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MAJOR ARTICLE

Viremia Does Not Independently Predict Cardiovascular Disease in People With HIV: A RESPOND Cohort Study

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Background. HIV viremia has been considered a cardiovascular disease (CVD) risk factor, but many studies have had insufficient data on potential confounders. We explored the association between viremia and CVD after adjusting for established risk factors and analyzed whether consideration of viremia would improve CVD prediction.

Methods. Adults from RESPOND were followed from the first date with available data until the first of rigorously defined CVD, loss to follow-up, death, or administrative censoring. We first analyzed the associations between 6 measures of viremia (time-updated, before antiretroviral therapy [ART], viremia category, and measures of cumulative viremia) and CVD after adjusting for the variables in the D:A:D CVD score (age, sex/gender, smoking, family history, diabetes, recent abacavir, CD4 count, blood pressure, cholesterol, high-density lipoprotein, cumulative use of stavudine, didanosine, indinavir, lopinavir, and darunavir). We subsequently compared predictive performance with and without viremia in 5-fold internal cross-validation.

Results. A total of 547 events were observed in 17 497 persons (median follow-up, 6.8 years). Although some viremia variables were associated with CVD in univariable analyses, there were no statistically significant associations after adjusting for potential confounders, neither for measures of current viral load, pre-ART viral load, highest viremia category during ART, nor cumulative viremia (modeled both as total cumulative viremia, cumulative viremia during ART, and recent cumulative viremia). Consistently, none of the viremia variables improved prediction capacity.

Conclusions. In this large international cohort, HIV viremia was not associated with CVD when adjusting for established risk factors. Our results did not show viremia to be predictive of CVD among people with HIV.

Keywords. cardiovascular diseases; HIV viremia; myocardial infarction; prediction; stroke.

People with HIV have increased risk of cardiovascular disease (CVD) [1]. Although the age-standardized incidence of CVD has declined rapidly over the past 20 years [2], the total burden of CVD among people with HIV is increasing as people with HIV live longer [3]. CVD prevention is thus an important part of HIV care. Guidelines recommend estimation of cardiovascular risk to inform risk-benefit discussions of preventive treatment [3, 4]. Although scores developed for the general population (such as SCORE2 in Europe [5] or the American College of Cardiology/American Heart Association (ACC/AHA) score in the United States [6]) can be used, they do not capture HIV-specific risk factors, such as previous or current immunosuppression [7] or exposure to antiretrovirals with reported associations with CVD [8–10]. The D:A:D CVD score was developed for this purpose in 2010 with an update in 2016 [11, 12] but attempts to validate this in separate cohorts have not convincingly showed improved prediction compared with general scores [13].

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Higher exposure to HIV viremia has been associated with higher CVD risk in some [14–16], but not all [17], observational studies, and degree of virologic nonsuppression has also been linked with progression of coronary artery stenosis [18]. Thus, the AHA mentions prolonged viremia as a "HIV-Related CVD Risk Enhancing Factor," which indicates the risk is higher than estimated [3]. Still, these studies may have had insufficient information on potential confounders, such as smoking, blood pressure, lipid levels, and family history.

With this in mind, we aimed to analyze whether viremia was associated with incident CVD after adjusting for established risk factors (the variables in the D:A:D CVD risk score). Subsequently, we developed prediction models including viremia exposure and compared the predictive capacity with the D:A:D CVD score, to see if consideration of viremia would add predictive value for CVD risk assessment among people with HIV.

METHODS

We used data from the RESPOND consortium, which includes people with HIV from 19 cohorts across Europe and Australia [19]. We included participants aged >18 years who were under follow-up after January 2012 and with a viral load (VL) and CD4 cell count measured in the period 12 months before to 3 months after baseline. Participants with a recorded prior CVD were excluded from the main analysis. Following RESPOND practice, we only included participants from cohorts with sufficient completeness regarding CVD outcomes, smoking, hypertension, and chronic kidney disease (CKD) (Supplementary Methods).

All participants consented to contributing data following local requirements. Data are securely stored at the RESPOND Coordinating Centre in Copenhagen, Denmark, with approval from the Danish Data Protection Agency (approval number 2012-58-0004, RH-2018-15, 26/1/2018). The researchers had access to pseudo-anonymized data.

