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The Prevalence and Burden of Non-AIDS Comorbidities Among Women Living With or at Risk for Human Immunodeficiency Virus Infection in the United States

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(See the Editorial Commentary by Huaman and Fichtenbaum on pages 1312–3.)

Background. The prevalence and burden of age-related non-AIDS comorbidities (NACMs) are poorly characterized among women living with HIV (WLWH).

Methods. Virologically suppressed WLWH and HIV-seronegative participants followed in the Women's Interagency HIV Study (WIHS) through at least 2009 (when >80% of WLWH used antiretroviral therapy) were included, with outcomes measured through 31 March 2018. Covariates, NACM number, and prevalence were summarized at most recent WIHS visit. We used linear regression models to determine NACM burden by HIV serostatus and age.

Results. Among 3232 women (2309 WLWH, 923 HIV-seronegative) with median observation of 15.3 years, median age and body mass index (BMI) were 50 years and 30 kg/m^2, respectively; 65% were black; 70% ever used cigarettes. WLWH had a higher mean NACM number than HIV-seronegative women (3.6 vs 3.0, $P < .0001$) and higher prevalence of psychiatric illness, dyslipidemia, non-AIDS cancer, kidney, liver, and bone disease (all $P < .01$). Prevalent hypertension, diabetes, and cardiovascular and lung disease did not differ by HIV serostatus. Estimated NACM burden was higher among WLWH versus HIV-seronegative women in those aged 40–49 ($P < .0001$) and ≥60 years ($P = .0009$) (HIV × age interaction, $P = .0978$). In adjusted analyses, NACM burden was associated with HIV, age, race, income, BMI, alcohol abstinence, cigarette, and crack/cocaine use; in WLWH, additional HIV-specific indices were not associated, aside from recent abacavir use.

Conclusions. Overall, NACM burden was high in the cohort, but higher in WLWH and in certain age groups. Non-HIV traditional risk factors were significantly associated with NACM burden in WLWH and should be prioritized in clinical guidelines for screening and intervention to mitigate comorbidity burden in this high-risk population.

Keywords. human immunodeficiency virus; women living with HIV; HIV and aging; non-AIDS comorbidities; comorbidity burden.

Combination antiretroviral therapy (cART) has resulted in tremendous improvements in mortality, and as such, nearly half of individuals with diagnosed human immunodeficiency virus (HIV) in the United States are now aged 50 years or older [1, 2]. In those with access to care and treated, age-associated non-AIDS comorbidities (NACMs) increasingly account for morbidity [3–5] and mortality [6, 7]. Compared with HIV-seronegative counterparts, persons living with HIV (PLWH) experience higher risk and severity of NACMs [3, 8], which may accrue at an earlier age [9, 10].

While women account for more than 50% of adults with HIV worldwide [11], they are underrepresented in HIV research [12]. Further, analyses do not always present sex-delineated outcomes [13]. Female-specific biological and sociobehavioral factors influence HIV acquisition, pathogenesis, reservoir, and treatment responses, and likely contribute to comorbidity development; however, additional investigation is warranted [14]. Large, multisite cohort studies describing "multimorbidity" in aging PLWH lack adequate representation of female participants (range, 13–21%) [3, 5, 10, 15]. This is especially concerning given

that NACM risk and burden may be amplified in women living with HIV (WLWH) compared with men [5, 16, 17].

A comprehensive understanding of the distribution of age-related comorbidities in WLWH is crucial to optimizing care for this unique aging population. Our objectives were to describe NACM burden and prevalence in WLWH, assess the effects of HIV serostatus and age on NACM burden, and describe risk factors associated with NACM in a large, geographically diverse, exclusively female cohort of WLWH and HIV-seronegative counterparts.

METHODS

The Women's Interagency HIV Study

We analyzed data from the Women's Interagency HIV Study (WIHS), the largest prospective US-based cohort of women living with or at risk for HIV infection [18]. Enrollment occurred in 4 waves (1994–1995, 2001–2002, 2011–2012, 2013–2015) from 11 cities (Atlanta, GA; Birmingham, AL; Bronx, NY; Brooklyn, NY; Chapel Hill, NC; Chicago, IL; Jackson, MS; Los Angeles, CA; Miami, FL; San Francisco, CA; Washington, DC). HIV-seropositive (HIV+) or HIV-seronegative (HIV−) women at risk of HIV acquisition (based on sexually transmitted infection history and/or sociobehavioral characteristics) were recruited, as described in more detail previously [18].

Women's Interagency HIV Study participants complete a biannual interviewer-administered questionnaire, standardized physical examination (including 3 seated blood pressure measurements in the participant's right arm using an automated Dinamap monitor [Dinamap Procare Series, GE Medical Systems]) and biospecimen collections. Sociodemographic and clinical information, medical and psychiatric comorbidities, medications, and health behaviors are assessed. Blood testing evaluates kidney and liver function, CD4 count, and HIV viral load. The WIHS study protocol has been approved by each site's institutional review board, and all participants have provided written informed consent.

Study Design

To focus our analysis on age-related NACMs in the era of effective HIV treatment (and to minimize the contribution of AIDS-related pathology), we included all WIHS participants with at least 2 full study visits completed between 2009 (when >80% of WLWH used cART) through the end of observation (31 March 2018) (Supplementary Figure). Longitudinal WIHS data from study enrollment through observation end were cross-sectionalized, such that covariates and NACM prevalence and burden were assessed as of the most recent visit for each participant.

