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MAJOR ARTICLE

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Background. Data on uptake of preventive measures for cardiovascular disease (CVD) in people with HIV are limited.

Methods. We determined the annual prevalence (2012–2021) of CVD preventive measures use for RESPOND participants with a very high (>10%) estimated D:A:D 10-year CVD risk who were eligible for each specific measure evaluated. We used binomial regression to assess factors associated with each preventative measure uptake.

Results. Between 2012 and 2021, the crude proportion of >10% estimated 10-year CVD risk individuals increased from 32.4% (n = 4272) to 52.1% (n = 5298). At the end of follow-up, among very high-risk individuals, 67.4% (1552/2303) with hypertension used antihypertensives, 55.9% (1562/2792) with dyslipidemia lipid-lowering drugs (LLDs), and 7.4% (159/2149) smokers ceased smoking, without significant changes over time. Conversely, a smaller proportion of individuals with diabetes received antidiabetics in later years (2012–2013: 60.3% [388/643] versus 2019–2020: 57.2% [459/803], global $P = .0028$). Use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) in those with hypertension or diabetes slightly declined before increasing again (42.1% [864/2052] versus 43.4% [1123/2585], global $P = .0009$). Individuals with ongoing viremia or intravenous drug use as HIV exposure group were less likely to cease smoking and use LLDs. Men ≥40 years and women ≥50 were more likely to use antihypertensives, ACEIs/ARBs, antidiabetics, and LLDs. The uptake of preventive measures was similar between sexes/genders.

Conclusions. The increasing proportion of individuals at very high estimated 10-year CVD risk without a corresponding increase in use of preventive measures calls for greater awareness of CVD risk management for people with HIV attending routine clinical care.

Keywords. cardiovascular disease; cohort; HIV.

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BACKGROUND

Cardiovascular disease (CVD) is a leading cause of mortality among people with HIV on antiretroviral therapy (ART) [1, 2]. While European guidelines until 2024 recommended annual CVD risk assessment in men ≥40 and women ≥50 years of age, current management guidelines recommend annual CVD risk assessment in all people with HIV ≥40 years of age [3, 4]. CVD risk models developed in the general population have been shown to systematically underestimate CVD risk in people with HIV [5]. Therefore, the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) created a model for people with HIV, including both traditional CVD risk factors and HIV-related factors, such as CD4 count and use of antiretrovirals (ARVs) previously associated with CVD [6].

The European AIDS Clinical Society (EACS) recommends initiation of preventive measures at a 10-year CVD risk >10%, including lifestyle interventions and focus on the use of antihypertensives in those with hypertension, antidiabetics in diabetics, and ART modifications where indicated. Current EACS recommendations recommend considering lipid-lowering drug (LLD) use also in low to moderate CVD risk individuals ≥40 years of age [4, 7]. Nonetheless, suboptimal CVD risk prevention and management strategies are well described both for people with and without HIV [8].

While some studies indicate CVD rates in people with well-treated HIV have approached those of the general population [9, 10], recent US data found an increasing myocardial infarction (MI) incidence gap in 2010–2017 when comparing people with and without HIV, highlighting the need for CVD prevention in an ageing population with HIV [11].

Previous investigations of CVD management were primarily conducted nationally in smaller observational studies [12] and focused on the use of individual measures, eg, statins or aspirin [13, 14], with limited data in subgroups of interest, including women or older individuals with HIV.

Based on the EACS guidelines' management principles, we assessed the utilization of multiple cardiovascular preventive measures in the International Cohort Consortium of Infectious Diseases (RESPOND) for people with HIV at very high CVD risk (>10%), stratified by clinically relevant subgroups.

METHODS

Study participants were from the RESPOND consortium, including people with HIV from 19 cohorts across Europe and Australia. Details on RESPOND were previously published [15].

RESPOND annually collects prospective clinical, paraclinical, and demographic data on all participants and for at least 5 years prior to enrollment.

The composite CVD endpoint includes type I myocardial infarctions, strokes, and invasive cardiovascular procedures (ICP; coronary angioplasty/stenting, coronary bypass surgery, carotid endarterectomy, carotid artery stenting).

Individuals included in this analysis were ≥18 years and had a CD4 count and viral load (VL) measurement in the 12 months before or 3 months after baseline with no prior CVD. Baseline was defined as the first date where a 10-year D:A:D CVD risk could be calculated after 1 January 2012 or cohort enrollment. To reduce potential bias from missing data, we only included cohorts with >70% data completeness for each variable contributing to the 10-year D:A:D CVD risk score [6]. We censored participants' follow ups at the earliest of the first CVD event, last visit, or 31 December 2021 (administrative censoring date).

Cardiovascular Disease Risk and Preventive Measures

Developed in a population similar to RESPOND and therefore likely well-fitted to our study population, we used the 10-year D:A:D CVD risk score to divide individuals into low (<1%), moderate (1–5%), high (5–10%), and very high (>10%) 10-year CVD risk. Based on a clinical standpoint and agreement of the RESPOND CVD working group, once an individual's estimated CVD risk reached >10%, the individual remained in that risk category throughout the study period.

Based on recommendations of the EACS Guidelines at the time of analysis [3], the preventive measures considered in this study were: weight loss, defined as in earlier RESPOND analyses as ≥7% loss of body weight in obese individuals (body mass index [BMI] > 30 kg/m^2) [16], smoking cessation in current smokers, and use of antidiabetic medication in individuals with diabetes, defined as blood glucose >11.1 mmol/L, HbA1c > 6.5%, antidiabetic medication initiation or clinical diagnosis [17]. We also determined LLD use in individuals with dyslipidemia, defined as a total cholesterol >240 mg/dL and/or high-density lipoprotein <35 mg/dL, triglycerides >200 mg/dL, or the initiation of LLDs, and use of antihypertensive medication in persons with hypertension defined as 2 consecutive systolic blood pressure (SBP) measurements ≥140 mmHg and/or 2 diastolic blood pressure (DBP) measurements ≥90 mmHg (performed on different days), a single SBP measurement ≥140 mmHg and/or DBP measurement ≥90 mmHg with antihypertensive use within 6 months of the measurement, or antihypertensive medication initiation without a recorded high BP [18]. Additionally, while also included as antihypertensive medication, we considered angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use in persons with hypertension or diabetes due to their indication in persons with proteinuria. As recommended for primary CVD prevention, we also assessed antiplatelet medication uptake in participants with diabetes.

