1.05)	1.00 (0.95–1.05)	1.00 (0.94–1.05)
Hypertension		0.97 (0.46–2.03)	1.00 (0.47–2.11)	1.06 (0.50–2.25)
Diabetes mellitus		1.62 (0.55–4.76)	1.73 (0.58–5.11)	1.78 (0.60–5.28)
Baseline year 1996–2005 (vs 2011–2016)			4.33 (1.29–14.5)	3.88 (1.15–13.1)
Baseline year 2006–2010 (vs 2011–2016)			2.19 (0.62–7.73)	2.12 (0.60–7.53)
Baseline ART use				1.02 (0.54–1.92)

ART indicates antiretroviral therapy; BMI, body mass index; CI, confidence interval; HF, heart failure; HR, hazard ratio.

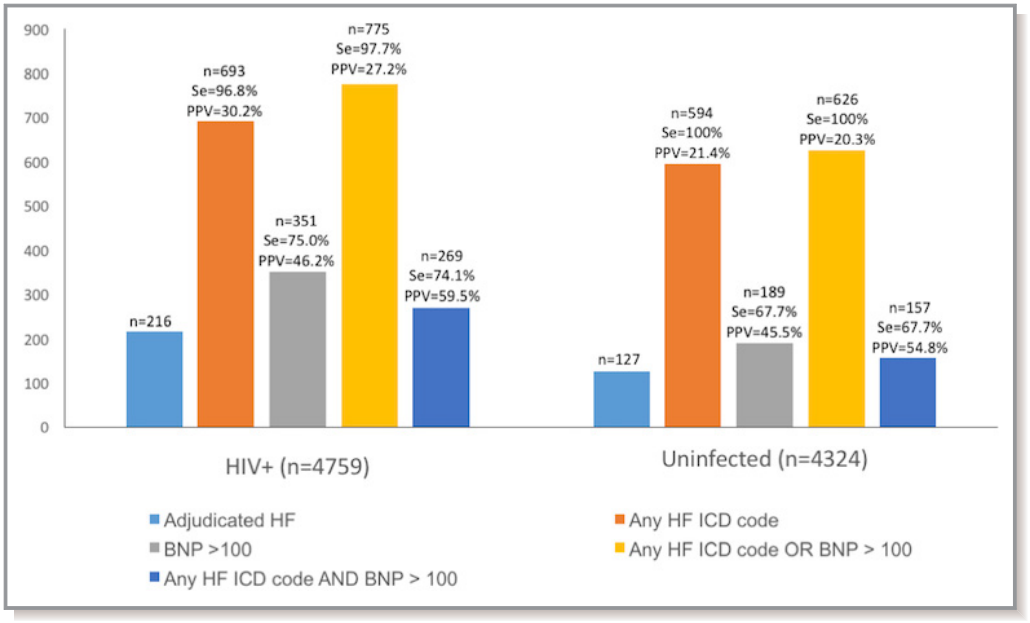

Figure 3. Characteristics of automated heart failure screening protocols in HIVE-4CVD (HIV Electronic Comprehensive Cohort of CVD Complications) relative to the adjudicated heart failure gold standard. BNP indicates B-type natriuretic peptide; HF, heart failure; *ICD*, *International Classification of Diseases*; PPV, positive predictive value; Se, sensitivity.

elevated BNP (odds ratio: 1.79–1.97) and physician-adjudicated HF (odds ratio: 1.77). This may have been driven by a relative excess in uninfected controls with HF diagnosis codes entered who were determined not to have HF (78.6% of controls with any *ICD* code for HF did not have adjudicated HF versus 69.8% of PLWH; Figure 3). Indeed, if HF diagnosis codes are systematically more likely to be entered for uninfected people than for PLWH with comparable symptoms and clinical scenarios, our adjudication protocol may have unmasked a greater relative difference in HF for PLWH versus uninfected controls than that observed in analyses relying on diagnosis codes alone.

