International Journal of Cardiology Cardiovascular Risk and Prevention 15 (2022) 200151

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention

Two decade trends in cardiovascular disease outcomes and cardiovascular risk factors among US veterans living with HIV

Mohammed Haji [a], Vrishali V. Lopes [b], Augustus Ge [b], Christopher Halladay [b], Cullen Soares [d], Nishant R. Shah [a,c,e], Christopher T. Longenecker [f], Michelle Lally [a,c], Gerald S. Bloomfield [g], Theresa I. Shireman [e], David Ross [h,i], Jennifer L. Sullivan [b,c,e], James L. Rudolph [a,b,c,e], Wen-Chih Wu [a,b,c,e], Sebhat Erqou [a,b,c,*]

[a] Department of Medicine, Brown University, Providence, RI, USA
[b] Center of Innovation in Long Term Services & Supports, Providence VA Medical Center, Providence, RI, USA
[c] Department of Medicine, Providence VA Medical Center, Providence, RI, USA
[d] Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
[e] Brown University School of Public Health, Brown University, Providence, RI, USA
[f] School of Medicine and Department of Global Health, University of Washington, Seattle, WA
[g] Duke Clinical Research Institute, Duke Global Health Institute and Department of Medicine, Duke University, Durham, NC, USA
[h] Office of Specialty Care Service, US Department of Veterans Affairs, USA
[i] Infectious Disease Section, Washington, DC Department of Veterans Affairs Medical Center, USA

ARTICLE INFO

Keywords:
HIV
Human immunodeficiency virus
Cardiovascular disease
CVD
Risk factors
Trend
Disease burden

ABSTRACT

Coomprhensive data on temporal trends in cardiovascular disease (CVD) risk factors and outcomes in people living with HIV are limited. Using retrospective data on 50,284 US Veterans living with HIV (VLWH) who received care in the VA from 2001 to 2019, we calculated the prevalence and incidence estimates of CVD risk factors and outcomes, as well as the average annual percent changes (AAPC) in the estimates. The mean age of the Veterans increased from 47.8 (9.1) years to 58.0 (12.4) years during the study period. The population remained predominantly (>95%) male and majority Black (~50%). The prevalence of the CVD outcomes increased progressively over the study period: coronary artery disease (3.9%–18.7%), peripheral artery disease (2.3%, 10.3%), ischemic cerebrovascular disease (1.1%–9.9%), and heart failure (2.4%–10.5%). There was a progressive increase in risk factor burden, except for smoking which declined after 2015. The AAPC in prevalence was statistically significant for the CVD outcomes and risk factors. When adjusted for age, the predicted prevalence of CVD risk factors and outcomes showed comparable (but attenuated) trends. There was generally a comparable (but attenuated) trend in incidence of CVD outcomes, procedures, and risk factors over the study period. The use of statins increased from 10.6% (2001) to 40.8% (2019). Antiretroviral therapy usage increased from 77.7% (2001) to 85.0% (2019). In conclusion, in a retrospective analysis of large-scale VA data we found the burden and incidence of several CVD risk factors and outcomes have increased among VLWH over the past 20 years.

1. Background

Prior epidemiological studies regarding cardiovascular disease (CVD) among people living with human immunodeficiency virus (PLWH) have largely focused on the association of human immunodeficiency virus (HIV) with CVD risk [1–13]. Yet, there are limited data investigating comprehensively the temporal trends of CVD outcomes and their risk factors among PLWH. Further research in this area is important because with greater survivorship, PLWH are experiencing a greater prevalence of age-related disease, such as CVD [14–16]. Along with increased life expectancy, this epidemiological transition has been also attributed to the increased prevalence of traditional and

Abbreviations: HIV, Human Immunodeficiency Virus; CVD, Cardiovascular disesae.

* Corresponding author. Division of Cardiology, Providence VA Medical Center, Providence, RI, USA.
E-mail address: sebhaterqou@gmail.com (S. Erqou).

https://doi.org/10.1016/j.ijcrp.2022.200151
Received 16 June 2022; Received in revised form 29 August 2022; Accepted 19 September 2022
Available online 29 September 2022

nontraditional CVD risk factors among PLWH [17,18]. In addition, the effects of anti-retroviral therapy (ART) causing metabolic derangements, including dyslipidemia and insulin resistance, are thought to be important contributors to the increasing CVD burden [19,20]. It is also postulated that low-grade inflammation associated with chronic HIV infection contributes to the increased risk of CVD in PLWH [22].

Therefore, to investigate the incidence, burden and trend in CVD outcomes and risk factors among PLWH, we performed a comprehensive retrospective analysis of the United States Veteran Health Administration (VHA) healthcare database over two decades from 2001 to 2019.

2. Methods

This study is a retrospective analysis of Veterans living with HIV (VLWH) who received healthcare within the VHA system defined as attendance of at least one primary care, infectious disease, or mental health visit during the study year. Individual patient data were obtained from the VHA Corporate Data Warehouse using the VHA Informatics and Computing Infrastructure. Information on the age of the general Veteran population for comparison was obtained from summary data on VHA users provided by the VHA Support Service Center [21]. The study was approved by the Providence VA Medical Center Institutional Review Board (IRB-2020-005). VLWH were identified based on the presence of International Classification of Diseases (ICD), Ninth Revision (ICD-9) and ICD, Tenth Revision (ICD-10) codes for asymptomatic or symptomatic HIV infection and AIDS in their electronic medical record, using a validated approach that was previously implemented by others and us [9,22–24]. Demographic variables (i.e., age, sex, ethnicity), were collected from chart data collection. Body mass index (BMI) was calculated from the weight and height from the first available time point at the respective study year.

To estimate the burden of disease, we defined CVD and its outcomes by the presence of at least one inpatient or outpatient ICD-9 or ICD-10 code or current procedural terminology code (primary or secondary) for either coronary artery disease (CAD), coronary artery revascularization procedures (i.e., coronary artery bypass grafting, percutaneous coronary intervention), peripheral artery disease (PAD), peripheral artery revascularization procedures, ischemic cerebrovascular disease (ICVD), or cerebrovascular procedures during or prior to the respective study year, based on previously used algorithms [25,26]. Heart Failure (HF) was defined similarly using ICD-9 and ICD-10 codes [27,28]. For disease incidence only ICD-9 or 10 codes occurring in the respective study year among individuals with no prior recorded diagnosis was taken.

The traditional risk factors of diabetes mellitus (DM), hypertension, and chronic kidney disease (CKD) as well as non-traditional factors of alcohol abuse, illicit drug use, and depression were also defined by the presence of at least one inpatient or outpatient ICD-9 or ICD- 10 code for the respective diagnoses, like CVD outcome above. Smoking status was obtained from uniform health factor data based on screening questionnaires administered in VHA clinics that delineated smoking status as active versus former, ornever smoker.

Information on ART and statin prescription dispensed at VHA pharmacies was obtained from the VA Pharmacy Benefits Management dataset. For Veterans who filled their medications in non-VA pharmacies, we used data from non-VA medication tables. To evaluate the efficacy of HIV therapy in our population, we obtained HIV viral loads and CD4 T-cell counts. Pharmacy data and laboratory values closest to the start of each respective study year within a 2-year time frame (i.e., 1 year before or after the start date of the respective study year) were used. The HIV viral load was dichotomized as undetectable ($<$75 copies/mL) versus detectable ($\geq$75 copies/mL). The mean CD4 count was dichotomized as $<$200 cells/μL versus $\geq$200 cells/μL.