Outcome

The outcome in our main analysis was a composite including myocardial infarction, stroke, and invasive cardiovascular procedures (percutaneous coronary intervention, coronary artery bypass graft surgery, and carotid endarterectomy/stenting). Events were reported using designated event forms and are centrally adjudicated against a predefined algorithm (https://chip.dk/Research/Studies/RESPOND). Participating cohorts were queried extensively for missing data.

Statistical Analysis

Association Between Viremia and CVD. Because the potential underlying relationship between viremia and CVD is unknown—and to decrease the risk that misspecification of viremia led us to incorrectly reject the hypothesis that viremia improves prediction—we considered 6 different measures of viremia exposure:

1. Most recent VL.
2. Pre-antiretroviral therapy (ART) VL, defined as the last recorded VL before initiation of ART.
3. Viremia category, based on all VL measurements >12 months after initiation of ART. Grouped as suppression (detection limit ≤200 copies/mL, to enable analysis of the whole cohort), low-level viremia (201–999 copies/mL), and nonsuppression (≥1000 copies/mL). Reclassification was only done to higher strata, so the variable reflected the highest category the individual has experienced since starting ART.
4. Cumulative viremia, viremia-copy-years calculated as the area under the curve of the logarithmic VL plot above 200 copies/mL with the trapezoidal rule, so that people with undetectable VLs do not accumulate viremia-copy-years over time [20, 21].
   (a) Including all available VLs.
   (b) Since start of ART, based on all VLs >12 months after initiation of ART.
   (c) Recent viremia copy-years, a sliding 3-year window.

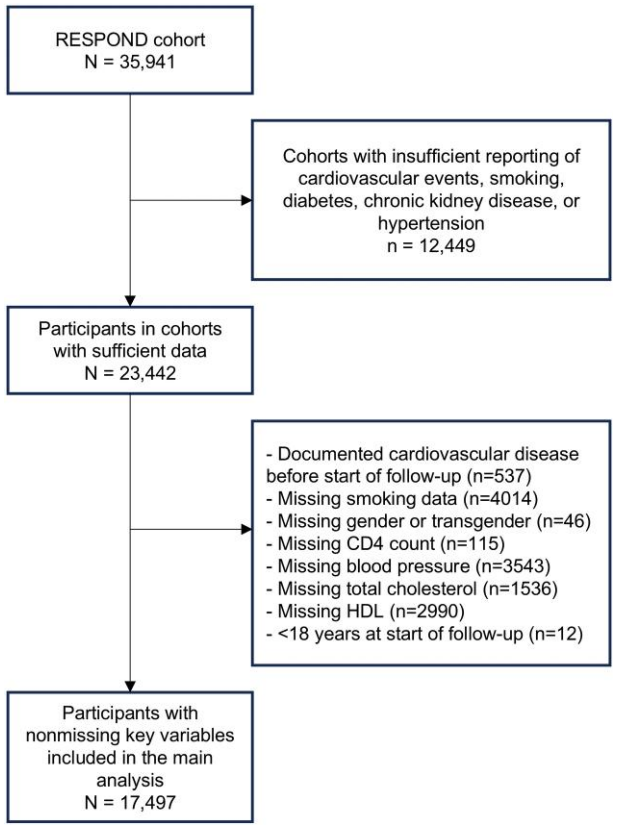

Figure 1. Exclusion flowchart. Abbreviation: HDL, high-density lipoprotein.

Table 1. Characteristics of Study Participants (N = 17 479)