Moreover, we assessed any discontinuation of ARVs previously associated with CVD, ritonavir-boosted lopinavir (LPV/r), boosted darunavir (DRV/b), and discontinuation of abacavir (ABC) for more than 6 months.

We defined medications using Anatomical Therapeutic Chemical [19] and HIV Cohorts Data Exchange Protocol [20] codes as received from participating RESPOND cohorts.

Statistical Analysis

We described the demographic and clinical characteristics of included participants at baseline and stratified them by the estimated 10-year CVD risk groups.

From 1 July 2012 to 1 July 2021, we determined the annual proportion of persons under follow-up at low, medium, high, and very high estimated CVD risk. To capture changes in risk and management over time, we calculated the annual prevalence of those eligible for each preventive measure among very

high CVD risk individuals (eg, antihypertensive treatment for those with hypertension). We then assessed the proportions of these individuals who received the respective measure within the following 12 months. If a participant stopped and later restarted (eg, restarted smoking and later quit again), they reentered the eligible pool and were reassessed in subsequent years. Due to insufficient follow-up in the latest calendar year up to administrative censoring, this approach was not feasible for 2021.

To determine factors associated with the uptake of each preventive measure among eligible individuals at very high risk, we used binomial regression with robust standard errors and generalized estimating equations to allow for repeated preventive measures within the same participant.

A priori, we stratified the assessment by clinically relevant subgroups. These included age, based on the EACS recommendations [3] to assess CVD risk annually for all men ≥ 40 years and women ≥ 50 without prior CVD. Other subgroups were sex, HIV transmission group (intravenous drug use [IDU] vs non-IDU), and VL (>200 vs ≤200 copies/mL). Since systematic CVD screening is a recommended part of routine HIV care for individuals with comorbidities and risk factors, we also stratified our analyses by diabetes and smoking status.

Regression models of preventive measure use were adjusted for age, sex, HIV acquisition risk, ethnicity, CD4 count, CD4 nadir, prior AIDS, prior cancer, prior chronic kidney disease, diabetes, hypertension, smoking status, BMI, ART status, prior exposure to drugs previously associated with CVD (LPV/r, DRV/b, IDV, ABC), baseline date, and calendar year. We also included integrase strand transfer inhibitors (INSTIs) based on recent RESPOND findings of an association between the INSTI class and CVD incidence [21]. Factors included as eligibility criteria were not included in the model of the respective intervention, eg, hypertension not included in models assessing ACEI/ARB use and, eg, prior LPV/r exposure not included for assessing LPV/r discontinuation. Additionally, we addressed potential regional differences by adding SCORE-2 charts' CVD risk regions [22] to all models.

An unknown category accounted for missing data for categorical variables in all models.

Sensitivity Analyses

We assessed the impact of multimorbidity on preventive measures' uptake by including an interaction term in our models between age and the number of prevalent comorbidities (considering hypertension, diabetes, dyslipidemia, and obesity).

Although RESPOND has shown consistently low loss to follow-up rates, helping to minimise bias and support the reliability of findings, we restricted the analysis to participants with follow-up for the entire study period. To be consistent with the original D:A:D CVD risk score derivation, we estimated 10-year CVD risk censoring exposure to ARVs at a maximum of 5 years.

We performed statistical analyses using SAS (Statistical Analysis Software, NC, USA) version 9.4.

RESULTS

Of 37 666 RESPOND participants, 10 135 were excluded as they were from cohorts with <70% data completeness or they had prior CVD, Figure 1. A further 4615 were excluded with missing data, such as sex or CD4 count, or without follow-up data, resulting in 22 916 participants in the analysis. Compared to the included participants, those excluded had lower CVD incidence rates; a larger proportion was female and had IDU or heterosexual contact as mode of HIV acquisition (Supplementary Table).

Baseline characteristics, stratified by 10-year CVD risk groups, are presented in Table 1. Compared to the overall participants, those at very high CVD risk (n = 6,060, 26.4%) had a lower proportion of VL >200 copies/mL, with fewer being ART-naïve at baseline. They had a higher proportion of traditional CVD risk factors and greater exposure to ARVs previously associated with CVD.

The crude proportions of individuals at very high estimated 10-year CVD risk increased from 32.4% (4272/13 199) in 2012% to 52.1% (5298/10 169) in 2021, Figure 2. Albeit CVD risk is multifactorial, increasing age and longer cumulative exposures to ARVs associated with CVD were the main contributors to these changes in very high estimated risk over time, while other risk factors remained more stable.

Temporal Trends

Among very high-risk individuals eligible for the specific prevention, within the latest follow-up period (2020–2021), 67.4% (1552/2303) of individuals with hypertension were on antihypertensive medication, and 55.9% (1562/2792) of those with dyslipidemia received LLDs. Smoking cessation occurred in 7.4% (159/2149) and 10.9% (51/469) of obese individuals lost ≥7% body weight. There were no statistically significant changes over time in using any of these CVD preventive measures when adjusting for potential risk factors (all global $P > .05$), Figure 3.

