Incident Non-AIDS Comorbidity Burden Among Women With or at Risk for Human Immunodeficiency Virus in the United States

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Background. Human immunodeficiency virus (HIV) infection may accelerate development of aging-related non-AIDS comorbidities (NACMs). The incidence of NACMs is poorly characterized among women living with HIV (WLWH).

Methods. WLWH and HIV-seronegative participants followed in the Women's Interagency HIV Study (WIHS) through 2009 (when >80% of WLWH used antiretroviral therapy) or onward were included, with outcomes measured through 31 March 2018. Sociodemographics, clinical covariates, and prevalent NACM were determined at enrollment. We used Poisson regression models to determine incident NACM burden (number of NACMs accrued through most recent WIHS visit out of 10 total NACMs assessed) by HIV serostatus and age.

Results. There were 3129 participants (2239 WLWH, 890 HIV seronegative) with 36 589 person-years of follow-up. At enrollment, median age was 37 years, 65% were black, and 47% currently smoked. In fully adjusted analyses, WLWH had a higher incident NACM rate compared with HIV-seronegative women (incidence rate ratio, 1.36 [95% confidence interval (CI), 1.02–1.81]). Incident NACM burden was higher among WLWH vs HIV-seronegative women in most age strata (HIV × age interaction: P = .0438), and women <25 years old had the greatest incidence rate ratio by HIV serostatus at 1.48 (95% CI, 1.19–1.84) compared with those in older age groups. Incident NACM burden was associated with traditional comorbidity risk factors but not HIV-specific indices.

Conclusions. Incident NACM burden was higher among WLWH than HIV-seronegative women. This difference was most dramatic among women aged <25 years, a group for whom routine comorbidity screening is not prioritized. Established non-HIV comorbidity risk factors were significantly associated with incident NACM burden. More data are needed to inform best practices for NACM screening, prevention, and management among WLWH, particularly young women.

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

Due to combination antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection has become a chronic condition for individuals with access to care [1]. Along with increased longevity, persons living with HIV (PLWH) experience a high burden of age-related non-AIDS comorbidities (NACMs) [2–6]. Compared with persons without HIV, NACMs occur disproportionately and prematurely among PLWH [7–9].

Multimorbidity is costly not only to the individual aging with HIV (ie, affected quality of life) [10], but to the healthcare system, leading to higher resource utilization and direct medical costs (ie, $300–$5000 more per patient month for PLWH with comorbidities than for those without) [11].

NACM risk appears to be greater among women living with HIV (WLWH) than men [5, 12, 13]. Biologic and sociobehavioral sex differences have been implicated in HIV acquisition, pathogenesis, reservoir establishment, responses to ART, and curative interventions, and while likely to influence comorbidity development, this remains poorly characterized [14]. Marcus et al demonstrated that NACM occurred 16 years earlier among insured PLWH than HIV-negative matched controls [9]. Differences by sex were found when examining overall and comorbidity-free life expectancy; however, female

representation was inadequate (12.3%) [9], as is frequently the case in research involving PLWH [14, 15]. To better understand the role of biologic sex and associated factors in premature NACM accrual among PLWH, comorbidity study, specifically among women, is crucial and has the potential to improve clinical outcomes [16].

We recently evaluated the prevalence of 10 NACMs among >3000 participants in the Women's Interagency HIV Study (WIHS), the largest prospective United States (US)–based cohort of WLWH and at-risk women without HIV [6]. Virologically suppressed WLWH had a higher mean NACM count than women without HIV overall, and among certain age groups. To understand the longitudinal effects of chronic HIV and age on NACMs among women, we performed a follow-up analysis of NACM incidence and associated factors among WIHS participants.

METHODS

The Women's Interagency HIV Study
The WIHS is a multicenter prospective US cohort established in 1993 to investigate the progression and sequelae of HIV infection among women. WLWH and at-risk women without HIV enrolled during 4 waves (1994–1995, 2001–2002, 2011–2012, 2013–2015) from 11 cities (Atlanta, Georgia; Birmingham, Alabama; Bronx, New York; Brooklyn, New York; Chapel Hill, North Carolina; Chicago, Illinois; Jackson, Mississippi; Los Angeles, California; San Francisco, California; Miami, Florida; Washington, District of Columbia). Women without HIV were recruited based on being at risk for HIV acquisition (eg, history of sexually transmitted infections, substance use) as previously described [17].

Study visits occurred at 6-month intervals and comprised standardized interviews, physical examinations, and biospecimen collection. Sociodemographics, clinical information including chronic comorbidities, medications, and health behaviors were assessed. Blood testing evaluated kidney and liver function, CD4 count, and HIV viral load. The WIHS protocol has been approved by each site's institutional review board, and all participants have provided informed consent.

Study Design
We performed a longitudinal assessment of WIHS participants from study enrollment through end of observation to measure incident NACMs and to evaluate the effects of HIV serostatus and age on NACMs over time. As previously described, women followed through 2009 (when >80% of WLWH used ART) or onward were included to focus on the development of age-related NACM in the era of highly effective ART [6]. For this analysis, participants were additionally required to have ≥2 study visits within 2 years of enrollment and ≥1 follow-up study visit after that period to define prevalent (disease present at baseline) and incident (disease occurrence after

baseline) NACMs, respectively (Supplementary Figure 1). Age, covariates, and prevalent NACMs were determined at the end of the 2-year baseline period. Incident NACMs were measured through the participant's last visit or 31 March 2018 if still enrolled.

Outcome Measures
The primary outcome was incident NACM burden, defined as the number of total NACMs per participant that developed over the course of observation. Ten NACMs were evaluated given their age association and significant contribution to morbidity and mortality in the general population and among PLWH: hypertension; dyslipidemia; cardiovascular disease (CVD); diabetes; chronic kidney disease (CKD); liver, bone, and lung disease; psychiatric illness; and non-AIDS cancer. NACMs were rigorously defined (Supplementary Table 1) using up to 3 data sources per comorbidity (self-reported diagnosis or medication use; clinical measurement; and/or laboratory evidence) [6]. For NACMs that may have existed intermittently over time (ie, CKD and depression), data from consecutive study visits were required [6]. NACMs were measured at baseline and at end of observation and were considered incident if present at the latter but not former time point.

