Human Immunodeficiency Virus Increases the Risk of Incident Heart Failure

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Background: Although the HIV can cause myocardial inflammation, the association of HIV infection with subsequent development of heart failure (HF) has not been extensively studied. This nationwide cohort study aimed to determine the risk of incident HF in people living with HIV/AIDS (PLWHA).

Methods: We identified PLWHA using the Taiwan Centers for Disease Control and Prevention HIV Surveillance System. An age- and sex-matched control group without HIV infection was selected from the Taiwan National Health Insurance Research Database for comparison. All patients were followed up until December 2014 and were observed for a new diagnosis of HF. A time-dependent Cox proportional hazards model was used to determine the association of HIV and highly active antiretroviral therapy with incident HF, with death as a competing risk event.

Results: Of the 120,765 patients (24,153 PLWHA and 96,612 matched controls), 641 (0.53%) had incident HF during a mean follow-up period of 5.84 years, including 192 (0.79%) PLWHA and 449 (0.46%) controls. Time to diagnosis of incident HF was significantly shorter in PLWHA than in those without HIV infection ($P < 0.001$, the log-rank test). After adjusting for age, sex, and comorbidities, HIV infection was found to be an independent risk factor for incident HF (adjusted hazard ratio, 1.52; 95% confidence interval: 1.27 to 1.82). As the duration of highly active antiretroviral therapy increased, the risk of HF decreased ($P = 0.014$).

Conclusions: HIV infection was an independent risk factor for incident HF. Clinicians need to be aware of the higher risk of HF in PLWHA.

Key Words: heart failure, human immunodeficiency virus, highly active antiretroviral treatment

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INTRODUCTION

More than 36.7 million people have been infected with HIV worldwide.[1] Moreover, 1.0 million people died of AIDS and other HIV-related illnesses worldwide in 2016.[1] With the success of highly active antiretroviral therapy (HAART), people living with HIV/AIDS (PLWHA) are aging, and more chronic diseases (eg, cardiovascular diseases) are being diagnosed in this population.

Heart failure (HF) in PLWHA can cause significant morbidity and mortality. The pathogenesis of HF is multifactorial, including incident coronary artery disease (CAD),[2] myocarditis,[2] myocardial fibrosis,[3] and cardiac steatosis.[4] Previous studies showed that PLWHA had a higher risk of incident CAD.[5] Cardiac magnetic resonance imaging and spectroscopy revealed that compared with HIV-uninfected individuals, PLWHA had a higher rate of myocardial fibrosis and cardiac steatosis.[6] Despite some evidence suggesting that PLWHA have a higher risk of HF, the association between HIV infection and the development of HF has not been extensively studied. Two previous studies showed that veterans infected with HIV had a 1.2–1.8 fold higher risk of HF than individuals not infected with HIV.[7,8] The higher risk of HF persisted among veterans who did not have a coronary heart disease before the incident HF event.[7] In women with HF, HIV infection increased the risk of HF readmission.[9] However, these previous studies on the association between HIV infection and HF enrolled either only veterans[7,8] or female PLWHA.[9]

HAART plays an important role in improving the survival in PLWHA. Some antiretroviral drugs (eg, zidovudine) can cause mitochondrial damage and focal myocardial necrosis, possibly increasing the risk of HF development.[11,12] However, studies determining the association between HAART and incident HF are limited. Alvi et al[13] followed up 394 antiretroviral therapy–treated PLWHA who were hospitalized with HF and found that PLWHA receiving HAART with protease inhibitors have increased 30-day HF

readmission. Therefore, we conducted a nationwide population-based cohort study to examine the association of HIV infection and HAART with the risk of incident HF during 2003–2014 in Taiwan.

METHODS

Data Source

This cohort study used 2003–2014 data from the Taiwan Centers for Disease Control HIV Surveillance Database. In Taiwan, medical professionals are required by law to report new HIV infections to TCDC within 24 hours of diagnosis. Reported HIV-infected cases in Taiwan are defined as having a positive HIV-1 Western blot or a positive polymerase chain reaction analysis results. Since 1997, all individuals in Taiwan infected with HIV have been offered HAART free of charge.[14] This study was approved by the institutional review board of Taipei City Hospital (TCHIRB-10410122-E).

Study Subjects

This cohort study linked the Taiwan Centers for Disease Control and Prevention (CDC) HIV surveillance database to the Taiwan National Health Insurance Research Database. PLWHA who were aged 15 years or older were selected from the TCDC HIV Surveillance Database from 2003 through 2014. PLWHA who had a HF diagnosis (*ICD-9-CM* codes 428) before HIV diagnosis were excluded.