Variables of the D:A:D CVD Risk Score	
Sex/gender[a]	…
Male	13 265 (76%)
Female	4232 (24%)
Age, y	45 (37, 52)
Smoking	…
Never	6428 (37%)
Past	2929 (17%)
Current	8140 (47%)
Family history of cardiovascular disease	…
Yes	636 (4%)
No	6592 (38%)
Missing	10 269 (59%)
Diabetes mellitus	…
Yes	992 (6%)
No	16 505 (94%)
Exposure to indinavir, ritonavir boosted lopinavir, and darunavir, y	0 (0, 1.4)
Exposure to abacavir last 6 mo	…
Yes	4046 (23%)
No	13 451 (77%)
Exposure to stavudine or didanosine, y	0 (0, 0)
CD4 count, cells/μL	558 (399, 746)
Systolic blood pressure, mm Hg	125 (116, 136)
Total cholesterol, mmol/L	4.9 (4.2, 5.6)
HDL, mmol/L	1.2 (1.0, 1.5)
Other variables	
Chronic kidney disease	…
Yes	370 (2%)
No	17 002 (97%)
Missing	125 (1%)
Body mass index	…
<18.5 kg/m^2	600 (3%)
18.5–21 kg/m^2	2252 (13%)
21–25 kg/m^2	6160 (35%)
25–30 kg/m^2	4116 (24%)
≥30 kg/m^2	1348 (8%)
Missing	3021 (17%)
HIV transmission group	…
Men who have sex with men	8096 (46%)
Injecting drug use	2612 (15%)
Heterosexual	5855 (33%)
Other	934 (5%)
Ethnicity	…
White	13 297 (76%)
Black	1489 (9%)
Other	894 (5%)
Unknown or missing	1817 (10%)
Exposure to integrase strand transfer inhibitors	…
0 mo	15 411 (88%)
0–6 mo	1400 (8%)
6–12 mo	276 (2%)
1–2 y	199 (1%)
2–3 y	98 (1%)
≥3 y	113 (1%)
Any lipid-lowering therapy	4747 (27%)
Any antiplatelet therapy	1970 (11%)
Treatment experienced at start of follow-up	16 711 (96%)
Time between starting ART and start of follow-up for treatment-experienced participants, y	6.9 (2.3, 13.8)

Table 1. Continued

Viremia exposure at end of follow-up	
Time-updated viral load, copies/mL	≤200 (≤200, ≤ 200)
Time updated viral load >200 copies/mL	645 (4%)
Pre-ART VL, log_{10} copies/mL	4.8 (4.1, 5.3)
Viremia category during ART	…
Suppression ≤200 copies/mL	9641 (57%)
Low-level viremia 201–999 copies/mL	1582 (9%)
Nonsuppression ≥1000 copies/mL	5842 (34%)
Cumulative viremia including all VLs, log_{10} copy × year/mL	2.7 (0.6, 10.7)
Cumulative viremia during ART, log_{10} copy × year/mL	0 (0, 3.7)
Recent cumulative viremia, log_{10} copy × year/mL	0 (0, 0)

Results are n (%) or median (interquartile range). Time-updated variables (expect viremia exposure) are reported at start of follow-up. Viremia category during ART was defined as the highest exposure since 12 mo after ART initiation.

Abbreviations: ART, antiretroviral therapy; HDL, high-density lipoprotein; VL, viral load.

[a]Sex/gender is not collected consistently in the cohorts contributing to RESPOND. The resulting variable includes gender when available or else sex.

We fitted Cox proportional hazard models including the variables in the D:A:D CVD risk score [12]: age, sex/gender (male/female), smoking (never/past/current), family history of CVD (yes/no/missing), diabetes mellitus (yes/no), cumulative exposure to the protease inhibitors indinavir, ritonavir boosted lopinavir, or darunavir (per year), recent exposure to abacavir (within the past 6 months, yes/no), cumulative exposure to the nucleoside reverse transcriptase inhibitors stavudine or didanosine (per year), CD4 cell count, systolic blood pressure, total cholesterol, and high-density lipoprotein. All variables were handled as time-updated variables with the last value carried forward; models were stratified by SCORE2 region. Age, CD4 count, blood pressure, and lipids were analyzed after logarithmic transformation. We analyzed the association between viremia exposure and CVD in 6 separate univariable models, as well as after adjustment for the variables of the D:A:D CVD score. In an extended model, we further adjusted for variables that are likely relevant [10] but not included in the D:A:D CVD model: CKD (defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2 for those with a first eGFR ≥60 mL/min/1.73 m^2 or a 25% decline for those with a first eGFR <60 mL/min/1.73 m^2), body mass index (BMI), transmission group, ethnicity, and integrase strand transfer inhibitors (INSTI).

Participants were followed from the first date with available data after the latest of 2012 or local cohort enrollment until the first of the first CVD event, death, loss to follow-up (>730 days without any VL measurement), or administrative censoring 31 December 2021. We included a missing data category for family history and required the variables sex/gender and smoking to be nonmissing. We required at least 1 nonmissing observation for the continuous variables.