We performed a repeated cross-sectional analysis at 5 representative time points (2001, 2005, 2010, 2015 and 2019) and present detailed characteristics of the participants including estimates of prevalence. We calculated the 95% confidence intervals (CIs) for the respective years assuming binomial distribution of the prevalence estimates. Continuous variables (age, BMI) are presented as mean and standard deviation. In addition, we assessed annual prevalence and incidence of CVD outcomes and risk factors from 2001 to 2019 and calculated annualized average precent changes (AAPC) over the study period.

As the average age of the HIV population increased significantly over the study period, we calculated age-adjusted risk factor and disease prevalence to allow assessment of the change in burden over time after accounting for the effect of age. This was done by fitting a logistic regression model for each risk factor and CVD outcome for the respective study year separately, with age as the independent variable. We then computed the predicted prevalence (95% CI) of the risk factors and outcomes adjusted to age 54.3 years (the average age for all the VLWH included in the study from 2001 to 2019). Additionally, we present data on prevalence of CVD outcomes, traditional factors, and statin use stratified by ART use status.

The main outcome variables, i.e., CVD outcomes and CVD risk factors, which were determined based on presence or absence of ICD codes, had no missingness. Accordingly, the predicted prevalence estimates of CVD risk factors and outcomes adjusted for age were calculated in logistic regression models without needing to implement imputations techniques. The percentage of participants with missing data for BMI, viral load and CD4 count, are shown in Supplement Table 1. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) software. AAPCs were calculated using Joinpoint Desktop Software available from the National Cancer Institute (**Joinpoint version 4.9.1.0**). Illustrative graphs were plotted using Microsoft Excel.

3. Results

50,284 unique VLWH received care in the VHA from 2001 to 2019. Over the study period, the number of VLWH who received care in the VA health care system increased from 16,258 in 2001 to 31,812 in 2019 (Table 1). During the same period, the mean (SD) age of the VLWH increased steadily from 47.8 (9.1) years in 2001 to 58.0 (12.4) years in 2019 (Supplement Figure 1). By contrast, the average age of newly diagnosed VLWH remained relatively stable over the same period (47.6 [9.9] years in 2001 and 49.2 [15.0] years in 2019). The population remained predominantly male (97.4% in 2001, 96.2% in 2019) with predominantly Black (51.2% in 2001, 50.3% in 2019), and White (41.6% in 2001, 42.8% in 2019) ethnic backgrounds (Table 1).

In this study, the prevalence of CVD outcomes in the VLWH population, including CAD, PAD, ICVD, and HF increased progressively from 2001 to 2019 along with an overall significant increase in the AAPC (Fig. 1, Table 2). The prevalence of CAD and coronary procedures showed the highest increase from 3.9% to 18.7% with an AAPC of 11.2% (95% CI, 10.0–12.4) and from 0.4% to 3.7% with an AAPC of 16.3% (14.6–18.0), respectively. The prevalence of MI increased from 1.9% in 2000 to 8.2% in 2019 with an AAPC of 11.6% (10.4–12.8). PAD and ICVD prevalence increased from 2.3% to 10.3% with an AAPC of 11.0% (10.0–12.0), and from 1.1% to 9.9% with an AAPC of 15.8% (15.2–16.3), respectively, over the same period. Similarly, the prevalence of HF increased from 2.4% in 2001 to 10.5% in 2019 with an AAPC of 10.3% (8.9–11.7) (Table 1, Table 2, Figs. 1, Fig. 2A, 3A).

From 2001 to 2019, there was also an increase in the prevalence in three of the four traditional CVD risk factors: DM (10.6% to26.3%; AAPC, 5.9% [5.6–6.2]), hypertension (28.6% to 64.0%; AAPC, 6.0% [5.7–6.3]), and CKD (2.6% to22.5%; AAPC, 14.5% [13.5–15.5]) There was also an increase in the average BMI from 25.8 in 2001 to 27.3 kg/m^2 in 2019 with minimal missing data reported in Supplemental Table 2. On the other hand, the prevalence of current smoking status initially uptrended from 14.5% in 2001 to 26.7% in 2010, was relatively stable ~26% between 2010 and 2014, and then down-trended to 17.0% by 2019. The AAPC from 2000 to 2015 was 5.0% (4.0–6.0) and from 2015

Table 1
Characteristics of veterans with HIV by study year (2001–2019).

Variable	Year, 2001	Year, 2005	Year, 2010	Year, 2015	Year, 2019
	N = 16,258	N = 22,461	N = 26,173	N = 30,325	N = 31,812
Age (years)	**47.8** (9.1)	**51.1** (9.5)	**54.1** (10.2)	**56.3** (11.4)	**58.0** (12.4)
Male	**97.4%** (97.1–97.6%)	**97.3%** (97.1–97.5%)	**96.8%** (96.6–97.1%)	**96.5%** (96.3–96.7%)	**96.2%** (96.0–96.4%)
White	**41.6%** (40.9–42.4%)	**42.4%** (41.8–43.1%)	**42.8%** (42.2–43.4%)	**42.6%** (42.1–43.2%)	**42.8%** (42.2–43.3%)
Black	**51.2%** (50.4–52.0%)	**51.1%** (50.4–51.8%)	**51.0%** (50.4–51.6%)	**50.7%** (50.1–51.3%)	**50.3%** (49.8–50.9%)
BMI (kg/m^2) Mean (SD)[a]	**25.8** (5.0)	**26.1** (5.23)	**26.7** (5.3)	**27.0** (5.4)	**27.3** (5.4)
CAD	**3.9%** (3.6–4.2%)	**9.3%** (9.0–9.7%)	**13.0%** (12.6–13.4%)	**15.2%** (14.8–15.6%)	**18.7%** (18.2–19.1%)
MI	**1.9%** (1.7–2.1%)	**4.2%** (3.9–4.5%)	**5.9%** (5.6–6.2%)	**7.2%** (6.9–7.5%)	**8.2%** (7.9–8.5%)
PAD	**2.3%** (2.1–2.6%)	**5.3%** (5.0–5.5%)	**7.7%** (7.4–8.1%)	**9.6%** (9.3–9.9%)	**10.3%** (10.0–10.6%)
ICVD	**1.1%** (0.9–1.3%)	**2.9%** (2.7–3.1%)	**5.3%** (5.0–5.6%)	**8.2%** (7.9–8.5%)	**9.9%** (9.6–10.3%)
HF	**2.4%** (2.2–2.7%)	**4.9%** (4.6–5.2%)	**6.7%** (6.4–7.0%)	**8.2%** (7.9–8.5%)	**10.5%** (10.2–10.9%)
CAD Procedures	**0.4%** (0.3–0.5%)	**1.4%** (1.3–1.6%)	**2.6%** (2.4–2.8%)	**3.3%** (3.1–3.5%)	**3.7%** (3.4–3.9%)
PAD Procedures	**0.2%** (0.1–0.2%)	**0.7%** (0.5–0.8%)	**1.9%** (1.7–2.0%)	**2.5%** (2.3–2.7%)	**2.2%** (2.0–2.4%)
ICVD Procedures	**0.03%** (0.0–0.1%)	**0.1%** (0.10–0.20%)	**0.3%** (0.2–0.4%)	**0.4%** (0.3–0.5%)	**0.5%** (0.4–0.6%)
DM	**10.6%** (10.2–11.1%)	**16.0%** (15.6–16.5%)	**20.3%** (19.8–20.8%)	**23.1%** (22.6–23.6%)	**26.3%** (25.8–26.8%)
Hypertension	**28.6%** (27.9–29.2%)	**46.3%** (45.6–46.9%)	**57.6%** (0.70–58.0%)	**61.0%** (60.4–61.5%)	**64.0%** (63.5–64.5%)
CKD	**2.6%** (2.4–2.9%)	**5.5%** (5.20–5.80%)	**11.3%** (11.0–11.7%)	**16.4%** (16.0–16.8%)	**22.5%** (22.1–23.0%)
Smoker	**14.5%** (14.0–15.0%)	**21.6%** (21.1–22.1%)	**26.7%** (26.2–27.2%)	**24.6%** (24.2–25.1%)	**17.0%** (16.6–17.4%).
Depression	**19.6%** (19.0–20.2%)	**21.8%** (21.2–22.3%)	**25.3%** (24.8–25.8%)	**27.9%** (27.4–28.4%)	**28.7%** (28.2–29.2%)
Alcohol	**15.8%** (15.3–16.4%)	**14.7%** (14.3–15.2%)	**14.3%** (13.9–14.8%)	**14.1%** (13.7–14.5%)	**12.3%** (11.9–12.7%)
Drug	**20.4%** (19.8–21.0%)	**19.6%** (19.1–20.1%)	**18.6%** (18.2–19.1%)	**17.8%** (17.4–18.3%)	**16.0%** (15.6–16.4%)
Statin Use	**10.6%** (10.1–11.1%)	**19.3%** (18.8–19.9%)	**28.4%** (27.9–29.0%)	**32.0%** (31.5–32.5%)	**40.8%** (40.3–41.3%)
ART	**77.7%** (77.0–78.3%)	**73.8%** (73.3–74.4%)	**81.0%** (80.5–81.4%)	**84.1%** (83.7–84.5%)	**85.0%** (84.6–85.4%)
PI	**22.2%** (21.5–22.8%)	**29.9%** (29.0–30.5%)	**42.7%** (42.1–43.3%)	**32.9%** (32.3–33.4%)	**15.3%** (14.9–15.7%)
VL $\leq$ 75 (copies/ml)[a]	**25.4%** (24.4–26.3%)	**18.9%** (18.2–19.6%)	**55.6%** (54.9–56.3%)	**79.8%** (79.3–80.3%)	**85.8%** (85.3–86.2%)
CD4 > 200 (cells/ul)[a]	**73.5%** (72.8–74.2%)	**72.5%** (71.7–73.2%)	**86.3%** (85.8–86.7%)	**90.3%** (90.0–90.7%)	**92.9%** (92.6–93.2%)