In contrast, we surprisingly observed a significant decrease in antidiabetic medication use in later years; 60.3% (388/643) of people with diabetes received antidiabetic medication in 2012–2013 compared to 57.2% (459/803) in 2020–2021 (global $P = .028$). Similarly, the proportion of participants with diabetes on antiplatelet medication slightly decreased from 15.2% (98/643) to 13.2% (106/803) (global $P = .017$). The proportion of individuals using ACEIs/ARBs was U-shaped (42.1% in 2012–2013 vs 43.4% in 2020–2021, global $P = .009$), with >95% of those individuals having hypertension. Discontinuation rates increased over time for DRV/b (7.2% vs 10.3%), LPV/r (15.0% vs 21.4%), and ABC for >6 months, although ABC discontinuation decreased in the latest follow-up period (2.4% in 2012%–2013%

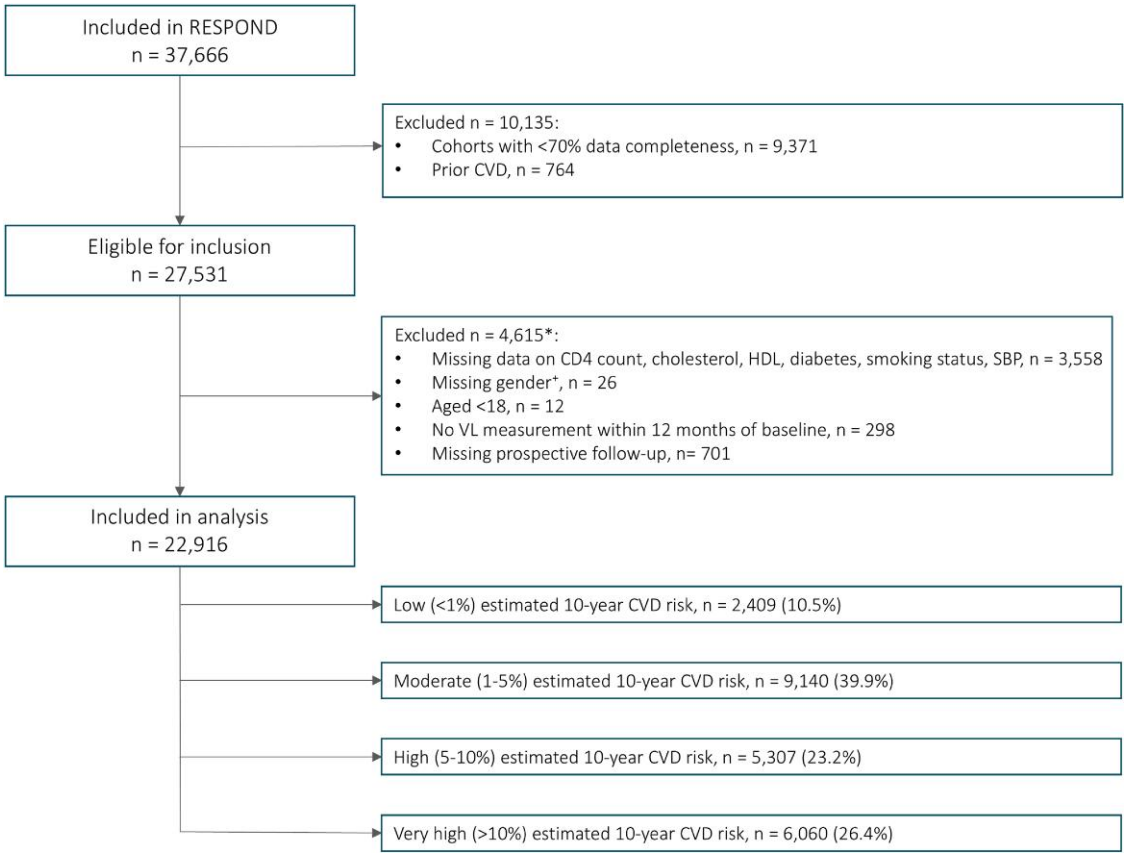


Figure 1. Exclusion flowchart. *More than 1 reason can apply. +Including transgender. Estimated CVD risk score categories were assessed at baseline. CVD, cardiovascular disease; HDL, high-density lipoprotein; SBP, systolic blood pressure; VL, viral load.

vs 8.9% in 2019–2020, 2.1% in 2020–2021; $P < .001$ for all ARVs).

Subpopulations

In adjusted regression models, men ≥40 and women ≥50 years (vs <40/<50) were more likely to use antihypertensive medication, ACEIs/ARBs, and LLDs, Figure 4. Similarly, individuals with diabetes, compared to those without, were more likely to use antihypertensive medication, LLDs and cease smoking.

Smoking cessation and LLD use, however, were less likely in participants with viremia (vs VL <200 copies/mL) and IDU as HIV acquisition (vs non-IDU). Other than women being less likely to receive ACEIs/ARBs, preventive measure use was similar between sexes/genders.

Compared to low CVD risk regions, individuals from a moderate CVD risk region were less likely to use antidiabetic medication, stop smoking, and discontinue ABC but more likely to use antihypertensive medication, ACEIs/ARBs, and discontinue DRV/b, Supplementary Figure. Participants from high CVD risk regions were less likely to discontinue LPV/r and ABC and those from very high-risk regions were additionally less likely to use LLDs and stop smoking.

Sensitivity Analyses

Compared to those without concomitant comorbidities, having an increasing number of comorbidities significantly increased the likelihood of receiving antihypertensive, antidiabetic, antiplatelet medication, LLDs, and ACEIs/ARBs (data not shown, all multivariable $P < .001$). There was no evidence of an interaction between uptake of each preventive measure, concomitant comorbidities, and age ($P > .10$), suggesting a similar effect of multimorbidity on preventive measure use for younger and older individuals.

Censoring ARV exposure at 5 years and assessing only participants under follow-up during the entire study period did not change our findings.