Outcome Measures

We selected 10 NACMs due to their known age association and significant contribution to morbidity and mortality in the general population (Supplementary Table 1). Our primary outcome was NACM burden, defined as the number of total NACMs per participant. Our secondary outcomes were the prevalence of each NACM, defined as the presence of the condition as of the participant's most recent visit. Non-AIDS comorbidities were defined using up to 3 potential data sources: self-reported diagnosis or medication, clinical measurement, and/or laboratory evidence. Use of pathology and/or imaging modalities to define NACMs (eg, biopsies for cancer, bone densitometry for osteopenia/osteoporosis, transient elastography for liver disease, etc) was not employed given a lack of availability of these data. Non-AIDS comorbidities were assigned if a participant had any history of the comorbidity at the most recent visit, with the exception of certain comorbidities defined by measurements with the potential to fluctuate over time (eg, chronic kidney disease [CKD] and depression), for which criteria were required on 2 or more consecutive visits to satisfy the NACM definition. Once a participant met criteria for a comorbidity, that comorbidity was considered prevalent.

Statistical Analysis

We compared demographic and clinical characteristics of women by HIV serostatus using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Chi-square tests and 2-sample *t* tests assessed the association of HIV serostatus with the prevalence of each comorbidity and NACM burden, respectively. For the entire cohort and then stratified by HIV serostatus, we assessed for a linear trend by ranked age category (<40, 40–49, 50–59, ≥60 years) using the Wilcoxon test (for individual NACM prevalence) and unadjusted linear regression (for NACM burden).

We performed separate, partially adjusted logistic regression (outcome = individual NACM prevalence) and partially adjusted linear regression (outcome = NACM burden) analyses to assess for associations of HIV serostatus and age; models included HIV serostatus, categorized age, and an HIV × age interaction term and no other covariates.

For the primary outcome (NACM burden), we used a "fully adjusted" linear regression model, controlling for important covariates (derived from the literature or univariate analyses), in addition to HIV serostatus, categorized age, and an HIV × age interaction term to determine model-based estimates of mean NACM burden by HIV × age category and covariates. A separate adjusted linear regression model including only WLWH was performed to assess the effect of age- and HIV-specific indices, controlling for the same covariates as the "fully adjusted" model, on NACM burden. Any variables used to define individual NACMs were not included as covariates in adjusted models. Model fit was assessed through residual plots for linear regression and Hosmer-Lemeshow test for logistic regression.

To evaluate co-occurring NACM dyads, all possible pairs of comorbidities were assessed for prevalence (overall, by HIV serostatus, and by age category, and within each HIV × age

category combination) and then ranked in order of co-occurrence regardless of the presence of additional comorbidities.

All analyses were conducted in SAS version 9.4 (SAS Institute) and significance was set at α = 0.05.

RESULTS

Participant Characteristics
Among 3232 women (2309 HIV+, 923 HIV−) included in our analysis (Supplementary Figure) with a median observation of 15.3 years, median age was 50 years and 65% were black (Table 1). Compared with WLWH, HIV-seronegative women had higher systolic blood pressure (126 vs 122 mmHg), a body mass index (BMI) of 30 kg/m^2 or greater (57% vs 46%), and current use of cigarettes (44% vs 36%), alcohol (57% vs 41%), and crack/cocaine (9% vs 6%) (all $P < .0001$). Women living with HIV had a higher prevalence of chronic hepatitis C (13% vs 9%, $P = .0026$) and hepatitis B viral infection (2% vs 1%, $P = .0148$) and worse kidney function than HIV-seronegative women (Table 1). Educational level and median depressive symptoms score did not significantly differ by HIV serostatus. Women living with HIV had a median CD4 count of 615 cells/mm^3, 81% had virologic suppression, and median time since cART initiation was 12.5 years.

Non-AIDS Comorbidity Burden and Prevalence
Mean (SD) NACM burden increased with each older age category (<40, 40–49, 50–59, ≥60 years)—1.7 (1.4), 2.7 (1.8), 4.0 (2.0), and 5.2 (1.9) ($P < .0001$)—as did the prevalence of each individual NACM ($P < .0001$) (Supplementary Table 2). Women living with HIV had a higher mean NACM burden than HIV-seronegative women, 3.6 versus 3.0 ($P < .0001$), and the following comorbidities were more prevalent in WLWH versus HIV-seronegative women (all $P < .01$): psychiatric illness (57%/48%), liver disease (45%/26%), dyslipidemia (40%/35%), bone disease (40%/33%), CKD (15%/7%) and non-AIDS cancer (11%/7%) (Supplementary Table 3). The prevalence of hypertension (66%/64%), lung disease (41%/42%), diabetes (22%/24%), and cardiovascular disease (19%/19%) did not significantly differ by HIV serostatus.

Non-AIDS Comorbidity Burden by HIV Serostatus and Age Group
Figure 1 shows the distribution of categorized NACM burden by HIV serostatus and age group. In partially adjusted models, WLWH had greater NACM burden compared with HIV-seronegative women, although this was significant only for those aged 40–49 years ($P < .0001$) and 60 years or older ($P = .0028$) (HIV × age interaction, $P = .0206$) (Table 2). The estimated mean difference in NACM (HIV+/HIV−) for women aged 40–49, 50–59, and 60 years or older, compared with those aged less than 40 years of the same HIV serostatus, was 1.17 (95% confidence interval [CI], .92–1.41)/.73 (95% CI, .40–1.06), 2.35 (95% CI, 2.11–2.58)/2.35 (95% CI, 2.03–2.68), 3.65

(95% CI, 3.37–3.93)/3.18 (95% CI, 2.77–3.58), respectively (all $P < .0001$).