Note: Values are % (95% confidence interval).
ART – anti-retroviral therapy; PI – protease inhibitors; VL –HIV viral load; CD4 – CD4 T-cell count; DM – diabetes mellitus; CKD - chronic kidney disease; Smoking – current smoker; BMI – body mass index; Alcohol – alcohol abuse; Drug – illicit drug use; CAD – coronary artery disease; MI – myocardial infarction; PAD-peripheral arterial disease; ICVD – ischemic cerebrovascular disease; HF – heart failure.
[a] Data with Missing values – see Supplemental Table 2.

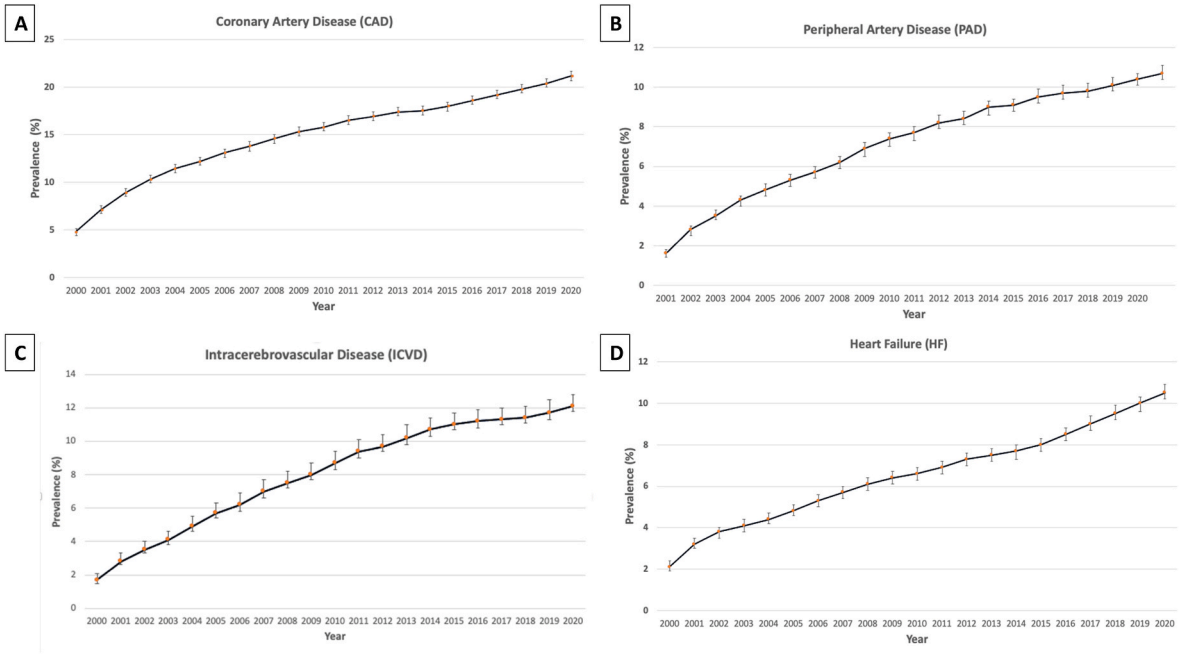

Fig. 1. Annual Trends in Prevalence of (A) CAD, (B) PAD, (C) ICVD, and (D) HF from 2001 to 2019. The dots represent prevalence point estimates; Error bars represent 95% confidence intervals. CAD - coronary artery disease, MI - myocardial infarction, PAD - peripheral arterial disease, ICVD - ischemic cerebrovascular disease, HF -heart failure.

to 2019 was −6.1% (−22.6–13.8) (Table 2, Fig. 4A). The prevalence of history of depression increased over the period from 19.6% in 2001 to 28.7% in 2019 with AAPC of 2.2% (1.5–2.9) while alcohol use and drug use declined from 15.8% to 12.3% and 20.4% to16.0%. respectively, over the same period (Table 1, Supplement Figure 2).

The age-adjusted trends in prevalence showed a similar progressively increasing, but attenuated, trend of CVD outcomes from 2001 to 2019, except for PAD which showed slight decrease in 2019 compared to

Table 2
Annual Average Percent Change (AAPC) of Prevalence and Incidence for CVD Outcomes, and Risk Factors Among Veterans Living with HIV from 2000 to 2019.