Independent Variables
For analysis, age at baseline was categorized into 5-year increments from <25 to ≥55 years for all NACMs except for CKD and non-AIDS cancer, where age was collapsed into 10-year increments from <30 to ≥50 years because of the rarity of these conditions.

Statistical Analysis
We compared baseline demographic and clinical characteristics of women by HIV serostatus using χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. For each individual NACM, the number and percentage of incident cases, total length of follow-up time (in person-years [PY]), and raw incidence rate (calculated as number of cases/PY × 1000) was computed, both overall and stratified by HIV serostatus. For incident NACM burden, the total number of incident comorbidities, total length of follow-up time (in PY), and raw incidence rate (calculated as total number of comorbidities/PY) was computed, both overall and stratified by HIV serostatus.

For each individual NACM and incident NACM burden, separate Poisson regression models using robust variance estimation were used to generate model-based incidence rate ratios (IRRs) and corresponding 95% confidence intervals (CIs) for independent variables of interest from (1) unadjusted (contained only HIV serostatus) and (2) partially adjusted (additionally included categorized baseline age and HIV × age interaction) models. For the primary outcome of incident NACM burden, a fully adjusted model that controlled for

important covariates plus the partially adjusted model terms was utilized. Model-based mean estimates were exponentiated to get the estimated mean incidence rate and 95% CI for each level of the independent variable of interest. Pre-planned contrasts compared HIV serostatus within each age category in the full model. A separate multivariable full model including only WLWH assessed the effect of HIV-specific indices, adjusting for the same covariates, on incident NACM burden. Model fit was assessed through deviance/degrees of freedom goodness-of-fit test and residual plots.

Analyses used SAS version 9.4 software. Significance level was set at $\alpha = .05$.

RESULTS

Participant Characteristics at Baseline
There were 3129 participants (2239 WLWH, 890 women without HIV) included in the analysis (Supplementary Figure 1) with a total of 36 589 PY of follow-up. At baseline, median age was 37 years and 65% were black (Table 1). Compared with WLWH, women without HIV had significantly higher body mass index (BMI) ≥ 30 kg/m^2 (47% vs 40%, $P = .0008$) and current use of cigarettes (54% vs 44%), crack/cocaine (15% vs 10%), and alcohol (57% vs 47%) (all $P < .0001$). WLWH were significantly more likely to use antihypertensive medication (20% vs 16%, $P = .0118$) and to have prevalent chronic hepatitis C virus infection (12% vs 9%, $P = .0051$), hepatitis B virus infection (2% vs 1%, $P = .0216$), and worse kidney function (estimated glomerular filtration rate of 99.3 vs 101.5 mL/minute/1.73 m^2, $P = .0099$) than women without HIV (Table 1). Education level, annual household income, and median depressive symptom score did not significantly differ by HIV serostatus. At baseline, WLWH had a median CD4 count of 484 cells/μL, 69% were on ART, and 45% were virologically suppressed.

Prevalent and Incident NACM Burden
Figure 1 shows the distribution of women with prevalent NACMs at baseline and incident NACMs at the end of follow-up by HIV serostatus. Of 10 NACMs evaluated, mean NACM burden at baseline was higher among WLWH than women without HIV (1.4 vs 1.2, $P = .0063$), though only prevalent liver disease (26% vs 16%, $P < .0001$) and psychiatric illness (26% vs 21%, $P = .0028$) differed by HIV serostatus (Supplementary Table 2). The unadjusted incident NACM rate by HIV serostatus and age is shown in Supplementary Figure 2.

In partially adjusted models, incident NACM burden was greater in WLWH compared with women without HIV (0.19/PY vs 0.16/PY; IRR 1.21 [95% CI, 1.13–1.29]) (Table 2). The incidence was higher among WLWH than women without HIV for CKD (IRR, 3.14 [95% CI, 1.80–5.49]), liver disease (IRR, 2.56 [95% CI, 1.85–3.54]), psychiatric illness (IRR, 1.38 [95% CI, 1.02–1.86]), dyslipidemia (IRR 1.36 [95% CI, 1.14–1.62]),

and bone disease (IRR, 1.35 [95% CI, 1.14–1.58]). However, incident hypertension, diabetes, CVD, lung disease, and non-AIDS cancer did not differ significantly by HIV serostatus (Table 2). Supplementary Table 3 shows the incidence of individual NACM and incident NACM burden stratified by HIV serostatus and age (for incident burden, HIV × age interaction: $P = .0063$).

Fully Adjusted Incident NACM Burden by HIV and Age
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, baseline age group, and HIV × age), WLWH had a significantly higher incident NACM rate compared with women without HIV (IRR, 1.36 [95% CI, 1.02–1.81]). The incident NACM burden was significantly higher among WLWH compared with women without HIV in most age strata (Figure 2; HIV × age interaction: $P = .0438$). Women aged <25 years had the greatest IRR at 1.48 (95% CI, 1.19–1.84) vs those aged 25–29 (IRR, 1.31 [95% CI, 1.09–1.57]), 30–34 (IRR, 1.25 [95% CI, 1.09–1.43]), 35–39 (IRR, 1.12 [95% CI, 1.003–1.25]), 40–44 (IRR, 1.01 [95% CI, .90–1.14]), 45–49 (IRR, 1.28 [95% CI, 1.08–1.53]), 50–54 (IRR, 1.18 [95% CI, .95–1.46]), and ≥ 55 years (IRR, 1.36 [95% CI, 1.02–1.81]).

