

Sex differences in cardiovascular disease in people with and without HIV

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Objective: This study aims to assess the association between HIV infection and cardiovascular disease (CVD) incidence, with a focus on sex differences and the role of immune status.

Design: Retrospective cohort study using electronic health records from the All of Us (AoU) Research Program. We identified people with HIV (PWH) and matched them to people without HIV (PWoH) using propensity score matching (PSM) (1:5) by sex, age, and race/ethnicity. The matched cohort was then restricted to participants who were free of CVD before the index date.

Methods: We used Cox proportional hazards models, including an interaction term between sex and HIV status, to assess sex differences in the association between HIV status and incident CVD, adjusting for potential confounders. Subgroup analyses evaluated effect modification by viral suppression (HIV RNA < 50 copies/ml) and preserved immune function (CD4⁺ cell count > 500 cells/ μ l).

Results: After PSM, we identified 4803 PWH without preexisting CVD and matched them with 24 276 PWoH. Compared to their matched PWoH, women with HIV had an elevated adjusted hazard ratio (aHR) for CVD [aHR = 1.933, 95% confidence interval (CI): 1.709–2.188] than men with HIV (aHR = 1.435, 95% CI: 1.313–1.568). In subgroup analyses, compared with women without HIV, women with HIV remained at higher risk of CVD despite viral suppression (aHR = 1.929, 95% CI: 1.565–2.378) or preserved immune function (aHR = 1.813, 95% CI: 1.455–2.259). In contrast, no significant differences were observed between men with HIV and well controlled men without HIV (aHR = 1.133, 95% CI: 0.964–1.332).

Conclusion: Understanding sex-specific drivers of CVD risk is crucial for developing targeted interventions to prevent CVD in women with HIV and men with HIV.

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AIDS 2026, **40**:1703–1711

Keywords: cardiovascular disease, HIV, preserved immune function, sex differences, viral suppression

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Received: 11 February 2026; revised: 28 May 2026; accepted: 29 May 2026.

DOI:10.1097/QAD.0000000000004567

Introduction

With the widespread use of combination antiretroviral therapy (ART), HIV infection has transformed from an accelerated fatal disease into a chronic disease associated with an increased risk of heart and circulatory system disorders, including myocardial infarction, heart failure, pulmonary hypertension, stroke, and sudden cardiac death [1–3]. People with HIV (PWH) have a 1.5–2.0-fold increased risk for cardiovascular disease (CVD), which has arisen as the leading cause of mortality in this population [4,5]. The increased CVD prevalence among PWH is driven by complex interactions among traditional CVD risk factors (e.g. tobacco use, obesity, diabetes mellitus, and hypertension), HIV-specific factors (e.g. chronic infection, inflammation, and immune activation), ART treatment, and healthcare access disparities [5]. A meta-analysis of 793 635 PWH found the global burden of HIV-related CVD had tripled during the past 20 years, and it is estimated that 78% of PWH will have subclinical or clinical CVD by the year 2030 [6,7].

There are potential sex differences in CVD among PWH due to a combination of behavioral factors (e.g. smoking) and biological factors (e.g. immune response to HIV and immunomodulatory effects of antiretroviral therapy) [8–10]. A narrative review of CVD in women with HIV suggested that HIV increases the risk of CVD in women more than in men, which was explained by that certain cardiometabolic risk factors (e.g. metabolic syndrome and obesity) are more prevalent in women with HIV than in men with HIV [4]. It was also explained that some other risk factors, such as hypertension and hyperlipidemia, are undertreated in women with HIV compared with men with HIV [4]. However, a large cohort study conducted among 105 958 PWH using administrative and claims data found that the risk for atherosclerotic CVD in women with HIV was lower than that in men with HIV [10]. These conflicting findings highlight the need for further research to clarify sex differences in HIV-related CVD risk [11,12].

