

Cumulative Human Immunodeficiency Virus (HIV)-1 Viremia Is Associated With Increased Risk of Multimorbidity Among US Women With HIV, 1997–2019

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Background. To evaluate the effect of cumulative human immunodeficiency virus (HIV)-1 viremia on aging-related multimorbidity among women with HIV (WWH), we analyzed data collected prospectively among women who achieved viral suppression after antiretroviral therapy (ART) initiation (1997–2019).

Methods. We included WWH with ≥ 2 plasma HIV-1 viral loads (VL) < 200 copies/mL within a 2-year period (baseline) following self-reported ART use. Primary outcome was multimorbidity (≥ 2 nonacquired immune deficiency syndrome comorbidities [NACM] of 5 total assessed). The trapezoidal rule calculated viremia copy-years (VCY) as area-under-the-VL-curve. Cox proportional hazard models estimated the association of time-updated cumulative VCY with incident multimorbidity and with incidence of each NACM, adjusting for important covariates (eg, age, CD4 count, etc).

Results. Eight hundred six WWH contributed 6368 women-years, with median 12 (Q1–Q3, 7–23) VL per participant. At baseline, median age was 39 years, 56% were Black, and median CD4 was 534 cells/mm³. Median time-updated cumulative VCY was 5.4 (Q1–Q3, 4.7–6.9) log₁₀ copy-years/mL. Of 211 (26%) WWH who developed multimorbidity, 162 (77%) had incident hypertension, 133 (63%) had dyslipidemia, 60 (28%) had diabetes, 52 (25%) had cardiovascular disease, and 32 (15%) had kidney disease. Compared with WWH who had time-updated cumulative VCY < 5 log₁₀, the adjusted hazard ratio of multimorbidity was 1.99 (95% confidence interval [CI], 1.29–3.08) and 3.78 (95% CI, 2.17–6.58) for those with VCY 5–6.9 and ≥ 7 log₁₀ copy-years/mL, respectively ($P < .0001$). Higher time-updated cumulative VCY increased the risk of each NACM.

Conclusions. Among ART-treated WWH, greater cumulative viremia increased the risk of multimorbidity and of developing each NACM, and hence this may be a prognostically useful biomarker for NACM risk assessment in this population.

Keywords. cumulative HIV-1 viremia; multimorbidity; non-AIDS comorbidities; viremia copy-years; women with HIV.

In 2019, 52% of US persons with human immunodeficiency virus (PWH) were aged ≥ 50 years [1]. Despite increased lifespan attributed to antiretroviral therapy (ART), PWH live 16.3 fewer

healthy years than persons without human immunodeficiency virus (HIV) [2]. Compared with persons without HIV, PWH experience a higher prevalence and earlier onset of aging-related nonacquired immune deficiency syndrome comorbidities (NACM), eg, cardiovascular and kidney disease, leading to premature multimorbidity in this population [3, 4, 5]. Among PWH, data suggest that women are at greater NACM risk than men [5, 6, 7, 8] and that young women with HIV (WWH) are uniquely at risk [9].

The risk and severity of NACM among PWH is multifactorial, mediated by an overrepresentation of traditional risk factors and HIV-related contributors. Human immunodeficiency virus-associated chronic inflammation and immune activation play a key role, driven in part by ongoing low-level viral replication at reservoir sites despite ART-induced virologic suppression

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[10, 11]. Furthermore, ART-treated PWH may experience intermittent viral nonsuppression [12, 13, 14], which may further heighten the inflammatory state that exists among PWH with controlled HIV, potentially contributing to deleterious end-organ effects [11, 15]. At any given HIV-1 ribonucleic acid viral load (VL), women have greater immune activation and higher systemic levels of inflammatory biomarkers than men [16], possibly impacting differential NACM risk by sex observed in PWH [17].

Measures of cumulative HIV-1 viremia have been associated with mortality among ART-treated PWH [18, 19, 20, 21, 22] (even independent of CD4 count) [23], and with individual NACM including myocardial infarction [18, 24], hypertension [25], renal insufficiency [26, 27], and non-acquired immune deficiency syndrome (AIDS) cancer [28]. However, previous studies evaluating cumulative HIV-1 viremia as a prognosticator of non-AIDS mortality and morbidity have comprised male-predominant cohorts and have not assessed the effect of virologic nonsuppression on aging-related multimorbidity.

Our objective was to evaluate the relationship between cumulative HIV-1 viremia and multimorbidity risk among ART-treated WWH prospectively followed in a multisite longitudinal women's cohort.

METHODS

Study Population

We analyzed data from the Women's Interagency HIV Study (WIHS), a multicenter US observational cohort established in 1993 to investigate the impact of HIV on women. Women with HIV and socio-demographically comparable women at risk of HIV were enrolled during 4 waves (1994–1995, 2001–2002, 2011–2012, 2013–2015) in 11 geographically diverse cities [29]. Semiannual study visits comprised in-depth interviews, physical examinations, and biospecimen collection, generating robust longitudinal data allowing for detailed profiling of chronic comorbidities, medication (including ART) and substance use, and HIV-1 suppression over time.

Patient Consent Statement

The WIHS protocol was approved by each site's Institutional Review Board. All participants provided written informed consent.