	AAPC of Prevalence	P-Value	AAPC of Incidence	P-value
CAD	**11.2** (10–12.4)	<0.001	**0.7** (−0.4–1.9)	0.204
MI	**11.6** (10.4–12.8)	<0.001	**0.4** (−0.3–1.2)	0.207
PAD	**11.0** (10.0–12.0)	<0.001	**−0.6** (−1.5–0.4)	0.227
ICVD	**15.8** (15.2–16.3)	<0.001	**4.8** (3.6–6.0)	<0.001
HF	**10.3** (8.9–11.7)	<0.001	**2.0** (1.2–2.8)	<0.001
CAD Procedures	**16.3** (14.6–18.0)	<0.001	**2.7** (0.1–5.4)	0.041
PAD Procedures	**17.4** (15.8–18.9)	<0.001	**3.7** (−5.5–13.9)	0.441
ICVD Procedures	**21.8** (15.9–28.1)	<0.001	**6.1** (2.4–9.9)	0.002
DM	**5.9** (5.6–6.2)	<0.001	**−0.9** (−2.8–1.0)	0.365
Hypertension	**6.0** (5.7–6.3)	<0.001	**−1.4** (−2.5–−0.4)	0.008
CKD	**14.5** (13.5–15.5)	<0.001	**6.2** (4.9–7.6)	<0.001
Depression	**2.2** (1.5–2.9)	<0.001	N/A	N/A
Smoker[a] (2000–2015)	**5.0** (4.0–6.0)	<0.001	N/A	N/A
Smoker[a] (2015–2019)	**−6.1** (−22.6–13.8)	0.373	N/A	N/A

AAPC - Annual Percent Change in Prevalence with 95% Confidence interval.
DM – diabetes mellitus; CKD - chronic kidney disease; CAD – coronary artery disease, MI – myocardial infarction; PAD-peripheral arterial disease; ICVD – ischemic cerebrovascular disease; HF – heart failure.
N/A – For data that was inaccessible for appropriate calculations.
[a] Current smoking was defined based health factor data collected in patient medical records during clinical encounters.

2015 (Table 3, Fig. 2B). On the other hand, trends in age-adjusted prevalence of CVD procedures generally flattened or tapered after 2010, in particular for ICVD procedures (Table 3, Fig. 3B). The trend of age-adjusted prevalence of 3 CVD risk factors was attenuated but persisted: DM increased from 13.5% to 20.9%, hypertension from 36.5% to 59.0%, and CKD from 3.2% to 17.0% from 2001 to 2019 (Table 3, Fig. 4B).

Supplement Table 2 shows the annual incidence of CVD, CVDprocedures and traditional CVD risk factors for each year from 2001 to 2019 along with weighted average annual incidence values. These annual incidence values were used to calculate the AAPC in incidence presented in Table 2. CAD had the highest average annual incidence at 2.3%, however the AAPC in incidence was not statistically significant (AAPC, 0.7% [−0.4 – 1.9], p = 0.2). On the other hand, the average annual incidence for ICVD was 1.2% with an AAPC of incidence of 4.8% (3.6–6.0) was significant. Likewise, the average annual incidence of HF was 1.5% with an AAPC of incidence of 2% (1.2–2.8). From the traditional risk factors, the average annual incidence of CKD was 2.8% with a AAPC of incidence of 6.2% (4.9–7.6). Hypertension had the highest average annual incidence of 11.7%, but an overall decline in AAPC of incidence of −1.4% (−2.5 to −0.4). The other CVD outcomes and risk factors had positive average percent incidences, but non-significant trends in theAAPCs of their incidences.

Over the study period the use of statins increased from 10.6% in 2001 to 40.8% in 2019.

ART usage overall increased from 77.7% to 85.0% from 2001 to 2019 (Table 1). By contrast the use of Protease Inhibitors (PI), increased initially from 2001 to 2010 (from 22.2% to 42.7%), and then subsequently decreased progressively to 15.3% by 2019. The percentage of VLWH with viral load <75 copies/mL increased from 25.4% in 2001 to 85.8% in 2019. The percentage of patients with CD4≥200 cells/μL increased from 73.5% to 92.9% from 2001 to 2019 (Table 1).

Supplement Table 3 shows the trends in CVD risk factors and CVD outcome burden stratified by ART use. In general, the increase in risk factors burden followed comparable trend between the two groups, except for statin treatment where there was slightly slower increase in statin uptake among those not on ART compared to those on ART.

4. Discussion

Using a retrospective cross-sectional analyses of electronic healthcare data on over 50,000 VLWH that received care in the VA during the period 2001 to 2019, we found that the average age of VLWH increased by 10 years. We also noted an increasing burden in CVD outcomes (CAD, MI, PAD, ICVD, and HF), CVD related procedures, and CVD traditional risk factors (DM, hypertension, and CKD). The increasing burden was attenuated but persistent even after accounting for the increasing age of VLWH. There was similar significant increase in incidence of ICVD, ICVD procedures, CAD procedures, HF, and CKD, while the other trends in incidence were not statistically significant, and the incidence of hypertension actually showed a slight but significant decline. On the other hand, smoking status of VLWH initially increased until 2010, was relatively stable between 2010 and 2015, and declined after that. In addition, there was an increase in prevalence of depression, but a decreasing burden of alcohol use and drug use among VLWH by 2019. There was also an increase in statin prescriptions, likely consistent with the increasing recognition of CVD risk in the HIV population. In all, this description of two decades of epidemiologic patterns among VLWH

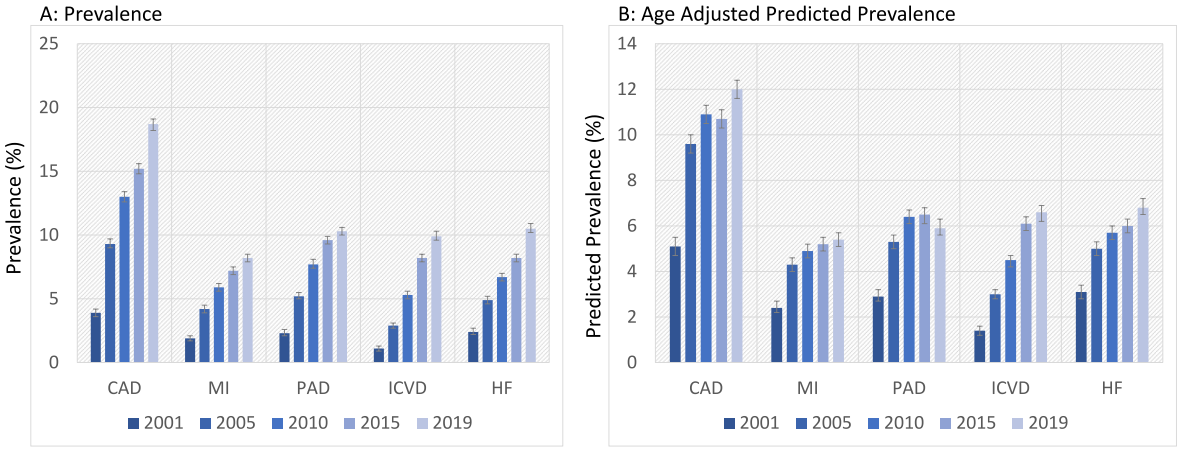

Fig. 2. Trends in (A) Prevalence and (B) Age-Adjusted* Predicted Prevalence of CVD outcomes among Veterans with HIV (2001–19) with 95% confidence intervals. *Adjusted to age 54.3 years Bar graphs represent prevalence; Error bars represent 95% confidence intervals; the color codes represent the years 2001, 2005, 2010, 2015, 2019. CAD - coronary artery disease, MI - myocardial infarction, PAD - peripheral arterial disease, ICVD - ischemic cerebrovascular disease, HF -heart failure. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Predicted prevalence of CVD risk factors and outcomes among veterans with HIV after adjustment for age[a] by study year (2000–2019).

