Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Lauren Frances Collins, MD Date

The Prevalence and Burden of Non-AIDS Comorbidities

Among Women Living with or at-risk for HIV Infection in the United States

By

Lauren F. Collins, MD

Master of Science

Clinical Research

_____

Ighovwerha Ofotokun, MD, MSc
Advisor

_____

Anandi N. Sheth, MD, MSc
Committee Member

_____

Matthew Magee, PhD
Committee Member

Accepted:

_____

Lisa A. Tedesco, PhD
Dean of the James T. Laney School of Graduate Studies

_____

Date

The Prevalence and Burden of Non-AIDS Comorbidities Among Women Living with or at-risk for HIV Infection in the United States

By

Lauren F. Collins, MD

BS, University of Georgia, 2009

MD, Boston University School of Medicine, 2014

Advisor: Ighovwerha Ofotokun, MD, MSc

An abstract of

A thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Master of Science

in Clinical Research

2020

ABSTRACT

The Prevalence and Burden of Non-AIDS Comorbidities

Among Women Living with or at-risk for HIV Infection in the United States

By Lauren F. Collins

Background: Due to the success of combination antiretroviral therapy (cART), persons living with HIV are living longer. Age-associated non-AIDS comorbidities (NACM) increasingly account for morbidity and mortality in this population. Compared with HIV-seronegative counterparts, NACM occur up to a decade earlier among HIV-seropositive individuals, and women living with HIV (WLWH) may be at greater NACM risk than men. The epidemiology of NACM, however, is poorly characterized among WLWH. The objectives of this research were to describe NACM burden and prevalence, assess the effects of HIV serostatus and age on NACM burden, and describe risk factors associated with NACM, in a large U.S. cohort of women living with or at-risk for HIV infection.

Methods: Virologically-suppressed WLWH and HIV-seronegative participants followed in the Women's Interagency HIV Study (WIHS) through ≥2009 (when >80% WLWH used cART) were included, with outcomes measured through 3/31/2018. 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 3,232 women (2,309 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<0.0001) and higher prevalence of psychiatric illness, dyslipidemia, non-AIDS cancer, kidney, liver and bone disease (all p<0.01). Prevalent hypertension, diabetes, cardiovascular and lung disease did not differ by HIV serostatus. Estimated NACM burden was higher among WLWH vs. HIV-seronegative women in those aged 40-49 (p<0.0001) and ≥60 years (p=0.0009) (HIV*age interaction p=0.0978). 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.

The Prevalence and Burden of Non-AIDS Comorbidities Among Women Living with or at-risk for HIV Infection in the United States

By

Lauren F. Collins, MD

BS, University of Georgia, 2009

MD, Boston University School of Medicine, 2014

Advisor: Ighovwerha Ofotokun, MD, MSc

A thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Master of Science

in Clinical Research

2020

ACKNOWLEDGMENTS

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS), now the MACS/WIHS Combined Cohort Study (MWCCS). The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), with additional co-funding from the Eunice Kennedy Shriver National Institute Of Child Health & Human Development (NICHD), National Human Genome Research Institute (NHGRI), National Institute On Aging (NIA), National Institute Of Dental & Craniofacial Research (NIDCR), National Institute Of Allergy And Infectious Diseases (NIAID), National Institute Of Neurological Disorders And Stroke (NINDS), National Institute Of Mental Health (NIMH), National Institute On Drug Abuse (NIDA), National Institute Of Nursing Research (NINR), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). MWCCS data collection is also supported by UL1-TR000004 (UCSF CTSA), P30-AI-050409 (Atlanta CFAR), P30-AI-050410 (UNC CFAR), and P30-AI-027767 (UAB CFAR). This work was also supported by the Emory Specialized Center of Research Excellence (SCORE) on Sex Differences (grant number U54AG062334; to IO). LFC is also supported by the National Center for Advancing Translational Sciences (NCATS) of the NIH (award numbers UL1TR002378 and TL1TR002382).

I would like to thank my lead mentor, Dr. Igho Ofotokun, my co-mentor, Dr. Anandi Sheth, my thesis chair, Dr. Matthew Magee, as well as MSCR Executive committee members Drs. Henry Blumberg, Tom Ziegler, Jessica Alvarez, and Vas Michopoulos. In

addition, I would like to thank MSCR program faculty Dr. Mitch Klein and Dr. Amita Manatunga for their teaching. I also thank Dr. Christina Mehta (Emory) and Dr. Susanna (Naggie) for their mentorship throughout my MSCR training. My co-authors for this study and their respective WIHS sites are Anandi Sheth (Emory), Christina Mehta (Emory), Elizabeth Golub (Johns Hopkins), Kathryn Anastos (Montefiore), Audrey French (Rush), Seble Kassaye (Georgetown), Tonya Taylor (SUNY Downstate), Margaret Fischl (University of Miami), Adaora Adimora (University of North Carolina at Chapel Hill), Mirjam-Colette Kempf (University of Alabama at Birmingham), Frank Palella (Northwestern), Phyllis Tien (University of California at San Francisco) and Igho Ofotokun (Emory). I would also like to sincerely thank the WIHS participants and staff at all sites for their contributions.

TABLE OF CONTENTS

INTRODUCTION 1

BACKGROUND 2

METHODS 6

RESULTS 12

DISCUSSION/CONCLUSIONS 15

REFERENCES 21

TABLES AND FIGURES 27

INTRODUCTION

Combination antiretroviral therapy (cART) has resulted in tremendous improvements in mortality, and as such, nearly half of individuals with diagnosed HIV in the US are now aged ≥50 years[1,2]. In those with access to care and treated, age-associated non-AIDS comorbidities (NACM) 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 NACM[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 biologic and sociobehavioral factors influence HIV acquisition, pathogenesis, reservoir, treatment responses, and likely contribute to comorbidity development, however additional study 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.

BACKGROUND

Age-related non-AIDS comorbidities (NACM) are rising among persons living with HIV (PLWH). Due to combination antiretroviral therapy (cART), PLWH are living longer. The Centers for Disease Control and Prevention estimates nearly half of individuals diagnosed with HIV in the U.S. are ≥50 years old[1]. Among those with access to care and treated, NACM increasingly account for morbidity[3–5] and mortality[2,6,7]. Compared with persons without HIV, PLWH experience a higher burden of NACM including cardiovascular disease (CVD), chronic kidney disease (CKD), liver disease, bone disease, non-AIDS cancer and neurocognitive impairment[3–5,8,18]. A recent cross-sectional analysis of MarketScan data including 36,298 PLWH found that the proportion of assessed NACM, including hypertension, hyperlipidemia, and endocrine disease, significantly increased in this population from 2003 to 2013[4]. These data are supported by several other multisite cohort studies describing the rise of "multimorbidity" among PLWH in the era of cART[3,5,10,15].

The burden of NACM in PLWH is concerning not only to the individual, but to the overall healthcare system in terms of utilization and direct medical costs (i.e., $300-$5,000 more per patient month in PLWH with comorbidities than those without HIV)[19,20]. The escalation of NACM among aging PLWH brings about unique challenges to HIV care delivery, including the need for innovative tools for NACM screening, prevention and mitigation, as well as for a multidisciplinary approach for comorbidity management, and for consideration of economic impacts on the healthcare system that must be addressed.

NACM accrue at an early age in PLWH and traditional risk assessment tools are

insensitive in this population. Epidemiologic data indicate PLWH are at risk of earlier accrual of NACM than seronegative counterparts[9,10,21]. Compared with the general population, NACM may be diagnosed up to a decade earlier in PLWH[9,10,21]. There are several possible etiologies driving "premature aging" observed among PLWH, compared with the general population, including HIV-associated chronic inflammation and immune activation, cART exposure and toxicity, other viral co-infections, and elevated sociobehavioral-derived comorbidity risk factors such as increased rates of smoking and depressed socioeconomics[9,22,23]. This underscores the need for preventive strategies targeting both HIV-related and "traditional" non-HIV risk factors to mitigate the premature onset of age-associated NACM among PLWH[24,25]. It is also important to recognize that routine health screening tools developed in the general population—such as for CVD and bone fracture risk—underperform in PLWH[26–29], such that existing strategies fail to identify substantial numbers of PLWH with elevated NACM risk who could potentially benefit from risk-modification interventions. A better of understanding of the effect of age on NACM risk could help inform the development of comorbidity screening tools and guidance for PLWH, in whom NACM occur more frequently and at a younger age.