Non-AIDS Comorbidity Burden Adjusting for Demographic and Clinical Factors
Univariate analysis of factors associated with NACM burden can be found in Supplementary Table 4. In fully adjusted models controlling for race, BMI, education, income, marital status, own residence, and current use of cigarettes, alcohol, and crack/cocaine (in addition to HIV, age, HIV × age), the estimated mean NACM burden differed by HIV serostatus and age group (Figure 2). Non-AIDS comorbidity burden was higher among WLWH compared with HIV-seronegative women in those aged 40–49 years ($P < .0001$) and 60 years or older ($P = .0009$), but not in those aged less than 40 years ($P = .1420$) and 50–59 years ($P = .0888$). The association between HIV serostatus and age on NACM burden approached significance (HIV × age interaction, $P = .0978$). In addition, estimated mean NACM burden was significantly higher in women who were older, of white race, and who had HIV, BMI of 30 kg/m^2 or higher, income of $24 000 or less, and reported cigarette use, crack/cocaine use, or alcohol abstinence (Table 3).

In an adjusted model including only WLWH (controlling for the aforementioned covariates and HIV-specific indices), recent use of abacavir was the only HIV-related characteristic associated with NACM burden (mean, 3.7 vs 3.3; $P < .0001$). Other characteristics, including current and nadir CD4 count, measures of HIV virologic suppression, time since cART initiation, and protease inhibitor use, were not associated with NACM burden in WLWH (Supplementary Table 5).

Non-AIDS Comorbidity Dyads
Figure 3 shows the 3 most common co-occurring NACM dyads in women, stratified by HIV serostatus and categorized age. The co-occurrence of hypertension-psychiatric illness ranked in the top 2 for each HIV × age stratification and was prevalent in 60% of all women aged 60 years or older (Supplementary Table 6). In WLWH, the co-occurrence of hypertension and liver disease was the next most prevalent, occurring in 33% overall and 64% of those aged 60 years or older. This pattern differed from HIV-seronegative women in whom hypertension–lung disease and hypertension–dyslipidemia were the next most common comorbidity dyads depending on age category.

DISCUSSION

In this exclusively female, geographically diverse, US-based cohort of 3232 participants with a median observation of 15.3 years, the burden of NACM was high in WLWH and at-risk HIV-seronegative women, but significantly higher in WLWH overall and in certain age groups. Human immunodeficiency virus infection modified the effect of age on NACM burden, although this interaction was attenuated when adjusting for covariates.

Table 1. Demographic and Clinical Characteristics of Women Living With or at Risk for Human Immunodeficiency Virus (HIV) Infection at End of Observation in the Women's Interagency HIV Study

Characteristics	Entire Cohort[a] (N = 3232)	HIV Positive (n = 2309)	HIV Negative (n = 923)	P[b]
Age, y	50 (43–56)	51 (44–57)	49 (41–55)	<.0001
Age group, n (%)				<.0001
<40 y	520 (16)	315 (14)	205 (22)	
40–49 y	996 (31)	711 (31)	285 (31)	
50–59 y	1241 (38)	936 (41)	305 (33)	
≥60 y	475 (15)	347 (15)	128 (14)	
Observation time, y	15.3 (4.0–18.2)	15.3 (4.0–18.4)	15.3 (4.0–17.9)	.6365
Race/ethnicity, n (%)				.0478
White, non-Hispanic	356 (11)	273 (12)	83 (9)	
Black, non-Hispanic	2108 (65)	1486 (64)	622 (67)	
Hispanic	657 (20)	477 (21)	180 (20)	
Other	111 (3)	73 (3)	38 (4)	
WIHS enrollment wave, n (%)				<.0001
1994–1995	1183 (37)	887 (38)	296 (32)	
2001–2002	867 (27)	559 (24)	308 (33)	
2011–2012	363 (11)	271 (12)	92 (10)	
2013–2015	819 (25)	592 (26)	227 (25)	
BMI, n (%)				<.0001
<30 kg/m^2	1547 (51)	1172 (54)	375 (43)	
≥30	1492 (49)	1004 (46)	488 (57)	
SBP, mmHg	123 (111–138)	122 (110–136)	126 (115–141)	<.0001
DBP, mmHg	75 (68–83)	75 (68–83)	76 (69–84)	.0024
Antihypertensive medication use, n (%)	1298 (40)	951 (41)	347 (38)	.0599
Lipid-lowering medication use, n (%)	578 (18)	430 (19)	148 (16)	.0829
eGFR, mL/min per 1.73 m^2 (CKD-EPI)	94.3 (75.4–110.3)	91.7 (72.6–108.4)	99.6 (84.0–114.4)	<.0001
CES-D score[c]	9 (3–19)	9 (3–19)	8 (3–19)	.6481
Education, n (%)				.1795
≤High school	2093 (65)	1513 (66)	580 (63)	
>High school	1132 (35)	793 (34)	339 (37)	
Income, n (%)				.0198
<$12 000	1515 (50)	1091 (50)	424 (49)	
$12 001–$24 000	703 (23)	521 (24)	182 (21)	
>$24 000	828 (27)	562 (26)	266 (31)	
Insured, n (%)	3011 (94)	2245 (98)	766 (83)	<.0001
Marital status, n (%)				.0038
Married/partner	886 (29)	629 (28)	257 (29)	
Divorced/widowed/separated	914 (30)	690 (31)	224 (25)	
Never married/other	1295 (42)	894 (40)	401 (45)	
Own residence, n (%)	2686 (83)	1973 (86)	713 (77)	<.0001
Cigarette use, n (%)				<.0001
Never	1020 (32)	786 (34)	234 (25)	
Current	1230 (38)	820 (36)	410 (44)	
Former	980 (30)	701 (30)	279 (30)	
Current alcohol use, n (%)				<.0001
None	1735 (54)	1339 (58)	396 (43)	
1–7 drinks/wk	1200 (37)	807 (35)	393 (43)	
>7 drinks/wk	280 (9)	147 (6)	133 (14)	
Marijuana use, n (%)				<.0001
Never	985 (31)	782 (34)	203 (22)	
Current	677 (21)	450 (20)	227 (25)	
Former	1551 (48)	1059 (46)	492 (53)	
Crack/cocaine use, n (%)				<.0001
Never	2239 (70)	1669 (73)	570 (62)	
Current	218 (7)	133 (6)	85 (9)	
Former	758 (24)	491 (21)	267 (29)	