	Year = 2001	Year = 2005	Year = 2010	Year = 2015	Year = 2019
CAD	**5.1%** (4.7–5.5%)	**9.6%** (9.2–10%)	**10.9%** (10.5–11.3%)	**10.7%** (10.3–11.1%)	**12.0%** (11.6–12.4%)
MI	**2.4%** (2.2–2.7%)	**4.3%** (4.0–4.6%)	**4.9%** (4.6–5.2%)	**5.2%** (4.9–5.5%)	**5.4%** (5.1–5.7%)
PAD	**2.9%** (2.7–3.2%)	**5.3%** (5.0–5.6%)	**6.4%** (6.1–6.7%)	**6.5%** (6.1–6.8%)	**5.9%** (5.6–6.3%)
ICVD	**1.4%** (1.2–1.6%)	**3.0%** (2.7–3.2%)	**4.5%** (4.2–4.7%)	**6.1%** (5.8–6.4%)	**6.6%** (6.2–6.9%)
HF	**3.1%** (2.8–3.4%)	**5.0%** (4.7–5.3%)	**5.7%** (5.4–6.0%)	**6.0%** (5.7–6.3%)	**6.8%** (6.5–7.2%)
CAD Procedures	**0.5%** (0.4–0.7%)	**1.4%** (1.3–1.6%)	**2.1%** (1.9–2.3%)	**2.1%** (1.9–2.3%)	**2.1%** (1.9–2.3%)
PAD Procedures	**0.2%** (0.1–0.3%)	**0.6%** (0.5–0.8%)	**1.5%** (1.3–1.7%)	**1.7%** (1.5–1.9%)	**1.3%** (1.1–1.4%)
ICVD Procedures	**0.0%** (0.0–0.1%)	**0.1%** (0.1–0.2%)	**0.2%** (0.2–0.3%)	**0.2%** (0.1–0.2%)	**0.2%** (0.1–0.2%)
DM	**13.5%** (12.9–14.1%)	**17.3%** (16.7–17.8%)	**18.8%** (18.3–19.3%)	**19.3%** (18.8–19.8%)	**20.9%** (20.4–21.4%)
Hypertension	**36.5%** (35.6–37.4%)	**51.8%** (51.1–52.5%)	**58.6%** (58.0–59.2%)	**58.4%** (57.8–59.0%)	**59.0%** (58.4–59.6%)
CKD	**3.2%** (2.9–3.6%)	**5.7%** (5.4–6.1%)	**10.1%** (9.7–10.5%)	**12.9%** (12.5–13.4%)	**17.0%** (16.5–17.5%)

Note: Values are % (95% confidence interval).
DM – diabetes mellitus; CKD - chronic kidney disease; CAD – coronary artery disease, MI – myocardial infarction; PAD-peripheral arterial disease; ICVD – ischemic cerebrovascular disease; HF – heart failure.
[a] Adjusted to age 54.3 years.

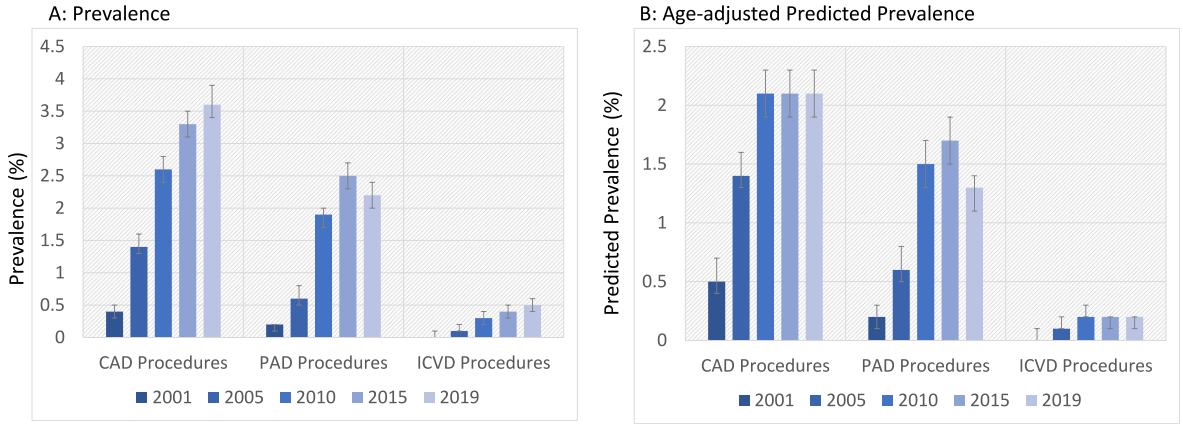

Fig. 3. Trends in (A) Prevalence and (B) Age Adjusted* Predicted Prevalence of CVD Procedures among Veterans with HIV (2001–19) with 95% confidence intervals *Adjusted to age 54.3 years Bar graphs represent prevalence; Error bars represent 95% confidence intervals; the color codes represent the years 2001, 2005, 2010, 2015, 2019. CAD - coronary artery disease, PAD - peripheral arterial disease, ICVD - ischemic cerebrovascular disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

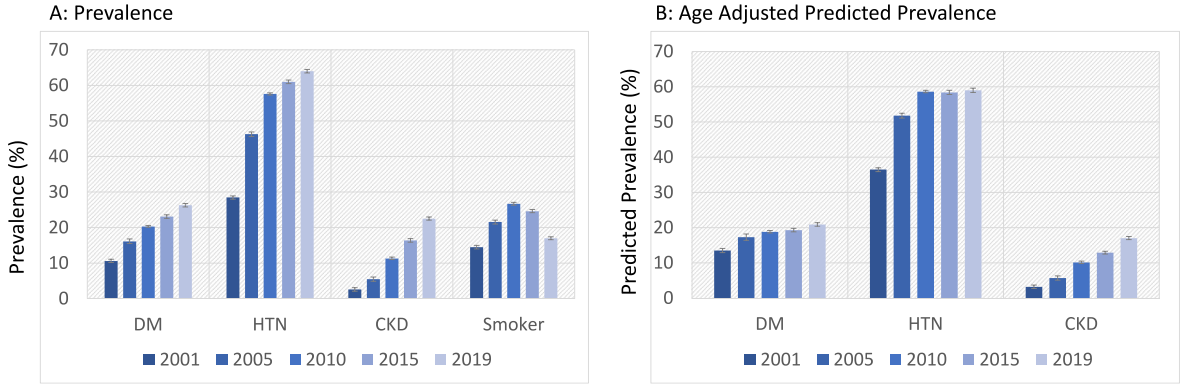

Fig. 4. Trends in (A) Prevalence and (B) Age-Adjusted Predicted* Prevalence of Traditional CVD Risk Factors among Veterans with HIV (2001–19) with 95% confidence intervals *Adjusted to age 54.3 years Bar graphs represent prevalence; Error bars represent 95% confidence intervals; the color codes represent the years 2001, 2005, 2010, 2015, 2019. DM - diabetes mellites, HTN - hypertension, CKD - chronic kidney disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

raises further attention to the need for primary and secondary prevention strategies to reduce the burden of CVD among PLWH.

