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FULL RESEARCH PAPER
Risk Prediction/Assessment & Stratification

Cardiovascular risk assessment in people living with HIV compared to the general population

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Aims We prospectively assessed and compared the accuracy of cardiovascular risk scores in people living with HIV (PLWH) and individuals from the general population.

Methods and results The Systematic Coronary Risk Evaluation Score 2 (SCORE2), the Pooled Cohort Equations (PCE), and the HIV-specific Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) score were calculated in participants free from atherosclerotic cardiovascular disease (ASCVD) between 2003 and 2009. In total, 6373 [mean age, 40.6 years (SD, 9.9)] PLWH from the Swiss HIV Cohort Study (SHCS) and 5403 [52.8 years (SD, 10.7)] individuals from the CoLaus|PsyCoLaus study were eligible for analysis. We tested discrimination and calibration, and the value of adding HIV-specific factors to scores using the net reclassification improvement (NRI). During mean follow-ups of 13.5 (SD, 4.1) in SHCS and 9.9 (SD, 2.3) years in CoLaus|PsyCoLaus study, 533 (8.4%) and 374 (6.9%) people developed an incident ASCVD, respectively. This translated into age-adjusted incidence rates of 12.9 and 7.5 per 1000 person-year, respectively. In SHCS, SCORE2, PCE, and D:A:D presented comparable discriminative capacities [area under the receiver operating characteristic curve of 0.745 (95% confidence interval, CI, 0.723–0.767), 0.757 (95% CI, 0.736–0.777), and 0.763 (95% CI, 0.743–0.783)]. Adding HIV-specific variables (CD4 nadir and abacavir exposure) to SCORE2 and PCE resulted in an NRI of −0.1% (95% CI, −1.24 to 1, $P = 0.83$) and of 2.7% (95% CI, 0.3–5.1, $P = 0.03$), respectively.

Conclusions PLWH present a two-fold higher rate of incident ASCVD compared to individuals from the general population. SCORE2 and PCE, which are clinically easier to use (reduced set of variables without adding HIV-specific factors), are valid to predict ASCVD in PLWH.

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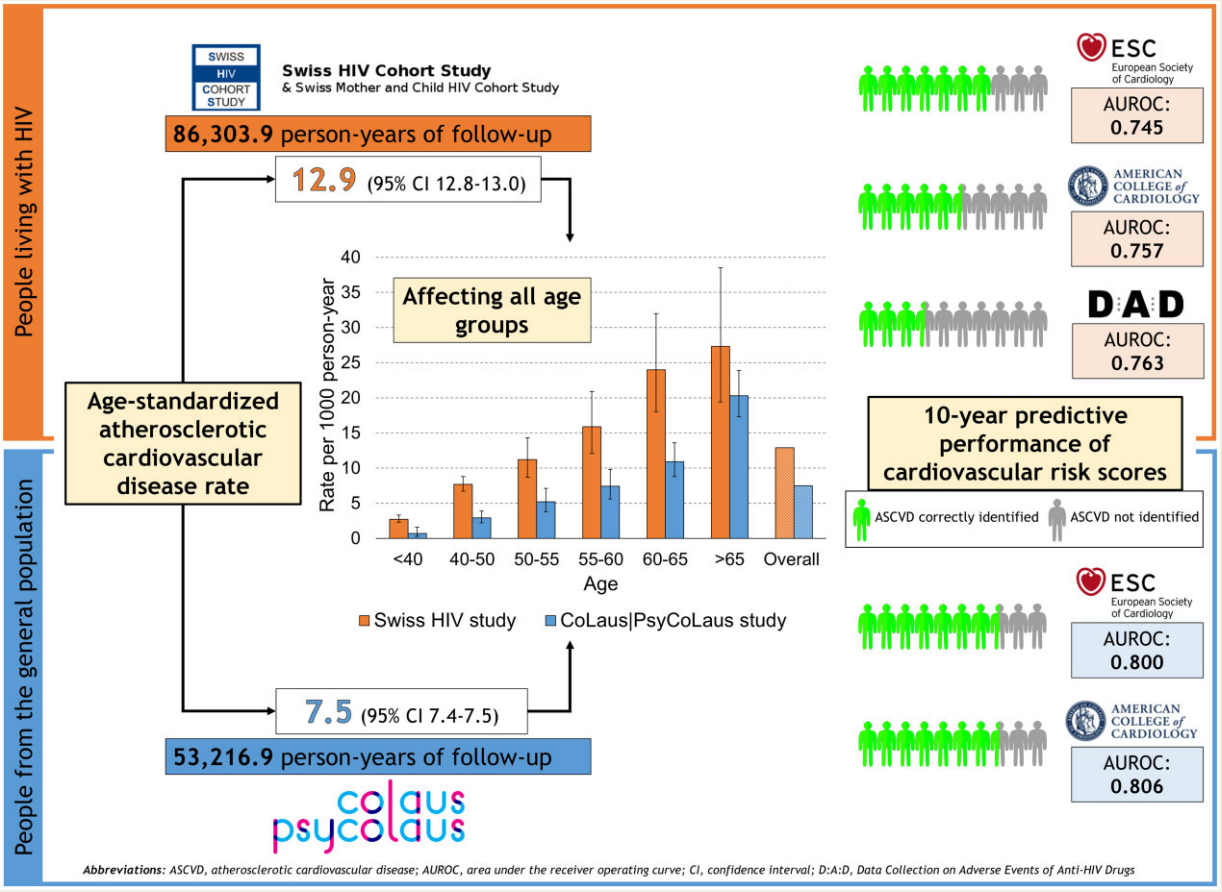
Graphical Abstract



Keywords Cardiovascular • Prevention • Risk score • HIV • PLWH • Discrimination • Calibration

Introduction

Atherosclerotic cardiovascular disease (ASCVD) prevention and treatment represent a major clinical challenge in people living with HIV (PLWH), who are now facing age-associated conditions under highly efficient combination antiretroviral therapy (cART).[1,2] The performance of cardiovascular risk scores developed for the general population in PLWH is debated,[3–6] and it remains unclear which score is appropriate in clinical practice.