Study Design

We performed a longitudinal assessment of WWH who demonstrated HIV-1 suppression after reported ART use. Antiretroviral therapy was defined as any regimen of ≥ 3 agents that included at least 1 protease inhibitor (PI), nonnucleoside reverse-transcriptase inhibitor (NNRTI), or integrase strand transfer inhibitor (INSTI) based on guideline-based recommendations over the study time period and supported by prior

literature [23]. Women with HIV were included if the first suppressed VL after reported ART was followed by a second suppressed VL assessed over 3 study visits within a 2-year "baseline" period. This time interval allowed for robust NACM ascertainment; women with ≥ 1 NACM present at end of baseline were excluded. Thus, we included only women who had suppressed HIV and zero comorbidities at the end of the baseline period. Study observation occurred from the last visit of the baseline period through primary outcome (ie, the visit in which a participant met criteria for a second incident NACM), censorship due to death, last observed visit, or most recent WIHS visit through 2019.

Outcome Measures

The primary outcome was incident multimorbidity defined as ≥ 2 NACM accrued over observation of 5 total assessed: hypertension, dyslipidemia, diabetes, cardiovascular disease (CVD), and chronic kidney disease (CKD). These specific NACM were chosen given their association with age, shared causal pathways, and vascular impact among PWH. Non-acquired immune deficiency syndrome (AIDS) comorbidities were defined by using ≥ 3 data sources per comorbidity: (1) self-reported diagnosis or medication use, (2) clinical measurement, and/or (3) laboratory evidence as previously described [5, 9]. Secondary outcomes included incidence of each NACM over observation.

Human Immunodeficiency Virus-1 Viral Load Data

Viral loads were measured during semiannual study visits. If a VL was not measured during a given study visit ($< 6.7\%$ of total visits), we imputed the VL using the last previously obtained measurement [23]. Given the variation in VL assay sensitivity over time, we defined viral suppression as < 200 copies/mL. Viral load results below the limit of detection were assigned a value of one half the limit for that assay; notably, in the most recent years of the WIHS, assay limit of detection was < 20 copies/mL. Values were capped at 1 000 000 copies/mL to minimize extreme outlier effects [18, 19].

Viremia Copy-Years

The independent variable was cumulative HIV-1 viremia, primarily assessed as viremia copy-years (VCY), a longitudinal measure akin to "pack-years" of smoking. Cumulative VCY was calculated using the trapezoidal rule as the area-under-the-VL-curve in 1-month increments [19, 20], starting with the VL measured in the last visit of the baseline period through the VL measured at time of outcome, censorship, or latest WIHS visit. A hypothetical value of 10 000 copy-years/mL viremia could represent having a VL of 10 000 copies/mL for 1 year or of 1000 copies/mL for 10 years [19].

We assessed 2 cumulative VCY measures: "overall" VCY, the sum of all area-under-the-curve 1-month segments accrued

over entire observation (assessed at end-of-observation); and “time-updated” VCY, the sum of all prior area-under-the-curve 1-month segments up through the current year (assessed annually). For our primary analysis, we \log_{10} -transformed the time-updated VCY measurement and categorized this value into 3 tiers of viral exposure (<5, 5–6.9, or $\geq 7 \log_{10}$ copy-years/mL) based on the distribution of our data and consistent with prior literature [19]. We also assessed intervals of time-updated VCY ranging from years 1 to 8 after baseline or preceding end of observation (Supplementary Material) [23].

Other Human Immunodeficiency Virus-1 Viremia Measures

As alternatives to VCY, we evaluated VL data as single timepoint (ie, measured pre-ART, pre-baseline, and at last observation) and other cumulative measures, including the percentage of person-years [PY] and of visits with VL ≥ 200 or ≥ 50 copies/mL and of participants with VL <200 or <50 copies/mL at every visit. Time-updated %PY with VL ≥ 200 or ≥ 50 copies/mL was also calculated (Supplementary Material). A VL threshold above/below 50 (in addition to 200) copies/mL was assessed considering improved assay sensitivity over time and the potential clinical implications of low-level viremia.

Statistical Analysis

Counts, relative frequency (percentage) for categorical variables and median, quartile 1 and 3 (Q1–Q3) were used to describe the cohort. We used the Kruskal-Wallis test to evaluate the association between cumulative time-updated HIV-1 exposure (ie, VCY; %PY VL ≥ 200 and ≥ 50 copies/mL) and baseline characteristics (eg, age group, race/ethnicity, etc) to assess for relevant differences in viremia indices by participant characteristics.

We used Cox proportional hazard (PH) survival models with time-varying covariates to assess the association of categorized time-updated \log_{10} -VCY with time to multimorbidity. Models were weighted to account for preceding time-updated VCY and study visit nonattendance (Supplementary Material). Weighted models were adjusted for age, race/ethnicity, CD4 count, CD4 nadir, ART type, ART adherence, baseline visit year, WIHS recruitment wave, and WIHS enrollment site. Weighted time-dependent Cox PH models were adjusted for age, race/ethnicity, body mass index (BMI), annual household income, cigarette use, alcohol use, crack/cocaine use, CD4 count, CD4 nadir, ART type, baseline visit year, and prior year VCY.

The association of HIV-1 viremia measures with time to multimorbidity was explored by using covariate-adjusted Cox PH models (for single timepoint or cumulative end-of-observation measurements) or by using weighted, covariate-adjusted time-dependent Cox PH models (for cumulative time-updated measurements). Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) are reported from all Cox

PH models. The PH assumption was checked by assessing the interaction between each categorical covariate and year.

Akaike information criterion (AIC) scores were used to compare the performance of various HIV-1 viremia index models in predicting incident multimorbidity. The performance of each model (lower AIC = better fit) [30] was only compared with other models within the same domain of measurement (ie, single timepoint, cumulative end-of-observation, time-updated) given interdomain model differences in the number of observations and weights used.

We used similar weighted and covariate-adjusted time-dependent Cox PH models to assess the association of time-updated \log_{10} -VCY with the incidence of each NACM; only WWH who did not have the respective comorbidity at baseline were included. The VCY categories were collapsed into <5 or $\geq 5 \log_{10}$ copy-years/mL for improved model fit. Analyses were performed using SAS v9.4 with significance set at $\alpha = 0.05$.