The burden of NACM among women living with HIV (WLWH) remains largely unknown though may be greater than among men. While women represent a substantial constituency of the aging HIV population (>50% worldwide), WLWH are historically understudied in HIV research[13]. The several large, multisite cohort studies describing "multimorbidity" in aging PLWH severely lack adequate representation of

female participants (range: 13-21%)[3,5,10,15]. Given that various aspects of biologic sex (e.g., anatomy, genetics, sex hormones, immunology, microbiome, response to cART, behaviors and access to care) likely influence the development of age-associated NACM[14], sex-delineated comorbidity research is crucial to informing sex-tailored clinical guidance on comorbidity screening and management among PLWH.

Importantly, recently published sex-stratified data from the HIV Outpatient Study demonstrated a higher NACM burden in WLWH than men living with HIV (median 3.9 vs. 3.4, respectively, of 11 NACM assessed, $p<0.05$)[5]. These data are consistent with prior reports of higher risk of cardiovascular and cerebrovascular events in PLWH compared with seronegative individuals, that was amplified in women compared with men[16,17]. These findings provide compelling evidence that WLWH may experience unique risk in terms of NACM development, and that defining the epidemiology of NACM among women with and without HIV specifically is urgently need to tailor sex-delineated HIV care.

NACM may co-occur in unique patterns among PLWH. Recent studies suggest comorbidities in PLWH occur in nonrandom patterns[30–32]. A recent analysis of NACM data from >20,000 PLWH in North America revealed that hypertension and hyperlipidemia most commonly co-occur, however, the composition of co-occurring comorbidity dyads and triads may be changing over time[15]. Nonrandom patterns of co-occurring NACM may reflect known pathologic mechanisms and shared risk factors, such as hypertension and diabetes mellitus both leading to CKD, however, evolving NACM epidemiology may unveil previously unknown pathophysiologic pathways[30,32].

Understanding NACM co-occurrence is therefore important to suggest common pathophysiology that could potentially be targeted for comorbidity screening, prevention and management interventions, and to address shared risk factors to mitigate NACM development or progression in the era of increasing multimorbidity among PLWH[4,15].

METHODS

Hypothesis and Specific Aims

This analysis was conducted with the following three specific aims:

(1) To describe the burden of NACM (defined as the total number of comorbidities per individual) and the prevalence of each NACM (per cohort) among women, stratified by HIV serostatus and age.

(2) To assess for associations of HIV serostatus and age on NACM prevalence and burden among women.

(3) To describe co-occurring prevalent NACM dyads, overall and stratified by HIV serostatus and age.

Our overall hypothesis was that WLWH experience a higher frequency and number of NACM than HIV-seronegative women, and that HIV serostatus and age interact synergistically on NACM burden.

The Women's Interagency HIV Study (WIHS)

We analyzed data from the WIHS, the largest prospective US-based cohort of women living with or at-risk for HIV infection[33]. Enrollment occurred in 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, 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 previously[33].

WIHS participants complete a biannual interviewer-administered questionnaire, standardized physical exam (including three 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 NACM in the era of effective HIV treatment (and to minimize the contribution of AIDS-related pathology), we included all WIHS participants with at least two full study visits completed between 2009 (when >80% WLWH used cART) through end of observation (March 31, 2018; Supplemental 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 NACM due to their known age-association and significant contribution to morbidity and mortality in the general population (Supplemental Table 1). Our primary outcome was NACM burden, defined as the number of total NACM per participant (i.e., count from 0 to 10). Our secondary outcomes were the prevalence of

each NACM, defined as presence of the condition as of the participant's most recent visit. NACM were defined using up to three potential data sources: self-reported diagnosis or medication, clinical measurement, and/or laboratory evidence. Use of pathology and/or imaging modalities to define NACM (e.g., biopsies for cancer, bone densitometry for osteopenia or osteoporosis, transient elastography for liver disease, etc.) was not employed given lack of availability of these data. NACM 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 (e.g., CKD and depression), for which criteria were required on ≥2 consecutive visits to satisfy the NACM definition. Once a participant met criteria for a comorbidity, that comorbidity was considered prevalent.

Additional general covariates included age (continuous), age group (<40, 40-49, 50-59, ≥60 years), observation time in study (continuous), WIHS enrollment wave (1994/95, 2001/02, 2011/12, 2013/15), race/ethnicity (White/non-Hispanic, Black/non-Hispanic, Hispanic, Other), body mass index (BMI) (<30 or ≥30 kg/m^2), education (<high school or ≥high school), annual household income (<$12,000, $12,000-$24,000, or >$24,000), marital status (had a partner, never partner/other, or married/partner), participant owns residence (yes or no), cigarette use (current, former, or never), current alcohol use (none, 1-7 drinks/week, or >7 drinks/week), and crack/cocaine use (current, former, or never). HIV-specific covariates included most recent CD4 cell count (<500 or ≥500 cells/mm^3), CD4 cell count nadir (<200 or ≥200 cells/mm^3), time since cART initiation (<10 years or ≥10 years), proportion of study visits that HIV RNA was suppressed from initial WIHS visit (<50% or ≥50%), protease inhibitor use in the last six

months (yes or no) and abacavir use in the last six months (yes or no). HIV RNA suppression was defined as viral load <200 copies/ml and/or less than the lower limit of assay quantification.

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 two sample t-tests assessed the association of HIV serostatus with prevalence of each comorbidity and NACM burden, respectively. We performed unadjusted logistic regression to generate odds ratios and 95% confidence intervals for each prevalent NACM by HIV serostatus:

$$\text{Model: Log } (p/1\text{-}p) = ß_0 + ß_1 x_1$$

p = probability of each NACM (ex. hypertension) = 1

x_1 = HIV serostatus

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).

Partially-adjusted models:

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.

(1) NACM prevalence:

$$\text{Model: Log } (p/1\text{-}p) = ß_0 + ß_1x_1 + ß_2x_2 + ß_3x_1{*}x_2$$

p = probability of each NACM (ex. hypertension) = 1

x_1 = HIV serostatus, x_2 = age category

(2) NACM burden:

$$\text{Model: } \hat{y} = ß_0 + ß_1x_1 + ß_2x_2 + ß_3x_1{*}x_2$$

$\hat{y}$ = estimated mean NACM burden (i.e., count, 0-10)

x_1 = HIV serostatus, x_2 = age category

Fully-adjusted models:

For the primary outcome (NACM burden), we used a "fully-adjusted" linear regression model, controlling for important covariates (derived from 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.

$$\text{Model: } \hat{y} = ß_0 + ß_1x_1 + ß_2x_2 + ß_3x_1{*}x_2 + ß_4x_3 + \ldots$$

$\hat{y}$ = estimated mean NACM burden (i.e., count, 0-10)

x_1 = HIV serostatus, x_2 = age category, x_3 = additional 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 NACM were not included as covariates in adjusted models (e.g., systolic blood pressure given this metric was used to define hypertension, etc.). 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.

Missing data were assumed to be missing at random and not imputed. All analyses were conducted in SAS v9.4 and significance was set at $\alpha=0.05$.

RESULTS

Participant Characteristics

Among 3,232 women (2,309 HIV+, 923 HIV-) included in our analysis (Supplemental Figure) with 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), BMI ≥30 kg/m^2 (57% vs. 46%) and current use of cigarettes (44% vs. 36%), alcohol (57% vs. 41%) and crack/cocaine (9% vs. 6%) (all p<0.0001). WLWH had a higher prevalence of chronic hepatitis C (13% vs. 9%, p=0.0026) and hepatitis B viral infection (2% vs. 1%, p=0.0148) and worse kidney function than HIV-seronegative women (Table 1). Education level and median depressive symptoms score did not significantly differ by HIV serostatus. WLWH had a median CD4 count of 615 cells/mm^3, 81% had virologic suppression and median time since cART initiation was 12.5 years.