The Systematic COronary Risk Evaluation 2 (SCORE2) and the Pooled Cohort Equations (PCE), recommended for cardiovascular risk assessment by the European and North American guidelines on primary prevention, respectively,[7,8] were established based on population-based cohorts without PLWH. To date, studies that have investigated predictive performance of available cardiovascular risk scores have shown an underprediction of risk when applied to PLWH.[3–5,9–11] The robustness of these studies were limited by short follow-up periods, limited sample sizes and absence of comparison with people living without HIV. The Data-Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study derived a specific risk prediction model for PLWH in 2010, the D:A:D score.[12] This score includes information on antiretroviral drugs use (lopinavir, indinavir, and abacavir), which have been associated with increased cardiovascular risk. An updated D:A:D score was proposed in 2016, including CD4+ T cells count (a low level having been observationally associated with ASCVD).[2,13] However, the D:A:D score was only tested using a 5-year follow-up,[12,13] questioning its capacity to accurately predict ASCVD over a 10-year period. One North American study assessed 10-year predictive performance of cardiovascular risk scores and demonstrated good discrimination performances of the D:A:D score, but 10-year follow-up was achieved in only 30.3% ($N = 692$) of the study population.[3]

Overall, there is a lack of comprehensive and contemporary studies assessing cardiovascular risk scores in PLWH with adequate follow-up and with comparison with people living without HIV. This study first sought to compare the predictive performance of SCORE2, PCE and

D:A:D scores in two cohorts including PLWH and individuals from the general population. Second, we tested whether adding HIV-specific factors to scores developed for the general population improved their predictive capacity.

Methods

Study participants

We used data from two prospective studies, the Swiss HIV Cohort Study (SHCS) and the CoLaus|PsyCoLaus study. SHCS is a systematic longitudinal multi-centric and ongoing study enrolling PLWH in Switzerland since 1988, independently of the stage of the disease, the degree of immunosuppression or whether the individual is receiving cART.[14] The cumulative number of participants in 2020 was 20 802 [median age at registration 35 [interquartile range (IQR), 29–43], 27.3% women]. At enrolment, sociodemographic data as well as specific data (results of earlier HIV tests, most probable mode of HIV transmission, history of antiretroviral treatment, smoking history, hypertension, and diabetes awareness and treatment) are registered. Follow-up consists in a visit with a physician and a laboratory analysis every 6 months. HIV viral load and CD4+ T cells levels are prospectively assessed every 6 months. Time exposure to any antiretroviral medication is documented. All incident cases of myocardial infarction, invasive cardiovascular procedure (coronary angioplasty and/or stenting, coronary artery bypass grafting, and carotid endarterectomy), stroke and death are systematically reported to the SHCS coordinating office through event checking chart forms for central validation by senior physician and coding.[15,16]

The CoLaus|PsyCoLaus study is a Swiss population-based prospective cohort investigating clinical, psychological, genetic, and social determinants of cardiovascular diseases.[17] Between 2003 and 2006, 6733 subjects (age range 35–75 years, 54% women) were recruited from a random sample of the population of the city of Lausanne for baseline extensive phenotyping with clinical assessment, questionnaires on health and lifestyle, and blood sampling. Periodic resurveys of the whole cohort were conducted over a 15-year follow-up. Appropriate medical records of participants who declared an incident ASCVD and/or ASCVD-related procedure were prospectively collected, as well as information on cause of death. ASCVD and causes of death were independently adjudicated by trained specialists (i.e. cardiologists, neurologists and internists). The complete procedure has been described previously.[18]

The SHCS was approved by ethical committees of each participating institutions and all participants provided written informed consent. The Institutional Ethics Committee of the University of Lausanne approved the CoLaus|PsyCoLaus study and all participants provided written informed consent.

Inclusion criteria

We included individuals aged more than 18 years free from prevalent ASCVD at baseline. People from non-Caucasian and non-African ethnicities were excluded due to their small number in CoLaus|PsyCoLaus study ($n = 331$). Exclusion criteria are described in the Supplementary material online.

For comparison purposes and to minimize secular trends and treatment bias, only prospective data collected from 2003 were used in SHCS. Additionally, for SHCS, we included all individuals present in the cohort until 2009, thus guaranteeing a 10-year follow-up.

Cardiovascular risk scores and outcomes

We compared three cardiovascular risk scores, namely SCORE2 (including SCORE2-OP, for people aged >65 years), PCE and D:A:D (see Supplementary material online, *Table S1*). We used low-risk region recalibrated models of SCORE2 and SCORE2-OP (hereafter SCORE2).[19,20] PCE was recalibrated as previously proposed,[21] whereas D:A:D was already calibrated for SHCS sample.[12] The scores were computed for each participant at baseline, with the exception of D:A:D which was only computed for PLWH. We applied criteria of the European Society of Cardiology (ESC)[7] and of the American College of Cardiology/American Heart Association (ACC/AHA)[8] to reclassify individuals in higher categories of risk. We did not account for microalbuminuria, which was not available in our dataset. As the three scores predict different cardiovascular outcomes, we used a common set of cardiovascular outcomes for comparison purposes, namely ASCVD, as already performed by others,[18,22] and recommended by the 2021 ESC and the 2019 ACC/AHA cardiovascular preventive guidelines.[7,8] ASCVD comprised: (i) fatal or non-fatal acute myocardial infarction, (ii) sudden cardiac death or cardiovascular death, (iii) symptomatic coronary artery disease with >50% stenosis revascularized by either percutaneous coronary intervention or coronary artery bypass graft, and (iv) fatal and non-fatal ischaemic stroke (including transient ischaemic attack). During the follow-up period and in both cohorts separately, first incident ASCVD were prospectively collected and independently adjudicated (as described in *Study participants* section) according to established recommendations and similar definitions detailed elsewhere.[16,18]

Statistical analysis

For each cohort separately and according to incident ASCVD, baseline participants' characteristics were expressed as number (percentage) for categorical variables and as mean ± standard deviation (SD) for continuous variables, stratified by sex. The Pearson χ^2 (for categorical variables) or ANOVA (for continuous variables) was used to evaluate differences in characteristics. If a continuous variable was not normally distributed, results were expressed as median with interquartile range (IQR) and differences in subjects were assessed using Kruskal–Wallis test.

Low-density lipoprotein cholesterol (LDL-C) levels were calculated according to the Friedewald equation. We used Martin's formula to estimate LDL-C levels in participants with triglycerides above 10.3 mmol/L (400 mg/dL).[23]

ASCVD rates were calculated, in both cohorts, by dividing the number of first events by the person-years during the observation period (i.e. until the event, death, or end of follow-up). Rates were expressed per 1000 person-years. Age-standardization on the Swiss general population was based on data provided by the Swiss Federal Statistical Office (https://www.bfs.admin.ch, 23 November 2021). Participants experiencing an ASCVD were subsequently censored for the rest of the study period to prevent double-counting of participants presenting additional ASCVD events.