Extensive evidence has shown that improved CVD incidence in PWH is likely related to viral suppression and optimal immune function [13]. However, most studies on CVD incidence compared PWH as a single group against individuals without HIV, failing to recognize the sex-specific immunologic heterogeneity within PWH [3]. A retrospective cohort study of 9082 PWH in South Carolina found that CVD incidence was lower among individuals with a higher percentage of days with viral suppression and higher most recent CD4⁺ cell counts [14]. Nonetheless, chronic HIV infection, regardless of virologic control, is related to persistent inflammation and a prothrombotic state, especially among women with HIV [15,16]. As a result, even women with HIV and men with HIV with well controlled HIV are at greater risk than people without HIV (PWoH) [16,17]. Given the

growing number of PWH achieving viral suppression and preserved immune function due to ART advancement, elucidating sex differences in HIV-related CVD in this population is critically important for identifying risk factors in specific HIV groups and potentially informing sex-specific CVD prevention strategies [18,19]. Using nationwide real-world data and sex-stratified assessment methods, this study aimed to explore the sex differences in the association between HIV and CVD in well controlled PWH and their matched seronegative counterparts.

Methods

Data source

We used multisourced data [that is, electronic health records (EHR) and survey data] from the latest All of Us (AoU) controlled tier data, version 8, which included participants enrolled from 6 May 2018, to 1 October 2023 [20]. The AoU Research Program is a National Institutes of Health (NIH)-funded community-engaged program aiming to improve health by partnering with one million participants, more than 80% of whom were from historically underrepresented communities in biomedical research in the United States [20]. All US adults (aged 18 years and older) who are not in prison and could provide consent to participate are eligible for participation in AoU. Participants were recruited either online or through partner healthcare practitioner organizations [20]. Specifically, AoU collected various data types, including survey responses, EHRs, physical measurements, whole genome sequences, genotyping arrays, Fitbit records, and structural variants. All registered researchers could access these data with a secure internet connection.

Study cohort

For each adult (≥ 18 years) PWH we identified in AoU [21], we used a propensity score matching (PSM) approach to match five PWoH based on sex, age group, and race/ethnicity [22]. Criteria for matching were decided based on well documented demographic disparities in CVD within the general population [23]. For PWH, the index date was the first indicator date of HIV (i.e. index date), which could be diagnosis codes, drug exposure related to HIV, or lab results, determined by a predefined comprehensive HIV phenotyping algorithm [21]. We assigned individuals without HIV the same index date as their matched counterparts. Then, we further restricted the PWH and the matched PWoH cohort to participants who were free of CVD before the index date. The follow-up was from the index date until the earliest occurrence of a study endpoint: CVD diagnosis, death, or the study end date. All analyses were conducted following the ethical guidelines posted in the AoU Code of Conduct.

Definition of cardiovascular disease

The outcome of interest, CVD, was defined as a composite of coronary artery disease or stroke (hemorrhagic or ischemic). We identify coronary artery disease using the *International Classification of Diseases, Ninth/Tenth (ICD-9/10) Revision* diagnostic codes and procedure codes following the MidSouth Clinical Data Research Network Coronary Heart Disease Algorithm from the 'condition', 'occurrence', and 'procedure' domain in the EHR data [24]. A similar approach using previously validated ICD-9/10 codes in EHR was used to identify stroke cases [25]. The list of ICD-9/10 codes and procedure codes was presented in Supplemental Table 1, <http://links.lww.com/QAD/D916>.

