Incident Non-AIDS Comorbidity Burden among Women with or at-risk for HIV in the U.S.

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Summary of article: Among women in the U.S., the burden of incident non-AIDS comorbidities was higher for those living with HIV compared with those without HIV, and this difference was greatest for young women, a group not prioritized in routine comorbidity screening.

ABSTRACT

Background: HIV infection may accelerate development of aging-related non-AIDS comorbidities (NACM). The incidence of NACM 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) were included, with outcomes measured through 3/31/2018. Sociodemographics, clinical covariates and prevalent NACM were determined at enrollment. We used Poisson regression models to determine incident NACM burden (number of NACM accrued through most recent WIHS visit out of ten total NACM assessed) by HIV serostatus and age.

Results: There were 3,129 participants (2239 WLWH, 890 HIV-seronegative) with 36,589 person-years of follow-up. At enrollment, median age was 37 years, 65% were black, 47% currently smoked. In fully-adjusted analyses, WLWH had a higher incident NACM rate compared with HIV-seronegative women (IRR 1.36, 95% CI 1.02-1.81). Incident NACM burden was higher among WLWH versus HIV-seronegative women in most age strata (HIV*age interaction p=0.0438) 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

Introduction

Due to combination antiretroviral therapy (ART), 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 (NACM)[2–6]. Compared with persons without HIV, NACM occur disproportionately and prematurely among PLWH[7–9]. Multimorbidity is costly not only to the individual aging with HIV (i.e., affected quality of life)[10], but to the healthcare system, leading to higher resource utilization and direct medical costs (i.e., $300-$5,000 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 NACM among >3,000 participants in the Women's Interagency HIV Study (WIHS), the largest prospective U.S.-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 NACM among women, we performed a follow-up analysis of NACM incidence and associated factors among WIHS participants.

Methods

The Women's Interagency HIV Study (WIHS)

The WIHS is a multicenter prospective U.S. cohort established in 1993 to investigate the progression and sequelae of HIV infection among women. WLWH and at-risk women without HIV enrolled during four 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, D.C.). Women without HIV were recruited based on being at-risk for HIV acquisition (i.e., history of sexually transmitted infections, substance use, etc.) as previously described[17].

Study visits occurred at six-month intervals and comprise standardized interviews, physical examinations and biospecimen collection. Sociodemographics, clinical information including chronic comorbidities, medications, and health behaviors are assessed. Blood testing evaluates 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 NACM and to evaluate the effects of HIV serostatus and age on NACM 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 two 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) NACM, respectively (Supplemental Figure 1). Age, covariates, and prevalent NACM were determined at the end of the two-year baseline period. Incident NACM were measured through the participant's last visit or 3/31/2018 if still enrolled.

Outcome Measures

The primary outcome was incident NACM burden defined as the number of total NACM per participant that developed over the course of observation. Ten NACM 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, non-AIDS cancer. NACM were rigorously defined (Supplemental Table 1) using up to three data sources per comorbidity (self-reported diagnosis or medication use; clinical measurement; and/or laboratory evidence)[6]. For NACM that may have existed intermittently over time (i.e., CKD and depression), data from consecutive study visits was required[6]. NACM 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 NACM 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 chi-square 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*1,000) 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 (IRR) and corresponding 95% confidence intervals (CI) for independent variables of interest from 1) unadjusted (contained only HIV serostatus), 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/df goodness-of-fit test and residual plots.

Analyses used SAS v9.4. Significance level was set at $\alpha=0.05$.