Prior epidemiological studies have demonstrated that PLWH have higher risk of various CVD outcomes [1,5–12]. A 2012 prospective cohort followed PLWH for 20 months showed an increased prevalence of CVD and its risk factors, notably CAD and hypertension [29]. The authors additionally predicted a 10-year Framingham CVD risk of 16.4% in their aging (>45 years) HIV patients versus 4.2% in those who were ≤45 years. In our study, we observed the unadjusted prevalence of CAD rise from 4% to 18% over 2 decades with an annual percent increase of prevalence of 11%, which is comparable to their predicted 10-year estimation. A meta-analysis of CVD in PLWH that evaluated the global

burden of CVD in this population from 1990 to 2015 estimated a tripling of CVD in this patient population, especially in low-middle income nations [30]. In our study, we also observe similar trends. For instance, after adjusting for age, we found that CAD and PAD prevalence increased two-fold, while ICVD increased approximately five-fold from 2001 to 2019. The exact estimates of CVD burdenin our study differ from the estimates by these prior studies possibly due to differences in populations characteristics, outcome ascertaiment apporach, and study timeframe. I

Our study also reports incidence and shows a positive average percent incidence for CVD outcomes, their associated procedures, and traditional risk factors from 2001 to 2019. However, unlike the AAPC of prevalence, the AAPC in incidence reached statistical significance only ICVD, ICVD procedures, HF and CKD. This indicates that most new cases of CVD are occurring at a consistent rate in the last 2 decades, contributing to the significant rise in prevalence of CVD among VLWH as they live longer and grow older in age.

As mentioned, age has been attributed as one of the major contributors for the rise in CVD burden in PLWH. In this study we made adjustement for age, and the predicted trends still demonstrated an overall attenuated but increasing burden inCVD outcomes and CVD risk factors. This suggests that age is not the sole contributor to the observed increase intrend in CVD outcome and risk factor burden in this population. As PLWH survive to older ages, the cumulative effect of long-term usage of ART and persistent inflammation may also contribute to the increased burden of CVD in this population. In this study, we found a rise in the use of ART during the study period, as well as the increasing percentages of patients with CD4 $>$ 200 cells/ul and viral load $\leq$75 copies/ml. Despite a transition away from Protease inhibitors (PI), which are commonly associated with metabolic derangements [19], we observed a rise in CVD and metabolic risk factors (i.e. DM, BMI), possibly suggesting a delayed effect or the role of other ART regimens or other traditional and nontraditional factors also affecting the metabolic profile of PLWH. Moreover, despite low viral loads, underlying inflammatory markers, such as IL-6 and hsCRP have been shown to be elevated in PLWH and may also contribute to CVD risk [31,32]. One study that used the monoclonal antibody canakinumab to target IL-1 Beta (a pro-inflammatory cytokine) in PLWH observed an overall reduction in inflammatory markers and arterial wall and bone marrow inflammation, which are linked to atherogenesis [32].

The rise in CVD outcome burden among PLWH is also linked to the rise in prevalence of traditional CVD risk factors (DM, hypertension, CKD) in this population. Although ART t and chronic inflammation may also have a role in this rise, common factors such as lifestyle, diet, and exercise habits likely contribute to the rise in CVD burden over time. Due to the longitudinal nature of this study, it is important to consider if changes in risk factor definitions including those for diabetes and hypertension, contributed to changes in the prevalence over time. The Joint National Committee (JNC) on hypertension articles VI (1997) to VIII (2014), have all defined hypertension as systolic blood pressure (SBP) $>$ 140 and diastolic blood pressure (DBP) $>$ 90 [33]. Most recently in 2017, the American College of Cardiology and American Heart Association changed their definition to SBP $>$130 and DBP $>$80 [34]. Although this definition change may have contributed to practice change, the effect was likely small as we observed only an increase in prevalence of hypertension by 3% from 2015 to 2019 and an overall decrease in annual percent change in incidence. Similarly, the definition by the American Diabetes Association for DM has remained a fasting glucose $>$126 mg/dL ($>$7.0 mmol/L) from 1997 to 2021 and starting in 2010 also included hemoglobin A1C $>$ 6.5% to the definition [35,36]. Although the addition of hemoglobin A1C to the definition of DM may have improved rates of screening, this change did not translate into more new diagnoses of DM within our population as evidenced by the non-significant increase in the AAPC of incidence for DM.

Additionally, our study also noted a rise in depression among VLWH, which is a non-traditional risk factor increasingly linked to the incidence of CVD and CVD-related mortality [37]. The etiology of this relationship is not understood, but the correlation is well characterized [38]. Mental health disease is highly prevalent among Veterans and PLWH [39,40]. The VHA healthcare system provides many mental health resources, including, but not limited to multiple health providers, social workers, and individual or group therapy sessions. This is different from other healthcare networks where receiving mental health services may be more difficult. Yet in our study of VLWH, the prevalence of depression continues to rise along with the CVD burden, suggesting that mental health disease may also be a contributor to the rise in CVD among VLWH.

Importantly, we saw a decline in the prevalence of smoking use among VLWH. Similar to mental health services, the VHA healthcare system has developed and implemented a robust smoking cessation campaign that includes providing education materials, no co-payments for cessation counseling, easier access to nicotine replacement therapy, and training for providers [41,42]. These changes broadened smoking cessation efforts from specialty focused clinics to the primary care setting and may explain the decrease in the number of smokers in our patient population, which is different from the general population of PLWH [41,42]. This is an important step in helping reduce the burden of CVD among VLWH, however there were will be a log before the reduction of smoking begins to impact the prevalence and incidence of CVD in VLWH

By describing the temporal rise in CVD and its risk factors, we hope to encourage physicians to have increased vigilance for CVD and its associated risk factors among PLWH. Recent studies have shown only a limited percentage of PLWH achieving ideal cardiovascular health [43]. While smoking, alcohol use and substance use appear to be on the decline among VLHW, they should still sould be encouraged to work on lifestyle modifications, including but not limited to weight loss, exercise, and diet. Along with behavioral change, medical therapy for primary and secondary prevention of CVD will be essential. Some studies have shown that statins in PLWH may slow progression of noncalcified plaque and carotid intima thickness [44]. Most recently, a 2021 study of PLWH showed that the subset of their patients who were on statins (31% of the study population) had lower levels of proinflammatory cytokines [45]. In the present study, we found a consistent increase in the use of statins in PLWH, which may be attributed to increased awareness of CVD, but also changing guidelines. In 2013, the American Heart Association (AHA)/American College of Cardiology (ACC) released new guidelines for statin use that reduced the threshold to start treatment and recognized HIV as a risk enhancer for atherosclerotic CVD [46–48]. Despite the potential utility of statins and increasing trend in usage seen in the present analyses, statins are still commonly underused in PLWH [49–51], which is an important area of focus in improving cardiovascular care quality for PLWH. Ongoing studies in this area are expected to clarify the role of statins for primary CVD prevention in middle-aged PLWH at low to moderate risk [52].

A strength of this study is that it is based on a single large-scale healthcare datae comprising of over 50,000 PLWH observed over a period of two decades. The longitudinal nature of the study allowed us to evaluate trends in the prevalence and incidence of CVD and associated procedures, as well as several factors that are associated with CVD, including traditional and non-traditional risk factors. Additionally, most of the study population trended towards having more optimal control of HIV infection, which is representative of the current and future population of PLWH. Moreover, by adjusting for age, we attempted to assess some of the trends in CVD and risk factor burden independent of the rising age trend in this population. This study will contribute to the growing body of evidence demonstrating an increasing burden of CVD outcomes and risk factors among VLWH.