Table 1. **Continued**

Characteristics	Entire Cohort[a] (N = 3232)	HIV Positive (n = 2309)	HIV Negative (n = 923)	P[b]
Opioid use (heroin/methadone), n (%)	…	…	…	<.0001
Never	2822 (88)	2056 (90)	766 (83)	
Current	58 (2)	38 (2)	20 (2)	
Former	335 (10)	199 (9)	136 (15)	
Injection drug use, n (%)		…	…	.4479
Never	2622 (82)	1866 (81)	756 (82)	
Current	29 (1)	18 (1)	11 (1)	
Former	563 (18)	408 (18)	155 (17)	
Noninjection drug use, n (%)		…	…	<.0001
Never	820 (26)	659 (29)	161 (17)	
Current	796 (25)	525 (23)	271 (29)	
Former	1597 (50)	1107 (48)	490 (53)	
Chronic HBV, n (%)	66 (2)	56 (2)	10 (1)	.0148
Chronic HCV, n (%)	393 (12)	306 (13)	87 (9)	.0026
CD4 count, cells/mm^3	…	615 (400–855)	…	
CD4 nadir, cells/mm^3	…	280 (160–414)	…	
HIV viral load, n (%)	…	…	…	
Suppressed[d]	…	1773 (81)	…	
200–999 copies/mL	…	106 (5)	…	
≥1000 copies/mL	…	311 (14)	…	
Proportion visits HIV suppressed,[d] %	…	…	…	
From baseline visit	…	69% (44–94%)	…	
On/after 2009	…	91% (60–100%)	…	
Year initiated cART, n (%)	…	…	…	
1995–1999	…	865 (37)	…	
2000–2003	…	305 (13)	…	
2004–2008	…	364 (16)	…	
≥2009	…	702 (30)	…	
Never initiated cART, n (%)	…	73 (3)	…	
Time since cART initiation, years	…	12.5 (7.0–17.1)	…	
Antiretroviral class,[e] n (%)	…	…	…	
PI	…	769 (33)	…	
NNRTI	…	591 (26)	…	
INSTI	…	746 (32)	…	
Other	…	24 (1)	…	
Not on therapy	…	179 (8)	…	
Specified NRTI,[f] n (%)	…	…	…	
ABC	…	479 (24)	…	
TDF	…	1156 (57)	…	
TAF	…	480 (24)	…	
Antiretroviral adherence, n (%)	…	…	…	
≥95%	…	1746 (82)	…	
<95%	…	381 (18)	…	

Data are presented as median (Q1–Q3) or n (%). Column percentages may not total 100 due to rounding.

Abbreviations: ABC, abacavir; BMI, body mass index; cART, combined antiretroviral therapy; CES-D, Center for Epidemiologic Studies–Depression; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SBP, systolic blood pressure; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; WIHS, Women's Interagency HIV Study.

[a]Data missing for the following: SBP (n = 169), DBP (n = 169), CES-D (n = 36), CD4 count (n = 81), CD4 nadir (n = 92), time since cART initiation (n = 75).
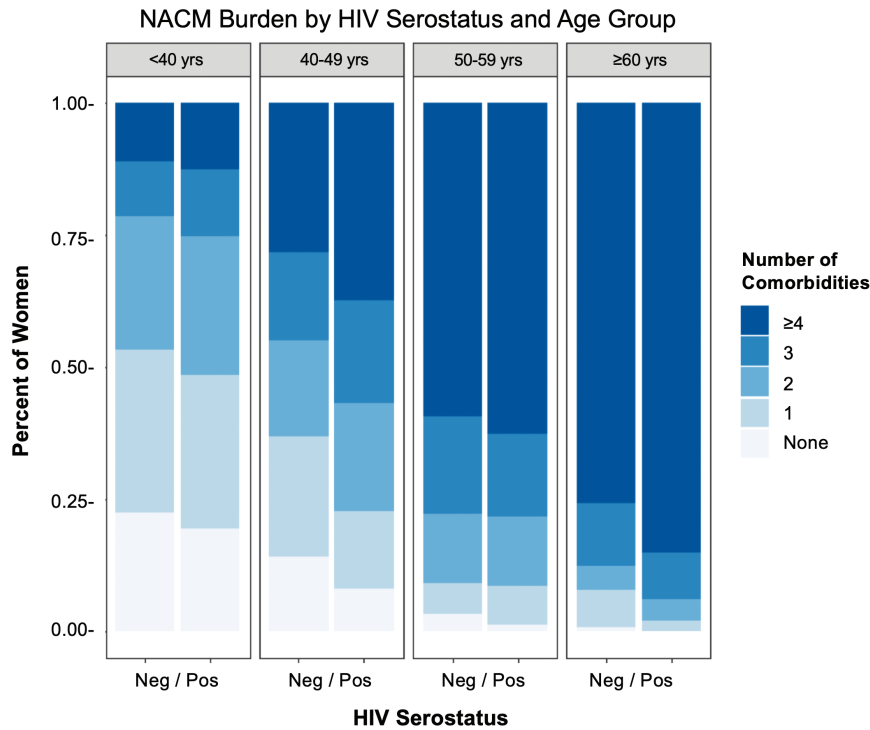
[b]χ^2 test performed for categorical variables and Wilcoxon rank-sum test for continuous variables.