Results

Participant Characteristics at Baseline

There were 3,129 participants (2,239 WLWH, 890 women without HIV) included in the analysis (Supplemental 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*=0.0008) and current use of cigarettes (54% vs. 44%), crack/cocaine (15% vs. 10%) and alcohol (57% vs. 47%) (all *p*<0.0001). WLWH were significantly more likely to use anti-hypertensive medication (20% vs. 16%, *p*=0.0118), have prevalent chronic hepatitis C virus infection (12% vs. 9%, *p*=0.0051), hepatitis B virus infection (2% vs. 1%, *p*=0.0216), and worse kidney function (estimated glomerular filtration rate of 99.3 vs. 101.5 ml/min/1.73 m^2, *p*=0.0099) than women without HIV (Table 1). Education level, annual household income and median depressive symptoms score did not significantly differ by HIV serostatus. At baseline, WLWH had a median CD4 count of 484 cells/mm^3, 69% were on ART and 45% were virologically suppressed.

Prevalent and Incident NACM Burden

Figure 1 shows the distribution of women with prevalent NACM at baseline and incident NACM at the end of follow-up by HIV serostatus. Of 10 NACM evaluated, mean NACM burden at baseline was higher among WLWH than women without HIV (1.4 vs. 1.2, *p*=0.0063), though only prevalent liver disease (26% vs. 16%, *p*<0.0001) and psychiatric illness (26% vs. 21%, *p*=0.0028) differed by HIV serostatus (Supplemental Table 2). The unadjusted incident NACM rate by HIV serostatus and age is shown in Supplemental 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). Supplemental 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*=0.0063).

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, 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*=0.0438). Women aged <25 years had the greatest IRR at 1.48 (95% CI 1.19-1.84) versus 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 0.90-1.14), 45-49 (IRR 1.28; 95% CI 1.08-1.53), 50-54 (IRR 1.18; 95% CI 0.95-1.46), ≥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 (Supplemental Table 4).

Discussion

In this large, multicenter U.S.-based prospective observational cohort of women with and without HIV that included >36,000 person-years of follow-up, we found that WLWH had a significantly higher burden of incident NACM 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 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 (i.e., as young as in their twenties), 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 NACM 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 twenties 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 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 versus 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 HIV-related factors. This underscores the important contribution of social determinants of health in driving 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 co-infections compared with the general population, the type and duration of ART exposure, and HIV-associated chronic inflammation and immune activation hastening the natural aging process[11]. Elevations in inflammatory biomarkers (i.e., hs-CRP, IL-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 co-infections, 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 pro-inflammatory state thereby compounding the systemic inflammation of chronic HIV[32,37]. While pre-menopausal status in the general population is protective against the development of several NACM, e.g., 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 NACM 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 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.

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Table 1. Baseline Demographic and Clinical Data of Women living with or at-risk for HIV Infection at the Time of Enrollment in the Women's Interagency HIV Study (WIHS)[a]

Characteristic, median (Q1-Q3) or n (%)	**Entire cohort[b] (n=3129)**	**HIV+ (n=2239)**	**HIV- (n=890)**	*P* value[c]
Age, *yrs*	37 (31-45)	38 (32-45)	36 (28-44)	<0.0001
Age group, *yrs*				<0.0001
<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, *yrs*	14.3 (3-17.2)	14.3 (3-17.4)	14.4 (3.2-16.7)	0.8321
Race/ethnicity				0.1110
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				<0.0001
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				0.0008
<30	1779 (58)	1317 (60)	462 (53)	
≥30	1288 (42)	882 (40)	406 (47)	
SBP, *mmHg*	116 (107-127)	115 (107-127)	116 (108-128)	0.0742
DBP, *mmHg*	74 (68-80)	74 (68-81)	73 (68-80)	0.1379
Anti-hypertensive medication use	579 (19)	439 (20)	140 (16)	0.0118
Lipid-lowering medication use	155 (5)	108 (5)	47 (5)	0.5966
eGFR, ml/min per 1.73 m^2 (CKD-EPI)	100 (85.4-117)	99.3 (84.2-116.4)	101.5 (87.6-118.8)	0.0099
CES-D score[d]	12 (5-22)	12 (5-23)	12 (5-22)	0.2353
Education				0.1848
≤HS	2025 (65)	1466 (66)	559 (63)	
>HS	1099 (35)	771 (34)	328 (37)	