Regarding limitations, first, the study population was predominantly male and received care in an integrated VHA health system, which is not a global representation of all PLWH. Nonetheless, our findings are consistent with currently available data and knowledge about HIV and

CVD. Second, the CVD outcomes and risk factors diagnoses were obtained through ICD codes within the VA healthcare database and not through direct adjudication of electronic health records. However, the approach we used has been previously implemented in the VHA health record system with good results [25,26]. Third, as the analyses were based on VHA health record data, relevant diagnoses outside the VHA system may have been missed and under-represented. However, we have included data on health care that was provided in the community that was paid for by the VHA (Fee-basis files). In the future, complementing the VHA health data with Medicare data can make the results more comprehensive. Fourth, the composition of the study population in each cross-sectional study year was different but was also not independent (as some patients die or are lost from the system and new patients are added). Therefore, the study did not follow a single cohort through the period of interest. This allowed us to maximize the available data on burden of risk factors and disease among VLWH. A complementary approach following the same cohort for an extended period may allow for further insight on temporal relationship of CVD in PLWH.

In conclusion, through a comprehensive, retrospective longitudinal analysis of an integrated healthcare system data, our study further advances the notion that the burden of CVD and risk factors is overall rising among PLWH, also with general rising or stable incidence of these outcomes and risk factors. As this population experiences increased survivorship, our study helps to further highlight the need for increased vigilance in managing traditional and non-traditional risk factors that contribute to the burden of CVD. Further studies, including non-veteran populations and larger proportions of females, additionally looking at data on more factors related to ideal cardiovascular health (e.g., exercise) and preventative measures (e.g., hypertension treatment), will help to highlight potential targets for intervention. Ultimately, such endeavors will enable initiation of evidence-based interventions to ensure PLWH do not fall through the cracks in missing preventative therapies that have potential to curb morbidity and mortality.

Funding disclosure

The research reported/outlined here was supported by the Department of Veterans Affairs, Veterans Health Administration, VISN 1 Career Development Award to SE. SE is also funded by Center for Aids Research, The Rhode Island Foundation, and Lifespan Cardiovascular Institute. JLR, WW, SE, VL, CH, AG, and JS are funded by the VA Health Services Research and Development Center of Innovation in Long Term Services and Supports (CIN 13–419; C19-20-213). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Author contributions

Conceptualization (SE, WW, ML, TIS, NS); Data curation (AG, CH); Formal analysis (AG, CH); Funding acquisition (SE, WW, JLR); Investigation (SE, MH); Methodology (SE, WW, JLR, JLS); Project administration (AG, CH); Resources (JLR, WW); Software (AG, CH); Supervision (SE); Validation (SE); Visualization (MH, NS, CS); Roles/Writing - original draft (MH); Writing - review & editing (SE, NL, NS, CS, CTL, JSB, JBE, TIS, DR, ML, JLS, JLR, WW).

Declaration of competing interest

All authors declared none.

Acknowledgement

The VHA for the research support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2022.200151.

References

[1] M.J. Feinstein, et al., Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American heart association, Circulation 140 (2019) e98–e124, https://doi.org/10.1161/cir.0000000000000695.
[2] C. Antiretroviral Therapy Cohort, Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies, Lancet HIV 4 (2017) e349–e356, https://doi.org/10.1016/S2352-3018(17)30066-8.
[3] R. Weber, et al., Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study, HIV Med. 14 (2013) 195–207, https://doi.org/10.1111/j.1468-1293.2012.01051.x.
[4] N. Wada, et al., Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984-2008, Am. J. Epidemiol. 177 (2013) 116–125, https://doi.org/10.1093/aje/kws321.
[5] K. So-Armah, M.S. Freiberg, HIV and cardiovascular disease: update on clinical events, special populations, and novel biomarkers, Curr. HIV AIDS Rep. 15 (2018) 233–244, https://doi.org/10.1007/s11904-018-0400-5.
[6] A.A. Butt, et al., Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease, Arch. Intern. Med. 171 (2011) 737–743, https://doi.org/10.1001/archinternmed.2011.151.
[7] J.A. Beckman, et al., Association of human immunodeficiency virus infection and risk of peripheral artery disease, Circulation 138 (2018) 255–265, https://doi.org/10.1161/circulationaha.117.032647.
[8] K.A. Armah, et al., Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans, Clin. Infect. Dis. 58 (2014) 121–129, https://doi.org/10.1093/cid/cit652.
[9] M.S. Freiberg, et al., Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: results from the veterans aging cohort study, JAMA Cardiol. 2 (2017) 536–546, https://doi.org/10.1001/jamacardio.2017.0264.
[10] M.S. Freiberg, et al., HIV infection and the risk of acute myocardial infarction, JAMA Intern. Med. 173 (2013) 614–622, https://doi.org/10.1001/jamainternmed.2013.3728.
[11] J.J. Sico, et al., HIV status and the risk of ischemic stroke among men, Neurology 84 (2015) 1933–1940, https://doi.org/10.1212/WNL.0000000000001560.
[12] M.S. Freiberg, K. So-Armah, HIV and cardiovascular disease: we need a mechanism, and we need a plan, J. Am. Heart Assoc. 4 (2016), e003411, https://doi.org/10.1161/JAHA.116.003411.
[13] A. Alonso, et al., HIV infection and incidence of cardiovascular diseases: an analysis of a large healthcare database, J. Am. Heart Assoc. 8 (2019), e012241, https://doi.org/10.1161/jaha.119.012241.
[14] A.S.V. Shah, et al., Global burden of atherosclerotic cardiovascular disease in people living with HIV: systematic review and meta-analysis, Circulation 138 (2018) 1100–1112, https://doi.org/10.1161/CIRCULATIONAHA.117.033369.
[15] P. Morlat, et al., Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000, AIDS 28 (2014) 1181–1191, https://doi.org/10.1097/QAD.0000000000000222.
[16] E. Cerrato, et al., Cardiovascular disease in HIV patients: from bench to bedside and backwards, Open Heart 2 (2015), e000174, https://doi.org/10.1136/openhrt-2014-000174.
[17] F. Boccara, Cardiovascular health in an aging HIV population, AIDS 31 (Suppl 2) (2017) S157–S163, https://doi.org/10.1097/qad.0000000000001384.
[18] M.V. Zanni, J. Schouten, S.K. Grinspoon, P. Reiss, Risk of coronary heart disease in patients with HIV infection, Nat. Rev. Cardiol. 11 (2014) 728–741, https://doi.org/10.1038/nrcardio.2014.167.
[19] N. Friis-Moller, et al., Cardiovascular disease risk factors in HIV patients–association with antiretroviral therapy. Results from the DAD study, AIDS 17 (2003) 1179–1193, https://doi.org/10.1097/01.aids.0000060358.78202.c1.
[20] S.G. Deeks, R. Tracy, D.C. Douek, Systemic effects of inflammation on health during chronic HIV infection, Immunity 39 (2013) 633–645, https://doi.org/10.1016/j.immuni.2013.10.001.
[21] U.D.o.V. Affairs, VHA Support Services Center Capital Assets, VSSC), 2020.
[22] K.A. McGinnis, et al., Understanding racial disparities in HIV using data from the veterans aging cohort 3-site study and VA administrative data, Am. J. Publ. Health 93 (2003) 1728–1733, https://doi.org/10.2105/ajph.93.10.1728.
[23] S. Erqou, et al., Heart failure outcomes and associated factors among veterans with human immunodeficiency virus infection, JACC Heart Fail. 8 (2020) 501–511, https://doi.org/10.1016/j.jchf.2019.12.007.
[24] S. Erqou, et al., Age at diagnosis of heart failure in United States veterans with and without HIV infection, J. Am. Heart Assoc. 10 (2021), e018983, https://doi.org/10.1161/JAHA.120.018983.
[25] C.L. McBride, et al., Statin prescription rates and their facility-level variation in patients with peripheral artery disease and ischemic cerebrovascular disease: insights from the Department of Veterans Affairs, Vasc. Med. 23 (2018) 232–240, https://doi.org/10.1177/1358863x18758914.