The control group was selected from the Taiwan National Health Insurance Research Database. In Taiwan, more than 99% of Taiwanese citizens have been covered by the National Health Insurance Program since 1995.[15] The control group in this study was matched by age, sex, and date of enrollment (±7 days). Four controls were randomly selected for each HIV patient.[16,17] Control subjects were excluded if (1) they had been reported to TCDC as HIV-infected cases or (2) they had received a diagnostic code for HF before inclusion into the study. The HIV patients and control groups were both followed up until a diagnosis of HF, death, or December 31, 2014. The death events were determined by the death certificate database of Taiwan. In Taiwan, it is regulated by the law that within 30 days after a patient dies, his or her death certificate must be registered by the physician in charge according to *ICD-9-CM* or *ICD-10-CM* codes. The cause-of-death coding in Taiwan is considered very accurate because trained medical registrars review and code all death certificates at the central office of the National Death Certification Registry.[18]

Outcome Variable

The outcome "new diagnosis of HF" was defined as the presence of an appropriate *ICD-9-CM* code (428).[19] A person was considered to have a new onset of HF only if the condition occurred in an inpatient setting or 3 or more outpatient visits in Taiwan. The validation of the diagnosis of HF has previously been reported, with an accuracy of around 97.6%.[19]

Control Variables

Control variables included sociodemographics, comorbidities, HAART, AIDS status, and opportunistic infections (OIs) after the diagnosis of HIV. Sociodemographic variables included income level and urbanization. Income level was calculated from the average monthly income of the insured person and grouped into 3 levels: low [≤19,200 New Taiwan Dollars (NTD)], intermediate (19,201 NTD to <40,000 NTD), and high (≥40,000 NTD). Urbanization was categorized as urban and rural area. Comorbidities included CAD (*ICD-9* code 410-414), dyslipidemia (*ICD-9* code 272), diabetes (*ICD-9* code 250), chronic kidney disease (CKD; *ICD-9* code 580-587), hypertension (HTN; *ICD-9* code 401-405), cancer (*ICD-9* code 140-208), cerebral vascular disease (CVD; *ICD-9* code 430–437), sleep apnea (*ICD-9* code 780.51, 780.53, and 780.57), and hepatitis C virus (HCV) infection (*ICD-9* code 070.41, 070.44, 070.51, and 070.54, V02.62). The OIs after the diagnosis of HIV included *Mycobacterium tuberculosis* infection (*ICD-9* code 011-018), disseminated *M. avium* complex infection (*ICD-9-CM* code 0312), *Pneumocystis jirovecii* pneumonia (*ICD-9* code 1363), *Penicillium marneffei* infection (*ICD-9-CM* code 1179), cytomegalovirus (*ICD-9* code 078.5), candidiasis (*ICD-9* code 112), herpes simplex (*ICD-9* code 054), and herpes zoster (*ICD-9* code 053). A person was considered to have a comorbidity or OI only if the condition occurred in an inpatient setting or 3 or more outpatient visits.[20]

Patients with HIV were considered to receive HAART if they received HAART before the new onset of HF. The classes of HAART included nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase inhibitors. AIDS status was defined by a CD4 lymphocyte count of < 200 cells/mm^3 or by any other AIDS-defining condition in an individual with HIV infection.[21]

Statistical Analysis

First, the demographic data of the study subjects were analyzed. Continuous data are presented as mean ± SD, and a 2-sample *t* test was used to compare outcomes between groups. Categorical data were analyzed using the Pearson χ^2 test where appropriate.

The incidence of HF per 100,000 person-years was calculated in patients with and without HIV infection. The relative hazards (RHs) of incident HF in PLWHA were estimated from Cox proportional hazards models as comparing with patients without HIV infection.

To determine the association between HIV infection and incident HF, a Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for age, sex, and comorbidities. In these models, we used competing risk Cox proportional hazards regression to determine the risk of HF in study subjects, in which HF competes with the risk of death.[22] Also, to evaluate the association between HAART and incident HF, a time-dependent Cox proportional hazards model was also used to identify risk factors for incident HF within PLWHA. In these models, HAART and AIDS status were regarded as time-dependent covariables,[23] whereas other confounders such as

age, sex, and comorbidities, which were collected at baseline, were considered as fixed covariates. Moreover, a time-dependent Cox proportional hazards model was used to determine the short-term and long-term effects of HAART on incident HF in PLWHA. Adjusted HRs (AHRs) with 95% CIs are reported to indicate the strength and direction of associations.