DISCUSSION

Within the large, multinational RESPOND cohort consortium, the crude proportion of people with HIV at a very high estimated 10-year CVD risk increased by almost 20% from 2012 to 2021, primarily due to ageing and longer cumulative use of ARVs associated with increased CVD risk. Meanwhile, the uptake of most CVD preventive measures did not increase

Table 1. Baseline Characteristics, Overall and Stratified by Estimated 10-year D:A:D CVD Risk Score Category

				Low CVD Risk		Medium CVD Risk		High CVD Risk		Very High CVD Risk	
		All		<1%		1–5%		5–10%		>10%	
		n	%	n	%	n	%	n	%	n	%
All		**22 916**	**100**	**2409**	**100**	**9140**	**100**	**5307**	**100**	**6060**	**100**
Sex/Gender	Male	17 200	75.1	1343	55.7	6344	69.4	4193	79.0	5320	87.8
	Female	5716	24.9	1066	44.3	2796	30.6	1114	21.0	740	12.2
Risk of HIV acquisition	MSM	10 540	46.0	1070	44.4	4143	45.3	2489	46.9	2838	46.8
	IDU	3199	14.0	118	4.9	1144	12.5	877	16.5	1060	17.5
	Heterosexual	7871	34.3	1019	42.3	3405	37.3	1651	31.1	1796	29.6
	Other	1306	5.7	202	8.4	448	4.9	290	5.5	366	6.0
Ethnicity	White	17 208	75.1	1488	61.8	6503	71.1	4192	79.0	5025	82.9
	Other[a]	3230	14.1	646	26.8	1675	18.3	538	10.1	371	6.1
CVD risk region[b]	Low	11 295	49.3	980	40.7	4142	45.3	2777	52.3	3396	56.0
	Moderate	8719	38.0	1052	43.7	3569	39.0	1923	36.2	2175	35.9
	High	1879	8.2	210	8.7	893	9.8	413	7.8	363	6.0
	Very high	1023	4.5	167	6.9	536	5.9	194	3.7	126	2.1
Viral load (cp/mL)	>200	4209	18.4	913	37.9	2097	22.9	720	13.6	479	7.9
	<200	18 707	81.6	1496	62.1	7043	77.1	4587	86.4	5581	92.1
Prior AIDS	No	18 070	78.9	2235	92.8	7697	84.2	4027	75.9	4111	67.8
	Yes	4846	21.1	174	7.2	1443	15.8	1280	24.1	1949	32.2
Prior CKD	No	22 119	96.5	2349	97.5	8957	98.0	5158	97.2	5655	93.3
	Yes	530	2.3	2	0.1	53	0.6	108	2.0	367	6.1
Diabetes	No	21 663	94.5	2401	99.7	9035	98.9	5120	96.5	5107	84.3
	Yes	1253	5.5	8	0.3	105	1.1	187	3.5	953	15.7
Hypertension	No	18 601	81.2	2336	97.0	8314	91.0	4193	79.0	3758	62.0
	Yes	4315	18.8	73	3.0	826	9.0	1114	21.0	2302	38.0
Smoking status	Never	8455	36.9	1576	65.4	4003	43.8	1564	29.5	1312	21.7
	Current	10 128	44.2	528	21.9	3511	38.4	2610	49.2	3479	57.4
	Previous	4333	18.9	305	12.7	1626	17.8	1133	21.3	1269	20.9
Dyslipidemia	No	13 137	57.3	1933	80.2	6189	67.7	2760	52.0	2255	37.2
	Yes	9779	42.7	476	19.8	2951	32.3	2547	48.0	3805	62.8
BMI (kg/m^2)	≤18	548	2.4	84	3.5	202	2.2	117	2.2	145	2.4
	18–25	12 198	53.2	1456	60.4	5036	55.1	2725	51.3	2981	49.2
	25–30	5765	25.2	406	16.9	2139	23.4	1478	27.9	1742	28.7
	>30	1959	8.5	167	6.9	766	8.4	453	8.5	573	9.5
ART naïve	No	20 631	90.0	1813	75.3	7954	87.0	4970	93.6	5894	97.3
	Yes	2285	10.0	596	24.7	1186	13.0	337	6.4	166	2.7
Prior exp. Lopinavir	No	16 919	73.8	2021.0	83.9	7192	78.7	3836.0	72.3	3870	63.9
	Yes	5997	26.2	388.0	16.1	1948	21.3	1471.0	27.7	2190	36.1

Table 1. Continued

				Low CVD Risk		Medium CVD Risk		High CVD Risk		Very High CVD Risk	
		All		<1%		1–5%		5–10%		>10%	
		n	%	n	%	n	%	n	%	n	%
Prior exp. Darunavir	No	19 079	83.3	2053	85.2	7673	83.9	4416	83.2	4937	81.5
	Yes	3837	16.7	356	14.8	1467	16.1	891	16.8	1123	18.5
Prior exp. Indinavir	No	19 411	84.7	2384	99.0	8575	93.8	4389	82.7	4063	67.0
	Yes	3505	15.3	25	1.0	565	6.2	918	17.3	1997	33.0
Prior exp. Abacavir	No	15 223	85.3	2056	66.4	6924	75.8	3356	63.2	2887	47.6
	Yes	7693	14.7	353	33.6	2216	24.2	1951	36.8	3173	52.4
Prior exp. INSTI	No	19 763	81.1	1953	86.2	7743	84.7	4670	88.0	5397	89.1
	Yes	3153	18.9	456	13.8	1397	15.3	637	12.0	663	10.9
		Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age		45	(37, 52)	29	(25, 32)	40	(35, 45)	48	(44, 48)	55	(50, 62)
CD4 count		555	(390, 746)	532	(393, 721)	549	(386, 731)	568	(568, 396)	560	(391, 766)
CD4 nadir (cells/mm^3)		240	(120, 375)	344	(229, 496)	270	(159, 408)	218	(104, 340)	174	(70, 288)
Baseline		jan-12	(jan-12, apr-15)	may-13	(jan-12, jun-16)	mar-12	(jan-12, sep-15)	jan-12	(jan-12, nov-14)	jan-12	(jan-12, jul-14)

P values for comparison of baseline characteristics between the estimated risk score categories were 0.01 for risk of HIV acquisition and <0.001 for all other categories.