RESULTS

Participant Characteristics

Of the 3677 WWH followed in the WIHS over the study observation (1997–2019), 1124 were excluded due to ≥ 1 NACM prevalence at baseline, with other exclusions shown in Supplementary Figure 1. Among 806 WWH included, contributing a total of 6368 women-years of follow up, baseline characteristics were median or percentage: age 39 (Q1–Q3, 34–44) years, 56% non-Hispanic Black, 62% ever used cigarettes, 32% had a BMI ≥ 30 kg/m², CD4 count 534 (Q1–Q3, 368–707) cells/mm³, and CD4 nadir 204 (Q1–Q3, 89–300) cells/mm³. Reported ART regimen type included use of a PI, NNRTI, or INSTI among 54%, 35%, and 12% of WWH, respectively (Table 1).

Human Immunodeficiency Virus-1 Viral Load Summary Data

Over the observation period, participants contributed a median of 12 (Q1–Q3, 7–23) VL measurements with 182 (Q1–Q3, 167–197) days between measurements (Table 2). Median VL pre-ART was 14 000 (Q1–Q3, 21 000–59 000) and at last observation was 10 (Q1–Q3, 10–41) copies/mL. Table 2 provides the median end-of-observation %PY and %visits with VL ≥ 200 and ≥ 50 copies/mL. Overall, 338 (42%) and 240 (30%) participants had VL <200 and <50 copies/mL, respectively, at every study visit during observation.

Cumulative Human Immunodeficiency Virus-1 Viremia

At the end-of-observation period, the median overall VCY was 5.5 (Q1–Q3, 4.7–7.0) \log_{10} copy-years/mL and time-updated VCY was 5.4 (Q1–Q3, 4.7–6.9) \log_{10} copy-years/mL. Interval measures of time-updated VCY in years 1–8 after baseline or preceding end-of-observation period are shown in Table 2. Median time-updated %PY with VL ≥ 200 or ≥ 50 copies/mL

Table 1. Baseline Demographic and Clinical Characteristics of Women With HIV Who Achieved Viral Suppression After Reported Initiation of Antiretroviral Therapy Enrolled in the Women's Interagency HIV Study (1997–2019)

Characteristic Median (Q1–Q3) or N (%) ^a	WWH (N=806)
Age, years	39 (3–44)
Age group, years	...
<30	88 (10.9)
30–34	140 (17.4)
35–39	213 (26.4)
40–44	176 (21.8)
≥45	189 (23.5)
Observation time, years	6.5 (3.3–12.4)
Race/ethnicity	...
White, non-Hispanic	101 (12.5)
Black, non-Hispanic	451 (56.0)
Hispanic	224 (27.8)
Else, non-Hispanic	30 (3.7)
WIHS enrollment wave	...
1994–1995	342 (42.4)
2001–2002	241 (29.9)
2011–2012	75 (9.3)
2013–2015	148 (18.4)
Year observation started	...
1997–2002	261 (32.4)
2003–2008	268 (33.3)
2009–2014	115 (14.3)
2015–2018	162 (20.1)
Body mass index, kg/m ²	...
<30	544 (67.6)
≥30	261 (32.4)
Blood pressure, mmHg	...
Systolic blood pressure	112 (104, 120)
Diastolic blood pressure	70 (65, 77)
eGFR, mL/min per 1.73 m ² (CKD-EPI)	103.3 (87.4, 117.2)
CES-D score ^b	...
CES-D <16	547 (68.0)
CES-D ≥16	258 (32.0)
Education attained	...
> High school	282 (35.0)
≤ High school	523 (65.0)
Annual household income	...
<\$12 000	370 (47.8)
\$12 001–24 000	195 (25.2)
>\$24 000	209 (27.0)
Marital status	...
Married/partner	275 (35.1)
Had a partner	204 (26.1)
Never married/other	304 (38.8)
Residence status	...
Own residence	673 (83.6)
Not own residence	132 (16.4)
Cigarette use	...
Never	312 (38.8)
Current	292 (36.3)
Former	201 (25.0)
Current alcohol use	...
None	442 (55.3)
1–7 drinks/week	318 (39.8)

Table 1. Continued

Characteristic Median (Q1–Q3) or N (%) ^a	WWH (N=806)
>7 drinks/week	40 (5.0)
Marijuana use	...
Never	309 (38.7)
Current	121 (15.1)
Former	369 (46.2)
Crack/cocaine use	...
Never	646 (80.7)
Current	43 (5.4)
Former	112 (14.0)
Injection drug use	...
Never	672 (83.9)
Current	8 (1.0)
Former	121 (15.1)
Noninjection drug use	...
Never	274 (34.3)
Current	145 (18.2)
Former	380 (47.6)
Chronic HBV	25 (3.1)
Chronic HCV	92 (11.4)
ART regimen type ^c	...
Includes PI	433 (53.7)
Includes NNRTI	278 (34.5)
Includes INSTI	95 (11.8)
CD4 count, cells/mm ³	534 (368, 707)
CD4 nadir, cells/mm ³	204 (89, 300)
ART adherence (self-reported) ^d	...
≥95% of the time	603 (82.7)
<95% of the time	126 (17.3)

Abbreviations: ART, antiretroviral therapy; CES-D, Center for Epidemiologic Studies Depression; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; WIHS, Women's Interagency HIV Study; WWH, women with HIV.