[c]Range, 0–60; threshold for depressive symptoms, ≥16.

[d]HIV viral load <200 copies/mL and/or less than the lower limit of quantification of assay.

[e]Categorized hierarchically as PI > NNRTI > INSTI > other.

[f]Of those on any NRTI (n = 2033), not mutually exclusive.

Figure 1. Distribution of prevalent non-AIDS comorbidity burden by HIV serostatus and age group demonstrating that women living with HIV have a higher burden of comorbidities overall and specifically in age groups 40–49 and ≥60 years. Abbreviation: HIV, human immunodeficiency virus.

Factors significantly associated with NACM burden were HIV seropositivity, older age, white race, obesity, income $24 000 or lower, cigarette use, crack/cocaine use, and alcohol abstinence. For virologically suppressed WLWH, traditional comorbidity risk factors were more commonly associated with NACM burden than were HIV-related clinical indices. To our knowledge, this analysis is the first of its scale to comprehensively examine age-associated NACM prevalence and burden specifically in women. Given that more than 50% of the HIV population is female, and women have unique biological and sociobehavioral risk influencing comorbidity development, this work has broad implications for the clinical care of aging WLWH.

Table 2. Burden and Prevalence of Non-AIDS Comorbidities in Women Stratified by Human Immunodeficiency Virus Serostatus and Age Group

|	HIV Positive				HIV Negative				HIV × Age Interaction, P^b
NACM	<40 Years (n = 315)	40–49 Years (n = 711)	50–59 Years (n = 936)	≥60 Years[a] (n = 347)	<40 Years (n = 205)	40–49 Years (n = 285)	50–59 Years (n = 305)	≥60 Years[a] (n = 128)	
Hypertension	99 (31)	413 (58)	698 (75)	322 (93)	77 (38)	146 (51)	246 (81)	119 (93)	.0169
Psychiatric illness	122 (39)	385 (54)	574 (61)	231 (67)	65 (32)	120 (42)	187 (61)	73 (57)	.0816
Lung disease	91 (29)	249 (35)	442 (47)	172 (50)	68 (33)	103 (36)	157 (51)	64 (50)	.8503
Liver disease	76 (24)	239 (34)	482 (52)	233 (67)	21 (10)	63 (22)	94 (31)	59 (46)	.4073
Dyslipidemia	54 (17)	244 (34)	413 (44)	215 (62)	32 (16)	64 (22)	150 (49)	73 (57)	.0023
Bone disease	41 (13)	208 (29)	447 (48)	233 (67)	30 (15)	72 (25)	126 (41)	73 (57)	.3940
Diabetes mellitus, type 2	23 (7)	113 (16)	244 (26)	122 (35)	17 (8)	48 (17)	105 (34)	55 (43)	.5365
Cardiovascular disease	15 (5)	89 (13)	210 (22)	124 (36)	12 (6)	37 (13)	84 (28)	45 (35)	.6543
Chronic kidney disease	7 (2)	37 (5)	160 (17)	145 (42)	0 (0)	2 (<1)	26 (9)	33 (26)	.3004
Cancer, non-AIDS	8 (3)	64 (9)	119 (13)	60 (17)	7 (3)	11 (4)	32 (10)	18 (14)	.1914
Mean (SD) NACM burden	1.7 (1.4)	2.9 (1.8)	4.0 (2.0)	5.4 (1.9)	1.6 (1.4)	2.3 (1.8)	4.0 (2.0)	4.8 (2.0)	.0206

Data are presented as n (%) unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; NACM, non-AIDS comorbidity.

[a]Wilcoxon test performed for linear trend across (ordinal) age groups for categorical variables (ie, prevalence of each comorbidity) and unadjusted linear regression performed for continuous variables (ie, NACM burden) stratified by HIV serostatus: all P values were < .0001 for each prevalent comorbidity and NACM burden within each strata of HIV serostatus.

[b]Partially adjusted logistic regression performed for the prevalence of each comorbidity and partially adjusted linear regression for NACM burden with HIV serostatus, categorized age, and HIV × age interaction terms in the model.