Baseline was defined as the first date of 10-y CVD risk calculation after cohort enrollment or 1 January 2012.

Unknown categories are not shown.

Percentage of overall unknowns: ethnicity: 10.9, prior CKD: 1.6, BMI: 10.9.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; IDU, intravenous drug use; IQR, interquartile range; INSTI, integrase strand transfer inhibitor; MSM, men having sex with men.

[a]Refers to all non-White ethnicities.

[b]SCORE-2 charts developed by the European Society of Cardiology; based on the CVD incidence and mortality rate reported to the World Health Organisation, Australia was included as a moderate CVD risk region.

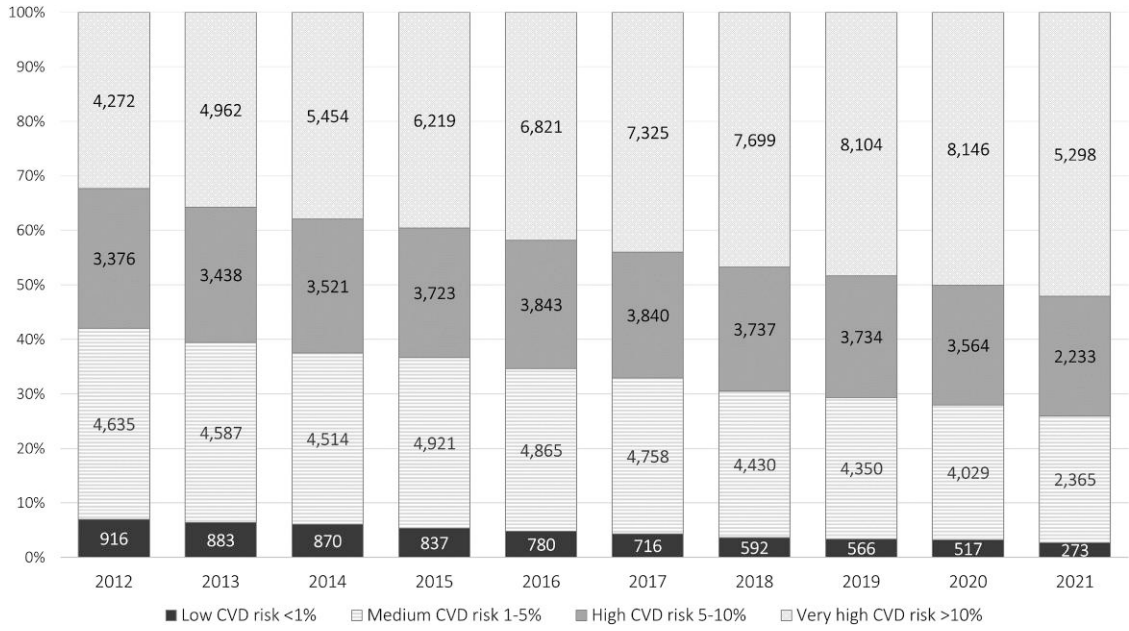


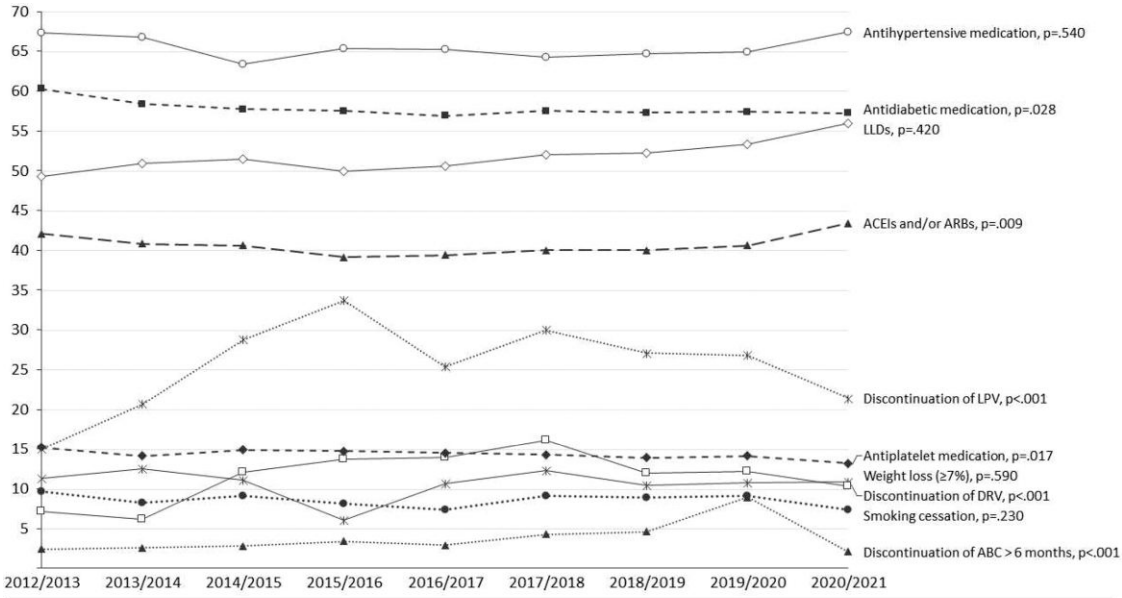
Figure 2. Temporal proportions of estimated 10-y D:A:D CVD risk. All proportions were assessed on 1 July of the calendar year and participants were not allowed to reverse to a lower risk category. Mean age increased from 47 y in 2012 to 51 y in 2020, mean cumulative exposure to nucleoside/nucleotide reverse transcriptase inhibitors increased from 8.6 y to 12.5 y, number of participants currently using abacavir increased from 23% (3037/13 199) to 36% (5950/16 256).

correspondingly, suggesting systematic underutilisation in at-risk participants.