For all analyses, the performance of the scores was tested by dichotomizing the predicted risk into low and intermediate versus high and very-high categories of risk.

Discrimination was assessed with sensibility, specificity, positive and negative predictive values, area under the receiver operating characteristic curve (AUROC), and Youden's index, with corresponding 95% confidence intervals (CIs), using incident ASCVD event during the period of interest.

Calibration was assessed with Brier score and the Hosmer–Lemeshow test. Furthermore, Cox prediction models for SCORE2, PCE,

and D:A:D were computed (using Stata command 'stmp2', fitting flexible parametric survival models) to generate calibration plots (using Stata command 'pmcalplot'). The proportional-hazards assumption was verified using Schoenfeld residuals. Model fit was assessed with Akaike's and Schwarz's Bayesian information criteria (AIC and BIC).

To allow further analyses, 10-year cardiovascular risk prediction was estimated based on Cox proportional-hazards model regressing the variables of either SCORE2 or PCE on incident ASCVD. We first explored the value of adding HIV-specific factors to SCORE2 and PCE. HIV-specific factors (baseline HIV viraemia, nadir CD4 T cells count, baseline CD4 T cells count, baseline CD4/CD8 ratio, abacavir use, nucleoside reverse transcriptase inhibitors and protease inhibitors exposure, and HIV associated-lipodystrophy) were separately included in the Cox equation and were selected for subsequent analysis if the derived hazard ratio (HR) was significant. AUROC and net reclassification improvement (NRI) were used to assess performance of SCORE2 and PCE before and after addition of the selected HIV-specific factors to the risk functions.[24]

Data were analysed using Stata version 16.0 for Windows (Stata Corp, College Station, TX, USA). Statistical testing was performed at the two-tailed α-level of 0.05.

Sensitivity analyses

First, we excluded individuals taking statin therapy at baseline to identify any bias due to on- and off-target effects of this treatment. Second, we stratified the analysis according to ethnicity, as non-Caucasian individuals (especially, sub-Saharan Africans) represent a large proportion of SHSC participants. Third, as CoLaus|PsyCoLaus study was initiated in 2003, we stratified PLWH according to their date of enrolment in SHCS (i.e. before 2003 vs. after 2003) to account for any difference in the management of ASCVD between those two periods. Fourth, we assessed discrimination and calibration as described above using scores score-validated age categories (i.e. 40–70 and over for SCORE2, 35–79 for PCE and 18–75 for D:A:D). As D:A:D score was initially validated to predict cardiovascular events at 5 years,[12] we additionally tested 5-years risk prediction (censoring events at 5-year follow-up) for each score.

Results

Study population and endpoints

From SHCS and CoLaus|PsyCoLaus studies, 6373 (28.4% women, 30.6% of the initial sample) and 5403 (53.5% women, 80.2% of the initial sample) individuals were eligible for analyses, respectively (Supplementary material online, *Figure S1*). The median follow-up time was of 13.5 (SD ±4.1) and 9.9 years (SD ±2.3) in SHCS and the CoLaus|PsyCoLaus study, respectively. Participants' characteristics at baseline are presented in *Table 1*. Participants from the SHCS were younger compared to those of the CoLaus|PsyCoLaus study, with a mean age of 40.6 (SD ±9.9) and 52.8 years (SD ±10.7), respectively. There were more individuals from African ethnicity in SHCS than in the CoLaus|PsCoLaus study (13.1% and 2.9%, respectively). Incident ASCVD occurred in 533 (8.4%) and 374 (6.9%) individuals during the follow-ups of SHCS and CoLaus|PsyCoLaus study, respectively. Participants experiencing ASCVD were approximately 10-year older, were more likely men or smokers, and had higher cholesterol and blood pressure values. Smoking and diabetes were more prevalent, and triglycerides levels higher in PLWH, although this population was younger. More than half of PLWH at high cardiovascular risk were taking lipid-lowering therapy, against 20% of uninfected individuals in the same category of risk. However, in the same category of risk, the number of CoLaus|PsyCoLaus participants reaching LDL-C targets was twice as high as that of PLWH (according to 2016 ESC guidelines, Supplementary material online, *Table S5*).[8] Regarding HIV-specific factors, PLWH experiencing an ASCVD had a lower viral load, were more likely to have had a CD4 nadir lower than 200 cells/mm^3 and were more likely to have been exposed to abacavir, lopinavir or indinavir. Distribution of risk categories by incident ASCVD is presented in Supplementary material online, *Table S2*.

The age-standardized ASCVD rate among PLWH was 12.9 (95% CI, 12.8–13.0) compared to 7.5 (95% CI, 7.4–7.5) per 1000 person-year ($P < 0.001$) among individuals from the general population (Supplementary material online, *Table S4* and *Figure 1*). The age-standardized rate of acute myocardial infarction was also substantially higher in the PLWH cohort [5.2 (95% CI, 5.1–5.2) vs. 2.1 (95% CI, 2.1–2.1) per 1000 person-year; $P < 0.001$]. Types of incident ASCVD and types of death in both cohorts are presented in Supplementary material online, *Table S3*. Mortality rate was globally higher among PLWH compared to individuals from the general population, with a rate of 9.8 vs. 7.1 per 1000 person-years ($P < 0.001$). Regarding cardiovascular death, incidence rate was higher among CoLaus|PsyCoLaus participants (1.3 vs. 0.7 per 1000 person-years; $P < 0.001$).

Cardiovascular risk prediction models

People living with HIV

D:A:D presented the highest specificity [90.2% (95% CI 89.4–91)], but a lower capacity to detect individuals at true cardiovascular risk compared to SCORE2 [sensitivities of 34.7% (95% CI, 30.7–38.9) and 72.2% (95% CI, 68.2–76), respectively]. SCORE2 and PCE presented the highest negative predictive value, with 96.1% (95% CI, 95.5–96.7) and 95.1% (95% CI, 94.4–95.7), respectively. Overall, discrimination of SCORE2, PCE and D:A:D were comparable, with an AUROC (95% CI) of 0.745 (0.723–0.767), 0.757 (0.736–0.777), and 0.763 (0.743–0.783), respectively (*Figure 2* and Supplementary material online, *Table S6*). Youden's index was also comparable across scores (Supplementary material online, *Table S6*).