NACM Burden and Prevalence

Mean NACM burden increased with each older age category (<40, 40-49, 50-59, ≥60 years): 1.7 (SD 1.4), 2.7 (SD 1.8), 4.0 (SD 2.0), 5.2 (SD 1.9) (p<0.0001); as did the prevalence of each individual NACM (p<0.0001) (Table 2). WLWH had a higher mean NACM burden than HIV-seronegative women: 3.6 vs. 3.0 (p<0.0001) and the following comorbidities were more prevalent in WLWH vs. HIV-seronegative women (all p<0.01): psychiatric illness (57%/48%), liver disease (45%/26%), dyslipidemia (40%/35%), bone disease (40%/33%), CKD (15%/7%) and non-AIDS cancer (11%/7%) (Table 3). The

prevalence of hypertension (66%/64%), lung disease (41%/42%), diabetes (22%/24%) and CVD (19%/19%) did not significantly differ by HIV serostatus.

NACM 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, though this was significant only for those aged 40-49 (p<0.0001) and ≥60 years (p=0.0028) (HIV*age interaction p=0.0206) (Table 4). The estimated mean difference in NACM (HIV+/HIV-) for women 40-49, 50-59, ≥60 years, compared to those aged <40 of the same HIV serostatus, was 1.17 (95%CI 0.92-1.41)/0.73 (95%CI 0.40-1.06), 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<0.0001).

NACM Burden Adjusting for Demographic and Clinical Factors

Univariate analysis of factors associated with NACM burden can be found in Table 5. 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). NACM burden was higher among WLWH compared with HIV-seronegative women in those aged 40-49 (p<0.0001) and ≥60 years (p=0.0009), but not in those aged <40 (p=0.1420) and 50-59 years (p=0.0888). The association between HIV serostatus and age on NACM burden approached significance (HIV*age interaction p=0.0978). In addition, estimated mean NACM burden was

significantly higher in women of who were older, white race, and who had HIV, BMI ≥30 kg/m^2, income ≤$24,000, and reported cigarette use, crack/cocaine use or alcohol abstinence (Table 6).

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<0.0001). 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 (Table 7).

NACM Dyads

Figure 3 shows the three 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 two for each HIV*age stratification, and was prevalent in 60% of all women ≥60 years (Supplemental Table 2). In WLWH, the co-occurrence of hypertension-liver disease was the next most prevalent, occurring in 33% overall and 64% of those aged ≥60 years. This pattern differed from HIV-seronegative women where 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 3,232 participants with 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. HIV infection modified the effect of age on NACM burden, though this interaction was attenuated when adjusting for covariates. Factors significantly associated with NACM burden were HIV seropositivity, older age, white race, obesity, income ≤$24,000, 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 >50% of the HIV population is female, and women have unique biologic and sociobehavioral risk influencing comorbidity development, this work has broad implications for the clinical care of aging WLWH.

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 13-21%, 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 US. For example, Palella et al reported the mean number of 11 NACM assessed in PLWH (19% female) aged 18-40, 41-50, 51-60, ≥61 years as 1.4, 2.1, 3.0 and 3.9, respectively[5]; 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 NACM in 267 WLWH compared with 276 HIV-seronegative women (iRR 1.58, 95% CI 1.38-1.81)[21]. Although the median number of NACM in WLWH was lower than we observed (2 [IQR: 1-4] vs. 3 [Q1-Q3: 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 in those aged 40-49 and ≥60 years. We demonstrated that HIV infection significantly modified the effect of age on NACM burden, though this was attenuated when adjusting for covariates. Epidemiologic data suggest PLWH are at risk of earlier accrual of NACM than seronegative counterparts, with NACM diagnosed up to a decade earlier in PLWH[9,10,21]. Discrepancy in NACM prevalence between PLWH and the general population may even precede the diagnosis of HIV[10], suggesting 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 NACM in WLWH than 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[21]. 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[34]. We did not find a relationship between NACM burden and measures of CD4 count, HIV virologic suppression, nor cART exposure other than recent abacavir use. This could reflect preferred use of abacavir over tenofovir disoproxil fumarate (prior to the advent of tenofovir alafenamide) in PLWH with certain comorbidities[35,36]. A recent examination of traditional and HIV-related factors contributing to several comorbidity outcomes found a substantial proportion of NACM could be prevented by interventions addressing smoking, elevated cholesterol and hypertension[25]. These findings, corroborated by other large cohorts of virologically-suppressed PLWH[5,10,30,31], 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 NACM evaluated, the most common in WIHS included hypertension, psychiatric illness, dyslipidemia, liver and lung disease, with most NACM significantly more prevalent in WLWH compared with HIV-seronegative women. Individual NACM prevalence ranging between 10-66% is modestly higher than that described among other cohorts of PLWH including WLWH[5,15,21], though similar to our data, the most commonly occurring NACM include hypertension, dyslipidemia, psychiatric illness and liver disease[3–5,21]. Observed differences by HIV serostatus in the prevalence of certain NACM is likely driven by the complex interplay of overrepresentation of mental health including substance use disorders in PLWH compared with the general population[23,37]; higher prevalence of viral hepatitis co-infection; viral- and cART-mediated effects on lipids, kidney and bone health[38–40]; and the poorly understood relationship between HIV and oncogenesis[41].

Recent studies suggest comorbidities in PLWH occur in non-random patterns[30–32]. 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[42], and has been shown to increase the risk of hypertension in women and be strongly associated with fatal CVD[43]. 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[15,32,44,45]. 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 all-cause mortality[46,47].

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 men living with HIV (median 3.9 vs. 3.4, respectively, $p<0.05$)[5]. This is consistent with prior reports of higher risk of cardiovascular and cerebrovascular events in PLWH, compared with HIV-seronegative individuals, that is amplified in women compared with men[16,17]. The role of biologic sex on development of age-associated comorbidities warrants further study, especially considering numerous potential mechanistic differences, e.g., 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 NACM in WLWH to demographically-similar HIV-seronegative women recruited in WIHS based on sociobehavioral characteristics associated with risk of HIV acquisition[33]. In our study, HIV-seronegative women had significantly higher BMI, blood pressure and substance use compared with WLWH. It is well-established these characteristics predispose to age-related comorbidities[48]. Therefore, it is possible that 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 eight measured) in 5355 participants (55% women, mean age 68 years)[42]. In their study, 62% of women reported multimorbidity, compared with 98% of WLWH and 92% of HIV-seronegative women in WIHS aged ≥60 years. Similarly in the Australian Longitudinal Study on Women's Health[49], while 46% of >10,000 women aged 45-50 years reported ≥2 chronic comorbidities of 18 assessed, WIHS participants aged 40-49 years reported ≥2 NACM 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 four 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 NACM, especially considering the possibility of switches over time and non-adherence. Lastly, since this study focused on prevalent NACM, we did not evaluate the role of menopause status or timing.

In conclusion, WLWH living in the US experienced a high overall burden of age-associated NACM compared with HIV-seronegative counterparts. HIV infection appears to modify the effect of aging on comorbidity burden in women, though 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, though dedicated characterization of respective unique biologic 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 <50 years, in whom NACM burden is already higher than in their HIV-seronegative counterparts.