Previous studies have also suggested inadequate CVD risk management in people with HIV [8]. However, these were typically smaller, single-country observational studies focused on individual measures of CVD prevention. In contrast, here, we provide a comprehensive overview of each component of the risk profile in very high-risk individuals in a multi-national cohort setting of well-characterised people with HIV [13, 14]. Evidence from the general population showed that even individuals at high CVD risk often receive suboptimal prevention, particularly in settings with limited healthcare access or inconsistent guideline implementation [23]. Given the complexity of our study's multinational design, our aim was not to formally compare with HIV-negative individuals but to assess how well very high-risk people with HIV are managed.

As expected from the ageing RESPOND population, we observed an increasing proportion of very high-risk individuals over time. With limited data on the effectiveness of specific CVD preventive interventions, the EACS Guidelines recommend a holistic approach to initiate all relevant interventions in very high CVD risk persons [3, 4]. A US/Canadian cohort collaboration from 2019 suggested that hypertension and dyslipidemia management has the largest impact on avoiding myocardial infarctions, although the impact of smoking cessation was likely underestimated by only considering whether participants ever smoked [24]. A 2014 D:A:D study suggested smoking cessation had the greatest impact among modifiable risk factors on subsequent CVD risk [25]. The REPRIEVE trial recently reported a 35% lower risk of CVD events in people with HIV with daily pitavastatin [26]. Contrary to our analysis, REPRIEVE focused on individuals at low to moderate CVD risk using the American College of Cardiology/American Heart Association Cohort Equation risk calculator developed in the general population and found a decreasing number needed to treat with increasing CVD risk category, which further stresses efforts to increase LLD use in a higher-risk population. Since our study period (2012–2021) predates recent updates in HIV guidelines recommending statin therapy for those with a CVD risk over 5%, future studies will be needed to assess statin eligibility and uptake based on updated thresholds, which would likely identify a larger proportion of people with HIV for statin therapy. Importantly, our results should not be interpreted to imply that LLDs should be withheld until an individual's CVD risk reaches 10%. Instead, it highlights LLD use is underutilized, even among those at very high risk.

Despite accumulating evidence suggesting higher rates of CVD and its risk factors in people with HIV compared to HIV-negative controls [27] and emphasis on CVD screening and management [27], we did not observe increased uptake over time for most traditional preventive measures in eligible participants with very high 10-year CVD risk. Antihypertensive medication (67%), antidiabetic medication (57%) and LLDs (56%) were the most frequently used cardio-preventive measures. Captured behavioral interventions were limited, with smoking cessation being the least frequent (10%), hence remaining a major



n	n	n	n	n	n	n	n	n	
1,773	2,045	2,271	2,442	2,692	2,937	3,161	3,267	2,303	Antihypertensives
643	728	813	877	926	1,021	1,088	1,121	803	Antidiabetic medication
2,658	2,910	3,148	3,470	3,696	3,943	4,207	4,196	2,792	LLDs
2,052	2,358	2,618	2,814	3,081	3,349	3,586	3,699	2,585	ACEIs and/or ARBs
643	728	813	877	926	1,021	1,088	1,121	803	Antiplatelets
602	584	507	430	319	240	170	123	70	Discontinuation LPV
663	876	1,087	1,254	1,319	1,301	1,210	1,136	706	Discontinuation DRV
1,389	1,594	1,774	2,076	2,373	2,462	2,442	2,288	1,355	Discontinuation ABC
328	408	441	472	501	571	653	694	469	Weight loss
2,178	2,376	2,562	2,859	3,170	3,322	3,357	3,271	2,149	Smoking cessation

Figure 3. Temporal proportions of CVD preventive measures use among eligible individuals with >10% estimated 10-y CVD risk. All *P* values are global, multivariate *P* values for each preventive measure with calendar years per 2-y groups. n = individuals eligible for each of the respective preventive measure. Antihypertensive medication also includes ACEIs and ARBs. ABC, abacavir; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; DRV, darunavir; LLD, lipid-lowering drug; LPV, lopinavir.

health concern. Successful smoking cessation will commonly require access to structured behavioural support and specialised services, which may be limited in some routine HIV care settings. Weight loss in obese individuals was infrequently attained (11%). Notably, while BMI changes were captured, RESPOND does not collect non-pharmacological interventions (eg, diet, exercise), which could have affected management strategies.

Unexpectedly, we found that use of antidiabetic medication declined over time by 3%. When assessing potentially predictive factors, only current smokers and individuals on LPV/r or ABC were less likely to use antidiabetics. To address potentially incomplete data reporting, we explored antidiabetic medication use by RESPOND cohorts and observed similar decreases over time across participating cohorts. Moreover, besides an expected increase in the use of contemporary drug classes in recent years, eg, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP1) agonists, we observed similar frequencies of antidiabetic drug classes over time. The reason for the declining use remains unknown but could include earlier detection with increased focus on non-pharmacological interventions (eg, diet, exercise) and concerns about polypharmacy [28].

In line with current European guidelines, we observed more prevalent discontinuation of LPV/b, DRV/b and ABC among the very-high risk individuals. We were unable to assess specifically whether participants discontinued these drugs only due to their current CVD risk status or whether these trends simply reflect increasing access and uptake of INSTIs over calendar time, but likely a combination [29].