All scores demonstrated similar calibration and model fit (Supplementary material online, *Table S6*). Calibration plots illustrated a better calibration of SCORE2 in the high-risk groups compared to PCE and D:A:D. However, all scores over-predicted ASCVD in the lower deciles of risk and under-predicted it in the higher deciles of risk, especially in the intermediate-risk groups (*Figure 3*).

Two HIV-specific factors were independently associated with the development of ASCVD, namely CD4 T cells nadir less than 200 cells/mm^3 [dichotomized as yes/no; HR 1.3 (95% CI, 1.1–1.6)] and exposure to abacavir [dichotomized as yes/no; HR 1.5 (95% CI, 1.2–1.8)]. Adding those factors to SCORE2 and PCE slightly improved AUROC but not significantly [0.752 (95% CI, 0.730–0.773) to 0.767 (95% CI, 0.748–0.787) and 0.816 (95% CI, 0.798–0.833) to 0.819 (95% CI, 0.802–0.838), respectively] (*Figure 4*). Adding CD4 T cells nadir and abacavir exposure variables to SCORE2 and PCE resulted in an NRI of −0.1% (95% CI, −1.2 to 1, $P = 0.83$) and of 2.7% (95% CI, 0.3–5.1, $P = 0.03$), respectively (Supplementary material online, *Figure S8*).

Table 1 Participants' characteristics at baseline (2003–2009) according to occurrence of an ASCVD, by study

	SHCS (*N* = 6373)				CoLaus|PsyCoLaus study (*N* = 5403)			
		ASCVD event (*N* = 533)				ASCVD event (*N* = 374)		
	All	No	Yes	*P*-value	All	No	Yes	*P*-value
Age, years	40.6 ± 9.9	**39.9 ± 9.5**	**47.7 ± 10.5**	<0.001	52.8 ± 10.7	**52.1 ± 10.5**	**61.3 ± 9.5**	<0.001
Female, *n* (%)	1807 (28.4)	**1729 (29.6)**	**78 (14.6)**	<0.001	2892 (53.5)	**2767 (55.0)**	**125 (33.4)**	<0.001
Caucasian, *n* (%)	5533 (86.8)	**5021 (86)**	**512 (96.1)**	<0.001	5250 (97.2)	4884 (97.1)	366 (97.9)	0.403
Lipids								
Total cholesterol, mmol/L (mean)	4.9 ± 1.3	**4.8 ± 1.3**	**5.4 ± 1.3**	<0.001	5.6 ± 1	**5.6 ± 1**	**5.7 ± 1**	0.003
LDL-C, mmol/L (mean)	2.8 ± 1.1	**2.8 ± 1.1**	**3.2 ± 1.1**	<0.001	3.3 ± 0.9	**3.3 ± 0.9**	**3.5 ± 0.9**	<0.001
HDL-C, mmol/L (mean)	1.2 ± 0.4	**1.2 ± 0.4**	**1.1 ± 0.4**	0.006	1.7 ± 0.4	**1.7 ± 0.4**	**1.5 ± 0.4**	<0.001
Triglycerides, mmol/L (mean)	2.1 ± 1.7	**2 ± 1.6**	**2.7 ± 1.9**	<0.001	1.4 ± 1.2	**1.3 ± 1.2**	**1.7 ± 1.1**	<0.001
Lipid lowering therapy, *n* (%)	1850 (29)	**1427 (24.4)**	**423 (79.4)**	<0.001	579 (10.7)	**492 (9.8)**	**87 (23.3)**	<0.001
Achieving LDL-C targets, *n* (%)[a]	597 (9.4)	**453 (7.8)**	**144 (27.0)**	<0.001	177 (3.3)	**152 (3.0)**	**25 (6.7)**	<0.001
Blood pressure and hypertension								
Systolic, mmHg (mean)	124 ± 16	**123 ± 16**	**130 ± 18**	<0.001	128 ± 18	**127 ± 17**	**140 ± 19**	<0.001
Diastolic, mmHg (mean)	79 ± 11	**79 ± 11**	**82 ± 11**	<0.001	79 ± 11	**79 ± 11**	**83 ± 12**	<0.001
Hypertension, *n* (%)	2810 (44.1)	**2368 (40.6)**	**442 (82.9)**	<0.001	1834 (33.9)	**1599 (31.8)**	**235 (62.8)**	<0.001
Anti-hypertensive treatment, *n* (%)	2096 (32.9)	**1696 (29)**	**400 (75.1)**	<0.001	872 (16.1)	**741 (14.7)**	**131 (35.0)**	<0.001
eGFR (CKD-EPI), mL/min/1.73 m^2 (mean)	100.5 ± 19.9	**101.3 ± 19.7**	**91.8 ± 19.5**	<0.001	85.8 ± 15.5	**86.2 ± 15.4**	**80.2 ± 16.4**	<0.001
BMI, kg/m^2 (mean)	23.4 ± 3.7	23.4 ± 3.7	23.6 ± 3.7	0.153	25.6 ± 4.4	**25.5 ± 4.3**	**27.4 ± 5.0**	<0.001
Smokers, *n* (%)	3167 (49.7)	**2865 (49.1)**	**302 (56.7)**	0.001	1431 (26.5)	1314 (26.1)	117 (31.3)	0.065
Diabetes mellitus, *n* (%)	621 (9.7)	**513 (8.8)**	**108 (20.3)**	<0.001	326 (6.0)	**261 (5.2)**	**65 (17.4)**	<0.001
Platelet aggregation inhibitors treatment, *n* (%)	1074 (16.9)	**621 (10.6)**	**453 (85)**	<0.001	829 (15.3)	**732 (14.6)**	**97 (25.9)**	<0.001
Time since HIV diagnosis, years (median)	4.5 (0.1–10.6)	**4.1 (0.1–10.5)**	**7.1 (2.1–12.7)**	<0.001	NA	NA	NA	NA
Log HIV viral load, copies/mL (median)	7.8 (0–10.9)	**8 (0–10.9)**	**4.4 (0–10.4)**	<0.001	NA	NA	NA	NA
HIV-RNA <50 copies/mL, *n* (%)	2320 (36.4)	**2067 (35.4)**	**253 (47.5)**	<0.001	NA	NA	NA	NA
Baseline CD4 T cells, cells/mm^3 (median)	407 (254–595)	408 (254–596)	404 (258–590)	0.723	NA	NA	NA	NA
CD4 T cells nadir, cells/mm^3 (median)[b]	220 (99–363)	**225 (104–367)**	**161 (65–306)**	<0.001	NA	NA	NA	NA
CD4/CD8, ratio (mean)	0.4 (0.3–0.7)	**0.4 (0.3–0.7)**	**0.4 (0.3–0.7)**	0.031	NA	NA	NA	NA
cART, *n* (%)	3646 (57.2)	**3249 (55.6)**	**397 (74.5)**	<0.001	NA	NA	NA	NA
NRTI treatment, *n* (%)	3583 (98.3)	3195 (98.3)	388 (97.7)	0.383	NA	NA	NA	NA
Abacavir, *n* (%)	909 (24.9)	**776 (23.9)**	**133 (33.5)**	<0.001	NA	NA	NA	NA
NNRTI treatment, *n* (%)	1313 (36)	1164 (35.8)	149 (37.5)	0.504	NA	NA	NA	NA
PI treatment, *n* (%)	2077 (57)	1838 (56.6)	239 (60.2)	0.168	NA	NA	NA	NA
Indinavir, *n* (%)	297 (8.2)	**253 (7.8)**	**44 (11.1)**	0.023	NA	NA	NA	NA
Lopinavir, *n* (%)	591 (16.2)	**506 (15.6)**	**85 (21.4)**	0.003	NA	NA	NA	NA
HIV-associated lipodystrophy, *n* (%)	1387 (21.8)	**1211 (20.7)**	**176 (33)**	<0.001	NA	NA	NA	NA
Hepatitis C infection, *n* (%)	1333 (20.9)	1236 (21.2)	97 (18.2)	0.107	NA	NA	NA	NA