Income				0.7486
<$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)	<0.0001
Marital status				<0.0001
Married/partner	1029 (33)	741 (33)	288 (32)	
Had a partner	803 (26)	617 (28)	186 (21)	
Never married/other	1296 (41)	881 (39)	415 (47)	
Owner of residence	2293 (73)	1720 (77)	573 (64)	<0.0001
Cigarette use				<0.0001
Never	1077 (35)	814 (37)	263 (30)	
Current	1451 (47)	977 (44)	474 (54)	
Former	568 (18)	428 (19)	140 (16)	
Current alcohol use				<0.0001
None	1535 (50)	1158 (52)	377 (43)	
1-7 drinks/week	1202 (39)	843 (38)	359 (41)	
>7 drinks/week	341 (11)	206 (9)	135 (16)	
Marijuana use				<0.0001
Never	1049 (34)	826 (37)	223 (25)	
Current	690 (22)	433 (20)	257 (29)	
Former	1354 (44)	957 (43)	397 (45)	
Crack/cocaine use				<0.0001
Never	2412 (78)	1787 (81)	625 (71)	
Current	350 (11)	218 (10)	132 (15)	
Former	333 (11)	213 (10)	120 (14)	
Opioid use (heroin/methadon				0.0031
Never				
Current	2869 (93)	2078 (94)	791 (90)	
Former	112 (4)	71 (3)	41 (5)	
	114 (4)	69 (3)	45 (5)	
Injection drug use				0.0862
Never	2548 (82)	1819 (82)	729 (83)	
Current	75 (2)	47 (2)	28 (3)	
Former	470 (15)	350 (16)	120 (14)	
Non-injection drug use				<0.0001
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)	0.0216
Chronic HCV	345 (11)	269 (12)	76 (9)	0.0051
CD4 cell count, *cells/mm*^{3}	- - -	484 (308-698)	- - -	- - -

CD4 nadir, *cells/mm*^{3}	- - -	280 (159-414)	- - -	- - -
HIV viral load	- - -		- - -	- - -
Suppressed[e]		971 (45)		
200-999 copies/ml		197 (9)		
≥1000 copies/ml		976 (46)		
Antiretroviral status	- - -		- - -	- - -
No therapy		709 (32)		
Mono/dual ART		421 (19)		
Combination ART		1109 (50)		

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; HS = high school; SBP= systolic blood pressure

[a]Column percents 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); CD4 nadir (n=82)

[c]Chi-square test performed for categorical variables and Wilcoxon rank sum for continuous variables