REFERENCES

1. Centers for Disease Control and Prevention. HIV Surveillance Report, 2017; vol. 29. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2018. Accessed [June 1, 2019].
2. Marcus, J. L. *et al.* Narrowing the Gap in Life Expectancy Between HIV-Infected and HIV-Uninfected Individuals With Access to Care. *J. Acquir. Immune Defic. Syndr.* **73**, 39–46 (2016).
3. Schouten, J. *et al.* 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.* **59**, 1787–1797 (2014).
4. Gallant, J., Hsue, P. Y., Shreay, S. & Meyer, N. Comorbidities Among US Patients With Prevalent HIV Infection-A Trend Analysis. *J. Infect. Dis.* **216**, 1525–1533 (2017).
5. Palella, F. J. *et al.* Non-AIDS comorbidity burden differs by sex, race, and insurance type in aging adults in HIV care. *AIDS* (2019) doi:10.1097/QAD.0000000000002349.
6. Palella, F. J. *et al.* Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J. Acquir. Immune Defic. Syndr.* **43**, 27–34 (2006).
7. Trickey, A. *et al.* Cause-Specific Mortality in HIV-Positive Patients Who Survived Ten Years after Starting Antiretroviral Therapy. *PLoS ONE* **11**, e0160460 (2016).
8. Onen, N. F. *et al.* Aging and HIV infection: a comparison between older HIV-infected persons and the general population. *HIV Clin Trials* **11**, 100–109 (2010).
9. Guaraldi, G. *et al.* Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin. Infect. Dis.* **53**, 1120–1126 (2011).

10. Ronit, A. *et al.* Non-AIDS Comorbid Conditions in Persons Living With Human Immunodeficiency Virus (HIV) Compared With Uninfected Individuals 10 Years Before HIV Diagnosis. *Clin. Infect. Dis.* **67**, 1291–1293 (2018).

11. UNAIDS Global AIDS Update. 2018. Available at: http://www.unaids.org/en/resources/fact-sheet. Accessed September 10, 2019.

12. Grewe, M. E., Ma, Y., Gilbertson, A., Rennie, S. & Tucker, J. D. Women in HIV cure research: multilevel interventions to improve sex equity in recruitment. *J Virus Erad* **2**, 49–51 (2016).

13. Gandhi, M. *et al.* 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.* **81**, e158–e160 (2019).

14. Scully, E. P. Sex Differences in HIV Infection. *Curr HIV/AIDS Rep* **15**, 136–146 (2018).

15. Wong, C. *et al.* Multimorbidity Among Persons Living with Human Immunodeficiency Virus in the United States. *Clin. Infect. Dis.* **66**, 1230–1238 (2018).

16. Triant, V. A., Lee, H., Hadigan, C. & Grinspoon, S. K. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J. Clin. Endocrinol. Metab.* **92**, 2506–2512 (2007).

17. Chow, F. C. *et al.* Elevated ischemic stroke risk among women living with HIV infection. *AIDS* **32**, 59–67 (2018).

18. Yang, H.-Y., Beymer, M. R. & Suen, S.-C. Chronic Disease Onset Among People Living with HIV and AIDS in a Large Private Insurance Claims Dataset. *Sci Rep* **9**, 18514 (2019).

19. Gallant, J., Hsue, P., Budd, D. & Meyer, N. Healthcare utilization and direct costs of non-infectious comorbidities in HIV-infected patients in the USA. *Curr Med Res Opin* **34**, 13–23 (2018).

20. Lerner, A. M., Eisinger, R. W. & Fauci, A. S. Comorbidities in Persons With HIV: The Lingering Challenge. *JAMA* (2019) doi:10.1001/jama.2019.19775.

21. Donaldson, M. A. *et al.* Comorbidity and polypharmacy among women living with HIV in British Columbia. *AIDS* (2019) doi:10.1097/QAD.0000000000002353.

22. Sokoya, T., Steel, H. C., Nieuwoudt, M. & Rossouw, T. M. HIV as a Cause of Immune Activation and Immunosenescence. *Mediators Inflamm.* **2017**, 6825493 (2017).

23. Mdodo, R. *et al.* Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. *Ann. Intern. Med.* **162**, 335–344 (2015).

24. Collins LF, Sheth AN, Mehta CC, Naggie S, Golub ET, Anastos K, French AL, Kassaye S, Taylor T, Fischl MA, Adimora AA, Kempft MC, Palella FJ, Tien PC, Ofotokun I. 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.* **In press**, (2020).

25. Althoff, K. N. *et al.* 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* **6**, e93–e104 (2019).

26. Thompson-Paul, A. M. *et al.* Cardiovascular Disease Risk Prediction in the HIV Outpatient Study. *Clin. Infect. Dis.* **63**, 1508–1516 (2016).

27. Yin, M. T. *et al.* Fracture Prediction With Modified-FRAX in Older HIV-Infected and Uninfected Men. *J. Acquir. Immune Defic. Syndr.* **72**, 513–520 (2016).

28. Yang, J. *et al.* Improved fracture prediction using different fracture risk assessment tool adjustments in HIV-infected women. *AIDS* **32**, 1699–1706 (2018).

29. Kapelios, C. J. *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) doi:10.1097/QAI.0000000000002286.

30. De Francesco, D. *et al.* Risk factors and impact of patterns of co-occurring comorbidities in people living with HIV. *AIDS* **33**, 1871–1880 (2019).

31. Maggi, P. *et al.* Clusterization of co-morbidities and multi-morbidities among persons living with HIV: a cross-sectional study. *BMC Infect. Dis.* **19**, 555 (2019).

32. De Francesco, D. *et al.* Patterns of Co-occurring Comorbidities in People Living With HIV. *Open Forum Infect Dis* **5**, ofy272 (2018).

33. Adimora, A. A. *et al.* Cohort Profile: The Women's Interagency HIV Study (WIHS). *Int J Epidemiol* **47**, 393–394i (2018).

34. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010–2016. HIV Surveillance Supplemental Report 2019;24(No. 1). http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published February 2019. Accessed [3/8/2019].

35. Wyatt, C. M. *et al.* Changes in proteinuria and albuminuria with initiation of antiretroviral therapy: data from a randomized trial comparing tenofovir disoproxil

fumarate/emtricitabine versus abacavir/lamivudine. *J. Acquir. Immune Defic. Syndr.* **67**, 36–44 (2014).

36. Güerri-Fernández, R. *et al.* Bone Density, Microarchitecture, and Tissue Quality After Long-Term Treatment With Tenofovir/Emtricitabine or Abacavir/Lamivudine. *J. Acquir. Immune Defic. Syndr.* **75**, 322–327 (2017).

37. Ciesla, J. A. & Roberts, J. E. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *Am J Psychiatry* **158**, 725–730 (2001).

38. Riddler, S. A. *et al.* Impact of HIV infection and HAART on serum lipids in men. *JAMA* **289**, 2978–2982 (2003).

39. Moran, C. A., Weitzmann, M. N. & Ofotokun, I. Bone Loss in HIV Infection. *Curr Treat Options Infect Dis* **9**, 52–67 (2017).

40. Nadkarni, G. N., Konstantinidis, I. & Wyatt, C. M. HIV and the aging kidney. *Curr Opin HIV AIDS* **9**, 340–345 (2014).

41. Deeken, J. F. *et al.* The rising challenge of non-AIDS-defining cancers in HIV-infected patients. *Clin. Infect. Dis.* **55**, 1228–1235 (2012).

42. Niedzwiedz, C. L., Katikireddi, S. V., Pell, J. P. & Smith, D. J. Sex differences in the association between salivary telomere length and multimorbidity within the US Health & Retirement Study. *Age Ageing* (2019) doi:10.1093/ageing/afz071.

43. Whang, W. *et al.* Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. *J. Am. Coll. Cardiol.* **53**, 950–958 (2009).

44. Wong, C. *et al.* First Occurrence of Diabetes, Chronic Kidney Disease, and Hypertension Among North American HIV-Infected Adults, 2000-2013. *Clin. Infect. Dis.* **64**, 459–467 (2017).

45. Zhang, Y., Chen, Y. & Ma, L. Depression and cardiovascular disease in elderly: Current understanding. *J Clin Neurosci* **47**, 1–5 (2018).