Results are expressed as number of participants (%), mean (±SD), or median (IQR). Percentages are expressed by column. *P*-values were computed using Pearson χ^2, ANOVA, or one-way ANOVA on ranks (Kruskal–Wallis test) when appropriate. Results are displayed in bold when statistically significant.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; cART, combination anti-retroviral therapy; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration Equation; eGFR, estimated glomerular filtration rate; HDL-C high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable or not available; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; RNA, ribonucleic acid.
[a]According to the 2016 ESC guidelines for the management of dyslipidaemia (https://doi.org/10.1093/eurheartj/ehw272), categorization of risk according to SCORE.
[b]Corresponds to the lowest reported value of CD4+ T cells count for each HIV-infected individuals before baseline.

Comparison with general population

AUROC of both SCORE2 and PCE were higher in the CoLaus|PsyCoLaus study than in SHCS [0.800 (95% CI, 0.777–0.822) and 0.806 (95% CI, 0.784–0.827), respectively]. The sensitivity of SCORE2 for incident ASCVD was similar in SHCS and CoLaus|PsyCoLaus study (Supplementary material online, *Table S6*). Regarding calibration, the predicted probability of ASCVD by either SCORE2 or PCE was good in the highest decile of risk (*Figure 3*).

Sensitivity analysis

Baseline patient's characteristics according to sex or ethnicity are presented in Supplementary material online, *Tables S7* and

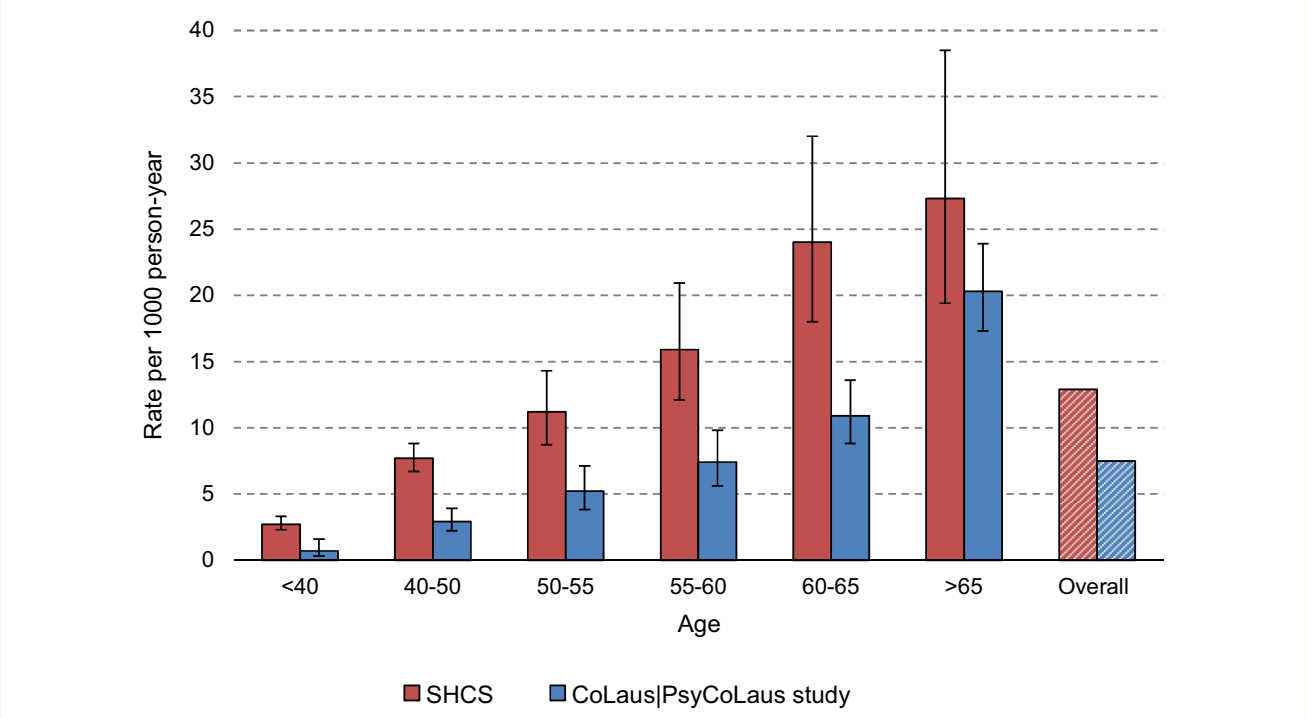


Figure 1 Atherosclerotic cardiovascular disease incidence rate according to age in Swiss HIV Cohort Study and CoLaus|PsyCoLaus study. Error bars illustrate 95% confidence intervals. Overall age-adjusted rates were obtained after standardization for the Swiss general population, based on data provided by the Swiss Federal Statistical Office (https://www.bfs.admin.ch, 23 November 2021).