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

[e]HIV viral load <200 copies/ml and/or <lower limit of quantification of assay

Table 2. Incidence Rates of Non-AIDS Comorbidities in Women by HIV serostatus

Cases/Total pop (%) *Person-time, yrs* *Rate per 1,000 PYs*	**Total**	**HIV+**	**HIV-**	**HIV+ vs HIV- Unadjusted IRR (95% CI)**[a]	**HIV+ vs HIV- Partially-adjusted IRR (95% CI)**[a]
Hypertension					
Incident cases	1260/2314 (54)	909/1643 (55)	351/671 (53)		
Person-time, yrs	19,119	13,513	5606	1.07 (0.95, 1.22)	0.91 (0.78, 1.06)
Incident rate	65.90	67.27	62.61		
Psychiatric illness					
Incident cases	940/2372 (40)	694/1665 (42)	246/707 (35)		
Person-time, yrs	20,458	13,831	6626	1.35 (1.16, 1.57)	1.38 (1.02, 1.86)
Incident rate	45.95	50.18	37.12		
Bone disease					
Incident cases	1057/2986 (35)	807/2137 (38)	250/849 (29)		
Person-time, yrs	29,281	20,561	8720	1.37 (1.20, 1.56)	1.35 (1.14, 1.58)
Incident rate	36.10	39.25	28.67		
Dyslipidemia					
Incident cases	938/2840 (33)	707/2030 (35)	231/810 (29)		
Person-time, yrs	27,703	19,253	8450	1.34 (1.17, 1.54)	1.36 (1.14, 1.62)
Incident rate	33.86	36.72	27.34		
Liver disease					
Incident cases	498/2399 (21)	406/1647 (25)	92/752 (12)		
Person-time, yrs	22,294	14,274	8020	2.48 (1.98, 3.11)	2.56 (1.85, 3.54)
Incident rate	22.34	28.44	11.47		
Lung disease					
Incident cases	461/2288 (20)	343/1658 (21)	118/630 (19)		
Person-time, yrs	23,199	16,627	6572	1.15 (0.93, 1.42)	1.03 (0.77, 1.38)
Incident rate	19.87	20.63	17.96		
DM2					
Incident cases	460/2877 (16)	328/2072 (16)	132/805 (16)		
Person-time, yrs	30,704	22,069	8635	0.97 (0.79, 1.19)	1.06 (0.80, 1.41)
Incident rate	14.98	14.86	15.29		
CVD					
Incident cases	467/2995 (16)	340/2149 (16)	127/846 (15)		
Person-time, yrs	32,691	23,342	9349	1.07 (0.88, 1.31)	1.06 (0.83, 1.36)
Incident rate	14.29	14.57	13.58		
CKD					
Incident cases	333/3063 (11)	286/2185 (13)	47/878 (5)		
Person-time, yrs	34,108	24,019	10,089	2.56 (1.89, 3.46)	3.14 (1.80, 5.49)[b]
Incident rate	9.76	11.91	4.66		
Cancer, non-AIDS					
Incident cases	167/2983 (6)	131/2125 (6)	36/858 (4)		
Person-time, yrs	33,698	23,821	9877	1.51 (1.05, 2.17)	1.39 (0.89, 2.18)[b]
Incident rate	4.96	5.50	3.65		

Incident NACM burden/PY					
Incident count	6581	4951	1630		
Person-time, yrs	36,589	26,131	10,458	1.22 (1.15, 1.29)	1.21 (1.13, 1.29)
Incident rate	0.1799	0.1895	0.1559		

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; DM2 = diabetes mellitus, type 2; IRR = incidence rate ratios

[a]Poisson regression analysis performed using robust variance estimation to generate IRR 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-yr increments from <25 to ≥55 years for all NACM except for CKD and non-AIDS cancer which were rare occurrences thus age collapsed into 10-yr increments from <30 to ≥50 years.

Table 3. Multivariable Analysis of Risk Factors at Study Enrollment Associated with the Incident Burden of Non-AIDS Comorbidities (NACM) in Women living with or at-risk for HIV Infection