Factors Associated With Incident NACM Burden
In fully adjusted models controlling for the aforementioned baseline covariates, the estimated incident NACM rate was significantly associated with traditional comorbidity risk factors identified in the general population. We observed higher incident NACM rates among women of white race, who had a BMI ≥ 30 kg/m^2, household income <$24 000, did not have their own residence, and reported current use of cigarettes or crack/cocaine (Table 3). Education status and current alcohol use were not associated with incident NACM burden. In an adjusted model including only WLWH (controlling for the aforementioned covariates and HIV-specific indices), enrollment CD4 count, CD4 nadir, ART status, and viral load were not significantly associated with the estimated incident NACM rate (Supplementary Table 4).

DISCUSSION

In this large, multicenter US-based prospective observational cohort of women with and without HIV that included >36 000 PY of follow-up, we found that WLWH had a significantly higher burden of incident NACMs than at-risk women without HIV. The difference in incident NACM rates by HIV serostatus was greatest among young women and in particular those aged <25 years, a group for whom routine comorbidity screening recommendations are not prioritized [18, 19]. Traditional, but not HIV-specific, comorbidity risk factors were significantly

Table 1. Baseline Demographic and Clinical Data of Women Living With or at Risk for Human Immunodeficiency Virus (HIV) Infection at the Time of Enrollment in the Women's Interagency HIV Study[a]

Characteristic	Entire Cohort[b] (N = 3129)	HIV Positive (n = 2239)	HIV Negative (n = 890)	P Value[c]
Age, y, median (Q1–Q3)	37 (31–45)	38 (32–45)	36 (28–44)	<.0001
Age group, y				<.0001
<25	222 (7)	95 (4)	127 (14)	
25–29	390 (12)	263 (12)	127 (14)	
30–34	602 (19)	458 (20)	144 (16)	
35–39	625 (20)	463 (21)	162 (18)	
40–44	496 (16)	378 (17)	118 (13)	
45–49	343 (11)	259 (12)	84 (9)	
50–54	265 (8)	189 (8)	76 (9)	
≥55	186 (6)	134 (6)	52 (6)	
Follow-up time, y, median (Q1–Q3)	14.3 (3–17.2)	14.3 (3–17.4)	14.4 (3.2–16.7)	.8321
Race/ethnicity				.1110
White, non-Hispanic	346 (11)	264 (12)	82 (9)	
Black, non-Hispanic	2033 (65)	1438 (64)	595 (67)	
Hispanic	642 (21)	465 (21)	177 (20)	
Other	108 (3)	72 (3)	36 (4)	
WIHS enrollment wave				<.0001
1994–1995	1149 (37)	862 (39)	287 (32)	
2001–2002	858 (27)	554 (25)	304 (34)	
2011–2012	333 (11)	250 (11)	83 (9)	
2013–2015	789 (25)	573 (26)	216 (24)	
BMI, kg/m^2				.0008
<30	1779 (58)	1317 (60)	462 (53)	
≥30	1288 (42)	882 (40)	406 (47)	
SBP, mm Hg, median (Q1–Q3)	116 (107–127)	115 (107–127)	116 (108–128)	.0742
DBP, mm Hg, median (Q1–Q3)	74 (68–80)	74 (68–81)	73 (68–80)	.1379
Antihypertensive medication use	579 (19)	439 (20)	140 (16)	.0118
Lipid-lowering medication use	155 (5)	108 (5)	47 (5)	.5966
eGFR, mL/min/1.73 m^2 (CKD-EPI), median (Q1–Q3)	100 (85.4–117)	99.3 (84.2–116.4)	101.5 (87.6–118.8)	.0099
CES-D score[d], median (Q1–Q3)	12 (5–22)	12 (5–23)	12 (5–22)	.2353
Education				.1848
High school or less	2025 (65)	1466 (66)	559 (63)	
More than high school	1099 (35)	771 (34)	328 (37)	
Income				.7486
<$12 000	1748 (56)	1262 (57)	486 (55)	
$12 001–$24 000	764 (25)	544 (24)	220 (25)	
>$24 000	591 (19)	418 (19)	173 (20)	
Insured	2490 (81)	1928 (87)	562 (64)	<.0001
Marital status	1029 (33)	741 (33)	288 (32)	<.0001
Married/partner	803 (26)	617 (28)	186 (21)	
Had a partner	1296 (41)	881 (39)	415 (47)	
Never married/other				
Owner of residence	2293 (73)	1720 (77)	573 (64)	<.0001
Cigarette use				<.0001
Never	1077 (35)	814 (37)	263 (30)	
Current	1451 (47)	977 (44)	474 (54)	
Former	568 (18)	428 (19)	140 (16)	
Current alcohol use				<.0001
None	1535 (50)	1158 (52)	377 (43)	
1–7 drinks/wk	1202 (39)	843 (38)	359 (41)	
>7 drinks/wk	341 (11)	206 (9)	135 (16)	
Marijuana use				<.0001
Never	1049 (34)	826 (37)	223 (25)	
Current	690 (22)	433 (20)	257 (29)	
Former	1354 (44)	957 (43)	397 (45)	