Covariates

A total of 19 covariates were selected based on existing literature regarding risk factors of CVD and data availability [26]. These covariates were categorized into three domains: demographic characteristics: age at enrollment (18–44, 45–54, 55–64, and 65+ years old), race (White, Black/African American, and Asian/other/unknown), and ethnicity (non-Hispanic and Hispanic); socioeconomic status: insurance status (with health insurance and without health insurance), income level (<\$25 000, \$25 000–\$50 000, and >\$50 000), education (less than high school and high school or more), employment status (employed/self-employed and unemployed), and marital status (married/living with partner, divorced/separated/widowed, and never married); health behaviors and comorbidities: BMI category (normal, overweight, obese, and unknown), ever smoking (yes and no), presence of a list of comorbid conditions [i.e. diabetes, hypertension, renal disease, liver disease, and hyperlipidemia (HLD)], presence of psychiatric diagnosis (i.e. depression, anxiety, and substance use disorder), and the prescription records of statin (yes and no). BMI was calculated using data from the 'physical measurement' domain, comorbidities and psychiatric diagnoses were identified through the 'conditions' and 'occurrence' domains, and prescription records were identified through the 'drug exposures' domain in EHR. All other socio-demographic variables and health risk behaviors were ascertained in self-reported survey data. Comorbidities were defined before the index date and were included as baseline covariates to account for preexisting differences in health status. For individuals with HIV, the index date was the date of first documented HIV diagnosis, and for people without HIV, the index date was assigned based on the matched counterpart. All covariates were ascertained at baseline and were included in the analysis as fixed rather than time-varying variables.

Statistical analysis

Descriptive statistics were used to describe the socio-demographic characteristics of the study population by HIV status before and after PSM, including mean (SD) for continuous variables and counts (proportions) for

categorical variables. We used exact PSM to balance the cohorts on key demographic characteristics, including sex, age group, and race/ethnicity. Variables included in the PSM were selected to balance key baseline characteristics between PWH and PWoH, while avoiding matching variables that may reflect downstream consequences associated with HIV infection. Although several comorbidities were associated with elevated CVD risk, these conditions were disproportionately prevalent among PWH. Including comorbidities in the matching process could therefore introduce overmatching, reduce sample size, and decrease estimation efficiency. Thus, other covariates were included in the multivariable regression model to control residual confounding. Standardized mean difference (SMD) was used to assess the balance of covariates between the PWH group and the matched PWoH group.

Cox proportional hazard models were used to examine the association of HIV status and sex with CVD incidence when adjusting for predefined covariates. To estimate sex differences in the association of HIV status with CVD incidence, we additionally included the interaction term between sex and HIV status. Additionally, subgroup analyses were conducted to assess the role of viral suppression (HIV RNA < 50 copies/ml) and immune status (CD4⁺ cell count > 500 cells/ μ l) in modifying the association between HIV and CVD risk. Viral suppression and immune status were assessed using the most recent viral load and CD4⁺ cell count before the study endpoint, that is, CVD diagnosis date, death, or the study end date, whichever occurs first. All analyses were conducted with R software in a secure informatics platform provided by NIH that enables users to access and analyze AoU data. A two-sided alpha of less than 0.05 was considered statistically significant.

Results

Before PSM, a total of 5067 PWH and 374 385 PWoH were identified. Compared with PWoH, PWH had a higher proportion of men (68.4 vs. 37.9), non-Hispanic Black (49.1 vs. 16.7%), with household income less than \$25 000 (53.3 vs. 23.7%), less than high school education (4.5 vs. 3.1%), unemployed (63.8 vs. 44.9%), and without health insurance (7.2 vs. 5.6%). After PSM, among a total of 5067 identified PWH and 25 335 matched PWoH, sex, age group, and race/ethnicity distributions were balanced between the two groups: 31.6% were female, 36.2% were aged 55–64, and 49.1% were non-Hispanic Black (SMD < 0.001 for all) (Table 1).

After further restricting PWH and PWoH cohort to participants who were free of CVD before the index date, a total of 4803 PWH and 24 276 PWoH were used for analysis. The mean follow-up duration for women with

Table 1. Sociodemographic characteristics among people with and without HIV before and after propensity score matching.