Predictive Models Including Viremia. We compared models including the variables of the D:A:D CVD score with 6 separate models including the D:A:D variables and each of the viremia variables. Calibration was assessed by comparing the predicted 5-year risk with the 5-year risk from the Kaplan-Meier estimate (we did not consider 10-year risk, since all participants had <10 years of follow-up). We assessed discrimination in 5-fold cross-validation, in which the dataset was randomly split into 5 subcohorts. In 5 separate steps, the model was then fitted using 4 of the subcohorts and tested against the fifth [22]. Harrell's C-statistic was calculated using the Stata command "somersd," which can handle time-varying variables, and summarized using a mean weighted by 1/variance [23].

Sensitivity Analyses. We performed the following prespecified sensitivity analyses: considering the 3 components of the composite outcome separately; having 50 copies/mL as the threshold for suppression (rather than 200 copies/mL) where that limit was used; adjusting for the D:A:D CVD risk score (5-year predicted risk) rather than the individual components; excluding the variable family history that we anticipated to have many missing values; rerunning the analyses including people both with and without prior CVD; and using restricted cubic splines to allow for nonlinear relationships between the continuous viremia variables and CVD. Since some variables in our models (CD4 count, diabetes, blood pressure, and lipids) might lie on the potential causal pathway between viremia and CVD, we performed a separate analysis where these were fixed at baseline.

RESULTS

Study Participants

Of 35 941 persons currently in the RESPOND cohort, 17 479 (49%) belonged to cohorts with sufficient reporting, had available data on key variables, and no prior CVD (Figure 1). A total of 74% of excluded persons were men, and at RESPOND enrollment, the median (interquartile range [IQR]) age was 43 (35, 51) years, the nadir CD4 count was 242 (110, 392) cells/μL, 57% had viral suppression <200 copies/mL, and 76% were ART experienced. These values can be compared with 76% men, 46 (37, 53) years, 237 (120, 369) cells/μL, 77% suppressed,