Our protocol for ascertaining HF was essential, given relatively poor agreement between administrative codes for HF and physician-adjudicated HF. We found relatively poor agreement of automated HF definitions (based on administrative codes and/or BNP levels) with physician-adjudicated HF end points, which is consistent with prior studies.[16,31–33] Compared with our adjudicated HF definition as the gold standard, the most sensitive automated definitions of HF yielded PPVs ranging from 20.3% to 30.2%; as expected, more selective definitions incorporating BNP levels traded decreased sensitivity (67.7–75.0%) for somewhat higher, but still likely inadequate, PPVs (45.5–59.5%). These relatively low PPVs imply that even with these selective definitions, ≥40% of those considered to have HF actually do not have HF based on physician adjudication. To accurately understand characteristics and ultimately pathophysiology underlying HF in a population, it is essential that as much as possible of the population defined as having HF actually has HF.

We found that higher HIV viremia and lower CD4+ T cell count were associated with significantly higher HF risks among PLWH. This largely corroborates our previous cross-sectional and longitudinal findings from the VACS that higher HIV viral load is associated with HF among PLWH.[14,18] This illustrates the public health importance of prompt HIV diagnosis, early ART initiation, and strict ART adherence in this population. Nevertheless, HF risks still appear to be greater among PLWH with low or undetectable viral loads and with CD4 counts ≥500 cells/mm^3 than among uninfected controls.[14] Taken together, these findings suggest that HIV-related viremia and immune dysfunction may be implicated in HIV-associated HF, but other factors appear to be involved as well. Inflammation and immune activation are hallmarks of chronic HIV infection, even in the absence of peripherally detectable HIV viremia,[29,34] and are involved in HF pathogenesis in the general population.[35] Although certain ART medications have been implicated in myocardial toxicity[36] and associated with elevated rates of HF,[14] less is known about the impact of newer antiretroviral therapies on the myocardium and HF risk. Our findings are also consistent with prior studies suggesting that suppression of HIV viral replication with effective ART is associated with lower risk of HF (in addition to preventing noncardiac events).[14,18]

Our use of adjudicated HF end points represents a key strength given the discrepancy between HF end points based

on physician adjudication versus automated definitions relying on administrative codes and/or laboratory markers. An additional strength is our use of a clinical cohort, which includes all eligible patients with data collected in the course of their inpatient and/or outpatient clinical care. This approach reflects a distinct, likely sicker, and possibly more "real-world" population compared with longitudinal cohort studies that require participants to be willing and able to attend frequent study visits.

There are also limitations to acknowledge. This study was performed at a single large urban medical system and relied on data collected in routine clinical care. Although the single-center nature of this study may limit its generalizability, our findings were largely consistent with those of previous studies examining myocardial dysfunction and nonadjudicated HF diagnoses among PLWH. Our reliance on data collected during routine clinical care was unavoidable given the nature of our clinical cohort; we sought to address potential inconsistencies in data collection and follow-up by frequency-matching PLWH with controls on demographics, zip code, and clinic location and by ensuring all participants had valid baseline dates based on initial clinical encounters and/or HIV diagnosis. Furthermore, although PLWH and controls were not explicitly matched on cardiovascular risk factors, levels of cardiovascular risk factors were largely similar for PLWH and controls. Based on the nature of our cohort and inconsistent collection of smoking and substance use data, we were unable to include these data in our analyses. This limitation is significant because people with alcohol and other substance use disorders may have several reasons for HF, and PLWH are more likely than uninfected people to have alcohol and substance use disorders. Consequently, this may represent a source of residual confounding. Although we had a substantially greater proportion of women than previous studies examining incident HF in HIV, we did not have adequate power to examine sex-specific differences in HF by HIV status. We also were not adequately powered to evaluate HF subtype (eg, reduced versus preserved ejection fraction) in this study, although this distinction is of great interest in future analyses of HF in HIV. Finally, although our comparison of automated and physician-adjudicated HF definitions presumes that physician-adjudicated HF is the gold standard, this is based on accepted data standards.[17]

Despite these limitations, our study represents the first to examine incident HF among PLWH using adjudicated HF end points. We found that PLWH have significantly greater rates of HF than uninfected controls, corroborating findings from previous analyses of administrative data suggesting an association between HIV and HF. We also found that automated definitions of HF had relatively low accuracy compared with physician-adjudicated HF end points for PLWH and uninfected people, underscoring the necessity of adjudication for accurate HF definition. These findings provide evidence to inform practitioners and public health officials caring for the aging HIV-infected population increasingly at risk for cardiovascular diseases.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Association between HIV Status and Incident Heart Failure with Adjustment for Duration of Clinical Diagnoses.