NOTE: Missing data: own residence (*n* = 1), income (*n* = 32), marital status (*n* = 23), drinking (*n* = 6), education (*n* = 1), CES-D (*n* = 1), cigarette use (*n* = 1), crack/cocaine use (*n* = 5), marijuana use (*n* = 7), intravenous drug use (*n* = 5), noninjection drug use (*n* = 7), ART adherence (*n* = 77), body mass index (*n* = 1), CD4 count (*n* = 14), systolic blood pressure (*n* = 1), diastolic blood pressure (*n* = 1).

^aData are presented as median (Q1, Q3) or *n*(%). Column percentages may not total 100 due to rounding.

^bRange 0–60; threshold for depressive symptoms, ≥16.

^cCategorized hierarchically as PI > NNRTI > INSTI, such that a regimen containing a PI and INSTI would be categorized in the PI group, for example.

^dParticipants were asked "In general, over the past 6 months, how often did you take your antiretrovirals as prescribed?" with response options of 100%, 95%–99%, 75%–94%, or <75% of the time (collapsed in table based on distribution of responses).

was 9.4 (Q1–Q3, 0–46.0) and 19.9 (Q1–Q3, 0–57.8), respectively. Table 3 shows the median time-updated VCY and time-updated %PY with VL ≥200 and ≥50 copies/mL stratified by baseline characteristics. Median time-updated VCY was significantly associated with age group, race/ethnicity, year observation started, BMI, depression score, annual household income, cigarette use, chronic hepatitis C virus, baseline CD4 count, CD4 nadir, and ART regimen type; findings were overall similar for median %PY with ≥200 and ≥50 copies/mL, with the exception of race/ethnicity, BMI, and baseline CD4 not being

Table 2. HIV-1 Viral Load Data and Measures of Viral Exposure (ie, Single Timepoint, Cumulative End-of-Observation, and Time-Updated) Among Women With HIV Who Achieved Viral Suppression After Reported Initiation of Antiretroviral Therapy Enrolled in the Women's Interagency HIV Study (1997–2019)

Variable	Median (Q1, Q3) or N (%)	WWH (N=806 ^a)
Viral load measurement data^b		
Number of VL measurements per participant	12 (7, 23)	
Number of days between VL measurements	182 (167, 197)	
Single timepoint HIV-1 indices		
Pre-ART VL, cp/mL ^c	14 000 (21 000, 59 000)	
Pre-ART VL, log ₁₀ cp/mL ^c	4.2 (3.3, 4.8)	
Pre-baseline period VL, cp/mL	526 (40, 11000)	
Pre-baseline period VL, log ₁₀ cp/mL	2.7 (1.6, 4.0)	
VL at last observation, cp/mL	10 (10, 41)	
VL at last observation, log ₁₀ cp/mL	1.0 (1.0, 1.6)	
Participants with VL <200 cp/mL at first observation, n (%)	806 (100.0)	
Participants with VL <50 cp/mL at first observation, n (%)	734 (91.1)	
Participants with VL <200 cp/mL at last observation, n (%)	658 (81.6)	
Participants with VL <50 cp/mL at last observation, n (%)	611 (75.8)	
Cumulative HIV-1 indices, end-of-observation		
Overall VCY, copy-years/mL	295 233 (49 587, 9 309 783)	
Overall VCY, log ₁₀ copy-years/mL	5.5 (4.7, 7.0)	
Total %PY with VL ≥200 cp/mL	7.5 (0.0, 39.7)	
Total %PY with VL ≥50 cp/mL	17.8 (0, 52.2)	
Total %visits with VL ≥200 cp/mL	7.7 (0.0, 33.3)	
Total %visits with VL ≥50 cp/mL	16.7 (0.0, 45.5)	
Participants with VL <200 cp/mL at all visits, n (%)	338 (41.9)	
Participants with VL <50 cp/mL at all visits, n (%)	240 (29.8)	
Cumulative HIV-1 indices, time-updated		
Time-updated VCY, log ₁₀ copy-years/mL	5.4 (4.7, 6.9)	
Time-updated VCY, log ₁₀ copy-years/mL	...	
<5	607 (75.3)	
5–6.9	167 (20.7)	
≥7	32 (4.0)	
Time-updated VCY, log ₁₀ copy-years/mL	...	
Intervals from baseline period onward:		
Baseline through 1 year (n=806)	4.2 (3.9, 5.0)	
Baseline through 2 year (n=785)	4.5 (4.4, 5.8)	
Baseline through 3 year (n=727)	4.8 (4.6, 6.3)	
Baseline through 4 year (n=633)	5.1 (4.7, 6.6)	
Baseline through 5 year (n=557)	5.4 (4.8, 6.9)	
Baseline through 6 year (n=505)	5.5 (4.9, 7.0)	
Baseline through 7 year (n=446)	5.7 (5.0, 7.1)	
Baseline through 8 year (n=390)	5.9 (5.1, 7.1)	
Time-updated VCY, log ₁₀ copy-years/mL	...	
Intervals from last observation retrograde:		
1 year preceding last observation (n=806)	3.5 (3.2, 4.1)	
2 year preceding last observation (n=785)	4.1 (3.8, 5.1)	
3 year preceding last observation (n=727)	4.5 (4.0, 5.7)	
4 year preceding last observation (n=633)	4.7 (4.2, 6.2)	
5 year preceding last observation (n=557)	4.9 (4.4, 6.5)	
6 year preceding last observation (n=505)	4.9 (4.5, 6.6)	
7 year preceding last observation (n=446)	5.2 (4.7, 6.8)	

Table 2. Continued

Variable	Median (Q1, Q3) or N (%)	WWH (N=806 ^a)
8 year preceding last observation (n=390)		5.3 (4.8, 7.0)
Time-updated %PY with VL ≥200 cp/mL		9.4 (0.0, 46.0)
Time-updated %PY with VL ≥50 cp/mL		19.9 (0.0, 57.8)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PY, person-years; VCY, viremia copy-years; VL, viral load; WWH, women with HIV.