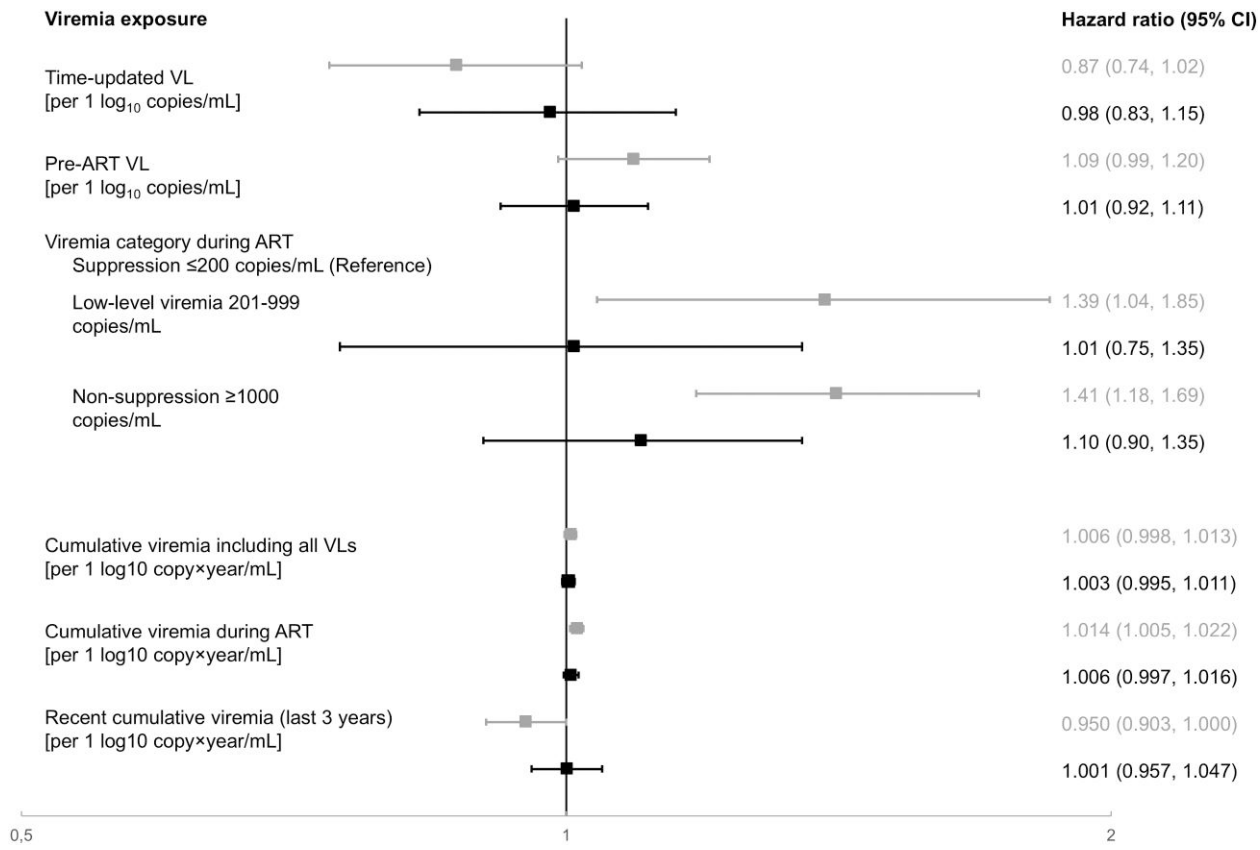

Figure 2. Associations between viremia variables and CVD events. Gray bars represent unadjusted estimates and black bars are adjusted for age, sex/gender, smoking, family history of cardiovascular diseases, diabetes, recent abacavir exposure, cumulative exposure to indinavir, ritonavir boosted lopinavir, or darunavir and stavudine or didanosine, respectively, CD4 count, systolic blood pressure, total cholesterol, and high-density lipoprotein (all time-updated) and stratified by SCORE2 risk stratum. Abbreviations: ART, antiretroviral therapy; CVD, cardiovascular disease; VL, viral load.

and 83% experienced among included participants. The overall proportion of having any recorded CVD event (also including events before start of follow-up) was higher among excluded than included persons (6% vs 4%). Characteristics of the included RESPOND participants are presented in Table 1.

Viremia Exposure

Most participants had a time-updated VL of ≤200 copies/mL, both at start (85%) and end of follow-up (96%). Considering all VL measurements >12 months after starting ART, 44% had at least 1 value of >200 copies/mL. The median (IQR) overall cumulative exposure to viremia was 2.7 (0.6, 10.7) $\log_{10}$ copy × year/mL. Only 11 711 (67%) had an available VL before start of ART; median pre-ART VL was 4.8 $\log_{10}$ copies/mL (Table 1). The median (IQR) number of VL measurements per year was 2.4 (1.9, 3.4), and participants had a total of 16 (8, 24) measurements.

Associations Between Viremia and Cardiovascular Events

During 109 381 person-years of follow-up (median, 6.8 years), 547 CVD events were observed. Most (39%) events were myocardial infarction, followed by stroke (31%) and invasive cardiovascular procedures (30%). Hazard ratios for the variables of the D:A:D CVD score were similar to Friis-Møller et al [12] (Supplementary Table 1).

Viremia variables related to viremia exposure after start of ART had statistically significant associations with CVD in univariable analysis. When adjusting for the variables of the D:A:D CVD score, however, there were no statistically significant associations (Figure 2). When only adjusting for age, sex/gender, and CD4 cell count, cumulative viremia during ART still had a statistically significant association with CVD, but this disappeared when adjusting for smoking, diabetes, blood pressure, and lipids. Further adjustment for CKD, BMI, transmission group, ethnicity, and INSTI use did not substantially affect the null associations between viremia and CVD (Table 2).

Prediction Models Including Viremia

None of the six different prediction models including viremia variables showed better calibration than the model containing only the variables of the D:A:D CVD score. Compared with the

Table 2. Proportional Hazard Models for Cardiovascular Events Depending on Viremia