Table 1. **Continued**

Characteristic	Entire Cohort[b] (N = 3129)	HIV Positive (n = 2239)	HIV Negative (n = 890)	P Value[c]
Crack/cocaine use				<.0001
Never	2412 (78)	1787 (81)	625 (71)	
Current	350 (11)	218 (10)	132 (15)	
Former	333 (11)	213 (10)	120 (14)	
Opioid use (heroin/methadone)				.0031
Never	2869 (93)	2078 (94)	791 (90)	
Current	112 (4)	71 (3)	41 (5)	
Former	114 (4)	69 (3)	45 (5)	
Injection drug use				.0862
Never	2548 (82)	1819 (82)	729 (83)	
Current	75 (2)	47 (2)	28 (3)	
Former	470 (15)	350 (16)	120 (14)	
Noninjection drug use				<.0001
Never	864 (28)	691 (31)	173 (20)	
Current	863 (28)	544 (25)	319 (36)	
Former	1366 (44)	981 (44)	385 (44)	
Chronic HBV	64 (2)	54 (2)	10 (1)	.0216
Chronic HCV	345 (11)	269 (12)	76 (9)	.0051
CD4 cell count, cells/µL, median (Q1–Q3)	…	484 (308–698)	…	
CD4 nadir, cells/µL, median (Q1–Q3)	…	280 (159–414)	…	
HIV viral load				
Suppressed[e]	…	971 (45)	…	
200–999 copies/mL	…	197 (9)	…	
≥1000 copies/mL	…	976 (46)	…	
ART status				
No therapy	…	709 (32)	…	
Mono/dual ART	…	421 (19)	…	
Combination ART	…	1109 (50)	…	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, combined antiretroviral therapy; BMI, body mass index; 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; HIV, human immunodeficiency virus; Q1, first quartile; Q3, third quartile; SBP, systolic blood pressure; WIHS, Women's Interagency HIV Study.

[a]Column percentages may not total 100 due to rounding.

[b]Data missing for BMI (n = 62), SBP (n = 2), DBP (n = 2), CES-D (n = 1), CD4 count (n = 82), and CD4 nadir (n = 82).

[c]χ^2 test performed for categorical variables and Wilcoxon rank-sum test for continuous variables.

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

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

associated with incident NACM burden among WLWH. These findings have broad-ranging implications for HIV care models and research priorities, and argue for additional study of NACM pathogenesis among WLWH specifically, and for sex-stratified comorbidity screening and prevention strategy development among PLWH to mitigate the elevated NACM risk in this population.

We previously showed in a cross-sectional analysis of the WIHS that the burden of prevalent NACM was significantly higher among WLWH than women without HIV overall and in certain age groups [6]. The current longitudinal study builds on those data by illustrating that women, regardless of HIV serostatus, began accruing comorbidities early in life (ie, as young as in their 20s), that incident NACM burden was higher among WLWH, and that the impact of living with HIV on comorbidity development may be most significant among young women. These findings substantiate that WLWH are susceptible to "premature" multimorbidity, as suggested by other male-predominant cohorts examining NACMs among PLWH [2, 3, 7], and that comorbidity risk assessment and intervention should optimally begin for women in their childbearing years.

The greatest difference in incident comorbidity burden by HIV serostatus occurred among women <25 years old. In comparison, among 39 000 PLWH and 387 785 HIV-negative adults insured through Kaiser Permanente, comorbidity-free life expectancy (assessed 2014–2016) at age 21 was 14.5 and 30.9 years, respectively [9]. Our data, among women specifically, revealed a difference in NACM incidence by HIV serostatus that commenced at least a decade earlier. This dramatic disparity in age at risk for comorbidity onset among the cohorts is likely due to differences in participant sociodemographics. While WIHS participants are predominantly urban women of color with a high

prevalence of obesity, substance use, and poverty [17], participants from other multisite cohorts examining multimorbidity among PLWH primarily comprise white men with stable access to care and higher income [2, 3, 9]. Additional studies are needed to investigate the interactions of sex, race, access to care, and other social determinants of health on mediating comorbidity development among PLWH [20].

Notably, women without HIV in our study also began accruing NACM as early as in their third decade of life. In a recent multicohort, multiethnic analysis of 32 833 participants (>50% female), women compared with men exhibited a significantly steeper increase in blood pressure trajectory that began as early as in their 20s and continued throughout their life [19]. It is possible that young women, regardless of HIV serostatus, may be particularly vulnerable to comorbidity incidence and progression [18, 19]. Along with female-specific biology, complex socioeconomic, environmental, and structural factors can affect physiology and coalesce to increase the risk of several comorbidities, and even premature mortality, among women compared with men [21].

Our data highlight the need to prioritize WLWH, particularly young women, for early NACM screening to identify those at highest risk of amassing comorbidities and to offer timely, targeted risk-modification interventions. Since PLWH experience multimorbidity at least a decade earlier than peers without HIV, age-anchored clinical guidance on comorbidity screening for the general adult population is inappropriate for use among PLWH. Such guidance misses the opportunity for early NACM detection among PLWH who may have decades of comorbidity-free life to preserve [10]. Furthermore, prior reports indicate that WLWH experience higher NACM burden and more severe disease than men [5, 12]; thus, sex attributes may differentially affect comorbidity onset and progression among PLWH compared with the general population. Primary care guidelines for PLWH [22] should consider more comprehensive and sex-stratified recommendations for comorbidity screening and prevention as data evolve on differential biologic risks and associated lifestyle factors driving NACM burden among WLWH vs men.