^aSample size unless otherwise specified.

^bFor VL results below the lower limit of detection, the value was set at one half the limit of detection; VL >1 000 000 were truncated to 1 000 000 copies/mL.

^cData missing for pre-ART VL (n=12).

significant associated with these HIV-1 viremia indices (Table 3).

Study Outcomes

A total of 211 (26%) WWH developed multimorbidity during the study observation, the remaining 595 (74%) were censored, either due to death (n=17) or not realizing multimorbidity by last observation (n=578). Of the 17 participants who were censored due to death, 3 (18%), 6 (35%), and 8 (47%) had a cumulative time-updated VCY of <5, 5–6.9, and >7 log₁₀ copy-years/mL, respectively; and 8 (47%) versus 9 (53%) had zero versus 1 NACM.

Among the 211 WWH who developed multimorbidity, the median NACM count of 5 total assessed was 2.0 (Q1–Q3, 2.0–2.0), including 162 (77%) participants who developed incident hypertension, 133 (63%) who developed incident dyslipidemia, 60 (28%) who developed incident diabetes, 52 (25%) who developed incident CVD, and 32 (15%) who developed incident CKD. The most common co-occurring NACM dyads were hypertension-dyslipidemia and hypertension-diabetes occurring in 85 (41%) and 37 (18%) participants, respectively (percentages not mutually exclusive).

Viral Exposure and Multimorbidity

In covariate-adjusted Cox PH models, the risk of multimorbidity was greater among WWH who had a time-updated VCY of 5–6.9 and ≥7 (aHR = 1.99, 95% CI = 1.29–3.08 and aHR = 3.78, 95% CI = 2.17–6.58, respectively) versus those with time-updated VCY <5 log₁₀ copy-years/mL (P < .0001) (Figure 1). Supplementary Table 1 reports these model results, including the specific hazard ratios of incident multimorbidity for additional HIV-specific and traditional risk factors included as covariates in the model.

The association of each HIV-1 viremia measure with multimorbidity risk was assessed using the AIC score (Supplementary Table 2). The best model fit (ie, lowest AIC) for multimorbidity risk-prediction was VL at last observation, overall log₁₀-VCY, and time-updated %PY with VL ≥50 copies/mL among single timepoint, cumulative end-of-observation, and time-updated measurements, respectively.

Table 3. Time-Updated Viremia Copy-Years and Time-Updated %Person-Years With Viral Load ≥ 200 and $\geq 5^\circ$ Copies/mL Stratified by Participant Characteristics at Baseline Among Women With HIV Who Achieved Viral Suppression After Reported Initiation of Antiretroviral Therapy Enrolled in the Women's Interagency HIV Study (1997–2019)

Characteristic	Median (Q1, Q3)	Time-Updated VCY, Log ₁₀ Copy-Years/mL	P Value ^a	Time-Updated %PY With VL ≥ 200 cp/mL	P Value ^a	Time-Updated %PY With VL ≥ 50 cp/mL	P Value ^a
Age group, years							
< 30	...	5.5 (4.9, 6.8)	<.0001	12.3 (0.0, 55.5)	<.0001	22.0 (2.5, 68.6)	<.0001
30–34	...	5.6 (4.8, 7.1)		12.6 (0.0, 48.4)		22.9 (0.0, 59.9)	
35–39	...	5.7 (4.9, 7.1)		12.6 (0.0, 50.5)		24.4 (0.0, 60.5)	
40–44	...	5.3 (4.8, 6.8)		8.1 (0.0, 42.8)		19.6 (0.0, 56.0)	
≥ 45	...	4.9 (4.3, 6.3)		0.0 (0.0, 28.5)		10.2 (0.0, 40.8)	
Race/ethnicity							
White, non-Hispanic	...	5.4 (4.8, 6.6)	.0012	10.8 (0.0, 37.3)	.1886	19.2 (0.0, 48.3)	.0584
Black, non-Hispanic	...	5.3 (4.6, 6.9)		7.3 (0.0, 49.7)		19.0 (0.0, 60.2)	
Hispanic	...	5.5 (4.9, 6.9)		11.3 (0.0, 46.0)		20.7 (0.0, 58.7)	
Other, non-Hispanic	...	5.6 (4.7, 6.5)		14.3 (0.0, 40.2)		29.7 (0.0, 51.3)	
Year observation started							
1997–2002	...	6.2 (5.2, 7.2)	<.0001	22.8 (0.0, 60.1)	<.0001	32.0 (9.0, 70.3)	<.0001
2003–2008	...	5.2 (4.8, 6.7)		5.5 (0.0, 36.8)		13.4 (0.0, 52.4)	
2009–2014	...	4.5 (4.1, 5.6)		0.0 (0.0, 21.7)		7.3 (0.0, 36.6)	
2015–2018	...	4.0 (3.8, 4.6)		0.0 (0.0, 0.00)		0.0 (0.0, 25.0)	
Body mass index, kg/m²							
< 30	...	5.5 (4.8, 6.9)	<.0001	10.1 (0.0, 43.1)	.4085	20.4 (0.0, 56.6)	.9797
≥ 30	...	5.2 (4.6, 6.8)		7.7 (0.0, 52.4)		18.5 (0.0, 61.3)	
CES-D score^b							
< 16	...	5.4 (4.6, 6.8)	<.0001	8.3 (0.0, 41.0)	<.0001	18.1 (0.0, 54.2)	<.0001
≥ 16	...	5.6 (4.8, 6.9)		13.0 (0.0, 53.3)		25.1 (0.0, 66.7)	
Annual household income							
<\$12 000	...	5.5 (4.8, 7.0)	<.0001	11.5 (0.0, 56.8)	<.0001	22.1 (0.0, 68.1)	<.0001
\$12 001–\$24 000	...	5.3 (4.8, 6.5)		6.3 (0.0, 40.4)		17.2 (0.0, 54.3)	
>\$24 000	...	5.5 (4.7, 6.9)		9.9 (0.0, 34.8)		20.0 (0.0, 49.8)	
Cigarette use							
Never	...	5.1 (4.6, 6.3)	<.0001	2.5 (0.0, 30.7)	<.0001	10.7 (0.0, 47.5)	<.0001
Current	...	5.8 (4.8, 7.1)		17.2 (0.0, 56.9)		29.3 (0.0, 68.0)	
Former	...	5.7 (4.8, 6.9)		13.1 (0.0, 45.3)		23.0 (0.0, 57.3)	
Chronic HCV							
Yes	...	6.0 (5.0, 7.1)	<.0001	19.5 (0.0, 56.8)	<.0001	31.7 (8.3, 66.3)	<.0001
No	...	5.3 (4.7, 6.8)		8.1 (0.0, 43.9)		18.0 (0.0, 56.8)	
Baseline CD4, cells/mm³							
< 500	...	5.4 (4.8, 6.9)	.0057	9.9 (0.0, 47.1)	.2422	20.6 (0.0, 58.8)	.0685
≥ 500	...	5.4 (4.6, 6.9)		9.1 (0.0, 45.2)		19.5 (0.0, 57.1)	
CD4 nadir, cells/mm³							
< 200	...	5.7 (4.9, 7.1)	<.0001	16.4 (0.0, 58.5)	<.0001	28.6 (0.0, 69.4)	<.0001
≥ 200	...	5.1 (4.6, 6.5)		3.3 (0.0, 29.3)		13.0 (0.0, 43.6)	
ART regimen type^c							
Includes PI	...	5.7 (4.9, 7.1)	<.0001	15.8 (0.0, 54.1)	<.0001	27.3 (0.0, 65.4)	<.0001
Includes NNRTI	...	5.2 (4.6, 6.4)		4.0 (0.0, 28.6)		12.0 (0.0, 43.7)	
Includes INSTI	...	4.1 (3.9, 5.8)		0.0 (0.0, 29.0)		0.0 (0.0, 44.8)	