	Model 1 Unadjusted	Model 2 Adjusted for Age, Sex/Gender, CD4 Count	Model 3 Further Adjusted for Smoking, Diabetes, Systolic Blood Pressure, Total Cholesterol, HDL	Model 4 (Adjusted for all D:A:D Variables) Further Adjusted for Family History, Abacavir, PI, NRTI	Model 5 Extended Model Further Adjusted for CKD, BMI, Transmission Group, Ethnicity, INSTI
Time-updated VL (per 1 log_{10} copies/mL)[a]	0.87 (0.74, 1.02)	0.98 (0.83, 1.16)	0.96 (0.82, 1.14)	0.98 (0.83, 1.15)	0.98 (0.83, 1.16)
Pre-ART VL (per 1 log_{10} copies/mL)[b]	1.09 (0.99, 1.20)	1.01 (0.93, 1.11)	1.01 (0.93, 1.11)	1.01 (0.92, 1.11)	1.01 (0.92, 1.10)
Viremia category during ART[c]	…	…	…	…	…
… Suppression (Reference)	1	1	1	1	1
… Low-level viremia 201–999 copies/mL	**1.39 (1.04, 1.85)**	1.08 (0.81, 1.43)	1.01 (0.76, 1.35)	1.01 (0.75, 1.35)	1.01 (0.75, 1.35)
… Nonsuppression ≥1000 copies/mL	**1.41 (1.18, 1.69)**	1.18 (0.98, 1.41)	1.12 (0.94, 1.35)	1.10 (0.90, 1.35)	1.10 (0.90, 1.35)
Cumulative viremia including all VLs (per 1 log_{10} copy × year/mL)[a]	1.006 (0.998, 1.013)	1.006 (0.998, 1.013)	1.003 (0.996, 1.011)	1.003 (0.995, 1.011)	1.003 (0.995, 1.011)
Cumulative viremia during ART (per 1 log_{10} copy × year/mL)[c]	**1.014 (1.005, 1.022)**	**1.010 (1.001, 1.019)**	1.007 (0.998, 1.016)	1.006 (0.997, 1.016)	1.006 (0.997, 1.016)
Recent cumulative viremia (per 1 log_{10} copy × year/mL)[d]	0.950 (0.903, 1.000)	1.005 (0.962, 1.051)	0.997 (0.953, 1.044)	1.001 (0.957, 1.047)	1.000 (0.956, 1.047)

Results are hazard ratio (95% confidence interval). All models are stratified by SCORE2 region. Statistically significant results are in bold.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CKD, chronic kidney disease; INSTI, integrase strand transfer inhibitor; HDL, high-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

[a]N = 17 497.

[b]N = 11 711.

[c]N = 17 065.

[d]N = 16 118.

Kaplan-Meier estimator, all models underestimated CVD risk for men and overestimated it for women. In five-fold cross validation, the model including the D:A:D CVD variables had a Harrell's C-statistic of 0.75, similar to all models with additional viremia variables (Table 3 and Supplementary Table 2).

Sensitivity Analyses

The overall conclusion that viremia exposure did not have a statistically significant association with CVD remained in all sensitivity analyses, including when we considered the 3 components of the composite outcome separately (Supplementary Table 3), when also including an additional 451 participants with a recorded prior CVD, and when excluding the variable "Family history of CVD," which was missing for 59% of the cohort. When we excluded participants who had an undetectable VL measured by an assay with a limit of quantification of >50 copies/mL and used this as the definition of suppression, 9708 participants remained. Of these, 55% had only suppressed VLs >12 months after starting ART, 27% had low-level viremia of 51–999 copies/mL as their highest viremia exposure, and 19% had at least 1 VL of ≥1000 copies/mL. There were no statistically significant associations between viremia variables and CVD (Supplementary Table 4). Modeling with restricted cubic splines did not indicate statistically significant departure from nonlinearity for the relationships between continuous viremia variables and CVD; tests for overall effect of viremia were also not statistically significant for all viremia measures (Supplementary Table 5). Last, adjusting for CD4 count, diabetes, blood pressure, and lipids fixed at baseline—rather than time-updated—yielded similar results as our main analysis.

DISCUSSION

We conducted an analysis of the RESPOND cohort with detailed information on cardiovascular risk profile and rigorously defined CVD endpoints and found no statistically significant associations between HIV viremia exposure and CVD when controlling for other factors, although we acknowledge that our results could be consistent with modest associations

Table 3. Prediction Models for Cardiovascular Events With and Without Viremia Variables

	Overall 2.44% (2.20%, 2.71%)	Males 2.83% (2.53%, 3.16%)	Females 1.26% (0.94%, 1.69%)	Overall
Kaplan-Meier Estimate of 5-y CVD Risk (95% CI)	Calibration (mean predicted 5-y risk)			Discrimination (Harrell's C)
D:A:D model	2.34%	2.64%	1.40%	0.75
D:A:D model + time-updated VL	2.34%	2.64%	1.40%	0.75
D:A:D model + pre-ART VL	2.20%	2.50%	1.26%	0.75
D:A:D model + viremia category	2.35%	2.47%	1.96%	0.75
D:A:D model + cumulative viremia including all VLs	2.34%	2.63%	1.40%	0.75
D:A:D model + cumulative viremia during ART	2.35%	2.47%	1.96%	0.75
D:A:D model + recent cumulative viremia	2.32%	2.37%	2.14%	0.75