Current risk assessment tools developed in the general population, such as for CVD and bone fracture risk, underperform among PLWH [23, 24], thus failing to identify substantial numbers of WLWH who may benefit from earlier interventions to mitigate premature NACM onset. Novel comorbidity screening and prevention tools that take into account HIV- and female-specific pathogenic processes are needed [25] and should be integrated into comprehensive strategies focused on aggressive modification of traditional comorbidity risk factors as well as HIV disease control. Corroborating prior studies [6, 26], incident NACM burden among WLWH was associated with elevated BMI, current substance use, and certain sociodemographics, but not with HIV-related factors. This underscores the important contribution of social determinants of health in driving
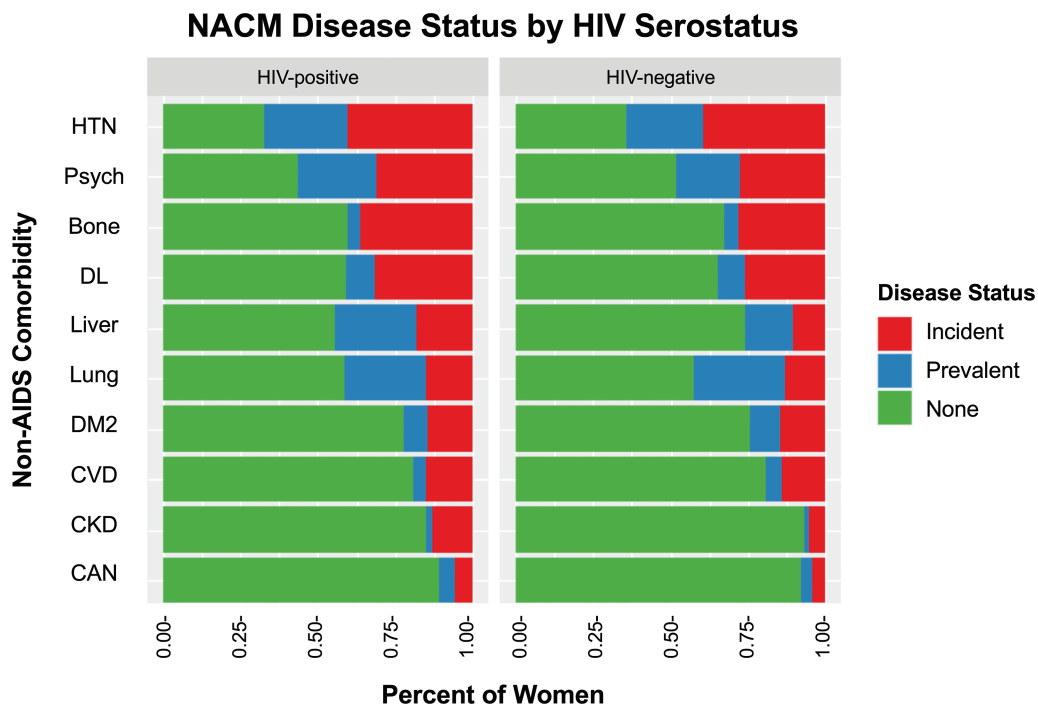

Figure 1. Distribution of women with prevalent (blue, disease present at baseline), incident (red, disease occurrence after baseline), or neither prevalent nor incident (green) non-AIDS comorbidities over the course of observation in the Women's Interagency HIV Study, stratified by human immunodeficiency virus serostatus. Abbreviations: Bone, bone disease; CAN, non-AIDS cancer; CKD, chronic kidney disease; CVD, cardiovascular disease; DL, dyslipidemia; DM2, type 2 diabetes mellitus; HIV, human immunodeficiency virus; HTN, hypertension; Liver, liver disease; Lung, lung disease; NACM, non-AIDS comorbidity; Psych, psychiatric illness.

Table 2. Incidence Rates of Non-AIDS Comorbidities in Women by Human Immunodeficiency Virus Serostatus

Comorbidity	Cases/Total Population (%), Person-Time, and Rate per 1000 PYs			Unadjusted IRR (95% CI)[a]	Partially Adjusted IRR (95% CI)[a]
	Total	HIV Positive	HIV Negative	HIV Positive vs HIV Negative	HIV Positive vs HIV Negative
Hypertension				1.07 (.95–1.22)	0.91 (.78–1.06)
Incident cases	1260/2314 (54)	909/1643 (55)	351/671 (53)		
Person-time, y	19 119	13 513	5606		
Incident rate	65.90	67.27	62.61		
Psychiatric illness				1.35 (1.16–1.57)	1.38 (1.02–1.86)
Incident cases	940/2372 (40)	694/1665 (42)	246/707 (35)		
Person-time, y	20 458	13 831	6626		
Incident rate	45.95	50.18	37.12		
Bone disease				1.37 (1.20–1.56)	1.35 (1.14–1.58)
Incident cases	1057/2986 (35)	807/2137 (38)	250/849 (29)		
Person-time, y	29 281	20 561	8720		
Incident rate	36.10	39.25	28.67		
Dyslipidemia				1.34 (1.17–1.54)	1.36 (1.14–1.62)
Incident cases	938/2840 (33)	707/2030 (35)	231/810 (29)		
Person-time, y	27 703	19 253	8450		
Incident rate	33.86	36.72	27.34		
Liver disease				2.48 (1.98–3.11)	2.56 (1.85–3.54)
Incident cases	498/2399 (21)	406/1647 (25)	92/752 (12)		
Person-time, y	22 294	14 274	8020		
Incident rate	22.34	28.44	11.47		
Lung disease				1.15 (.93–1.42)	1.03 (.77–1.38)
Incident cases	461/2288 (20)	343/1658 (21)	118/630 (19)		
Person-time, y	23 199	16 627	6572		
Incident rate	19.87	20.63	17.96		
Type 2 diabetes mellitus				0.97 (.79–1.19)	1.06 (.80–1.41)
Incident cases	460/2877 (16)	328/2072 (16)	132/805 (16)		
Person-time, y	30 704	22 069	8635		
Incident rate	14.98	14.86	15.29		
Cardiovascular disease				1.07 (.88–1.31)	1.06 (.83–1.36)
Incident cases	467/2995 (16)	340/2149 (16)	127/846 (15)		
Person-time, y	32 691	23 342	9349		
Incident rate	14.29	14.57	13.58		
Chronic kidney disease				2.56 (1.89–3.46)	3.14 (1.80–5.49)[b]
Incident cases	333/3063 (11)	286/2185 (13)	47/878 (5)		
Person-time, y	34 108	24 019	10 089		
Incident rate	9.76	11.91	4.66		
Cancer, non-AIDS				1.51 (1.05–2.17)	1.39 (.89–2.18)[b]
Incident cases	167/2983 (6)	131/2125 (6)	36/858 (4)		
Person-time, y	33 698	23 821	9877		
Incident rate	4.96	5.50	3.65		
Incident NACM burden/ PY				1.22 (1.15–1.29)	1.21 (1.13–1.29)
Incident count	6581	4951	1630		
Person-time, y	36 589	26 131	10 458		
Incident rate	0.1799	0.1895	0.1559		

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IRR, incidence rate ratio; NACM, non-AIDS comorbidity; PY, person-years.