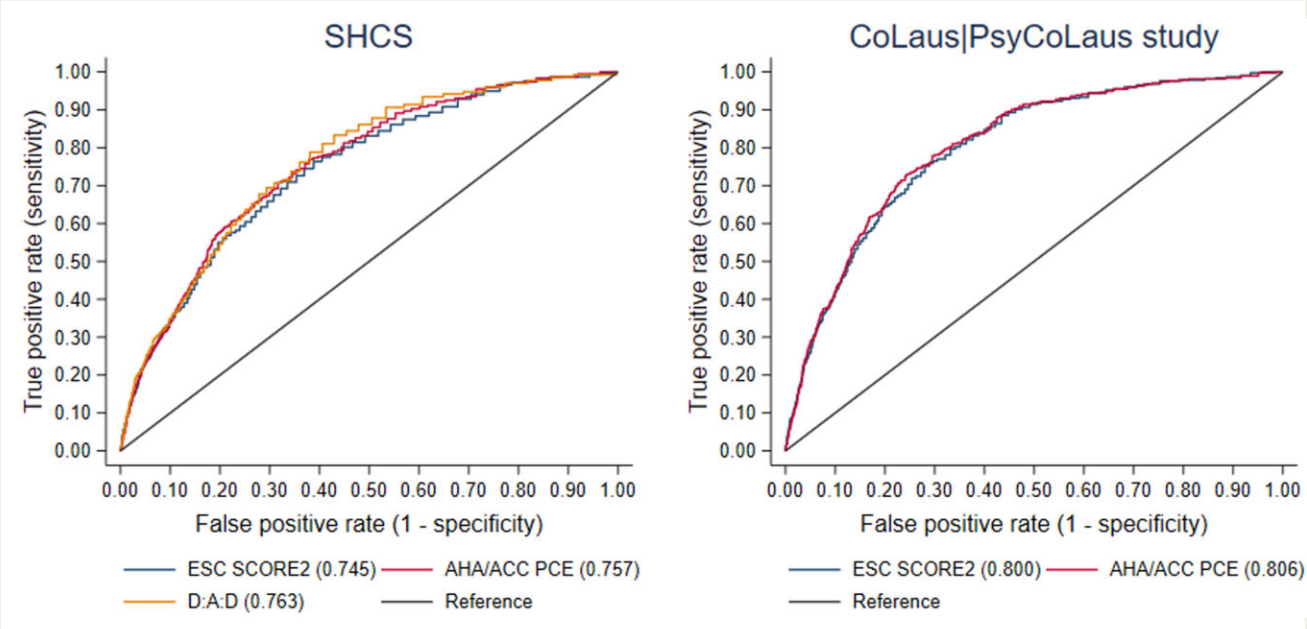


Figure 2 Receiver operating characteristics curves of ESC SCORE2, AHA/ACC PCE, and D:A:D scores to predict ASCVD, by study. Area under the receiver operating characteristic curves statistics are presented in parenthesis. All scores were dichotomized into low/intermediate vs. high/very high categories of risk. SHCS: 533 ASCVD events; CoLaus|PsyCoLaus: 372 ASCVD events. ACC, American College of Cardiology; AHA, American Heart Association; D:A:D, Data collection on Adverse Effects of Anti HIV Drugs; ESC, European Society of Cardiology; PCE, Pooled Cohort Equation; SCORE2, Systematic Coronary Risk Evaluation 2.