To examine the robustness of the main findings, subgroup and sensitivity analyses were conducted after stratifying study subjects by age, sex, and comorbidities. All data management and analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Participant Selection

A total of 25,061 individuals with HIV infection were reported to Taiwan CDC during the period from January 1, 2003, through December 31, 2014. After excluding those younger than 15 years (n = 33), those with antecedent HF (n = 324), and those with incomplete data (n = 551), the remaining 24,153 PLWHA were included in the analysis (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/B248). Another 96,612 subjects without HIV infection, matched for age and sex, were randomly selected for the control group. The overall mean (SD) age was 32.6 (9.9) years, and 93.83% of the subjects in the PLWHA were males. Mean (SD) follow-up time was 5.83 (3.38) years in the PLWHA and 5.84 (3.37) years in the control group. The demographic characteristics and comorbidities of the 2 groups are shown in Table 1. There were no significant differences in age or sex between groups. Compared with control subjects, PLWHA at baseline had a significantly higher proportion of CAD, CKD, malignancy, CVD, sleep apnea, and HCV infection, but had a significantly lower proportion of dyslipidemia and HTN.

Incident Rate of HF

During the study follow-up period, 641 individuals had a new onset of HF, including 192 (0.79%) PLWHA and 449 (0.46%) controls. The incidence rate of HF per 100,000 person-years was 136.34 in the PLWHA and 79.54 in the control group ($P < 0.001$). The RHs of incident HF was 1.63 [95% CI: 1.37 to 1.93] between PLWHA and the control group. Time to diagnosis of incident HF was significantly shorter in PLWHA than in those without HIV infection ($P < 0.001$, the log-rank test; Fig. 1).

Association of HIV Infection With Incident HF

A Cox proportional hazards model was used to identify independent risk factors for HF. After adjusting for age, sex, and comorbidities, HIV infection significantly increased the risk of incident HF (AHR 1.52; 95% CI: 1.27 to 1.82) (Table 2). Other risk factors associated with incident HF included older age, CAD, diabetes, CKD, HTN, and CVD.

Subgroup and Sensitivity Analysis for the Association Between HIV Infection and HF

This study conducted the subgroup analysis to evaluate the association between HIV and HF, after adjustment for patient demographics and comorbidities. HIV infection was significantly associated with a higher risk of HF in all patients' subgroups, except those who were aged 50 years or older and those with high income (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/B248). Among the subgroup subjects, female PLWHA had the highest risk of incident HF, followed by those living in urban areas.

Association of HAART With Incident HF Within PLWHA

The incidence rate of HF was 163.01 in PLWHA receiving HAART and 108.62 per 100,000 person-years in PLWHA not receiving HAART ($P < 0.001$) (Table 3). The univariate analysis showed that PLWHA receiving HAART had a significantly higher risk of incident HF than those not receiving HAART (HR 1.68; 95% CI: 1.24 to 2.28). After adjusting for age, sex, comorbidities, and OIs after the HIV

TABLE 1. Characteristics of the PLWHA and Matched Controls

Characteristics	No. (%) of Subjects* PLWHA, n = 24,153	Control, n = 96,612	*P*
Age, yrs			
Mean ± SD	32.6 ± 9.87	32.6 ± 9.87	0.999
15–49	22,618 (93.64)	90,468 (93.64)	0.981
≥50	1535 (6.36)	6144 (6.36)	
Sex			
Female	1482 (6.14)	5928 (6.14)	1
Male	22,671 (93.86)	90,684 (93.86)	
Income level			
Low	14,207 (58.82)	33,773 (34.96)	<0.001
Intermediate	8200 (33.95)	43,750 (45.28)	
High	1746 (7.23)	19,089 (19.76)	
Urbanization			
Rural	19,611 (81.19)	78,355 (81.1)	0.744
Urban	4542 (18.81)	18,257 (18.9)	
Comorbidity			
CAD	277 (1.15)	1267 (1.31)	0.042
Dyslipidemia	665 (2.75)	4330 (4.48)	<0.001
Diabetes	571 (2.36)	2319 (2.4)	0.742
CKD	234 (0.97)	663 (0.69)	<0.001
HTN	976 (4.04)	4910 (5.08)	<0.001
Cancer	295 (1.22)	866 (0.9)	<0.001
CVD	209 (0.87)	714 (0.74)	0.044
Sleep apnea	136 (0.56)	297 (0.31)	<0.001
HCV infection	584 (2.42)	395 (0.41)	<0.001
Outcome			
New onset of HF	192 (0.79)	449 (0.46)	<0.001
Incidence of HF†	136.34	79.54	<0.001
Follow-up yrs, mean (SD)	5.83 ± 3.38	5.84 ± 3.37	0.596

*Unless stated otherwise.
†Events per 100,000 person-years.