[a]Poisson regression analysis performed using robust variance estimation to generate IRRs of each NACM and incident NACM burden using unadjusted (HIV serostatus) or partially adjusted (HIV serostatus, baseline age group, HIV × age interaction) models.

[b]Age at baseline was categorized into 5-year increments from <25 to ≥55 years for all NACMs except for chronic kidney disease and non-AIDS cancer, which were rare occurrences and thus age-collapsed into 10-year increments from <30 to ≥50 years.

comorbidity burden among WLWH, as also found for women without HIV, and argues for increased attention and resources dedicated to improving women's health systematically, especially for those from high-risk communities [27].

The early occurrence of multimorbidity among WLWH is likely multifactorial, related to a higher prevalence of traditional comorbidity risk factors and viral coinfections compared with the general population, the type and duration of ART exposure,
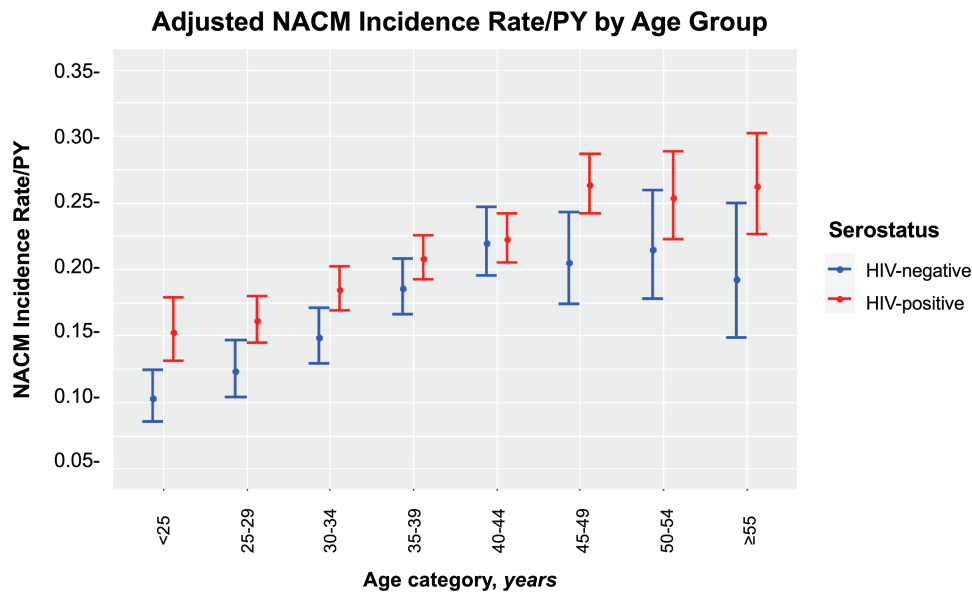
Adjusted NACM Incidence Rate/PY by Age Group

Figure 2. Incident non-AIDS comorbidity (NACM) burden per person-year (PY) by human immunodeficiency virus (HIV) serostatus and baseline age in 5-year increments. In addition to HIV serostatus, baseline age group, and HIV × age interaction, the adjusted model included the following characteristics assessed during the enrollment period: race, body mass index, household income, residence, marital status, education, smoking history, current alcohol use, history of crack/cocaine use, enrollment wave in the Women's Interagency HIV Study.

and HIV-associated chronic inflammation and immune activation hastening the natural aging process [11]. Elevations in inflammatory biomarkers (ie, high-sensitivity C-reactive protein, interleukin 6, D-dimer) have been associated with NACM events and all-cause mortality among PLWH on suppressive ART [28, 29]. While only 45% of WLWH in this analysis were virologically suppressed at baseline, the vast majority (>80%) were suppressed by end of observation. Measures of longitudinal HIV viremia have been associated with incident myocardial infarction and mortality among male-predominant cohorts of PLWH [30, 31]. However, the effect of cumulative viremia on incident comorbidity burden and its relationship to chronic inflammation and immune activation warrants additional investigation.

Female-specific anatomic, chromosomal, immunologic, hormonal, and lifestyle factors likely interplay in a complex fashion to expedite aging and comorbidity incidence among WLWH [14, 32]. "Immunoaging," the natural waning of immunity occurring with advanced age, is accelerated by HIV [33]. Among PLWH, despite ART-induced virologic suppression, immunoaging is attributed to persistent systemic inflammation as well as ongoing T-cell activation (from residual HIV replication, chronic viral coinfections, and translocated gut microbial products) and is associated with dysfunctional immunometabolism, dysregulated coagulation, and inflammatory vasculopathy [34–36]. Such mechanisms have been implicated in contributing to early NACM accrual among PLWH, which may be exacerbated by estrogen insufficiency among WLWH [32]. A hallmark of natural aging in women,

hypoestrogenism leads to a proinflammatory state, thereby compounding the systemic inflammation of chronic HIV [32, 37]. While premenopausal status in the general population is protective against the development of several NACMs (eg, CVD and osteoporosis) [38, 39], this biologic benefit may be attenuated among WLWH who may experience menopause earlier and more severely [40].

This study warrants mention of limitations. First, some of the NACMs relied on self-report due to lack of available objective measures for confirmation, such as tissue pathology or imaging results [6]. This could have resulted in underestimation of incident NACM burden. Second, given the study objective to describe NACM accumulation over the life course of women, time-varying factors, such as the onset of menopause or obesity, were not evaluated. Third, we were not able to assess the longitudinal effects of using different antiretroviral classes, considering the effects of ART switching and nonadherence. Finally, nor were we able to describe the relationship between time-updated HIV viremia and incident NACM given the scope of this analysis.