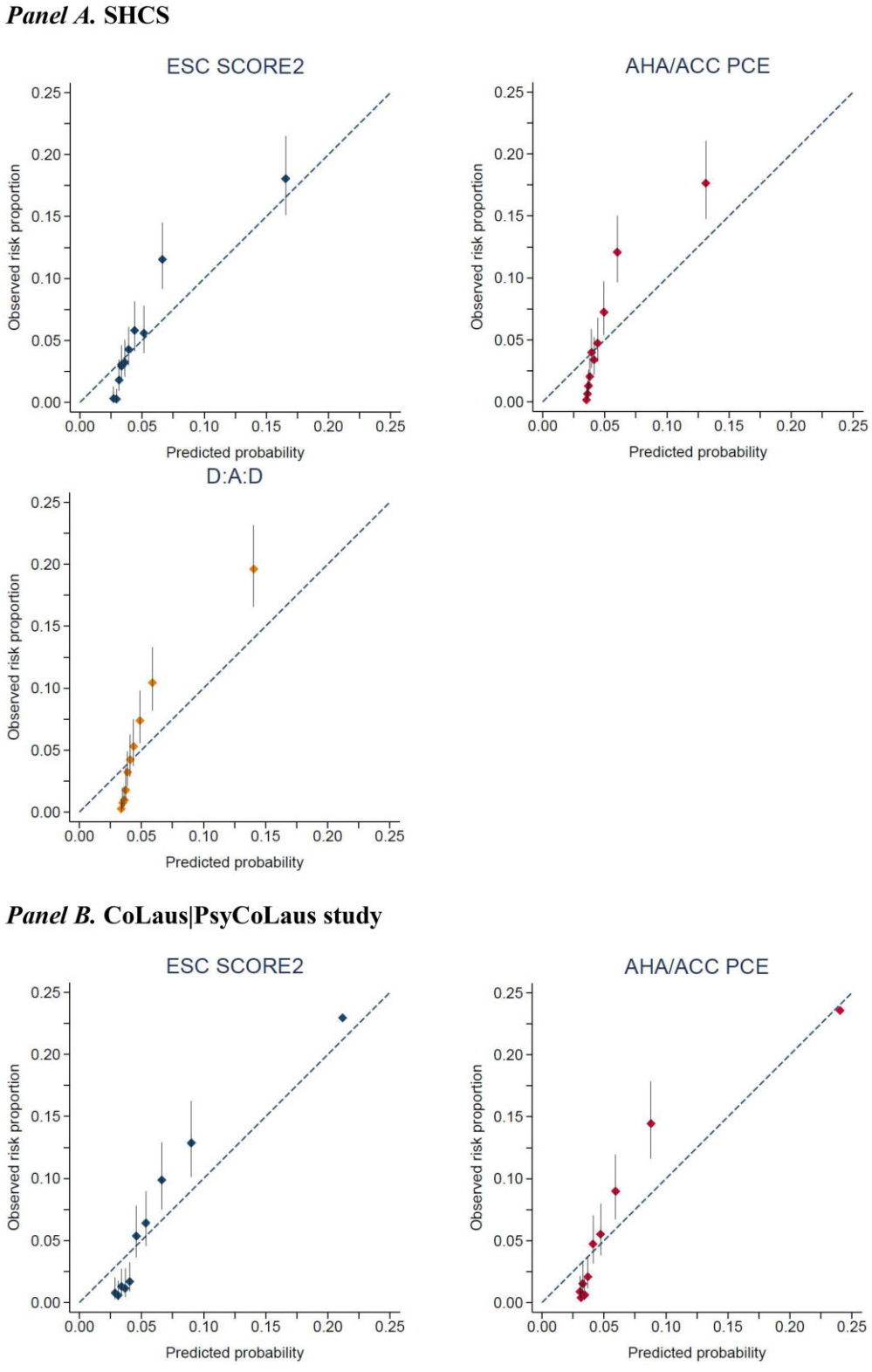


Figure 3 Predicted and observed ASCVD, by scores. (*A*) SHCS. (*B*) CoLaus|PsyCoLaus study. Calibration plots of cardiovascular risk scores (*N* = 6373 for SHCS, *N* = 5403 for CoLaus|PsyCoLaus). Observed risk scores outcome (i.e. common set of ASCVD) in the risk prediction model analysis were calculated using Kaplan–Meier estimates. Participants are divided into 10 deciles of risk represented by diamonds. Vertical bars indicate 95% confidence intervals. ACC, American College of Cardiology; AHA, American Heart Association; D:A:D, Data collection on Adverse Effects of Anti HIV Drugs; ESC, European Society of Cardiology; PCE, Pooled Cohort Equation; SCORE2, Systematic Coronary Risk Evaluation 2.

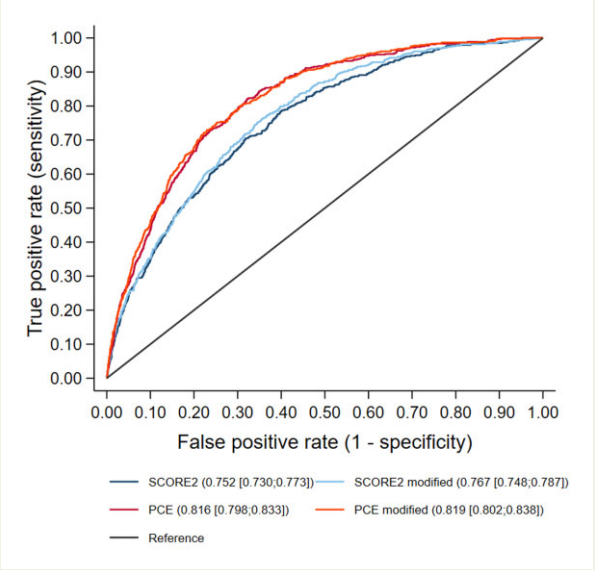


Figure 4 Comparison of conventional and modified (adding HIV-specific risk factors) ESC SCORE2 and AHA/ACC PCE scores in predicting ASCVD in people living with HIV in SHCS. Ten-year cardiovascular risk was estimated by Cox proportional-hazards model regressing ASCVD (yes/no) on risk factors of the different scores. For ESC SCORE2 and AHA/ACC PCE, modified scores were computed by adding CD4 nadir <200 cells/mm^3 (yes/no) and exposure to Abacavir (yes/no) to the Cox regressions in addition to the traditional variables. Area under the receiver operating characteristics curves statistics are presented in parenthesis with corresponding 95% confidence intervals. Because the scores shown in this figure were computed with Cox proportional-hazards models, their predictive performance should not be compared to the original ones, nor compared each another. ACC, American College of Cardiology; AHA, American Heart Association; D:A:D, Data collection on Adverse Effects of Anti HIV Drugs; ESC, European Society of Cardiology; PCE, Pooled Cohort Equation; SCORE2, Systematic Coronary Risk Evaluation 2.

S8, respectively. Baseline characteristics of PLWH according to their date of enrolment in SHCS (before or after 2003) are presented in Supplementary material online, *Table S9*. The sensitivity of SCORE2, PCE, and D:A:D scores to identify incident ASCVD in women was lower than in men, with similar AUROC (Supplementary material online, *Table S10*). In SHCS, calibration plots illustrated a better calibration of SCORE2 and D:A:D for women than PCE, which systematically underestimated risk prediction in the 10th decile of risk in this population (Supplementary material online, *Figure S5A*). The difference between sexes using PCE was reduced in the CoLaus|PsyCoLaus study (Supplementary material online, *Figure S5B*). Regarding ethnicity, SCORE2 and PCE underestimated risk in the higher deciles of risk in PLWH from African origin compared to D:A:D (Supplementary material online, *Figure S6A*). Hosmer–Lemeshow test *P*-value was not significant for SCORE2 in African participants in SHCS and CoLaus|PsyCoLaus study. The results remained consistent when separating SHCS individuals based on the period of enrolment (before and after 2003) (Supplementary material online, *Table S12* and *Figure 4*) and after exclusion of individuals using lipid-lowering therapy (Supplementary material online, *Table S13*).

When using score-validated age categories, predictive performances of SCORE2, PCE and D:A:D remained comparable (Supplementary material online, *Table S14*). Restricting follow-up to 5 years did not increased the performance of D:A:D (originally developed to predict outcomes over 5 years), which remained comparable to both SCORE2 and PCE (data not shown).

Discussion

Our findings, based on two contemporary cohorts with 10-year follow-up, provide evidence that PLWH continue to experience a two-fold higher incidence rate of ASCVD compared to people from the general population, notably myocardial infarction and especially in the young categories of age. Importantly, only a fifth of PLWH at high cardiovascular risk reached LDL-C targets, whereas a large proportion of them (55.2%) were taking a lipid-lowering therapy. In PLWH, SCORE2 and PCE were equivalent to D:A:D in predicting 10-year ASCVD risk. SCORE2 demonstrated better calibration in high-risk groups compared to PCE and D:A:D. Adding HIV-specific factors to SCORE2 and PCE marginally improved reclassification. As SCORE2, PCE, and D:A:D had similar performances in PLWH, they can be interchangeably used in comparable HIV populations, SCORE2 and PCE being easier to use with widely available variables.