Hazard Ratio (95% CI)			
Characteristic	Model Adjusted for Diagnoses (Original Model) (N=7371)	Characteristic	Model Adjusted for Diagnosis Duration (N=7371)
Human Immunodeficiency Virus (HIV)	2.10 (1.38-3.21)	Human Immunodeficiency Virus (HIV)	2.01 (1.32-3.06)
Baseline Age (years)	1.02 (1.01-1.04)	Baseline Age (years)	1.03 (1.01-1.05)
Sex (female)	1.22 (0.74-2.01)	Sex (female)	1.20 (0.73-1.97)
White race	Referent	White race	Referent
Black race	1.96 (1.25-3.08)	Black race	2.18 (1.39-3.42)
Other race	0.60 (0.31-1.16)	Other race	0.62 (0.32-1.19)
Baseline Body-Mass Index (kg/m^2)	1.02 (0.99-1.05)	Baseline Body-Mass Index (kg/m^2)	1.03 (1.00-1.05)
Hypertension	1.30 (0.81-2.08)	Hypertension duration (years)	0.78 (0.61-1.00)
Diabetes Mellitus	2.13 (1.20-3.75)	Diabetes Mellitus duration (years)	1.20 (0.88-1.65)
Hepatitis C Virus	0.70 (0.25-1.94)	Hepatitis C Virus duration (years)	0.77 (0.44-1.33)

Baseline year 1996-2005 (versus 2011-2016)	1.60 (0.83-3.08)	Baseline year 1996-2005 (versus 2011-2016)	1.63 (0.85-3.13)
Baseline year 2006-2010 (versus 2011-2016)	1.28 (0.66-2.50)	Baseline year 2006-2010 (versus 2011-2016)	1.32 (0.68-2.56)
Coronary Heart Disease	2.38 (1.38-4.11)	Coronary Heart Disease	3.16 (1.83-5.47)

Table S2. Heart Failure Incidence by Categorical CD4 Count.

Hazard Ratio (95% CI)			
Characteristic	Model 1 (N=4549)	Model 2 (N=3677)	Model 3 (N-3677)
CD4+ T Cell Count (cells/mm^3)			
>500	Referent	Referent	Referent
200-500	1.32 (0.78-2.25)	0.98 (0.51-1.86)	0.98 (0.52-1.87)
<200	2.36 (1.38-4.04)	1.79 (0.94-3.41)	1.84 (0.97-3.50)
Baseline Age (years)	1.04 (1.02-1.06)	1.02 (1.00-1.05)	1.02 (1.00-1.05)
Sex (female)	1.12 (0.67-1.88)	1.29 (0.66-2.51)	1.28 (0.66-2.51)
White race	1.13 (0.61-2.09)	1.30 (0.62-2.72)	1.23 (0.59-2.59)
Black race	2.86 (1.62-5.04)	2.47 (1.22-4.99)	2.45 (1.21-4.96)
Other race	Referent	Referent	Referent
Baseline Body-Mass Index (kilograms/meters^2)		0.99 (0.94-1.03)	0.99 (0.94-1.03)
Hypertension		1.10 (0.58-2.07)	1.13 (0.60-2.14)
Diabetes Mellitus		1.85 (0.76-4.53)	1.91 (0.78-4.67)
Hepatitis C Virus		0.82 (0.29-2.31)	0.81 (0.29-2.26)
Baseline year 1996-2005 (versus 2011-2016)			2.03 (0.91-4.52)
Baseline year 2006-2010 (versus 2011-2016)			1.32 (0.57-3.02)