Our results call for greater insights into patient/provider barriers to close this apparent management gap. Potential explanations for the observed underuse could include a lack of guideline knowledge and no shared-care agreement amongst healthcare providers about who manages comorbidities in people with HIV. Moreover, HIV guidelines have evolved over time, with eg, the EACS recommendations lowering the threshold for ART modification from 20% to 10% estimated 10-year CVD risk in 2019. This potentially may have led to greater focus on

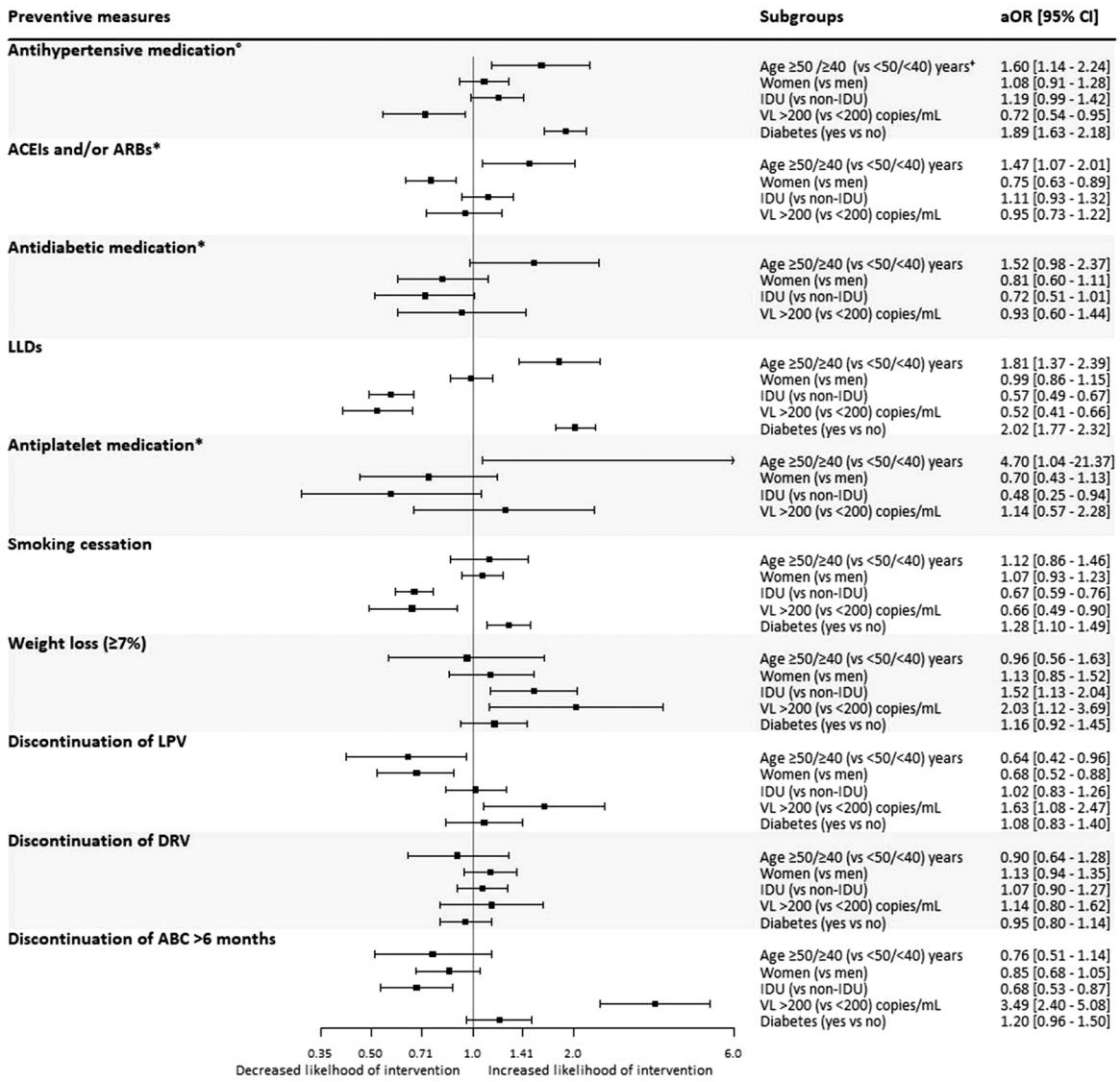


Figure 4. Adjusted odds ratios of CVD preventive measures use among eligible individuals with >10% estimated 10-y CVD risk for key subgroups. aOR adjusted for age (<40/≥40 men, < 50/≥50 women), sex/gender (male, female), ethnicity (white, other, unknown), SCORE-2 CVD risk region (low, moderate, high, very high), BMI (<30, ≥ 30 kg/m^2, unknown; not included for weight loss), HIV acquisition risk (MSM, IDU, heterosexual, other), CD4 cell count, CD4 nadir, ART experience (ART naïve, VL <200 copies/mL, VL >200 copies/mL), hypertension (yes, no; not included for antihypertensives and ACEIs/ARBs), diabetes (yes, no; not included for diabetic medication and ACEIs/ARBs), prior AIDS (yes, no), prior cancer (yes, no), prior CKD (yes, no), dyslipidaemia (yes, no; not included for LLDs), all fixed at baseline. Calendar year, current smoking status (current, past, never; not included for smoking cessation), cumulative exposure to LPV/r (not included for LPV/r discontinuation), DRV/b (not included for DRV/b discontinuation), and IDV, ABC use in the past 6 months (not included for ABC discontinuation), and INSTIs exposure (0, 0–6, 6–12, 12–24, 24–36, >36 m), all time updated. Use of antihypertensive medication, antidiabetic medication and LLDs was less likely in current smokers (vs non-smokers). Antihypertensive medication also include ACEIs and ARBs. +Age subgroup: < 40/≥40 y of age for men, < 50/≥50 for women. *Not including diabetes as a subgroup since it is part of the eligibility criteria for ACEIs/ARBs and antidiabetic medication. aORs included all observations within the study period, accounting for repeated measures through generalized estimating equations. ABC, abacavir; ACEI, angiotensin-converting enzyme inhibitor; aOR, adjusted odds ratio; ARB, angiotensin receptor blocker; ART, antiretroviral treatment; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DRV, darunavir; IDU, intravenous drug use; IDV, indinavir; INSTI, integrase strand transfer inhibitor; LLD, lipid-lowering drug; LPV, lopinavir; VL, viral load.

preventive interventions in recent years, whereas earlier efforts focused on those with even higher CVD risk. With some data suggesting an association between increasing tablet burden and decreased quality of life [30], concerns about adherence, drug–drug interactions, or polypharmacy may also have contributed. To help minimize CVD management gaps, RESPOND provides annual feedback to each participating cohort on its data quality and completeness, including percentages of individuals with comorbidities and respective medication uptake, eg, diabetes and use of antidiabetic medication. Additionally, while our study focused on annual uptake of preventive measures, future research should examine longitudinal adherence patterns.