Risk factor	**Estimated incident NACM rate (95% CI)**	**IRR (95% CI)**	*P* value[a]
HIV serostatus[b]			
Positive	0.21 (0.20, 0.22)	1.36 (1.02, 1.81)	<0.0001
Negative	0.17 (0.16, 0.18)	Ref	
Age group, *yrs*[b]			
≥55	0.22 (0.19, 0.26)	1.71 (1.41, 2.09)	<0.0001
50-54	0.23 (0.21, 0.26)	1.66 (1.38, 2.00)	
45-49	0.23 (0.21, 0.26)	1.72 (1.47, 2.02)	
40-44	0.22 (0.20, 0.24)	1.46 (1.25, 1.70)	
35-39	0.20 (0.18, 0.21)	1.36 (1.17, 1.58)	
30-34	0.17 (0.15, 0.18)	1.21 (1.04, 1.41)	
25-29	0.14 (0.13, 0.16)	1.06 (0.90, 1.25)	
<25	0.13 (0.11, 0.14)	Ref	
Body mass index, kg/m^2			
≥30	0.20 (0.19, 0.22)	1.15 (1.09, 1.21)	<0.0001
<30	0.18 (0.16, 0.19)	Ref	
Race			
Non-Hispanic AA	0.17 (0.16, 0.18)	0.83 (0.78, 0.89)	<0.0001
Hispanic	0.19 (0.17, 0.20)	0.89 (0.83, 0.97)	
Other non-Hispanic	0.19 (0.16, 0.22)	0.91 (0.78, 1.05)	
White	0.21 (0.19, 0.22)	Ref	
Education			
≤HS	0.19 (0.18, 0.20)	1.01 (0.96, 1.07)	0.6504
>HS	0.19 (0.17, 0.20)	Ref	
Income			
<$12,000	0.20 (0.19, 0.22)	1.12 (1.05, 1.20)	0.0002
$12,001-24,000	0.18 (0.17, 0.20)	1.02 (0.95, 1.10)	
>$24,000	0.18 (0.17, 0.19)	Ref	
Marital status			
Had a partner	0.19 (0.18, 0.20)	1.01 (0.96, 1.08)	0.1680
Never partner/other	0.18 (0.17, 0.20)	0.96 (0.91, 1.01)	
Married/partner	0.19 (0.17, 0.20)	Ref	
Own residence			
No	0.20 (0.18, 0.21)	1.08 (1.02, 1.14)	0.0067
Yes	0.18 (0.17, 0.19)	Ref	
Cigarette use			
Current	0.21 (0.19, 0.22)	1.19 (1.12, 1.27)	<0.0001
Former	0.19 (0.17, 0.20)	1.09 (1.02, 1.17)	
Never	0.17 (0.16, 0.19)	Ref	
Current alcohol use			
>7 drinks/week	0.19 (0.17, 0.20)	0.96 (0.88, 1.04)	0.1457

1-7 drinks/week	0.18 (0.17, 0.20)	0.95 (0.90, 1.00)	
None	0.19 (0.18, 0.21)	Ref	
Crack/cocaine use			
Current	0.20 (0.18, 0.21)	1.10 (1.02, 1.19)	0.0310
Former	0.19 (0.17, 0.21)	1.06 (0.99, 1.14)	
Never	0.18 (0.17, 0.19)	Ref	

Abbreviations: HS = high school; Ref = reference; IRR = incidence rate ratio

[a]Adjusted linear regression with all covariates listed included in the model plus WIHS enrollment wave and HIV*age interaction (p=0.0438 for the interaction term).

[b]Adjusted for HIV serostatus*age interaction

FIGURE LEGENDS:

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 (NACM) over the course of observation in the Women's Interagency HIV Study stratified by HIV serostatus.

(HTN = hypertension; Psych = psychiatric illness; Bone = bone disease; DL = dyslipidemia; Liver = liver disease; Lung = lung disease; DM2 = diabetes mellitus, type 2; CVD = cardiovascular disease; CKD = chronic kidney disease; CAN = non-AIDS cancer)

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

Figure 1

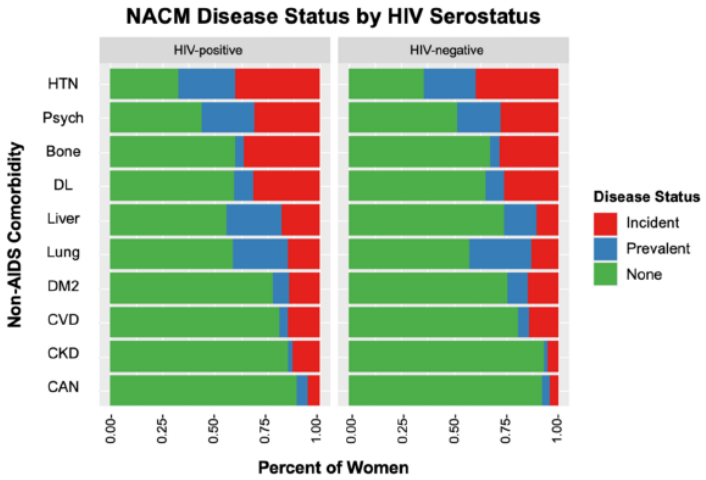

Figure 2