Abbreviations: ART, antiretroviral therapy; CES-D, Center for Epidemiologic Studies Depression; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; PY, person-years; NNRTI, nonnucleoside reverse-transcriptase inhibitor; VCY, viremia copy-years; VL, viral load.

NOTE: Missing data: income ($n=32$), CES-D ($n=1$), cigarette use ($n=1$), body mass index ($n=1$), CD4 count ($n=14$).

^aKruskal-Wallis test.

^bCES-D ≥ 16 indicates depressive symptoms.

^cCategorized hierarchically as PI > NNRTI > INSTI, such that a regimen containing a PI and INSTI would be categorized in the PI group, for example.

Viral Exposure and Specific Nonacquired Immune Deficiency Syndrome Comorbidities

Separate covariate-adjusted Cox PH models were used to assess the association of time-updated log₁₀-VCY with incidence of

each NACM (Figure 2; Supplementary Table 3). Women with HIV who had a time-updated VCY of ≥ 5 versus < 5 log₁₀ copy-years/mL had a significantly increased risk of each incident NACM: hypertension (aHR, 1.71; 95% CI, 1.29–2.27),

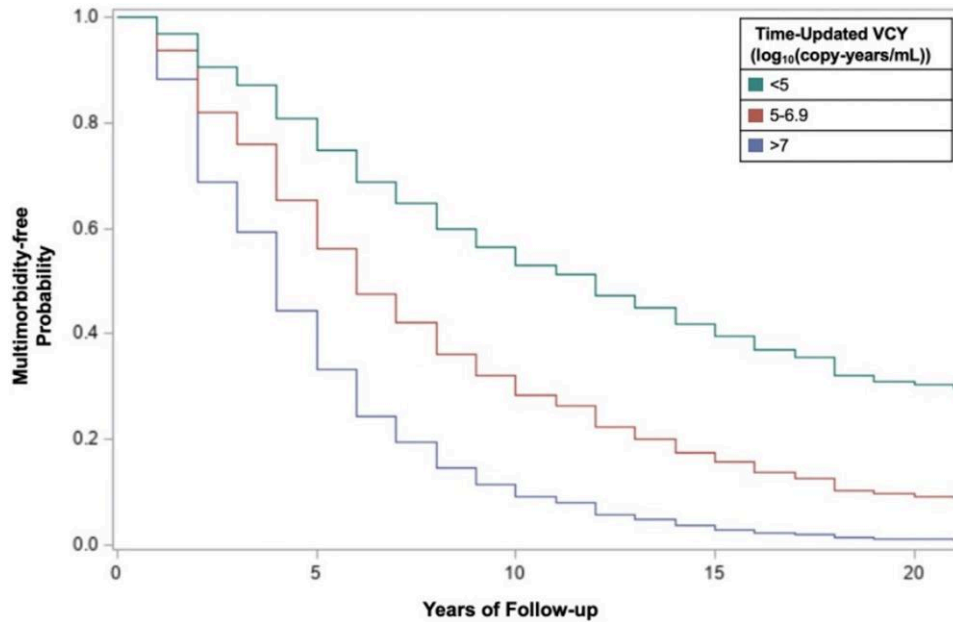


Figure 1. Cox proportional hazards survival curve of time to incident multimorbidity (≥ 2 nonacquired immune deficiency syndrome comorbidities accrued over observation of 5 total assessed: hypertension, dyslipidemia, diabetes, cardiovascular disease, chronic kidney disease) stratified by category of cumulative time-updated viremia copy-years (VCY) (see legend) among women with human immunodeficiency virus who achieved viral suppression after reported use of antiretroviral therapy ($n = 768$). The model was (1) adjusted for age, race/ethnicity, annual household income, cigarette use, alcohol use, crack/cocaine use, body mass index, CD4 count, CD4 nadir, antiretroviral therapy type, baseline visit year, and prior year VCY and was (2) weighted for prior time-updated VCY and study visit nonattendance.