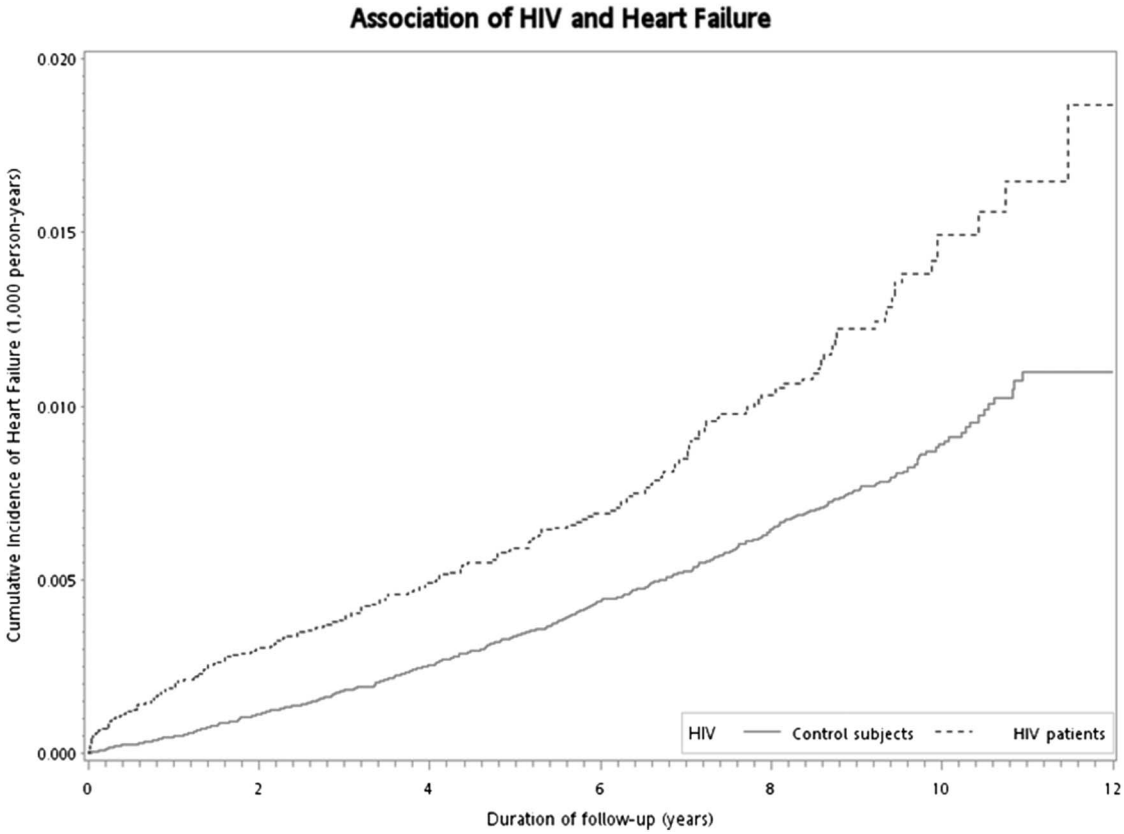

FIGURE 1. Kaplan–Meier curves for time to diagnosis of incident HF in patients with and without HIV infection.

diagnosis, a time-dependent Cox proportional hazards model showed that the RHs of incident HF were 1.35 (95% CI: 0.92 to 1.98) between PLWHA receiving HAART and those not.

This study evaluated the association between different classes of HAART and the risk of incident HF. After adjusting for age, sex, comorbidities, and OIs after the HIV diagnosis, a time-dependent Cox proportional hazards model showed that none of the classes of antiretroviral drugs were significantly associated with the risk of incident HF (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B248).

Short-Term and Long-Term Effects of HAART on Incident HF

A time-dependent Cox proportional hazards model was used to determine the short-term and long-term effects of HAART on incident HF among PLWHA. The incidence rates of HF per 100,000 person-years were 108.62, 200.74, 160.66, and 149.67 in PLWHA not receiving HAART, those receiving HAART within 1 year, those receiving HAART between 1 and 2 years, and after 2 years of treatment, respectively (Table 4). As the duration of HAART increased, the risk of HF decreased ($P = 0.014$). After adjusting for age, sex, comorbidities, and OIs after the HIV diagnosis, compared with PLWHA not receiving HAART, the RH of incident HF was 1.63 (95% CI: 0.95 to 2.80) in PLWHA receiving HAART within 1 year of treatment, 1.73 (95% CI: 0.96 to 3.10) in PLWHA receiving HAART between 1 and 2 years, and 1.08 (95% CI: 0.69 to 1.68) in PLWHA receiving HAART after 2 years of treatment.