In conclusion, this study is the first of its scale to comprehensively examine incident age-stratified comorbidity burden, and associated risk factors, among WLWH and at-risk women without HIV. The rate of NACM accrual was high for all women, though higher for WLWH, and associated with traditional comorbidity risk factors including social determinants of health. Strikingly, comorbidity incidence among women began in the third decade of life, suggesting high susceptibility to "premature aging" and supporting the need for earlier, more aggressive

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

Risk Factor	Estimated Incident NACM Rate (95% CI)	IRR (95% CI)	*P* Value[a]
HIV serostatus[b]			
Positive	0.21 (.20–.22)	1.36 (1.02–1.81)	<.0001
Negative	0.17 (.16–.18)	Ref	
Age group, y[b]			
≥55	0.22 (.19–.26)	1.71 (1.41–2.09)	<.0001
50–54	0.23 (.21–.26)	1.66 (1.38–2.00)	
45–49	0.23 (.21–.26)	1.72 (1.47–2.02)	
40–44	0.22 (.20–.24)	1.46 (1.25–1.70)	
35–39	0.20 (.18–.21)	1.36 (1.17–1.58)	
30–34	0.17 (.15–.18)	1.21 (1.04–1.41)	
25–29	0.14 (.13–.16)	1.06 (.90–1.25)	
<25	0.13 (.11–.14)	Ref	
BMI, kg/m^2			
≥30	0.20 (.19–.22)	1.15 (1.09–1.21)	<.0001
<30	0.18 (.16–.19)	Ref	
Race			
Non-Hispanic black	0.17 (.16–.18)	0.83 (.78–.89)	<.0001
Hispanic	0.19 (.17–.20)	0.89 (.83–.97)	
Other non-Hispanic	0.19 (.16–.22)	0.91 (.78–1.05)	
White	0.21 (.19–.22)	Ref	
Education			
High school or less	0.19 (.18–.20)	1.01 (.96–1.07)	.6504
More than high school	0.19 (.17–.20)	Ref	
Income			
<$12 000	0.20 (.19–.22)	1.12 (1.05–1.20)	.0002
$12 001–$24 000	0.18 (.17–.20)	1.02 (.95–1.10)	
>$24 000	0.18 (.17–.19)	Ref	
Marital status			
Had a partner	0.19 (.18–.20)	1.01 (.96–1.08)	.1680
Never partner/other	0.18 (.17–.20)	0.96 (.91–1.01)	
Married/partner	0.19 (.17–.20)	Ref	
Own residence			
No	0.20 (.18–.21)	1.08 (1.02–1.14)	.0067
Yes	0.18 (.17–.19)	Ref	
Cigarette use			
Current	0.21 (.19–.22)	1.19 (1.12–1.27)	<.0001
Former	0.19 (.17–.20)	1.09 (1.02–1.17)	
Never	0.17 (.16–.19)	Ref	
Current alcohol use			
>7 drinks/wk	0.19 (.17–.20)	0.96 (.88–1.04)	.1457
1–7 drinks/wk	0.18 (.17–.20)	0.95 (.90–1.00)	
None	0.19 (.18–.21)	Ref	
Crack/cocaine use			
Current	0.20 (.18–.21)	1.10 (1.02–1.19)	.0310
Former	0.19 (.17–.21)	1.06 (.99–1.14)	
Never	0.18 (.17–.19)	Ref	

Abbreviations: BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; IRR, incidence rate ratio; NACM, non-AIDS comorbidity; Ref, reference value.

[a]Adjusted linear regression with all covariates listed included in the model plus Women's Interagency HIV Study enrollment wave and HIV × age interaction (*P* = .0438 for the interaction term).

[b]Adjusted for HIV serostatus × age interaction.

NACM risk assessment and interventions for young WLWH and at-risk women that could be integrated into a broader women's health agenda during reproductive age. Implementation science, including innovative HIV- and female-specific clinical risk assessment and risk-reducing tools, tailored to the needs of young WLWH, will be paramount to address the synergy of HIV and premature multimorbidity, fueled by underlying social determinants, in this high-risk population.