46. Mills, J. C. *et al.* The Impact of Cumulative Depression along the HIV Care Continuum in Women Living with HIV during the Era of Universal Antiretroviral Treatment. *J. Acquir. Immune Defic. Syndr.* (2019) doi:10.1097/QAI.0000000000002140.

47. Mills, J. C. *et al.* Cumulative Burden of Depression and All-Cause Mortality in Women Living With Human Immunodeficiency Virus. *Clin. Infect. Dis.* **67**, 1575–1581 (2018).

48. Park, Y.-W. *et al.* The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch. Intern. Med.* **163**, 427–436 (2003).

49. Jackson, C. A., Dobson, A. J., Tooth, L. R. & Mishra, G. D. Lifestyle and Socioeconomic Determinants of Multimorbidity Patterns among Mid-Aged Women: A Longitudinal Study. *PLoS ONE* **11**, e0156804 (2016).

TABLES AND FIGURES

Table 1	Demographic and Clinical Characteristics of Women living with or at-risk for HIV Infection at End of Observation in the Women's Interagency HIV Study.	28
Table 2	The Burden and Prevalence of Non-AIDS Comorbidities in Women living with or at-risk for HIV Infection by Age Group.	31
Table 3	The Prevalence and Burden of Non-AIDS Comorbidities in Women living with or at-risk for HIV Infection.	32
Table 4	The Prevalence and Burden of Non-AIDS Comorbidities in Women Stratified by HIV serostatus and Age Group.	33
Table 5	Univariate Analysis of Risk Factors at End of Observation Associated with Non-AIDS Comorbidities Burden in Women living with or at-risk for HIV Infection.	34
Table 6	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 HIV Infection.	37
Table 7	Multivariable Analysis of HIV-specific Indices at End of Observation Associated with Non-AIDS Comorbidities Burden in Women living with HIV Infection.	39
Figure 1	Distribution of prevalent non-AIDS comorbidity burden by HIV serostatus and age group demonstrating women living with HIV have a higher burden of comorbidities overall and specifically in age groups 40-49 and ≥60 years.	40
Figure 2	Estimated number of non-AIDS comorbidities by HIV serostatus and age group, adjusted for HIV serostatus, categorized age, HIV*age in addition to the following demographic and clinical factors: race, BMI, education, income, marital status, own residence, and substance use (i.e., cigarettes, crack/cocaine and alcohol).	41
Figure 3	The three 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 (3) by each HIV*age stratum. The dyad of hypertension-psychiatric illness is represented in each stratification of HIV serostatus and age.	42
Supplemental Table 1	Definitions of Non-AIDS Comorbidities in Women living with or at-risk for HIV Infection.	43
Supplemental Table 2	Most Common Co-occurring Non-AIDS Comorbidity Dyads in Women living with or at-risk for HIV Infection.	44
Supplemental Figure	Flow diagram of participants in the Women's Interagency HIV Study (WIHS) eligible for this analysis.	46

Table 1. Demographic and Clinical Characteristics of Women living with or at-risk for HIV Infection at End of Observation in the Women's Interagency HIV Study (WIHS)[%]

Characteristic, median (Q1-Q3) or n (%)	**Entire cohort* (n=3232)**	**HIV+ (n=2309)**	**HIV- (n=923)**	*P* value[¶]
Age, *yrs*	50 (43-56)	51 (44-57)	49 (41-55)	<0.0001
Age group, *yrs*				<0.0001
<40	520 (16)	315 (14)	205 (22)	
40-49	996 (31)	711 (31)	285 (31)	
50-59	1241 (38)	936 (41)	305 (33)	
≥60	475 (15)	347 (15)	128 (14)	
Observation time, *yrs*	15.3 (4.0-18.2)	15.3 (4.0-18.4)	15.3 (4.0-17.9)	0.6365
Race/ethnicity				0.0478
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				<0.0001
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, kg/m^2				<0.0001
<30	1547 (51)	1172 (54)	375 (43)	
≥30	1492 (49)	1004 (46)	488 (57)	
SBP, *mmHg*	123 (111-138)	122 (110-136)	126 (115-141)	<0.0001
DBP, *mmHg*	75 (68-83)	75 (68-83)	76 (69-84)	0.0024
Anti-hypertensive medication use	1298 (40)	951 (41)	347 (38)	0.0599
Lipid-lowering medication use	578 (18)	430 (19)	148 (16)	0.0829
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)	<0.0001
CES-D score[†]	9 (3-19)	9 (3-19)	8 (3-19)	0.6481
Education				0.1795
≤HS	2093 (65)	1513 (66)	580 (63)	
>HS	1132 (35)	793 (34)	339 (37)	
Income				0.0198
<$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	3011 (94)	2245 (98)	766 (83)	<0.0001
Marital status				0.0038
Married/partner	886 (29)	629 (28)	257 (29)	
Had a partner	914 (30)	690 (31)	224 (25)	
Never married/other	1295 (42)	894 (40)	401 (45)	
Own residence	2686 (83)	1973 (86)	713 (77)	<0.0001
Cigarette use				<0.0001
Never	1020 (32)	786 (34)	234 (25)	
Current	1230 (38)	820 (36)	410 (44)	
Former	980 (30)	701 (30)	279 (30)	
Current alcohol use				<0.0001
None	1735 (54)	1339 (58)	396 (43)	
1-7 drinks/week	1200 (37)	807 (35)	393 (43)	
>7 drinks/week	280 (9)	147 (6)	133 (14)	
Marijuana use				<0.0001
Never	985 (31)	782 (34)	203 (22)	
Current	677 (21)	450 (20)	227 (25)	
Former	1551 (48)	1059 (46)	492 (53)	
Crack/cocaine use				<0.0001
Never	2239 (70)	1669 (73)	570 (62)	
Current	218 (7)	133 (6)	85 (9)	
Former	758 (24)	491 (21)	267 (29)	
Opioid use (heroin/methadone)				<0.0001
Never	2822 (88)	2056 (90)	766 (83)	
Current	58 (2)	38 (2)	20 (2)	
Former	335 (10)	199 (9)	136 (15)	
Injection drug use				0.4479
Never	2622 (82)	1866 (81)	756 (82)	
Current	29 (1)	18 (1)	11 (1)	
Former	563 (18)	408 (18)	155 (17)	
Non-injection drug use				<0.0001
Never	820 (26)	659 (29)	161 (17)	
Current	796 (25)	525 (23)	271 (29)	
Former	1597 (50)	1107 (48)	490 (53)	
Chronic HBV	66 (2)	56 (2)	10 (1)	0.0148
Chronic HCV	393 (12)	306 (13)	87 (9)	0.0026
CD4 count, *cells/mm^3*	- - -	615 (400-855)	- - -	- - -
CD4 nadir, *cells/mm^3*	- - -	280 (160-414)	- - -	- - -
HIV viral load	- - -		- - -	- - -
Suppressed‡		1773 (81)		
200-999 copies/ml		106 (5)		

≥1000 copies/ml		311 (14)		
Proportion visits HIV suppressed‡	- - -		- - -	- - -
From baseline visit		69% (44-94)		
On/after 2009		91% (60-100)		
Year initiated cART	- - -		- - -	- - -
1995-1999		865 (37)		
2000-2003		305 (13)		
2004-2008		364 (16)		
≥2009		702 (30)		
Never initiated cART		73 (3)		
Time since cART initiation, *yrs*	- - -	12.5 (7.0-17.1)	- - -	- - -
Antiretroviral class§	- - -		- - -	- - -
PI		769 (33)		
NNRTI		591 (26)		
INSTI		746 (32)		
Other		24 (1)		
Not on therapy		179 (8)		
Specified NRTI^	- - -		- - -	- - -
ABC		479 (24)		
TDF		1156 (57)		
TAF		480 (24)		
Antiretroviral adherence	- - -		- - -	- - -
≥95%		1746 (82)		
<95%		381 (18)		

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; HS = high school; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SBP= systolic blood pressure; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; WIHS = Women's Interagency HIV Study

*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)

¶Chi-square test performed for categorical variables and Wilcoxon rank sum for continuous variables