The D:A:D model includes age, sex/gender, smoking, family history of CVD, diabetes, recent abacavir exposure, protease inhibitor exposure, nucleoside reverse transcriptase inhibitor exposure, CD4 count, systolic blood pressure, total cholesterol, and high-density lipoprotein. All models were stratified by SCORE2 region. Discrimination was assessed in 5-fold cross-validation, and Harrell's C-statistic was summarized using mean and standard error weighted by 1/variance.

Abbreviations: ART, antiretroviral therapy; CVD, cardiovascular disease; VL, viral load.

between viremia and CVD. We further documented that incorporation of viremia history in prediction models neither improved discrimination nor calibration of CVD risk.

Several previous studies have reported associations between different measures of viremia exposure and 1 or more cardiovascular conditions. Cumulative viremia has been associated with myocardial infarctions [14, 24] and overall CVD [16, 25, 26]; baseline VL has been associated with myocardial infarctions [24], stroke [15, 27], and CVD deaths [28]; and time-updated VL has been associated with myocardial infarctions [24, 29], stroke [15, 30–32], overall CVD [33, 34], and CVD deaths [35]. There are also studies reporting null findings for the associations between time-updated viremia and myocardial infarction [17, 36], cumulative viremia and stroke [15], baseline VL and stroke [32], and baseline VL and overall CVD [7], but they are—to our knowledge—fewer. We believe there are 2 important considerations here. First, it is well-known that publication bias, where positive results are more likely to be published, has the potential to seriously distort the literature, and may mislead future research and clinical practice. Second, results from observational studies are highly dependent on the covariates included in the models, and it is possible that residual confounding is responsible for the previously reported associations between viremia and CVD. Residual confounding could occur when a potential confounder is unmeasured; as 2 examples, family history and type of ART are not included in Delaney et al. and Salinas et al. [14, 24] (although we saw the same lack of association when not including these factors) and many important CVD risk factors are lacking in some studies [16, 25, 28, 35]. Importantly, it could also result from misspecification of a potential confounder. Blood pressure and lipid levels have higher predictive values when included as continuous variables—as is done in the SCORE2 and AHA/ACC tools, as well as in the D:A:D CVD score [5, 6, 12]. Incorporating them as binary variables as in many of the studies mentioned previously [14, 15, 24, 26, 27, 29–34, 36] results in loss of information. The RESPOND cohort, with comprehensive data on relevant CVD risk factors for a large contemporary population, gives us a rare opportunity to analyze this research question. We have used rigorous methodology and while viremia after start of ART was associated with CVD in univariable analysis, we found no indication of an association between viremia and CVD when appropriately adjusting for other factors.

Another important difference between our study and some previous ones is the definition of CVD endpoints. We studied centrally validated events while some previous studies have used nonadjudicated administrative coding [16, 17, 24, 36]. Furthermore, we included hard clinical endpoints, whereas some previous studies have included (eg, type II myocardial infarctions) [14, 16, 17, 24, 36], which may have introduced noise because high VL is linked to type II infarctions, and the benefit of CVD prevention is much less clear for this heterogenous entity [37].

Apart from discrepancies in the statistical modelling and definition and validation of CVD endpoints, differences in study populations might also explain why associations between viremia and CVD have been found in some but not all studies [11]. We studied people on long-term ART, so our results are not generalizable to people not yet (or just recently) started on ART. In the START trial, comparing immediate and deferred ART initiation, there were numerically fewer CVD events among people starting ART immediately, but the number of events was small and the difference not statistically significant [38]. A post hoc analysis showed both positive and negative influence on CVD risk factors by immediate ART, suggesting a potentially neutral net effect [39]. Importantly, the authors were unable to account for potential changes in systemic inflammation, which is an important CVD risk factor for people with HIV [40]. Today, early ART is recommended for everyone, and the population of people on long-term ART is large and aging. Whether HIV viremia contributes to CVD risk for this group has been unclear, and our study suggests against any clinically significant contribution.