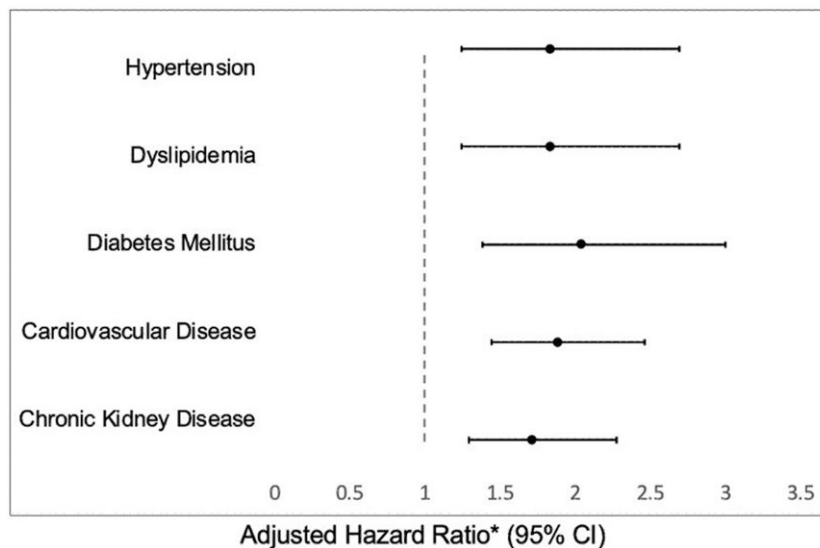


Figure 2. Adjusted hazard ratio and 95% confidence intervals (CI) from Cox proportional hazards survival models assessing the risk of 5 incident nonacquired immune deficiency syndrome comorbidities ([NACM] hypertension, dyslipidemia, diabetes, cardiovascular disease, and chronic kidney disease) among women with human immunodeficiency virus (HIV) after reported antiretroviral therapy use who had time-updated viremia copy-years (VCY) of ≥ 5 versus < 5 \log_{10} copy-years/mL. Note: A separate Cox proportional hazards survival analysis was performed for each specific NACM; sample sizes differed for each analysis based on the number of women with HIV who were risk-free of that specific NACM at baseline (see [Supplemental Material](#)).

dyslipidemia (aHR, 1.88; 95% CI, 1.44–2.46), diabetes (aHR, 1.83; 95% CI, 1.24–2.69), CVD (aHR, 2.04; 95% CI, 1.38–3.00), and CKD (aHR, 1.91; 95% CI, 1.26–2.88).

DISCUSSION

In this large, well characterized, and prospectively followed diverse cohort of US WWH who were observed in the years immediately after ART initiation, we evaluated the effect of cumulative HIV-1 viremia on a composite outcome of aging-related multimorbidity. In survival analyses adjusted for traditional and HIV-related comorbidity risk factors, greater time-updated VCY was associated with increased risk of multimorbidity among ART-treated WWH in a dose-dependent manner. Furthermore, in separate models evaluating incidence of each comorbidity, greater time-updated VCY increased the hazard of developing all 5 NACM assessed: hypertension, dyslipidemia, diabetes, CVD, and CKD. These data provide insights into possible shared mechanisms contributing to end-organ damage in WWH despite ART, and they suggest that measures of cumulative HIV-1 exposure may be prognostically useful biomarkers for NACM risk assessment in this population.

Despite a higher and earlier risk of NACM burden in PWH versus persons without HIV, existing comorbidity risk-assessment tools perform suboptimally in PWH [31, 32, 33, 34]. For example, routine CVD risk scores developed in the general population underestimate risk among PWH by 12%–20%, especially in women and younger persons [35]. Underperformance of current tools may be related to HIV-specific clinical factors (eg, CD4 count, VL measures, effects of ART use) not being considered in risk-estimation algorithms. It has been established that traditional risk factors including BMI, cigarette use, and social determinants of health contribute significantly to NACM development in PWH [5, 36]. In the current analysis, along with time-updated \log_{10} -VCY (which had the greatest hazard), older age, non-Hispanic White race, and INSTI-containing ART at baseline significantly increased the risk of incident multimorbidity. These findings suggest there may be additive benefit to focused evaluation and optimization of HIV-specific as well as traditional risk factors with the aim of mitigating NACM risk in PWH.

Robust data from male-predominant cohorts of PWH followed after ART initiation support the association of cumulative HIV-1 viremia with all-cause mortality [18, 19, 20, 21, 22, 23]. In the modern ART era, with life expectancy extended approximately 20 years since 2000 among PWH with access to care [2], it is critical to ascertain HIV care metrics not only predictive of death but also of aging-related NACM development. Recent analyses have demonstrated that cumulative HIV-1 viremia is associated with incident myocardial infarction [18, 24], hypertension [25], renal insufficiency [26, 27], and non-AIDS

cancer [28]. Our study uniquely adds to this growing body of literature by assessing multimorbidity as a composite outcome and by focusing on women, a group traditionally underrepresented in HIV research although uniquely at risk of NACM [5, 37, 38, 39].