DISCUSSION

This nationwide cohort study found that PLWHA had a significantly higher risk of developing incident HF compared with controls, after adjusting for demographic data and comorbidities.

Our study revealed robust associations between HIV infection and incident HF after stratifying patients by age, sex, and comorbidities. HIV infection significantly increased the risk of incident HF in all patients' subgroups, except those who were aged 50 years or older and those with high income.

This study found that PLWHA had a higher risk of HF than individuals not infected with HIV. A previous study showed that PLWHA had a higher prevalence of HF than individuals not infected with HIV (7.2% vs. 4.4%).[24] However, longitudinal studies that examine the association of HIV infection with the subsequent development of HF are limited. An early report from the Veterans Aging Cohort Study followed up 8486 male veterans (2391 patients with HIV and 6095 patients without HIV) and found that the HR for developing HF in patients infected with HIV was 1.81 (95% CI: 1.39 to 2.36).[7] The increased risk of HF in PLWHA persisted among those without CAD.[7] Another report from the Veterans Aging Cohort Study enrolled 98,015 veterans

TABLE 2. Univariate and Multivariate Analyses for the Factors Associated With Incident HF Among Subjects With and Without HIV Infection

Characteristic	No. of Patients	Incident HF	Follow-up Years	ID (95% CI)†	Univariate Analysis HR (95% CI)	Multivariate Analysis AHR (95% CI)
HIV infection						
No	96,612	449	564,529.03	79.54 (72.35 to 87.24)	1	1
Yes	24,153	192	140,821.68	136.34 (117.74 to 157.05)	1.63 (1.37 to 1.93)***	1.52 (1.27 to 1.82)***
Demographics						
Age, yrs						
15–49	113,086	419	658,903.45	63.59 (57.65 to 69.98)	1	1
≥50	7679	222	46,447.27	477.96 (417.15 to 545.14)	7.16 (6.07 to 8.43)***	2.94 (2.29 to 3.76)***
Sex						
Female	7410	54	54,864.24	98.42 (73.94 to 128.42)	1	1
Male	113,355	587	650,486.48	90.24 (83.09 to 97.84)	0.93 (0.7 to 1.23)	1.04 (0.78 to 1.38)
Income level						
Low	47,980	275	285,079.2	96.46 (85.40 to 108.57)	1	1
Intermediate	51,950	276	296,673.13	93.03 (82.38 to 104.68)	0.98 (0.83 to 1.16)	0.88 (0.74 to 1.05)
High	20,835	90	123,598.4	72.82 (58.55 to 89.50)	0.77 (0.61 to 0.98)*	0.74 (0.58 to 0.95)*
Urbanization						
Rural	97,966	479	567,701.52	84.38 (76.99 to 92.28)	1	1
Urban	22,799	162	137,649.2	117.69 (100.26 to 137.27)	1.38 (1.15 to 1.65)***	1.18 (0.98 to 1.42)
Comorbidity						
CAD						
No	119,221	540	697,173.96	77.46 (71.06 to 84.27)	1	1
Yes	1544	101	8176.76	1235.21 (1006.10 to 1500.89)	15.6 (12.6 to 19.31)***	2.81 (2.10 to 3.75)***
Dyslipidemia						
No	115,770	541	679,603.6	79.61 (73.04 to 86.60)	1	1
Yes	4995	100	25,747.12	388.39 (316.01 to 472.39)	4.95 (4 to 6.14)***	1.03 (0.78 to 1.35)
Diabetes						
No	117,875	528	689,670.02	76.56 (70.17 to 83.38)	1	1
Yes	2890	113	15,680.7	720.63 (593.90 to 866.40)	9.15 (7.46 to 11.21)***	1.94 (1.45 to 2.60)***
CKD						
No	119,868	598	700,747.26	85.34 (78.63 to 92.46)	1	1
Yes	897	43	4603.46	934.08 (676.00 to 1258.20)	9.86 (7.22 to 13.44)***	2.03 (1.40 to 2.95)***
HTN						
No	114,879	435	673,714.22	64.57 (58.64 to 70.93)	1	1
Yes	5886	206	31,636.5	651.15 (565.26 to 746.40)	9.87 (8.36 to 11.66)***	3.32 (2.46 to 4.47)***
Cancer						
No	119,604	627	699,290.97	89.66 (82.78 to 96.96)	1	1
Yes	1161	14	6059.75	231.03 (126.31 to 387.63)	2.15 (1.27 to 3.65)**	0.57 (0.31 to 1.03)
CVD						
No	119,842	590	700,558.47	84.22 (77.56 to 91.30)	1	1
Yes	923	51	4792.25	1064.22 (792.38 to 1399.25)	11.26 (8.41 to 15.06)***	1.60 (1.12 to 2.29)**
Sleep apnea						
No	120,332	637	703,647.68	90.53 (83.63 to 97.84)	1	1
Yes	433	4	1703.04	234.87 (64.00 to 601.37)	2.77 (1.04 to 7.40)*	1.08 (0.39 to 2.96)
HCV infection						
No	119,786	625	699,331.98	89.37 (82.50 to 96.66)	1	1
Yes	979	16	6018.74	265.84 (151.95 to 431.70)	2.77 (1.68 to 4.55)***	1.16 (0.68 to 2.00)