Furthermore, the SMART trial also provided data on the relationship between viremia and CVD [41]. People randomized

to structured ART interruptions had 60% higher hazards of CVD, but post hoc analysis indicated that this was not related to high VL [42]. Unlike in the SMART trial, people with viremia during ART in our study likely represent a mix of treatment interruptions (due to nonadherence or other reasons) and nonsuppressible viremia during ART, but our results are in agreement that other factors are more important for CVD than HIV viremia.

Traditional and non–HIV-specific CVD risk factors such as hypertension and smoking are central for CVD risk also for people with HIV [11, 12]. However, because some additional HIV-specific factors (such as use of certain antiretroviral agents [8–10] and immunosuppression [7]) have also been associated with increased CVD risk, it seems probable that an HIV-specific CVD risk estimator would perform better for people living with HIV. This has hitherto not been shown, however [13]. One explanation is that the D:A:D CVD score is likely to perform best in Europe/Australia where it was developed. Current guidelines, both in Europe and the United States recommend risk scores developed for the general population, with the disclaimer that the risk is likely underestimated [3, 4]. Underestimation has been particularly pronounced among women with HIV when assessed by the ACC/AHA score [43]. In contrast with this, the D:A:D CVD risk score did not show substantial underestimation for women when it was developed [12]. In our study, the D:A:D CVD risk score slightly overestimated risk for women, but since our cohort was predominately male, this analysis should be interpreted with caution. In men and woman alike, we found no indication that inclusion of a viremia variable would improve CVD prediction.

Our results corroborate previous findings by a smaller US study who did not find improved prediction when incorporating VL (at baseline) in their models for myocardial infarction [44]. When the D:A:D CVD model was developed, VL was considered as a binary variable (higher/lower than 50 copies/mL) and excluded because of nonsignificance [11]. Compared with these previous studies, we analyzed several additional parameterizations of viremia history (that have previously been reported as risk factors for CVD) without any indication that they improved prediction.

Limitations of our work include limited length of follow-up, so we estimated 5-year risk instead of 10-year, as in other scores [5, 6]. On the other hand, this enabled us to study this question in a recent dataset, with high relevance for people with HIV today. We were also not able to account for HIV RNA levels before diagnosis and cannot exclude that high exposure to HIV viremia during undiagnosed and untreated HIV is a risk factor for CVD. These unmeasured VLs are also unavailable to clinicians, however, and they are unlikely to be helpful for prediction. We studied a population of people receiving long-term ART, with relatively high CD4 counts and high degree of viral suppression; our results may not be generalizable to other settings. We also have relatively few people of non-White ancestry. The access to CVD prevention and treatment is generally high for people with HIV across Western and Northern Europe and Australia; our findings may not be generalizable to settings where this is not the case. The median age was 45 years at start of follow-up, so we have comparatively little data on older people with HIV. As follow-up of aging people with HIV accumulates in ours and others' cohorts, new studies on the prediction of CVD among older people with HIV are called for and planned. Moreover, estimation of cumulative exposure to viremia is highly dependent on sampling frequency, and our conclusions may not apply to settings with higher or lower sampling intensity (median, 2.4 per year). Only people with a known CVD risk profile and who were from cohorts with sufficient quality and completeness of the reporting of CVD events were included in the analysis; this resulted in exclusion of 51% of the eligible RESPOND cohort. Fewer had viral suppression and overall CVD occurrence was higher among excluded individuals, which may have resulted in selection bias and underrepresentation of people with high CVD risk; our results can thus be viewed as conservative estimates. Our data are observational, and we were not able to account for any intervention (pharmaceutical or nonpharmaceutical) that may have impacted CVD risk, including diet and exercise. Likewise, we cannot rule out residual confounding by unmeasured factors such as income level or educational attainment. Last, we had a large proportion of missing data for family history, but our findings were robust to removal of this variable in a sensitivity analysis. The main strengths of our study are a large sample size, comprehensive CVD risk profiles, and validated CVD endpoints. Our results were consistent in several sensitivity analyses.

In conclusion, though viral suppression undoubtedly is an important goal for HIV treatment, high exposure to viremia did not sway the risk of developing CVD in our data. When CVD risk stratifying people with HIV on long-term ART, clinicians should focus on other variables than HIV RNA levels.

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

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