†Range 0-60, threshold for depressive symptoms ≥16

‡HIV viral load <200 copies/ml and/or <lower limit of quantification of assay

§Categorized hierarchically as PI > NNRTI > INSTI > other

^Of those on any NRTI (n=2033), not mutually exclusive

%: Column percents may not total 100 due to rounding

Table 2. The Burden and Prevalence of Non-AIDS Comorbidities (NACM) in Women living with or at-risk for HIV Infection by Age Group

NACM, n (%)	**<40y (n=520)**	**40-49y (n=996)**	**50-59y (n=1241)**	**≥60y (n=475)**	*P* value*
Psychiatric illness	187 (36)	505 (51)	761 (61)	304 (64)	<0.0001
Hypertension	176 (34)	559 (56)	944 (76)	441 (93)	<0.0001
Lung disease	159 (31)	352 (35)	599 (48)	236 (50)	<0.0001
Liver disease	97 (19)	302 (30)	576 (46)	292 (61)	<0.0001
Dyslipidemia	86 (17)	308 (31)	563 (45)	288 (61)	<0.0001
Bone disease	71 (14)	280 (28)	573 (46)	306 (64)	<0.0001
Diabetes mellitus, type 2	40 (8)	161 (16)	349 (28)	177 (37)	<0.0001
Cardiovascular disease	27 (5)	126 (13)	294 (24)	169 (36)	<0.0001
Cancer, non-AIDS	15 (3)	75 (8)	151 (12)	78 (16)	<0.0001
Chronic kidney disease	7 (1)	39 (4)	186 (15)	178 (37)	<0.0001
Mean NACM burden (sd)	1.7 (1.4)	2.7 (1.8)	4.0 (2.0)	5.2 (1.9)	<0.0001

*Wilcoxon test performed for linear trend across (ordinal) age groups for categorical variables (e.g., prevalence of each comorbidity) and unadjusted linear regression performed for continuous variables (e.g., NACM burden)

Table 3. The Prevalence and Burden of Non-AIDS Comorbidities (NACM) in Women living with or at-risk for HIV Infection

NACM, n (%)	**Total (n=3232)**	**HIV+ (n=2309)**	**HIV- (n=923)**	*P* value*	**OR¶ HIV+/HIV- (95% CI)**
Hypertension	2120 (66)	1532 (66)	588 (64)	0.1530	1.12 (0.96, 1.32)
Psychiatric illness	1757 (54)	1312 (57)	445 (48)	<0.0001	1.41 (1.21, 1.65)
Lung disease	1346 (42)	954 (41)	392 (42)	0.5479	0.95 (0.82, 1.11)
Liver disease	1267 (39)	1030 (45)	237 (26)	<0.0001	2.33 (1.97, 2.76)
Dyslipidemia	1245 (39)	926 (40)	319 (35)	0.0034	1.27 (1.08, 1.49)
Bone disease	1230 (38)	929 (40)	301 (33)	<0.0001	1.39 (1.18, 1.63)
Type 2 DM	727 (22)	502 (22)	225 (24)	0.1050	0.86 (0.72, 1.03)
CVD	616 (19)	438 (19)	178 (19)	0.8365	0.98 (0.81, 1.19)
CKD	410 (13)	349 (15)	61 (7)	<0.0001	2.52 (1.90, 3.34)
Cancer, non-AIDS	319 (10)	251 (11)	68 (7)	0.0026	1.53 (1.16, 2.03)
Mean NACM burden (sd)	3.4 (2.2)	3.6 (2.1)	3.0 (2.1)	<0.0001	- - -

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; sd = standard deviation

*Chi-square test performed for categorical variables (i.e., prevalence of each comorbidity) and two sample t-test performed for continuous variable (i.e., NACM burden); ¶Unadjusted logistic regression performed to assess the odds of having each prevalent NACM for women living with HIV compared to those without HIV.

Table 4. The Prevalence and Burden of Non-AIDS Comorbidities (NACM) in Women Stratified by HIV serostatus and Age Group

	HIV+				**HIV-**				**HIV*age interaction**
NACM, n (%)	*<40 y (n=315)*	*40-49 y (n=711)*	*50-59 y (n=936)*	*≥60 y¶ (n=347)*	*<40 y (n=205)*	*40-49 y (n=285)*	*50-59 y (n=305)*	*≥60 y¶ (n=128)*	*P* value*
Hypertension	99 (31)	413 (58)	698 (75)	322 (93)	77 (38)	146 (51)	246 (81)	119 (93)	0.0169
Psychiatric illness	122 (39)	385 (54)	574 (61)	231 (67)	65 (32)	120 (42)	187 (61)	73 (57)	0.0816
Lung disease	91 (29)	249 (35)	442 (47)	172 (50)	68 (33)	103 (36)	157 (51)	64 (50)	0.8503
Liver disease	76 (24)	239 (34)	482 (52)	233 (67)	21 (10)	63 (22)	94 (31)	59 (46)	0.4073
Dyslipidemia	54 (17)	244 (34)	413 (44)	215 (62)	32 (16)	64 (22)	150 (49)	73 (57)	0.0023
Bone disease	41 (13)	208 (29)	447 (48)	233 (67)	30 (15)	72 (25)	126 (41)	73 (57)	0.3940
Type 2 DM	23 (7)	113 (16)	244 (26)	122 (35)	17 (8)	48 (17)	105 (34)	55 (43)	0.5365
CVD	15 (5)	89 (13)	210 (22)	124 (36)	12 (6)	37 (13)	84 (28)	45 (35)	0.6543
CKD	7 (2)	37 (5)	160 (17)	145 (42)	0 (0)	2 (<1)	26 (9)	33 (26)	0.3004
Cancer, non-AIDS	8 (3)	64 (9)	119 (13)	60 (17)	7 (3)	11 (4)	32 (10)	18 (14)	0.1914
Mean NACM burden (sd)	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)	0.0206

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; sd = standard deviation

¶Wilcoxon test performed for linear trend across (ordinal) age groups for categorical variables (i.e., prevalence of each comorbidity) and unadjusted linear regression performed for continuous variables (i.e., NACM burden) stratified by HIV serostatus: all *P* values were <0.0001 for each prevalent comorbidity and NACM burden within each strata of HIV serostatus; *partially-adjusted logistic regression performed for the prevalence of each comorbidity and partially-adjusted linear regression for NACM burden with HIV serostatus, categorized age, HIV*age interaction terms in the model.

Table 5. Univariate Analysis of Risk Factors at End of Observation Associated with Non-AIDS Comorbidities (NACM) Burden in Women living with or at-risk for HIV Infection

	Total (n=3232)	**HIV+ (n=2309)**	**HIV- (n=923)**	*P* value¶ (*Total, **HIV+, ***HIV-)
Risk factor	Median (Q1-Q3) NACM count			
Age, *yrs*				
<40	1 (1-2)	1 (1-2)	1 (1-2)	<0.0001*
40-49	3 (1-4)	3 (1-4)	2 (1-4)	<0.0001**
50-59	4 (3-5)	4 (3-5)	4 (2-5)	<0.0001***
≥60	5 (4-7)	5 (4-7)	5 (3-6)	
Race/ethnicity				
White, non-Hispanic	4 (2-6)	4 (3-6)	3 (2-5)	<0.0001*
Black, non-Hispanic	3 (2-5)	3 (2-5)	3 (1-4)	<0.0001**
Hispanic	3 (2-5)	3 (2-5)	3 (1-5)	0.6563***
Other	3 (2-5)	3 (2-5)	3 (1-5)	
WIHS enrollment wave				
1994—1995	5 (3-6)	5 (3-6)	4 (2-6)	<0.0001*
2001—2002	3 (1-4)	3 (2-5)	2 (1-4)	<0.0001**
2011—2012	3 (1-4)	3 (1-4)	3 (2-5)	<0.0001***
2013—2015	2 (1-4)	2 (1-4)	2 (1-4)	
BMI, kg/m^2				0.7051*
<30	3 (2-5)	3 (2-5)	3 (1-4)	0.2240**
≥30	3 (2-5)	3 (2-5)	3 (1-5)	0.0380***
Education				0.0002*
≤HS	3 (2-5)	3 (2-5)	3 (1-5)	0.0829**
>HS	3 (2-5)	3 (2-5)	2 (1-4)	0.0001***
Income				
<$12,000	4 (2-5)	4 (2-5)	4 (2-5)	<0.0001*
$12,001-24,000	3 (2-5)	3 (2-5)	3 (2-4)	<0.0001**
>$24,000	2 (1-4)	3 (2-4)	2 (1-3)	<0.0001***
Insured				<0.0001*
No	2 (1-3)	2 (1-4)	2 (1-3)	0.0034**
Yes	3 (2-5)	3 (2-5)	3 (1-5)	<0.0001***
Marital status				
Married/partner	3 (2-5)	3 (2-5)	3 (1-4)	<0.0001*
Had a partner	4 (2-5)	4 (2-5)	3 (2-5)	<0.0001**
Never partner/other	3 (2-5)	3 (2-5)	3 (1-4)	0.0010***
Own residence				0.2044*
No	3 (2-5)	3 (2-5)	3 (2-5)	0.1007**
Yes	3 (2-5)	3 (2-5)	3 (1-4)	0.2501***