*<0.05; **<0.01; and ***<0.001.
†Events per 100,000 person-years.
ID, incidence density.

(31,523 patients with HIV and 66,492 patients without HIV) and showed that veterans infected with HIV had an increased risk of HF with reduced ejection fraction (HR, 1.61; 95% CI: 1.40 to 1.86) or preserved ejection fraction (HR, 1.21; 95% CI: 1.03 to 1.41).[8] Janjua et al[9] revealed that compared with HIV-uninfected individuals, HIV infection increased the risk of HF readmission (HR, 2.58; 95 CI: 1.55 to 4.29) in female PLWHA. This study followed up 24,153 PLWHA and found

TABLE 3. Univariate and Multivariate Analyses for the Factors Associated With Incident HF Among PLWHA

Characteristic	No. of Patients	Incident HF	Follow-up Years	ID (95% CI)†	Univariate Analysis HR (95% CI)	Multivariate Analysis AHR (95% CI)
HAART						
No	6783	75	69,048.35	108.62 (85.44 to 136.16)	1	1
Yes	17,370	117	71,773.33	163.01 (134.82 to 195.37)	1.68 (1.24 to 2.28)***	1.35 (0.92 to 1.98)
AIDS status						
No	13,537	73	76,605.17	95.29 (74.70 to 119.82)	1	1
Yes	10,616	119	64,216.52	185.31 (153.51 to 221.75)	1.98 (1.46 to 2.68)***	1.41 (0.94 to 2.13)
Demographics						
Age, yrs						
15–49	22,618	139	131,569.85	105.65 (88.81 to 124.74)	1	1
≥50	1535	53	9251.84	572.86 (429.11 to 749.31)	4.89 (3.54 to 6.75)***	2.18 (1.34 to 3.53)**
Sex						
Female	1482	25	10,936.85	228.59 (147.93 to 337.44)	1	1
Male	22,671	167	129,884.83	128.58 (109.81 to 149.62)	0.55 (0.36 to 0.83)**	0.64 (0.41 to 0.98)*
Income level						
Low	14,207	119	85,326.93	139.46 (115.53 to 166.89)	1	1
Intermediate	8200	62	45,684.49	135.71 (104.05 to 173.98)	0.98 (0.72 to 1.33)	0.79 (0.57 to 1.08)
High	1746	11	9810.26	112.13 (55.97 to 200.63)	0.83 (0.45 to 1.53)	0.66 (0.35 to 1.27)
Urbanization						
Rural	19,611	129	110,857.17	116.37 (97.15 to 138.27)	1	1
Urban	4542	63	29,964.51	210.25 (161.56 to 269.00)	1.82 (1.34 to 2.47)***	1.74 (1.26 to 2.40)***
Comorbidity						
CAD						
No	23,876	174	139,328.69	124.88 (107.02 to 144.88)	1	1
Yes	277	18	1492.99	1205.63 (714.54 to 1905.42)	9.11 (5.60 to 14.8)***	1.86 (0.94 to 3.66)
Dyslipidemia						
No	23,488	174	137,771.33	126.30 (108.23 to 146.52)	1	1
Yes	665	18	3050.35	590.10 (349.73 to 932.61)	4.49 (2.76 to 7.31)***	1.01 (0.57 to 1.80)
Diabetes						
No	23,582	164	137,695.53	119.10 (101.57 to 138.79)	1	1
Yes	571	28	3126.16	895.67 (595.16 to 1294.49)	6.96 (4.66 to 10.4)***	2.10 (1.15 to 3.83)*
CKD						
No	23,919	183	139,606	131.08 (112.78 to 151.51)	1	1
Yes	234	9	1215.69	740.32 (338.52 to 1405.36)	5.02 (2.56 to 9.83)***	1.22 (0.55 to 2.69)
HTN						
No	23,177	150	135,795.74	110.46 (93.49 to 129.62)	1	1
Yes	976	42	5025.94	835.66 (602.27 to 1129.58)	6.82 (4.82 to 9.66)***	2.38 (1.30 to 4.36)**
Cancer						
No	23,858	188	139,168.21	135.09 (116.47 to 155.84)	1	1
Yes	295	4	1653.48	241.91 (65.91 to 619.40)	1.59 (0.59 to 4.28)	0.52 (0.18 to 1.49)
CVD						
No	23,944	176	139,674.43	126.01 (108.08 to 146.06)	1	1
Yes	209	16	1147.25	1394.64 (797.16 to 2264.81)	9.33 (5.45 to 16.0)***	2.45 (1.26 to 4.77)**
Sleep apnea						
No	24,017	190	140,317.12	135.41 (116.84 to 156.09)	1	1
Yes	136	2	504.56	396.38 (48.00 to 1431.88)	2.96 (0.74 to 11.9)	1.52 (0.31 to 7.39)
HCV infection						
No	23,569	180	136,853.85	131.53 (113.01 to 152.21)	1	1
Yes	584	12	3967.83	302.43 (156.27 to 528.29)	2.26 (1.26 to 4.05)**	1.79 (0.96 to 3.32)
OIs after HIV diagnosis						
TB infection						
No	22,831	175	131,193.78	133.39 (114.36 to 154.68)	1	1
Yes	1322	17	9627.9	176.57 (102.86 to 282.71)	1.32 (0.79 to 2.18)	0.83 (0.47 to 1.44)