Estimated Number of NACM by Age Group and HIV Serostatus,
Adjusted for Clinical and Demographic Factors

HIV Serostatus
- Negative
- Positive
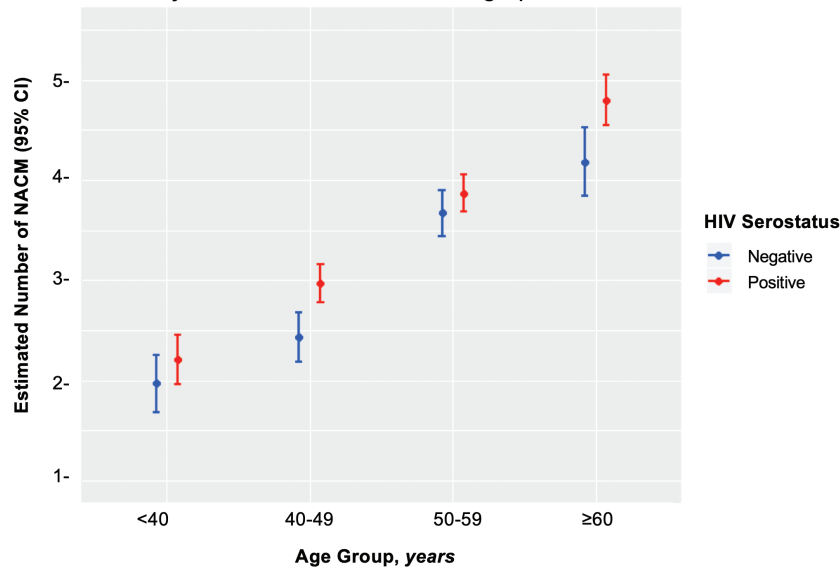
Estimated Number of NACM (95% CI)				
	<40 years	40-49 years	50-59 years	≥60 years
HIV+ women	2.21 (1.96-2.46)	2.97 (2.78-3.15)	3.87 (3.69-4.05)	4.80 (4.55-5.05)
HIV- women	1.97 (1.68-2.26)	2.44 (2.19-2.68)	3.67 (3.44-3.90)	4.19 (3.85-4.52)
P value (HIV+ vs HIV-)	0.1420	<0.0001	0.0888	0.0009

Figure 2. Estimated number of non-AIDS comorbidities by HIV serostatus and age group, adjusted for HIV serostatus, categorized age, HIV × age interaction, in addition to the following demographic and clinical factors: race, BMI, education, income, marital status, own residence, and substance use (eg, cigarettes, crack/cocaine and alcohol). Abbreviations: BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; NACM, non-AIDS comorbidities.

Our findings are consistent with several large cohorts of aging PLWH in developed countries reporting a high burden of NACM [3, 5, 10, 15]. Female representation in these studies ranged from 13% to 21%, the majority of participants were men who have sex with men, and the types and number of comorbidities evaluated varied. Considering these differences, we found a comparatively higher burden of NACM among virologically suppressed WLWH in the United States. For example, Palella et al [5] reported the mean number of 11 NACMs assessed in PLWH (19% female) aged 18–40, 41–50, 51–60, and 61 years or older as 1.4, 2.1, 3.0, and 3.9, respectively, compared with a mean NACM burden of 1.7, 2.9, 4.0, and 5.4 in similarly age-categorized WLWH in our analysis, respectively. Evaluation of 13 age-associated comorbidities among British Columbian women found a greater risk of NACMs in 267 WLWH compared with 276 HIV-seronegative women (incidence rate ratio, 1.58; 95% CI, 1.38–1.81) [19]. Although the median number of NACMs in WLWH was lower than what we observed (2 [interquartile range, 1–4] vs 3 [quartile 1–quartile 3, 2–5], respectively), this group similarly reported a significant interaction between HIV serostatus and age.

In our cross-sectional analysis, NACM burden was higher among WLWH compared with HIV-seronegative women in every age group and significantly so in those aged 40–49 and 60 years or older. We demonstrated that HIV infection significantly modified the effect of age on NACM burden, although this was attenuated when adjusting for covariates. Epidemiologic data suggest that PLWH are at risk of earlier accrual of NACM than their seronegative counterparts, with NACM diagnosed up to a decade earlier in PLWH [9, 10, 19]. Discrepancy in NACM prevalence between PLWH and the general population may even precede the diagnosis of HIV [10], suggesting that non-HIV risk factors may play an important role in the premature onset of age-associated comorbidities. Longitudinal analyses are needed to better understand if age has a greater effect on NACMs in WLWH than in HIV-seronegative women.

Our adjusted analyses of WLWH revealed "traditional" comorbidity risk factors were more commonly associated with multimorbidity than HIV-related clinical indices. The association of low income, cigarette use, and obesity with NACM risk has been previously demonstrated in WLWH [19]. In our analysis, the estimated mean NACM burden was higher in WLWH of white race compared with WLWH of minority races. This finding may represent differences in unmeasured factors such as race-mediated disparities in access to care that may have affected NACM identification [20]. We did not find a relationship between NACM burden and measures of CD4 count, HIV virologic suppression, or cART exposure other than recent abacavir use. This could reflect preferred use of abacavir over tenofovir disoproxil

Table 3. Multivariable Analysis of Risk Factors at End of Observation Associated With the Burden of Non-AIDS Comorbidities in Women Living With or at Risk for Human Immunodeficiency Virus Infection