Smoking use Never Current Former	 2 (1-4) 4 (2-5) 4 (2-5)	 2 (1-4) 4 (2-5) 4 (2-6)	 2 (1-3) 3 (2-5) 3 (1-5)	 <0.0001* <0.0001** <0.0001***
Current alcohol use None 1-7 drinks/week >7 drinks/week	 4 (2-5) 3 (1-4) 3 (2-4)	 4 (2-5) 3 (2-5) 3 (2-5)	 3 (2-5) 2 (1-4) 3 (2-4)	 <0.0001* 0.0013** <0.0001***
Marijuana use Never Current Former	 2 (1-4) 4 (2-5) 4 (2-5)	 2 (1-4) 4 (2-5) 4 (2-5)	 2 (1-4) 3 (1-4) 3 (2-5)	 <0.0001* <0.0001** <0.0001***
Crack/cocaine use Never Current Former	 3 (1-4) 4 (2-5) 4 (3-6)	 3 (2-5) 4 (2-5) 5 (3-6)	 2 (1-4) 3 (2-5) 4 (2-6)	 <0.0001* <0.0001** <0.0001***
Injection drug use Never Current Former	 3 (1-4) 5 (4-6) 5 (4-6)	 3 (2-5) 5 (4-6) 5 (4-6)	 2.5 (1-4) 5 (3-6) 4 (3-6)	 <0.0001* <0.0001** <0.0001***
CD4 count, *cells/mm^3* <500 ≥500	- - -	 4 (2-6) 3 (2-5)	- - -	0.0066**
CD4 nadir, *cells/mm^3* <200 ≥200	- - -	 4 (2-5) 3 (2-5)	- - -	0.0172**
HIV viral load Suppressed‡ 200-999 copies/ml ≥1000 copies/ml	- - -	 3 (2-5) 4 (2-5) 3 (2-5)	- - -	0.2681**
Proportion visits HIV suppressed‡ from baseline <50% ≥50%	- - -	 4 (2-5) 3 (2-5)	- - -	<0.0001**
Proportion visits HIV suppressed‡ on/after 2009 <90% ≥90%	- - -	 3 (2-5) 3 (2-5)	- - -	0.2229**

Time since cART initiation <10 years ≥10 years	- - -	 3 (1-4) 4 (2-6)	- - -	<0.0001**

INSTI use since last visit
  No
  Yes
	- - -	
		3 (2-5)
		4 (2-5)
			- - -	0.0012**

NNRTI use since last visit
  No
  Yes
	- - -	
		3 (2-5)
		3 (2-5)
			- - -	0.1856**

PI use since last visit
  No
  Yes
	- - -	
		3 (2-5)
		4 (2-5)
			- - -	0.0043**

Abacavir use
  No
  Yes
	- - -	
		3 (2-5)
		4 (2-6)
			- - -	<0.0001**

TDF use
  No
  Yes
	- - -	
		4 (2-5)
		3 (2-5)
			- - -	<0.0001**

TAF use
  No
  Yes
	- - -	
		3 (2-5)
		3 (2-5)
			- - -	0.3313**

Antiretroviral adherence <95% ≥95%	- - -	 3 (2-5) 3 (2-5)	- - -	0.3009**

Abbreviations: BMI = body mass index; cART = combined antiretroviral therapy; HS = high school; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide disoproxil; TDF = tenofovir fumarate disoproxil; WIHS = Women's Interagency HIV Study

¶Wilcoxon rank sum test for continuous variable (i.e., NACM burden), total and stratified by HIV serostatus

‡HIV viral load <200 copies/ml and/or <lower limit of quantification of assay

Table 6. Multivariable Analysis of Risk Factors at End of Observation Associated with the Burden of Non-AIDS Comorbidities (NACM) in Women living with or at-risk for HIV Infection

Risk factor	**Estimated mean number of NACM (95% CI)**	**Beta (±SE)**	*P* value*
HIV serostatus†			<0.0001
Positive	3.46 (3.30, 3.63)	0.40 (±0.08)	
Negative	3.07 (2.89, 3.24)	Ref	
Age group, *yrs*†			<0.0001
≥60	4.49 (4.25, 4.73)	2.40 (±0.14)	
50-59	3.77 (3.60, 3.94)	1.68 (±0.11)	
40-49	2.70 (2.52, 2.88)	0.61 (±0.10)	
<40	2.09 (1.88, 2.30)	Ref	
Race			<0.0001
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, kg/m^2			<0.0001
≥30	3.51 (3.34, 3.67)	0.48 (±0.06)	
<30	3.02 (2.86, 3.18)	Ref	
Education			0.3517
≤HS	3.23 (3.07, 3.39)	-0.07 (±0.07)	
>HS	3.30 (3.12, 3.47)	Ref	
Income			<0.0001
<$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			0.1108
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			0.2937
No	3.22 (3.02, 3.41)	-0.09 (±0.09)	
Yes	3.31 (3.16, 3.46)	Ref	
Cigarette use			<0.0001
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			0.0467
>7 drinks/week	3.15 (2.91, 3.39)	-0.24 (±0.12)	
1-7 drinks/week	3.26 (3.09, 3.42)	-0.13 (±0.07)	
None	3.39 (3.22, 3.56)	Ref	
Crack/cocaine use			<0.0001
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: HS = high school; Ref = reference; SE = standard error

†Adjusted for HIV serostatus*age interaction

*Adjusted linear regression with all covariates listed included in the model plus WIHS enrollment wave; assessing HIV*age interaction: p=0.0978

Table 7. Multivariable Analysis of HIV-specific Indices at End of Observation Associated with Non-AIDS Comorbidities (NACM) Burden in Women living with HIV Infection

HIV index	**Estimated mean number of NACM (95% CI)**	**Beta (±SE)**	*P* value*
CD4 count, *cells/mm^3*			0.0762
<500	3.62 (3.39, 3.85)	0.15 (±0.09)	
≥500	3.46 (3.23, 3.70)	Ref	
CD4 nadir, *cells/mm^3*			0.4425
<200	3.51 (3.26, 3.75)	-0.06 (±0.08)	
≥200	3.57 (3.35, 3.79)	Ref	
Time since cART initiation			0.1033
≥10 years	3.63 (3.39, 3.87)	0.18 (±0.11)	
<10 years	3.45 (3.21, 3.69)	Ref	
Proportion visits HIV suppressed‡ from initial WIHS visit			0.7676
<50%	3.53 (3.27, 3.78)	-0.03 (±0.10)	
≥50%	3.55 (3.33, 3.77)	Ref	
PI use in last 6 months			0.5666
Yes	3.56 (3.32, 3.81)	0.05 (±0.08)	
No	3.52 (3.30, 3.74)	Ref	
Abacavir use in last 6 months			<0.0001
Yes	3.76 (3.50, 4.02)	0.44 (±0.09)	
No	3.32 (3.11, 3.54)	Ref	