Variables	Before PSM ^a			After PSM ^a		
	Without HIV (N=37 385)	With HIV (N=5067)	SMD	Without HIV (N=25 335)	With HIV (N=5067)	SMD
Sex						
Female	232 494 (62.1)	1601 (31.6)	0.642	8005 (31.6)	1601 (31.6)	<0.001
Male	141 891 (37.9)	3466 (68.4)		17330 (68.4)	3466 (68.4)	
Age group (years)						
18–44	114 601 (30.6)	1225 (24.2)	0.442	6125 (24.2)	1225 (24.2)	<0.001
45–54	56 551 (15.1)	977 (19.3)		4885 (19.3)	977 (19.3)	
55–64	75 599 (20.2)	1835 (36.2)		9175 (36.2)	1835 (36.2)	
65+	127 634 (34.1)	1030 (20.3)		5150 (20.3)	1030 (20.3)	
Race						
White	200 624 (53.6)	1180 (23.3)	0.807	5900 (23.3)	1180 (23.3)	<0.001
Asian/other/unknown	111 250 (29.7)	1397 (27.6)		6985 (27.6)	1397 (27.6)	
Black or African American	62 511 (16.7)	2490 (49.1)		12450 (49.1)	2490 (49.1)	
Ethnicity						
Not Hispanic or Latino	8500 (82.1)	850 (82.1)	<0.001	20970 (84.3)	2097 (84.3)	<0.001
Hispanic or Latino	1850 (17.9)	185 (17.9)		3910 (15.7)	391 (15.7)	
Insurance status						
Yes	344 338 (92.0)	4514 (89.1)	0.101	21855 (86.3)	4514 (89.1)	0.097
No	20 859 (5.6)	367 (7.2)		2517 (9.9)	367 (7.2)	
Unknown	9188 (2.5)	186 (3.7)		963 (3.8)	186 (3.7)	
Household income (USD)						
<25k	88 849 (23.7)	2699 (53.3)	0.792	9133 (36.0)	2699 (53.3)	0.435
>50k	154 334 (41.2)	625 (12.3)		6897 (27.2)	625 (12.3)	
25–50k	56 711 (15.1)	659 (13.0)		3291 (13.0)	659 (13.0)	
Unknown	74 491 (19.9)	1084 (21.4)		6014 (23.7)	1084 (21.4)	
Education attainment						
High school degree or more	354 714 (94.7)	4613 (91.0)	0.153	23501 (92.8)	4613 (91.0)	0.064
Less than a high school degree	11 756 (3.1)	226 (4.5)		942 (3.7)	226 (4.5)	
Unknown	7915 (2.1)	228 (4.5)		892 (3.5)	228 (4.5)	
Employment status						
Employed for wages/self-employed	195 860 (52.3)	1572 (31.0)	0.445	11956 (47.2)	1572 (31.0)	0.336
Not employed for wages	167 997 (44.9)	3233 (63.8)		12303 (48.6)	3233 (63.8)	
Unknown	10 528 (2.8)	262 (5.2)		1076 (4.2)	262 (5.2)	
Marital status						
Divorced/separated/widowed	86 836 (23.2)	1230 (24.3)	0.672	6222 (24.6)	1230 (24.3)	0.424
Married/living with partner	191 467 (51.1)	1157 (22.8)		10256 (40.5)	1157 (22.8)	
Never married	87 257 (23.3)	2440 (48.2)		7958 (31.4)	2440 (48.2)	
Unknown	8825 (2.4)	240 (4.7)		899 (3.5)	240 (4.7)	
Cardiovascular disease diagnosis						
No	308 992 (82.5)	3763 (74.3)	0.202	20868 (82.4)	3763 (74.3)	0.198
Yes	65 393 (17.5)	1304 (25.7)		4467 (17.6)	1304 (25.7)	

PSM, propensity score matching; SMD, standardized mean difference.

^aThe propensity score matching is conducted at a 1:5 ratio based on an exact match on sex, age group, and race/ethnicity.