[26] A.R. Orkaby, et al., Association of statin use with all-cause and cardiovascular mortality in US veterans 75 Years and older, JAMA 324 (2020) 68–78, https://doi.org/10.1001/jama.2020.7848.
[27] A.M. Kucharska-Newton, et al., Identification of heart failure events in Medicare claims: the atherosclerosis risk in communities (ARIC) study, J. Card. Fail. 22 (2016) 48–55, https://doi.org/10.1016/j.cardfail.2015.07.013.
[28] R. Pfister, et al., Does ICD-10 hospital discharge code I50 identify people with heart failure? A validation study within the EPIC-Norfolk study, Int. J. Cardiol. 168 (2013) 4413–4414, https://doi.org/10.1016/j.ijcard.2013.05.031.
[29] S. Esser, et al., Prevalence of cardiovascular diseases in HIV-infected outpatients: results from a prospective, multicenter cohort study, Clin. Res. Cardiol. 102 (2013) 203–213, https://doi.org/10.1007/s00392-012-0519-0.
[30] F. Thienemann, K. Sliwa, J.K. Rockstroh, HIV and the heart: the impact of antiretroviral therapy: a global perspective, Eur. Heart J. 34 (2013) 3538–3546, https://doi.org/10.1093/eurheartj/eht388.
[31] B. Titanji, C. Gavegnano, P. Hsue, R. Schinazi, V.C. Marconi, Targeting inflammation to reduce atherosclerotic cardiovascular risk in people with HIV infection, J. Am. Heart Assoc. 9 (2020), e014873, https://doi.org/10.1161/JAHA.119.014873.
[32] P.Y. Hsue, et al., IL-1 beta inhibition reduces atherosclerotic inflammation in HIV infection, J. Am. Coll. Cardiol. 72 (2018) 2809–2811, https://doi.org/10.1016/j.jacc.2018.09.038.
[33] P.A. James, et al., Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint national committee (JNC 8), JAMA, J. Am. Med. Assoc. 311 (2014) 507–520, https://doi.org/10.1001/jama.2013.284427, 2014.
[34] P. Greenland, E. Peterson, The new 2017 ACC/AHA guidelines "up the pressure" on diagnosis and treatment of hypertension, JAMA, J. Am. Med. Assoc. 318 (2017) 2083–2084, https://doi.org/10.1001/jama.2017.18605.
[35] G. Puavilai, S. Chanprasertyotin, A. Sriphrapradaeng, Diagnostic criteria for diabetes mellitus and other categories of glucose intolerance: 1997 criteria by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (ADA), 1998 WHO consultation criteria, and 1985 WHO criteria. World Health Organization, Diabetes Res. Clin. Pract. 44 (1999) 21–26.
[36] Addendum. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021, Diabetes Care 44 (Suppl. 1) (2021) S15–S33, https://doi.org/10.2337/dc21-ad09. Diabetes care 44, dc21ad09-2182 2021.
[37] D.L. Hare, S.R. Toukhsati, P. Johansson, T. Jaarsma, Depression and cardiovascular disease: a clinical review, Eur. Heart J. 35 (2014) 1365–1372, https://doi.org/10.1093/eurheartj/eht462.
[38] B.M. Polanka, J. Berntson, E.A. Vrany, J.C. Stewart, Are cardiovascular risk factors stronger predictors of incident cardiovascular disease in U.S. Adults with versus without a history of clinical depression? Ann. Behav. Med. 52 (2018) 1036–1045, https://doi.org/10.1093/abm/kay007.
[39] A.M. Bengtson, et al., Depressive symptoms and engagement in human immunodeficiency virus care following antiretroviral therapy initiation, Clin. Infect. Dis. 68 (2019) 475–481, https://doi.org/10.1093/cid/ciy496.
[40] K. So-Armah, et al., Depression and all-cause mortality risk in HIV-infected and HIV-uninfected US veterans: a cohort study, HIV Med. 20 (2019) 317–329, https://doi.org/10.1111/hiv.12726.
[41] Institute of Medicine (U.S, Committee on smoking cessation in military and veteran populations, in: S. Bondurant, R. Wedge (Eds.), Combating Tobacco Use in Military and Veteran Populations, National Academies Press, 2009.
[42] K. Hamlett-Berry, et al., Evidence-based national initiatives to address tobacco use as a public health priority in the Veterans Health Administration, Mil. Med. 174 (2009) 29–34, https://doi.org/10.7205/milmed-d-00-3108.
[43] P.S. Douglas, et al., Cardiovascular risk and health among people with HIV eligible for primary prevention: insights from the REPRIEVE trial, Clin. Infect. Dis. (2021), https://doi.org/10.1093/cid/ciab552.
[44] C.T. Longenecker, A. Sattar, R. Gilkeson, G.A. McComsey, Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection, AIDS 30 (2016) 2195–2203, https://doi.org/10.1097/QAD.0000000000001167.
[45] S.K. Hussain, et al., Effect of statin use on inflammation and immune activation biomarkers in HIV-infected persons on effective antiretroviral therapy, AIDS Res. Hum. Retrovir. 37 (2021) 357–367, https://doi.org/10.1089/AID.2020.0127.
[46] N.J. Stone, et al., Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline, Ann. Intern. Med. 160 (2014) 339–343, https://doi.org/10.7326/M14-0126.
[47] Y.K. Cho, et al., ACC/AHA cholesterol guideline versus 2004 NCEP ATP III guideline in the prediction of coronary artery calcification progression in a Korean population, J. Am. Heart Assoc. 5 (2013), https://doi.org/10.1161/JAHA.116.003410, 2016.
[48] S.M. Grundy, et al., Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines, Circulation 110 (2004) 227–239, https://doi.org/10.1161/01.CIR.0000133317.49796.0E.
[49] M.S. Freiberg, et al., The association between the receipt of lipid lowering therapy and HIV status among veterans who met NCEP/ATP III criteria for the receipt of lipid lowering medication, J. Gen. Intern. Med. 24 (2009) 334–340, https://doi.org/10.1007/s11606-008-0891-7.
[50] J.A. Ladapo, et al., Disparities in the quality of cardiovascular care between HIV-infected versus HIV-uninfected adults in the United States: a cross-sectional study, J. Am. Heart Assoc. 6 (2017), https://doi.org/10.1161/jaha.117.007107.
[51] M.E. Clement, et al., Statin utilization and recommendations among HIV- and HCV-infected veterans: a cohort study, Clin. Infect. Dis. 63 (2016) 407–413, https://doi.org/10.1093/cid/ciw289.
[52] S.K. Grinspoon, et al., Rationale and design of the randomized trial to prevent vascular events in HIV (REPRIEVE), Am. Heart J. 212 (2019) 23–35, https://doi.org/10.1016/j.ahj.2018.12.016.