TABLE 3. (*Continued*) Univariate and Multivariate Analyses for the Factors Associated With Incident HF Among PLWHA

Characteristic	No. of Patients	Incident HF	Follow-up Years	ID (95% CI)†	Univariate Analysis HR (95% CI)	Multivariate Analysis AHR (95% CI)
Disseminated *M. avium* complex infection						
No	23,970	189	139,700.3	135.29 (116.69 to 156.01)	1	1
Yes	183	3	1121.39	267.53 (55.17 to 781.82)	1.89 (0.60 to 5.91)	1.80 (0.54 to 6.00)
Pneumocystis jirovecii pneumonia						
No	21,457	162	125,083.51	129.51 (110.34 to 151.06)	1	1
Yes	2696	30	15,738.18	190.62 (128.61 to 272.12)	1.40 (0.95 to 2.07)	1.04 (0.67 to 1.61)
Penicillium marneffei infection						
No	23,961	188	139,510.7	134.76 (116.18 to 155.46)	1	1
Yes	192	4	1310.98	305.12 (83.13 to 781.22)	1.68 (0.54 to 5.25)	1.18 (0.35 to 3.90)
Cytomegalovirus disease						
No	23,341	184	136,403.8	134.89 (116.11 to 155.86)	1	1
Yes	812	8	4417.89	181.08 (78.18 to 356.80)	1.24 (0.61 to 2.53)	0.74 (0.34 to 1.60)
Candidiasis						
No	21,561	160	125,083.4	127.91 (108.86 to 149.34)	1	1
Yes	2592	32	15,738.29	203.33 (139.07 to 287.04)	1.54 (1.05 to 2.26)*	1.15 (0.74 to 1.77)
Herpes simplex						
No	23,214	182	134,602.91	135.21 (116.28 to 156.35)	1	1
Yes	939	10	6218.78	160.80 (77.11 to 295.72)	1.24 (0.66 to 2.35)	1.11 (0.59 to 2.09)
Herpes zoster						
No	21,894	162	125,687.12	128.89 (109.81 to 150.34)	1	1
Yes	2259	30	15,134.56	198.22 (133.74 to 282.97)	1.62 (1.10 to 2.40)*	1.56 (1.04 to 2.32)*

*<0.05; **<0.01; and ***<0.001.
†Events per 100,000 person-years.
ID, incidence density; TB, tuberculosis.

that PLWHA had 1.5-fold higher risk of incident HF than patients not infected with HIV. The findings of our study suggest that HIV infection was an independent risk factor for incident HF.

HIV-related myocardial damage, fibrosis, and cardiac steatosis may account for the higher risk of incident HF in PLWHA. In vitro studies of human and rat cardiomyocytes, HIV can enter myocytes directly through pathways independent of a C–C chemokine receptor type 5.[10,25] The invasion of HIV into cardiac myocytes could cause myocardial inflammation and cytokine release.[26] HIV-related proinflammatory cytokines (eg, interleukin-1β and tumor necrosis factor-alpha) can promote expression of inducible nitric oxide synthase in cardiomyocytes.[27] High concentrations of nitric oxide and tumor necrosis factor-alpha could induce cardiomyocyte apoptosis[27] and lead to depressed heart function.[27]