Risk Factor	Estimated Mean Number of NACMs (95% CI)	B (±SE)	P[a]
HIV serostatus[b]			<.0001
Positive	3.46 (3.30, 3.63)	0.40 (±0.08)	
Negative	3.07 (2.89, 3.24)	Ref	
Age group[b]			<.0001
≥60 y	4.49 (4.25, 4.73)	2.40 (±0.14)	
50–59 y	3.77 (3.60, 3.94)	1.68 (±0.11)	
40–49 y	2.70 (2.52, 2.88)	0.61 (±0.10)	
<40 y	2.09 (1.88, 2.30)	Ref	
Race			<.0001
Non-Hispanic AA	3.09 (2.95, 3.22)	−0.40 (±0.11)	
Hispanic	3.00 (2.81, 3.18)	−0.50 (±0.12)	
Other non-Hispanic	3.48 (3.13, 3.83)	−0.02 (±0.20)	
White	3.49 (3.27, 3.72)	Ref	
Body mass index			<.0001
≥30 kg/m^2	3.51 (3.34, 3.67)	0.48 (±0.06)	
<30 kg/m^2	3.02 (2.86, 3.18)	Ref	
Education			.3517
≤High school	3.23 (3.07, 3.39)	−0.07 (±0.07)	
>High school	3.30 (3.12, 3.47)	Ref	
Income			<.0001
<$12 000	3.63 (3.46, 3.79)	0.84 (±0.08)	
$12 001–$24 000	3.38 (3.19, 3.57)	0.59 (±0.09)	
>$24 000	2.79 (2.60, 2.97)	Ref	
Marital status			.1108
Had a partner	3.35 (3.17, 3.53)	0.09 (±0.09)	
Never partner/other	3.18 (3.01, 3.36)	−0.07 (±0.08)	
Married/partner	3.26 (3.08, 3.44)	Ref	
Own residence			.2937
No	3.22 (3.02, 3.41)	−0.09 (±0.09)	
Yes	3.31 (3.16, 3.46)	Ref	
Cigarette use			<.0001
Current	3.61 (3.45, 3.78)	0.77 (±0.08)	
Former	3.33 (3.15, 3.51)	0.48 (±0.08)	
Never	2.85 (2.66, 3.04)	Ref	
Current alcohol use			.0467
>7 drinks/wk	3.15 (2.91, 3.39)	−0.24 (±0.12)	
1–7 drinks/wk	3.26 (3.09, 3.42)	−0.13 (±0.07)	
None	3.39 (3.22, 3.56)	Ref	
Crack/cocaine use			<.0001
Current	3.30 (3.04, 3.56)	0.24 (±0.13)	
Former	3.43 (3.25, 3.62)	0.38 (±0.08)	
Never	3.06 (2.91, 3.21)	Ref	

Abbreviations: AA, African American; HIV, human immunodeficiency virus; NACM, non-AIDS comorbidity; Ref, reference; WIHS, Women's Interagency HIV Study.

[a]Adjusted linear regression with all covariates listed included in the model plus WIHS enrollment wave; assessing HIV × age interaction: $P = .0978$.

[b]Adjusted for HIV serostatus × age interaction.
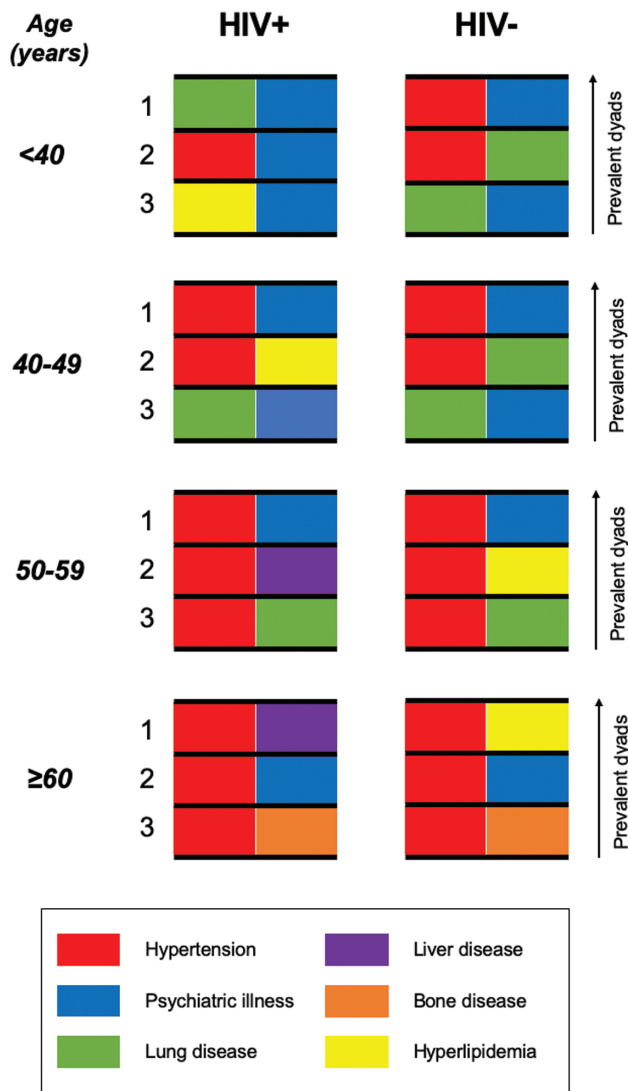
Figure 3. The 3 most common co-occurring non-AIDS comorbidity dyads in women living with or at risk for HIV infection, stratified by HIV serostatus and age group and ranked as most prevalent (1), second most prevalent (2), and third most prevalent (3) by each HIV × age stratum. The dyad of hypertension–psychiatric illness is represented in each stratification of HIV serostatus and age. Abbreviation: HIV, human immunodeficiency virus.

fumarate (prior to the advent of tenofovir alafenamide) in PLWH with certain comorbidities [21, 22]. A recent examination of traditional and HIV-related factors contributing to several comorbidity outcomes found a substantial proportion of NACMs could be prevented by interventions addressing smoking, elevated cholesterol, and hypertension [23]. These findings, corroborated by other large cohorts of virologically suppressed PLWH [5, 10, 24, 25], highlight the need for clinical strategies to screen, prevent, and/or intervene on traditional comorbidity risk factors to mitigate NACM development in aging WLWH.