HIV, women without HIV, men with HIV, and men without HIV was 10.02, 11.06, 9.61, and 10.51 years, respectively. Compared with PWOH, PWH were at significantly greater risk of developing CVD [adjusted hazard ratio (aHR) = 1.578, 95% CI: 1.467–1.698]. Subgroup analyses showed that this elevated risk persisted even among PWH with high CD4⁺ cell counts (CD4⁺ cell count >500 cells/ μ l) (aHR = 1.468, 95% CI: 1.284–1.678) and suppressed viral load (HIV RNA <50 copies/ml) (aHR = 1.355, 95% CI: 1.190–1.543), when comparing to PWOH. No significant sex differences in CVD incidence were observed in either the subgroup analyses or the overall population analysis (all $P > 0.05$) (Supplemental Table 2, <http://links.lww.com/QAD/D916>).

Compared to their matched PWOH, women with HIV had an elevated aHR for CVD (aHR = 1.933, 95% CI:

1.709–2.188) than men with HIV (aHR = 1.435, 95% CI: 1.313–1.568). Several other risk factors for CVD were identified, including unemployment status (aHR = 1.375, 95% CI: 1.277–1.480), diabetes (aHR = 1.321, 95% CI: 1.136–1.537), hypertension (aHR = 1.241, 95% CI: 1.086–1.418), renal disease (aHR = 2.128, 95% CI: 1.778–2.548), liver disease (aHR = 1.251, 95% CI: 1.030–1.520), hyperlipidemia (aHR = 1.241, 95% CI: 1.086–1.418), obesity (aHR = 1.293, 95% CI: 1.185–1.411), and alcohol use disorder (aHR = 1.263, 95% CI: 1.053–1.516) (Table 2).

In subgroup analyses, 1579 (31.2%) and 1686 (33.3%) PWH had CD4⁺ cell counts greater than 500 cells/ μ l and suppressed viral load, respectively. Among 1579 PWH with CD4⁺ cell counts greater than 500 cells/ μ l, 1072 (67.9%) were men and 507 (32.1%) were women. Among

Table 2. The Cox proportional hazard regression analysis with the interaction term between sex and HIV status.