References

1. Marcus JL, Chao CR, Leyden WA, et al. Narrowing the gap in life expectancy between HIV-infected and HIV-uninfected individuals with access to care. J Acquir Immune Defic Syndr **2016**; 73:39–46.
2. Gallant J, Hsue PY, Shreay S, Meyer N. Comorbidities among US patients with prevalent HIV infection—a trend analysis. J Infect Dis **2017**; 216:1525–33.
3. Wong C, Gange SJ, Moore RD, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Multimorbidity among persons living with human immunodeficiency virus in the United States. Clin Infect Dis **2018**; 66:1230–8.
4. Shiels MS, Islam JY, Rosenberg PS, Hall HI, Jacobson E, Engels EA. Projected cancer incidence rates and burden of incident cancer cases in HIV-infected adults in the United States through 2030. Ann Intern Med **2018**; 168:866–73.
5. Palella FJ, Hart R, Armon C, et al; HIV Outpatient Study (HOPS). Non-AIDS comorbidity burden differs by sex, race, and insurance type in aging adults in HIV care. AIDS **2019**; 33:2327–35.
6. Collins LF, Sheth AN, Christina Mehta C, et al. The prevalence and burden of non-AIDS comorbidities among women living with or at-risk for HIV infection in the United States. Clin Infect Dis **2020**; 72:1301–11.
7. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis **2011**; 53:1120–6.
8. Schouten J, Wit FW, Stolte IG, et al; AGEhIV Cohort Study Group. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis **2014**; 59:1787–97.
9. Marcus JL, Leyden WA, Alexeeff SE, et al. Comparison of overall and comorbidity-free life expectancy between insured adults with and without HIV infection, 2000-2016. JAMA Netw Open **2020**; 3:e207954.
10. Collins LF, Armstrong WS. What it means to age with HIV infection: years gained are not comorbidity free. JAMA Netw Open **2020**; 3:e208023.
11. Lerner AM, Eisinger RW, Fauci AS. Comorbidities in persons with HIV: the lingering challenge. JAMA **2019**; doi:10.1001/jama.2019.19775.
12. Chow FC, Regan S, Zanni MV, et al. Elevated ischemic stroke risk among women living with HIV infection. AIDS **2018**; 32:59–67.
13. Frazier EL, Sutton MY, Tie Y, Fagan J, Fanfair RN. Differences by sex in cardiovascular comorbid conditions among older adults (aged 50–64 or ≥65 years) receiving care for human immunodeficiency virus. Clin Infect Dis **2019**; 69:2091–100.
14. Scully EP. Sex differences in HIV infection. Curr HIV/AIDS Rep **2018**; 15:136–46.
15. Gandhi M, Smeaton LM, Vernon C, et al; Women's Health Inter-Network Scientific Committee (WHISC). Low rate of sex-specific analyses in presentations at the Conference on Retroviruses and Opportunistic Infections (CROI) meeting, 2018: room to improve. J Acquir Immune Defic Syndr **2019**; 81:e158–60.
16. Bartz D, Chitnis T, Kaiser UB, et al. Clinical advances in sex- and gender-informed medicine to improve the health of all: a review. JAMA Intern Med **2020**; 180:574–83.
17. Adimora AA, Ramirez C, Benning L, et al. Cohort profile: the Women's Interagency HIV Study (WIHS). Int J Epidemiol **2018**; 47:393–394i.
18. Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. Circulation **2019**; 139:1047–56.
19. Ji H, Kim A, Ebinger JE, et al. Sex differences in blood pressure trajectories over the life course. JAMA Cardiol **2020**; 5:19–26.
20. Silverstein M, Hsu HE, Bell A. Addressing social determinants to improve population health: the balance between clinical care and public health. JAMA **2019**; doi:10.1001/jama.2019.18055.
21. Heise L, Greene ME, Opper N, et al; Gender Equality, Norms, and Health Steering Committee. Gender inequality and restrictive gender norms: framing the challenges to health. Lancet **2019**; 393:2440–54.
22. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis **2020**; doi:10.1093/cid/ciaa1391.
23. Kapelios CJ, Argyris AA, Protogerou AD, et al. Progression of subclinical vascular damage in people living with HIV is not predicted by current cardiovascular risk scores: a prospective 3-year study. J Acquir Immune Defic Syndr **2020**; 83:504–12.
24. Yang J, Sharma A, Shi Q, et al. Improved fracture prediction using different fracture risk assessment tool adjustments in HIV-infected women. AIDS **2018**; 32:1699–706.

25. Moran CA, Sheth AN, Mehta CC, et al. The association of C-reactive protein with subclinical cardiovascular disease in HIV-infected and HIV-uninfected women. AIDS **2018**; 32:999–1006.

26. Althoff KN, Gebo KA, Moore RD, et al; North American AIDS Cohort Collaboration on Research and Design. Contributions of traditional and HIV-related risk factors on non-AIDS-defining cancer, myocardial infarction, and end-stage liver and renal diseases in adults with HIV in the USA and Canada: a collaboration of cohort studies. Lancet HIV **2019**; 6:e93–104.

27. Davidson KW, Kemper AR, Doubeni CA, et al. Developing primary care-based recommendations for social determinants of health: methods of the U.S. Preventive Services Task Force. Ann Intern Med **2020**; 173:461–7.

28. Angelidou K, Hunt PW, Landay AL, et al. Changes in inflammation but not in T-cell activation precede non-AIDS-defining events in a case-control study of patients on long-term antiretroviral therapy. J Infect Dis **2018**; 218:239–48.

29. Tien PC, Choi AI, Zolopa AR, et al. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. J Acquir Immune Defic Syndr **2010**; 55:316–22.

30. Salinas JL, Rentsch C, Marconi VC, et al. Baseline, time-updated, and cumulative HIV care metrics for predicting acute myocardial infarction and all-cause mortality. Clin Infect Dis **2016**; 63:1423–30.

31. Wang R, Haberlen SA, Palella FJ Jr, et al. Viremia copy-years and mortality among combination antiretroviral therapy-initiating HIV-positive individuals: how much viral load history is enough? AIDS **2018**; 32:2547–56.

32. Raghavan A, Rimmelin DE, Fitch KV, Zanni MV. Sex differences in select non-communicable HIV-associated comorbidities: exploring the role of systemic immune activation/inflammation. Curr HIV/AIDS Rep **2017**; 14:220–8.

33. Appay V, Sauce D. Assessing immune aging in HIV-infected patients. Virulence **2017**; 8:529–38.

34. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. Immunity **2013**; 39:633–45.

35. Butterfield TR, Landay AL, Anzinger JJ. Dysfunctional immunometabolism in HIV infection: contributing factors and implications for age-related comorbid diseases. Curr HIV/AIDS Rep **2020**; 17:125–37.

36. Duffau P, Wittkop L, Lazaro E, et al; ANRS CO3 Aquitaine Cohort Study Group. Association of immune-activation and senescence markers with non-AIDS-defining comorbidities in HIV-suppressed patients. AIDS **2015**; 29:2099–108.

37. Hewagama A, Patel D, Yarlagadda S, Strickland FM, Richardson BC. Stronger inflammatory/cytotoxic T-cell response in women identified by microarray analysis. Genes Immun **2009**; 10:509–16.

38. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biol Sex Differ **2017**; 8:33.

39. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. Nat Rev Endocrinol **2013**; 9:699–712.

40. Tariq S, Anderson J, Burns F, Delpech V, Gilson R, Sabin C. The menopause transition in women living with HIV: current evidence and future avenues of research. J Virus Erad **2016**; 2:114–6.