HIV-associated myocardial fibrosis may also account for the higher risk of incident HF in PLWHA. Myocardial fibrosis represents previous myocarditis and can cause cardiac dysfunction.[28] A previous magnetic resonance imaging study showed that 76% of asymptomatic HIV-infected patients had myocardial fibrosis, which was higher than 13% of HIV-uninfected patients.[6] Myocardial fibrosis can reduce ventricular compliance and lead to the progression to HF.[3]

Cardiac steatosis may also explain the higher risk of incident HF in PLWHA. A previous study found that HIV-infected individuals had 47% higher median myocardial lipid levels than HIV-uninfected individuals.[6] Animal studies found that lipid over storage in cardiac myocytes can produce lipotoxic intermediates that cause apoptosis, which can lead to the development of HF.[4,29]

HAART is essential for improving the outcomes in PLWHA. However, studies determining the association between HAART and the development of HF are limited. Alvi et al[13] followed up 394 PLWHA and reported that PLWHA with HF who were receiving a protease inhibitor had increased 30-day HF readmission. Our study found that none of the classes of HAART were significantly associated with the risk of incident HF in PLWHA. A previous study showed that PLWHA with a well-controlled viral load had a lower risk of incident HF.[7] Our study evaluated the short-term and long-term effects of HAART on incident HF and found that the incident rates of HF decreased as the duration of HAART increased.

TABLE 4. Short-Term and Long-Term Effects of HAART on Incident HF

Characteristic	No. of Patients	Incident HF	Follow-up Years	ID (95% CI)†	Univariate Analysis HR (95% CI)	Multivariate Analysis‡ AHR (95% CI)
Time since HAART initiation						
No HAART	6783	75	69,048.35	108.62 (85.44 to 136.16)	1	1
<1 yr	17,370	32	15,941.32	200.74 (137.30 to 283.38)	1.93 (1.21 to 3.10)*	1.63 (0.95 to 2.80)
1–2 yrs	14,474	21	13,070.85	160.66 (99.45 to 245.59)	2.09 (1.24 to 3.53)*	1.73 (0.96 to 3.10)
>2 yrs	11,760	64	42,761.16	149.67 (115.26 to 191.12)	1.43 (0.97 to 2.09)	1.08 (0.69 to 1.68)

*<0.01.
†Events per 100,000 person-years.
‡Adjusting for age, sex, comorbidities, and OIs after HIV diagnosis.
ID, incidence density.

This nationwide cohort study has several strengths. First, unlike previous cohort studies that included only veterans,[7,8] women,[9] or HIV-infected individuals from a single center,[13] our study was conducted in a general population from a nationally representative sample and thus has greater generalizability. Second, this nationwide population-based study traced all PLWHA and control patients with minimized referral bias because all medical care was covered by Taiwan National Health Insurance. Third, the timing of HAART in all patients was collected and HAART was regarded as a time-dependent variable in the analysis. Longitudinal studies that failed to account for changes in exposure during the study period will not be able to precisely estimate the effect of exposure on outcomes.[30]

This study nevertheless has some limitations. First, because of data limitation, we had no information on some important variables (eg, smoking, illicit drug use, and obesity) in the research subjects. Second, when a new HIV-infected individual was reported to Taiwan CDC, viral loads and CD4 counts—the index of advanced stage of HIV infection—were not required to be reported to the HIV Surveillance System. However, Taiwan CDC enforces medical professionals to report HIV-infected individuals' AIDS status—an indicator of immune status—within 24 hours of AIDS diagnosis. The multivariable analysis in our study controlled for AIDS status among all PLWHA and treated AIDS status as a time-dependent variable to mimic the real scenario regarding the immune status of HIV-infected individuals. Third, the diagnosis of HF relied on administrative claims data recorded by physicians or hospitals, and the outcome of HF may have been misclassified. However, a previous study found that the accuracy of the Taiwan NHIRD in recording HF diagnoses was high (97.6%).[19] Moreover, there is no reason to suspect that the validity of claims data would differ with a patient's HIV status. This nondifferential misclassification of outcome would bias the results toward a null association. Finally, to strengthen the diagnostic accuracy of incident HF, this study excluded HIV-infected individuals with prior HF in the analysis. However, some of the excluded HIV-infected individuals with prior HF may have already had the HIV infection before the first diagnosis of HF, which would underestimate the association between HIV infection and the development of HF in this study.

In conclusion, this nationwide long-term cohort study found a link between HIV infection and HF. HIV infection was found to be an independent risk factor for incident HF, after adjusting for demographic data and comorbidities. Because HF could cause significant morbidity in PLWHA, our study suggests that clinicians need to be aware of the higher risk of HF in this population.

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