Multimorbidity is a growing clinical phenotype in aging populations, including PWH, and is exacerbated in women [4, 6, 40]. Co-occurrence of NACM in PWH may be related to shared risk factors and/or common pathophysiology. We specifically evaluated 5 NACM that have been associated with HIV-associated chronic inflammation and immune activation [41, 42, 43], that frequently co-occur, and that have vascular impact [4, 44]. We found that among WWH, greater cumulative time-updated VCY despite reported ART use increased the risk of multimorbidity and incidence of 5 vascular-related NACM. These data (1) suggest that longitudinal HIV-1 viremia may contribute to vascular end-organ damage in PWH potentially involving a shared mechanistic pathway leading to multimorbidity and (2) support the hypothesis that cumulative viremia burden may affect sex differences in NACM risk among treated PWH.

Among a cohort of predominantly urban WWH of color (median age 39 years) with a high burden of adverse social determinants of health, median time-updated VCY was 5.4 \log_{10} copy-years/mL. This value is higher than previously reported in findings from largely male cohorts of PWH (range, 3.0–5.3 \log_{10} copy-years/mL) [19, 20, 21, 22, 23, 28]. In the HIV Outpatient Study, women had higher HIV-1 viral exposure than men [22], and previous WIHS data revealed younger age as a significant viremia risk factor [45]. Sex-differential drivers of viral exposure among treated PWH may include variability in antiretroviral drug exposure due to suboptimal adherence, food or drug interactions, drug pharmacokinetics (including drug penetration into cellular and/or tissue HIV reservoirs [46]), or socioeconomic strain disproportionately impacting women versus men [16, 47].

Despite apparent HIV-1 suppression, 18%–34% of PWH on ART experience low-level intermittent viremia [48]. Imperfect ART adherence has been associated with higher systemic levels of inflammatory and coagulopathy markers [15, 49, 50], with clinical impact among PWH including increased risk of incident NACM (particularly, CVD), outcome severity, and all-cause mortality [51, 52, 53, 54, 55]. More importantly, women versus men experience higher levels of immune activation and inflammation at the same VL level [16], which may contribute to higher NACM risk and severity, including the potential for premature multimorbidity [17]. Additional studies assessing sex differences in drivers of cumulative HIV-1 viremia and its effect on multimorbidity are needed, especially because the impact may be particularly consequential for young WWH [9], for whom the ideal timing of comorbidity risk assessment may be in the pre-/perimenopausal period [56].

Human immunodeficiency virus-1 viremia measures may serve as clinically accessible biomarkers of the long-term effects of chronic immune dysregulation driven by ongoing viral replication despite ART. Precisely which viral exposure measures may best prognosticate specific NACM or multimorbidity risk likely depends on many factors including specific comorbidity pathogenesis and possibly sex differences. In this analysis of WWH, time-updated VCY was significantly associated with increased multimorbidity risk in a dose-dependent manner (Figure 1; Supplementary Table 1). In evaluating different HIV-1 viremia measures for their relative prognosticative ability for multimorbidity, VL at last observation, overall VCY, and time-updated %PY with VL ≥ 50 copies/mL had the best model fit in the respective domains of single timepoint, cumulative end-of-observation, and time-updated measurements (Supplementary Table 2). These data suggest that incorporating HIV-1 viremia measures into existing or novel NACM risk-estimation tools may improve the accuracy of identifying ART-treated WWH at highest risk of developing multimorbidity. This would allow clinicians to offer targeted interventions such as intensified ART adherence counseling, lipid or blood pressure management, smoking cessation efforts, or other innovative NACM mitigation strategies such as those addressing persistent HIV-associated inflammation or underlying social determinants of health.

Strengths of our study included use of data from a large, multisite, well characterized women's cohort, thereby focusing on a high-priority population; extensive participant follow-up including semiannual VL measurements over decades; robust NACM assessment integrating several data elements; and a novel, clinically impactful primary outcome of multimorbidity.

Our study has several limitations. First, the determination of some NACM relied on self-reported conditions or medications, which could lead to an underestimation of certain NACM or differential findings related to healthcare access. Second, 6-month interval VL measurements do not capture real-time VL fluctuations, which inherently affect VCY calculations [57] and may represent more (or less) frequent VL monitoring than occurs in routine clinical care; nonetheless, calculating VCY using semiannual VL measurements (and lagging from the last available visit if missing; <6.7% of instances) was predictive of multimorbidity in this population of ART-treated WWH. Third, we were not able to assess the contribution of ART switching or nonadherence given that these characteristics were assessed only at baseline and not throughout follow up.

CONCLUSIONS

In conclusion, in a large, well characterized cohort of ART-treated women, greater cumulative time-updated HIV-1 viremia significantly increased the risk of multimorbidity and of the incidence of 5 vascular-related NACM. These data

suggest possible shared mechanisms driving several NACM, including a multimorbidity phenotype driven substantially by HIV-1 viremia, and support cumulative HIV-1 viremia as a prognostically useful biomarker for NACM risk assessment in WWH. Further investigation into the interplay of sex, HIV-1 viral exposure, persistent inflammation and immune activation, and traditional competing risks for specific NACM is urgently needed to better elucidate mechanisms mediating aging-related comorbidity burden among PWH in the modern ART era. These data could lead to the development or refining of sex-tailored, HIV-specific comorbidity screening and prevention strategies to identify individuals in greatest need of aggressive risk-modification interventions.

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.

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