Of the 10 NACMs evaluated, the most common in the WIHS included hypertension, psychiatric illness, dyslipidemia, and liver and lung disease, with most NACMs significantly more

prevalent in WLWH compared with HIV-seronegative women. The individual NACM prevalence ranging between 10% and 66% is modestly higher than that described among other cohorts of PLWH including WLWH [5, 15, 19], although similar to our data, the most commonly occurring NACMs include hypertension, dyslipidemia, psychiatric illness, and liver disease [3–5, 19]. Observed differences by HIV serostatus in the prevalence of certain NACMs are likely driven by the complex interplay of overrepresentation of mental health, including substance-use disorders in PLWH compared with the general population [26, 27]; higher prevalence of viral hepatitis coinfection; virally and cART-mediated effects on lipids, kidney, and bone health [28–30]; and the poorly understood relationship between HIV and oncogenesis [31].

Recent studies suggest that comorbidities in PLWH occur in nonrandom patterns [24, 25, 32]. Understanding NACM co-occurrence is therefore important for addressing shared risk factors in the era of increasing multimorbidity among PLWH [4, 15]. In WIHS women of all ages, we found the most common co-occurring NACM dyad was hypertension–psychiatric illness. Depression is more common in women than men [33] and has been shown to increase the risk of hypertension in women and be strongly associated with fatal cardiovascular disease [34]. In turn, hypertension may lead to incident depression and is frequently comorbid with diabetes, dyslipidemia, and CKD, both in the general population and in PLWH [15, 32, 35, 36]. It is paramount to aggressively screen for and manage hypertension and depression in WLWH as the cumulative burden of depression is linked not only to limited antiretroviral adherence but also to all-cause mortality [37, 38].

We dedicated our analysis to women as they represent a vital yet historically understudied constituency of the aging HIV population [13]. Recently published sex-stratified data demonstrated a higher NACM burden in WLWH than in men living with HIV (median, 3.9 vs 3.4, respectively; *P* < .05) [5]. This is consistent with prior reports of higher risk of cardiovascular and cerebrovascular events in PLWH, compared with HIV-seronegative individuals, which is amplified in women compared with men [16, 17]. The role of biological sex on the development of age-associated comorbidities warrants further study, especially considering numerous potential mechanistic differences (eg, anatomy, genetics, sex hormones, immunology, microbiome, response to cART, behaviors, and access to care) [14]. Further investigation characterizing sex differences in NACM prevalence and burden could serve to inform sex-tailored clinical guidance on comorbidity screening and management among PLWH.

Our study compared NACMs in WLWH with demographically similar HIV-seronegative women recruited in the WIHS based on sociobehavioral characteristics associated with risk of HIV acquisition [18]. In our study, HIV-seronegative women had significantly higher BMI, blood pressure, and substance use compared with WLWH. It is well established that these characteristics predispose to age-related comorbidities [39]. Therefore, it is possible that the observed differences in NACM burden by HIV serostatus may be even greater if WLWH were compared with HIV-seronegative women from a more generalized population. The US-based Health and Retirement Study assessed multimorbidity (≥2 age-associated health conditions of 8 measured) in 5355 participants (55% women; mean age, 68 years) [33]. In their study, 62% of women reported multimorbidity, compared with 98% of WLWH and 92% of HIV-seronegative women in the WIHS aged 60 years or older. Similarly, in the Australian Longitudinal Study on Women's Health [40], while 46% of more than 10 000 women aged 45–50 years reported 2 or more chronic comorbidities of 18 assessed, WIHS participants aged 40–49 years reported 2 or more NACMs among 75% of WLWH and 62% of HIV-seronegative women.

We acknowledge several additional limitations. Several diagnoses relied on self-report, which likely underestimated NACM prevalence and burden. Results of pathology and/or imaging modalities to supplement NACM definitions were not available. Given the chronic nature of HIV infection requiring routine medical visits, differences in self-reported NACM diagnoses or treatment could differ by HIV serostatus due to possible ascertainment bias. This may be counterbalanced by the overall poor health status of HIV-seronegative women in WIHS, when compared with a more generalized female population, which could have underestimated the effect of HIV serostatus on NACM burden. Women were included in our analysis from 4 different WIHS recruitment waves, each with varying enrollment criteria in terms of age, cART use, geography, etc; therefore, we adjusted for enrollment wave in multivariable analyses. Given the scope of our study, we were limited in assessing the contribution of specific cART types on individual NACMs, especially considering the possibility of switches over time and nonadherence. Last, since this study focused on prevalent NACMs, we did not evaluate the role of menopause status or timing.

In conclusion, WLWH living in the United States experienced a high overall burden of age-associated NACMs compared with HIV-seronegative counterparts. Human immunodeficiency virus appears to modify the effect of aging on comorbidity burden in women, although longitudinal studies examining the interaction of HIV and age on NACM accrual are needed. Our understanding of how women and men age with HIV is evolving, although dedicated characterization of respective unique biological and sociobehavioral profiles contributing to comorbidity risk is needed. Our study highlights the significant association between non-HIV traditional risk factors and multimorbidity in WLWH. Clinical care guidelines may consider additional emphasis on screening and intervention of social determinants of health and modifiable lifestyle factors to mitigate comorbidity risk in aging WLWH, including

those aged less than 50 years, in whom NACM burden is already higher than in their HIV-seronegative counterparts.

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