It is essential to understand if the observed trends differ in key subpopulations to direct further attention to any of these

groups. A systematic CVD assessment is a recommended part of the routine screening for men >40/women >50 years with HIV without prevalent CVD or with concomitant comorbidities [3]. Reassuringly, our study suggests greater likelihoods of antihypertensives, ACEIs/ARBs, and LLDs prescriptions in older at-risk participants.

Corresponding to clinical recommendations on diabetes's adverse impact on renal function [3, 4], people with diabetes were more likely to use antihypertensive medication, LLDs, and cease smoking.

Our analysis also indicated that multimorbidity subsequently increases usage of medical interventions independent of people's age. While greater awareness of CVD prevention in those with the highest absolute risk burden is reassuring, it highlights a gap in management in very high-risk individuals with a less evident risk profile.

In a D:A:D study from 1999 to 2013, women with prevalent CVD risk factors were less likely to receive LLDs and ICPs but more likely to receive antihypertensives compared to men [31]. In the more contemporary RESPOND consortium, we observed similar preventive measure uptake for men and women, except for a 25% lower likelihood of ACEIs/ARBs use in women. Notably, previous evidence in the general population suggested lower ACEI prescription rates in women, potentially due to experiencing CVD later in life or decreased awareness of appropriate treatment [32].

Low ART adherence may reflect a lower commitment to other concomitant treatments, such as CVD preventative medication; although not universal for all preventive measures considered, viraemic participants were less likely to receive LLDs. Similarly, people who inject drugs may attend less frequent clinical visits and CVD screening and have lower medication adherence, thereby lowering the usage of preventive measures, as observed for smoking cessation, antiplatelet medication, and LLDs. Our analysis highlights a need to focus on CVD risk management in these key subpopulations.

As expected, antihypertensive medication and ACEIs/ARBs use was more common in moderate and high CVD risk regions. In contrast, ABC discontinuation was lower in higher-risk regions and might suggest differences in national treatment guidelines, price, or access to clinical care.

Limitations

As an observational study, we cannot exclude the potential for residual confounding. While we included a wide range of characteristics, some risk factors and preventive measures are either not collected in RESPOND, eg, diet, physical activity and inflammation markers, or are incomplete, eg, family history of CVD. Further, most cohort studies, including RESPOND, do not systematically capture information on how CVD risk management is organised across healthcare systems. Data completeness in RESPOND is very high, especially for CVD-related factors, which is the main study focus, and undergoes meticulous cleaning and quality assurance. As described, we excluded participants with lower occurrence of CVD events from this analysis and, therefore, might have overestimated CVD risk in this study's population. Additionally, we could not capture adherence levels to prescribed measures and may under- or overestimate the impact of subsequent CVD risk. We estimated eligibility and preventative measure use each calendar year. However, individuals may have temporarily experienced changes in modifiable factors (eg, weight) during the 1-year follow-up. We were also unable to differentiate between intentional or unintentional weight loss, nor between loss of fat or lean mass. Further, while we investigated regional differences, we were unable to capture the impact of national recommendations in CVD risk assessment and management. Finally, we performed multiple statistical tests to consider extensive CVD risk assessments; *P*-values should therefore be interpreted carefully.

CONCLUSION

Despite a substantial and increasing proportion of people with HIV at very high estimated 10-year CVD risk, CVD preventive measures remain systematically underutilised across Europe and Australia. Older and multimorbid individuals were generally better managed, and sex differences were small. These findings call for greater awareness of CVD risk management and increased use of CVD preventive measures in very high-risk individuals.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. N. J., supervised by L. R., L. P., A. M., and B. N., conceived the idea and developed the project proposal and statistical analysis plan. All authors reviewed the proposal and analysis plan. A. M. performed the statistical analysis, which was reviewed by all authors. N. J. developed the first draft of the article and revised the subsequent versions. N. J., L. R., L. P., A. M., and B. N. reviewed all versions of the article and interpreted the data. F. W., M. V. D. V., H. F. G., M. S., E. W., J. K., A. L. R., P. N., A. C., A. A. M., K. P., J. H., S. H., H. G., F. R., L. Y., and J. L. contributed to the interpretation of data and reviewed the final draft of the article.

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Data sharing statement. The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk); for guidelines on how to submit research concepts, see the RESPOND governance and procedures point 6. The secretariat will direct the proposal to the relevant Scientific Interest Group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be assessed. Upon completion of the review, feedback will be provided to the proposer or proposers. In some circumstances, a revision of the concept might be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (up to 7 people who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definition can be found online. For any inquiries regarding data sharing, please contact the RESPOND secretariat (respond.rigshospitalet@regionh.dk).

Ethical statement. Participants are consented to share data with RESPOND according to local requirements. Participants are pseudonymised at enrollment by assigning a unique identifier by the participating cohort before data transfer to RESPOND. According to national or local requirements, all cohorts have approval to share data with RESPOND. Ethical approvals are obtained, if required, from the relevant bodies for collection and sharing of data. Data are stored on secure servers at the RESPOND coordinating centre in Copenhagen, Denmark, in accordance with current legislation and under approval by The Danish Data Protection Agency (approval number 2012-58-0004, RH-2018-15, 26/1/2018), under the EU General Data Protection Regulation (2016/679).

Role of funding sources. As per RESPOND governance, funders of the study were also academic collaborators, and employees or associates could be included as coauthors if they met the International Committee of Medical Journal Editors criteria. However, funding bodies (including employees and associates hereof) were not in a position to veto study design, data collection, data analysis, data interpretation, or writing of the manuscript.

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