Variables	The general population (N=29079) ^a		The high CD4 ⁺ group (N=9179) ^b		The viral suppression group (N=9785) ^c	
	aHR	95% CI	aHR	95% CI	aHR	95% CI
HIV status						
No	Ref		Ref		Ref	
Yes	1.435	(1.313–1.568)***	1.321	(1.121–1.557)***	1.133	(0.964–1.332)
Sex						
Male	Ref		Ref		Ref	
Female	0.872	(0.806–0.943)***	0.912	(0.794–1.046)	0.801	(0.704–0.911)***
Age group (years)						
18–44	Ref		Ref		Ref	
45–54	1.506	(1.315–1.725)***	1.575	(1.232–2.013)***	1.269	(1.010–1.595)*
55–64	1.808	(1.601–2.043)***	1.690	(1.354–2.109)***	1.513	(1.233–1.857)***
65+	1.882	(1.653–2.142)***	1.905	(1.508–2.406)***	1.659	(1.336–2.060)***
Race/ethnicity						
Non-Hispanic White	Ref		Ref		Ref	
Non-Hispanic Black	0.858	(0.792–0.93)***	0.805	(0.699–0.928)**	0.778	(0.676–0.895)***
Asian/other/unknown	0.914	(0.838–0.997)*	0.941	(0.808–1.095)	0.911	(0.786–1.055)
Insurance status						
Yes	Ref		Ref		Ref	
No	0.645	(0.561–0.741)***	0.637	(0.496–0.818)***	0.719	(0.571–0.904)**
Unknown	0.787	(0.651–0.951)*	0.858	(0.611–1.203)	0.926	(0.689–1.245)
Annual income level (\$)						
Less 25k	Ref		Ref		Ref	
25–50k	0.964	(0.873–1.064)	0.800	(0.669–0.956)*	0.997	(0.845–1.177)
Over 50k	0.806	(0.730–0.890)***	0.692	(0.585–0.820)***	0.738	(0.624–0.872)***
Unknown	1.119	(1.035–1.210)**	1.036	(0.905–1.187)	1.103	(0.970–1.254)
Highest education						
Over High School	Ref		Ref		Ref	
Less than High School	0.962	(0.829–1.116)	0.881	(0.685–1.134)	0.973	(0.772–1.226)
Unknown	0.870	(0.738–1.025)	0.919	(0.690–1.224)	0.986	(0.754–1.291)
Employment status						
Employed	Ref		Ref		Ref	
Unemployed	1.375	(1.277–1.480)***	1.289	(1.135–1.464)***	1.405	(1.243–1.587)***
Unknown	1.137	(0.949–1.362)	0.995	(0.712–1.390)	1.180	(0.876–1.591)
Marital status						
Married/living with a couple	Ref		Ref		Ref	
Divorced/separated/widowed	0.909	(0.841–0.983)*	0.923	(0.806–1.058)	0.915	(0.804–1.040)
Never married	0.827	(0.763–0.897)***	0.831	(0.718–0.962)*	0.831	(0.723–0.954)**
Unknown	0.955	(0.806–1.131)	0.940	(0.681–1.296)	0.886	(0.660–1.188)
Diabetes						
No	Ref		Ref		Ref	
Yes	1.321	(1.136–1.537)***	1.168	(0.856–1.594)	1.462	(1.096–1.950)**
Hypertension						
No	Ref		Ref		Ref	
Yes	2.235	(2.023–2.469)***	2.509	(2.083–3.023)***	2.543	(2.118–3.053)***
Renal disease						
No	Ref		Ref		Ref	
Yes	2.128	(1.778–2.548)***	2.020	(1.420–2.873)***	1.938	(1.390–2.702)***
Statin use						
No	Ref		Ref		Ref	
Yes	1.274	(1.112–1.461)***	1.097	(0.849–1.416)	1.177	(0.911–1.522)
Liver disease						
No	Ref		Ref		Ref	
Yes	1.251	(1.030–1.520)*	0.959	(0.650–1.415)	0.973	(0.648–1.462)
Ever smoke						
No	Ref		Ref		Ref	
Yes	1.055	(0.990–1.124)	0.999	(0.896–1.115)	1.082	(0.973–1.203)
Unknown	0.840	(0.709–0.997)*	0.896	(0.681–1.178)	0.810	(0.618–1.061)
Hyperlipidemia						
No	Ref		Ref		Ref	
Yes	1.241	(1.086–1.418)**	1.608	(1.257–2.057)***	1.437	(1.124–1.837)**
BMI level						
Underweight/normal	Ref		Ref		Ref	
Overweight	1.068	(0.972–1.174)	1.176	(0.991–1.396)	1.149	(0.980–1.346)
Obese	1.293	(1.185–1.411)***	1.387	(1.181–1.628)***	1.349	(1.163–1.564)***
Unknown	6.223	(5.658–6.845)***	7.808	(6.567–9.284)***	8.070	(6.840–9.523)***
Depression						
No	Ref		Ref		Ref	
Yes	1.085	(0.902–1.306)	1.036	(0.738–1.455)	0.847	(0.588–1.220)

Table 2 (continued)

Variables	The general population (N=29 079) ^a		The high CD4 ⁺ group (N=9179) ^b		The viral suppression group (N=9785) ^c	
	aHR	95% CI	aHR	95% CI	aHR	95% CI
Anxiety						
No	Ref		Ref		Ref	
Yes	1.145	(0.993–1.320)	1.185	(0.914–1.536)	1.279	(0.993–1.648)
Alcohol use disorder						
No	Ref		Ref		Ref	
Yes	1.263	(1.053–1.516)*	1.741	(1.207–2.511)**	1.129	(0.780–1.636)
HIV status * Sex ^d	1.348	(1.161–1.564)***	1.372	(1.048–1.797)*	1.703	(1.314–2.207)***
Female with HIV vs. female without HIV	1.933	(1.709–2.188)***	1.813	(1.455–2.259)***	1.929	(1.565–2.378)***
Male with HIV vs. male without HIV	1.435	(1.313–1.568)***	1.321	(1.121–1.557)***	1.133	(0.964–1.332)
Female with HIV vs. male with HIV	1.175	(1.031–1.340)*	1.252	(0.980, 1.597)	1.363	(1.080, 1.721)**
Female without HIV vs. male without HIV	0.872	(0.806–0.943)***	0.912	(0.794–1.046)	0.801	(0.704–0.911)***