We found a 73% increase in age-adjusted incidence rate ratio of ASCVD among PLWH compared to individuals from the general population, proportional to older data ranging from 40% to 100% and based on observational studies from 1990 to 2010 in high-income countries.[2] In our analysis, PLWH had the same ASCVD incidence rate than 10-year older individuals from the general population. While this difference could be explained by a higher prevalence of traditional cardiovascular risk factors in SHCS participants, our findings were contrasted. There were twice as many smokers in SHCS as in CoLaus|PsyCoLaus study and a higher prevalence of diabetes in PLWH, consistent with previous reports based on data around the 2000s.[25] Conversely, the impact of hypertension on ASCVD development in PLWH might have been mitigated by the fact that 60% of treated PLWH were normotensive, against 50% of treated individuals in the general population. Use of lipid-lowering therapy was higher in SHCS participants. However, fewer PLWH reached LDL-C targets according to their category of risk, which may result in an insufficient reduction in ASCVD risk in this population. This finding has been previously observationally reported, with lower than expected LDL-C reduction in PLWH according to the intensity of statin therapy.[26] Drug interactions and adherence to treatment might be potential issues. However, further research is warranted to assess specific determinants of the response to lipid-lowering drugs in PLWH compared to uninfected individuals.

Previous prospective studies[3,4,11] comparing the performance of cardiovascular risk scores among PLWH reported C-statistics

ranging from 0.71 to 0.76 for PCE and from 0.72 to 0.77 for D:A:D. These studies were limited by either limited follow-up or small samples size, and none of them conducted a prospective comparison with individuals from the general population. Our data provide evidence that SCORE2, the recent cardiovascular risk score developed for Europe, and PCE, its North American equivalent, are suboptimal in PLWH compared to people living without HIV in terms of discrimination and calibration. Furthermore, the gold-standard D:A:D score is not superior to both SCORE2 and PCE in PLWH. The new SCORE2 model demonstrated higher predictive performances than old SCORE when comparing our results to previous studies assessing SCORE in PLWH.[3,11] As SCORE2, PCE and D:A:D presented similar predictive capacities, SCORE2 and PCE could be recommended for cardiovascular risk assessment in PLWH, especially due to the fact that they include a more limited set of variables, which is useful in clinical practice. PCE should be used with caution in HIV-infected women, amongst whom calibration was lower compared to SCORE2 and D:A:D. Due to the high burden of ASCVD in PLWH, cardiovascular risk tools are crucial to identify individuals at high risk and to assist in patient counselling. PLWH represent a heterogeneous group concerning cardiovascular risk and may benefit from tailored strategies depending on their risk profile. The ongoing randomized trial to prevent vascular events in HIV (REPRIEVE)[27] is the first prospective randomized controlled trial testing a preventive strategy among PLWH and will certainly provide important clarifications.

The addition of HIV-specific factors failed to substantially improve the predictive performance of both SCORE2 and PCE. This finding is consistent with a recent multi-centric HIV cohort study from North America, comprising 11 288 PLWH (mean age 41.6 years, 18% women, 70% under cART, mean follow-up of 4.1 years).[4] The predictive performance of PCE was not improved by adding HIV viral load, CD4 T cells count, antiretroviral therapy and protease inhibitor variables to the algorithm. Although specific HIV factors have been linked to ASCVD, little is known on how they affect ASCVD progression compared to traditional risk factors. Baseline variables such as CD4 T cells level and abacavir use may not capture the complex influence of chronic inflammation, immune dysregulation and cART on ASCVD. Moreover, traditional risk factors may affect differently ASCVD progression among PLWH compared to people living without HIV and this remained to be investigated. Additionally, continuous improvements in risk equations rely on regular recalibrations, also integrating populations less frequently investigated such as women and people from different ethnical backgrounds. Further refinements may also be based on integrating genetic data into risk estimation.[28]

Limitations should be considered while interpreting our results. First, our analysis is based on observational data and we did not account for medical interventions that might have changed ASCVD development. Second, the closer follow-up in SHCS participants, compared to CoLaus|PsyCoLaus study, might have contributed to a higher rate of ASCVD in PLWH. Nevertheless, CoLaus|PsCoLaus participants were fully informed of the main aim of the study that is to specifically investigate cardiovascular disease and were asked multiple times during the follow-up about the occurrence of any ASCVD, minimizing their underreporting. For both studies, we had no information on the type of coronary lesions or subtype of infarction, rendering more precise analyses and comparison not possible. Third, the proportion of PLWH under cART at baseline was relatively low (57.2%) in line with guidelines that evolved until 2015 when World Health Organisation recommended to start treatment in everyone living with HIV.[29] Therefore, the complex influence of cART on cardiovascular risk profile should be kept in mind when comparing our results with HIV populations with a higher proportion of people under cART. Finally, the CoLaus|PsyCoLaus study, as opposed to SHCS, is a monocentric population-based study, which might limit the extrapolation of the results to whole Switzerland or countries with different prevalence of cardiovascular risk factors or disease. However, based on previous findings and official statistical data, there is no evidence for large differences in terms of prevalence of cardiovascular risk factors, ASCVD incidence or cardiovascular death rate across Switzerland compared to other European countries.[18,30,31]

Conclusion

PLWH are still presenting a two-fold higher incidence rate of ASCVD compared to individuals from the general population, making the implementation and validation of prevention tools an urgent need. In people taking lipid-lowering treatments, PLWH less often reached LDL-C targets compared to individuals from the general population in the same category of risk. Using either SCORE2 or PCE in PLWH is valid to predict ASCVD, notably due to their set of variables that are easier to use compared to more complex scores integrating HIV-specific data. Adding HIV-specific factors to scores developed for the general population did not result in a clinically significant improvement.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data Availability Statement

According to the Swiss law, data cannot be shared if data subjects have not agreed or data is too sensitive to share. Investigators with a request for selected data should send a proposal to the respective SHCS address (www.shcs.ch/contact). The provision of data will be considered by the Scientific Board of the SHCS and the study team and is subject to Swiss legal and ethical regulations, and is outlined in a material and data transfer agreement.

The CoLaus|PsyCoLaus cohort data used in this study cannot be fully shared as they contain potentially sensitive patient information. As discussed with the competent authority, the Research Ethic Committee of the Canton of Vaud, transferring or directly sharing this data would be a violation of the Swiss legislation aiming to protect the personal rights of participants. Non-identifiable, individual-level data are available for interested researchers, who meet the criteria for access to confidential data sharing, from the CoLaus Datacenter (CHUV, Lausanne, Switzerland). Instructions for gaining access to the CoLaus data used in this study are available at https://www.colaus-psycolaus.ch/professionals/how-to-collaborate.

Conflict of interest: none declared.

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