aHR, adjusted hazard ratio; CI, confidence interval.**p* < 0.05, ***p* < 0.01, ****p* < 0.001.
^aAll people with HIV (PWH) and people without HIV (PWoH) after propensity score matching.
^bSubgroup analysis: PWH with high CD4⁺ cell count (>500 cells/ μ l) and matched PWoH.
^cSubgroup analysis: PWH with low viral load (HIV RNA <50 copies/ml) and matched PWoH.
^dThe interaction term between HIV status and sex.

1686 PWH with suppressed viral load, 1150 (68.2%) were men and 536 (31.8%) were women. Compared with women without HIV, women with HIV remained at higher risk of CVD despite viral suppression (aHR = 1.929, 95% CI: 1.565–2.378) or preserved immune function (aHR = 1.813, 95% CI: 1.455–2.259). In contrast, no significant differences were observed between men with HIV and well controlled men without HIV (aHR = 1.133, 95% CI: 0.964–1.332) (Table 2).

Discussion

Consistent with prior studies, both women with HIV and men with HIV had a higher risk of CVD than their seronegative counterparts [13,27]. Our findings further suggest that the relative burden of CVD may be greater among women with HIV than among men with HIV, even among those with virological suppression and preserved immune function. This finding extends the current literature by indicating that excess CVD risk may persist in women with HIV despite favorable HIV-related clinical indicators. These results underscore the need for early and targeted prevention and treatment strategies to reduce CVD risk among women with HIV.

Women with HIV are at a greater risk of CVD than men with HIV, even after adjusting for certain traditional CVD risk factors and other comorbid conditions [28]. Specifically, women with HIV had a 1.933 times higher risk of CVD than women without HIV, while men with HIV had a 1.435-fold higher risk than men without HIV, aligning with previous research showing a general 1.5–2.0-fold increase in the risk of CVD among PWH compared to PWoH [6,29]. Prior studies have indicated

that women with HIV are less likely to receive guideline-recommended treatment for CVD risk factors, such as hypertension, dyslipidemia, and diabetes [30,31]. Additionally, women with HIV may experience more immune activation and greater ART-induced inflammation compared to men with HIV, which could contribute to their increased risk of CVD [1]. Therefore, unique biological sex-specific mechanisms appear to be an additional risk factor to consider when evaluating HIV acquisition and the risk of CVD morbidity [12,32]. For example, as suggested by Kovacs *et al.* [9], preserving endothelial function in PWH, particularly women with HIV, could be a critical target to reduce CVD morbidity and mortality. However, the exact mechanisms underlying the heightened CVD risk in women with HIV are still being explored, partially due to the historic underrepresentation of women in CVD research [33].

Despite achieving virological suppression and preserved immune function, women with HIV were still at a higher risk of CVD compared to women without HIV. PWH undergoing ART often experience lingering systemic inflammation, which has been linked to an increased risk for CVD due to its role in promoting atherosclerosis [34,35]. For instance, intestinal damage and bacterial translocation, resulting from the depletion of CD4⁺ T cells, continue to be major contributors to CVD even when HIV viral suppression is attained through ART [36]. In a Danish HIV cohort study, PWH were followed prospectively for over 15 years, and a major decline in CD4⁺ cell count was found to be associated with increased risks of CVD and mortality among virally suppressed PWH [37]. Emerging data suggest that women appear to experience less reduction in inflammation levels after ART initiation, despite lower pretreatment viral load and greater improvement in CD4⁺ cell counts than men [38]. For example, in the PEAELS study (AIDS Clinical

Trials Group A5174) based on a US cohort, women had less decrease in hs-CRP and sCD14 levels compared to men after 48 weeks of ART [38]. Additionally, estrogen depletion is also a well documented driver of CVD and loss of bone mineral density in the general population, and limited studies suggested that the increased risk of CVD in women with HIV than men with HIV could be due to menopausal changes, regardless of the virological status and immune function [39].

The elevated CVD risk among women with HIV could also be partially explained by menopause experienced by older women. A systematic review found that the age at menopause for PWH across studies ranges from 46 to 50 years, while more than 70% of women with HIV in our study were older than 45 years [40]. With the growing number of aging women with HIV, it is crucial to develop integrated and holistic care models to address the specific needs of this growing demographic. These findings emphasize the importance of thorough screening and interventions for CVD risk among women with HIV, irrespective of their virological status and immune function.

The current study has several strengths, including using large-scale population-based real-world data across the United States and subgroup analyses considering the impact of immune status. However, some limitations need to be acknowledged. First, due to substantial missing biomarker data in the EHR, we were unable to adjust for some important biomarkers (e.g., IL-6 and D-dimer), which would have provided further insight into the mechanisms behind sex differences in CVD risk [41]. Second, over 90% of participants had health insurance, which may limit the generalizability of the findings to women and men without health insurance. Third, comorbidities were defined before the index date and included as baseline covariates to account for preexisting differences in health status. However, if these factors are measured after the index date, they may serve as part of causal pathways leading to the outcome, and this issue will be further investigated in future studies. Fourth, we used the most recent viral load and CD4⁺ cell count before the study endpoint to define viral suppression status and immune status in the subgroup analysis. Because these measures may not fully capture changes in virologic control and immune function during follow-up, the subgroup findings should be interpreted with caution. Fifth, no adjustment was made for multiple comparisons. Because multiple exploratory analyses were conducted, the possibility of type I error cannot be excluded. Therefore, the findings should be considered hypothesis-generating and interpreted with caution.

In conclusion, the increased risk of CVD among women with HIV highlights the importance of tailored screening, intervention, and implementation strategies to mitigate the risk of CVD in this group, irrespective of their viral

suppression or preserved immune function. It is essential to further investigate the underlying mechanisms behind sex differences in HIV-related CVD risks among PWH to optimize HIV-specific and sex-specific CVD risk reduction strategies.

Acknowledgements

We gratefully acknowledge All of Us participants for their contributions; without them, this research would not have been possible. We also thank the National Institute of Health's All of Us Research Program for making available the participant and cohort data examined in this study. We gratefully appreciate Ruilie Cai and Jiajia Zhang's efforts in the computational phenotyping process in identifying the HIV cohort in All of Us.

Author's contribution: F.S. and X.Y.: conceptualization. F.S.: writing – original draft, writing – review and editing.

X.Y. and H.X.: methodology. H.X.: formal analysis. X.Y.: supervision. All authors: writing – review and editing.

Ethics approval and consent to participate: Only the authorized authors who completed AoU Responsible Conduct of Research training accessed the data from the Researcher Workbench. All research using data made available via the AoU Researcher Workbench has been designated as nonhuman subjects by the AoU Institutional Review Board. As the authors were not directly involved with the participants and Researcher Workbench employs a data passport model, IRB review was not required.

Availability of data and materials

The data that supports the findings of this study are available from the All of Us Researcher Workbench, but restrictions apply to the availability of these data. Access to the All of Us Researcher Workbench and data is free. All researchers must be authorized and approved via a three-step process that includes registration, completion of ethics training, and attestation to a data use agreement.

Funding: the research reported in this publication was supported by the Augusta SCORE pilot project (38920-6; X.Y.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders. Funders had no role in the design of the study, collection, analysis, and interpretation of the data.

Conflicts of interest

There are no conflicts of interest.

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