Abbreviations: cART = combined antiretroviral therapy; PI = protease inhibitor; SE = standard error; WIHS = Women's Interagency HIV Study

*Adjusted linear regression performed controlling for age (p<0.0001), race (p<0.0001), WIHS enrollment wave (p<0.0001), body mass index (p<0.0001), education (p=0.1031), income (p<0.0001), marital status (p=0.1649), own residence (p=0.5185), cigarette use (p<0.0001), current alcohol use (p=0.4295), crack/cocaine use (p=0.0055)

‡HIV viral load <200 copies/ml and/or <lower limit of quantification of assay

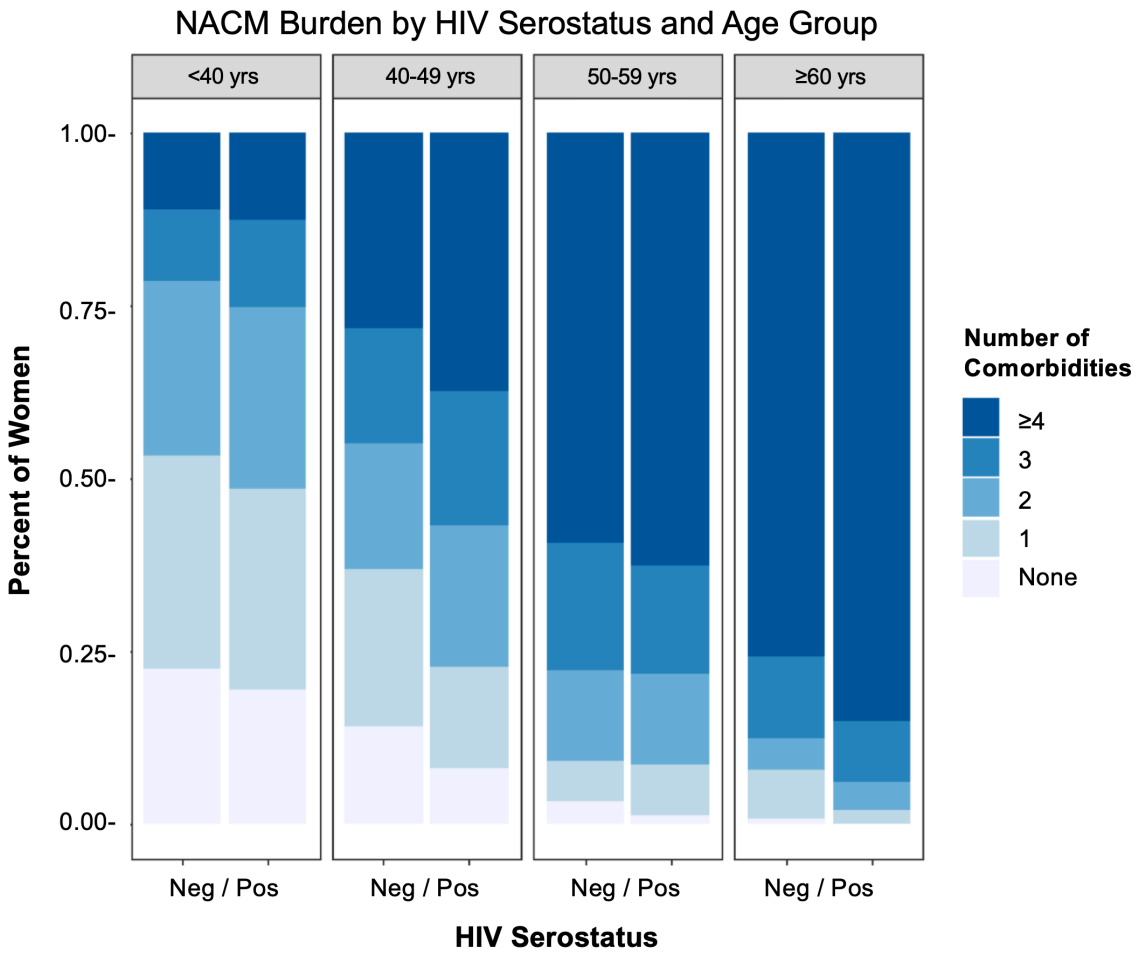
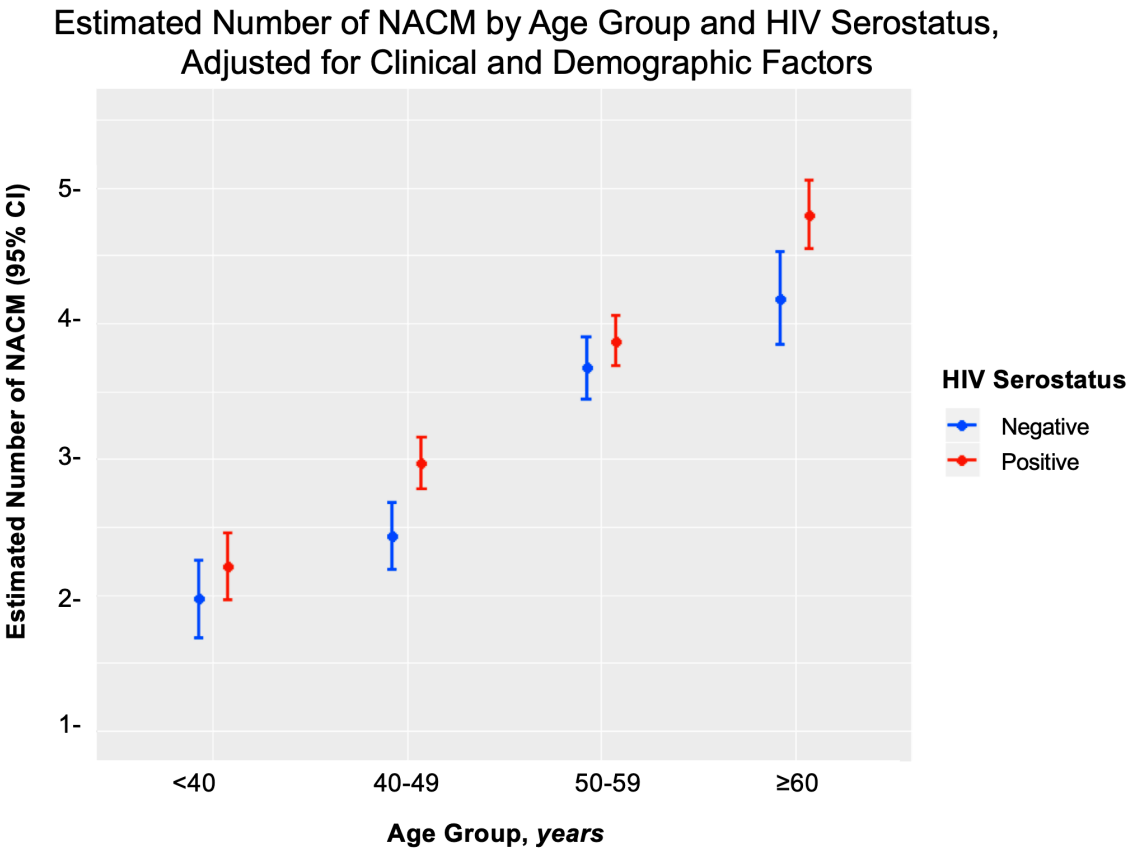


Figure 1. Distribution of prevalent non-AIDS comorbidity burden by HIV serostatus and age group demonstrating women living with HIV have a higher burden of comorbidities overall and specifically in age groups 40-49 and ≥60 years.



	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 in addition to the following demographic and clinical factors: race, BMI, education, income, marital status, own residence, and substance use (i.e., cigarettes, crack/cocaine and alcohol).

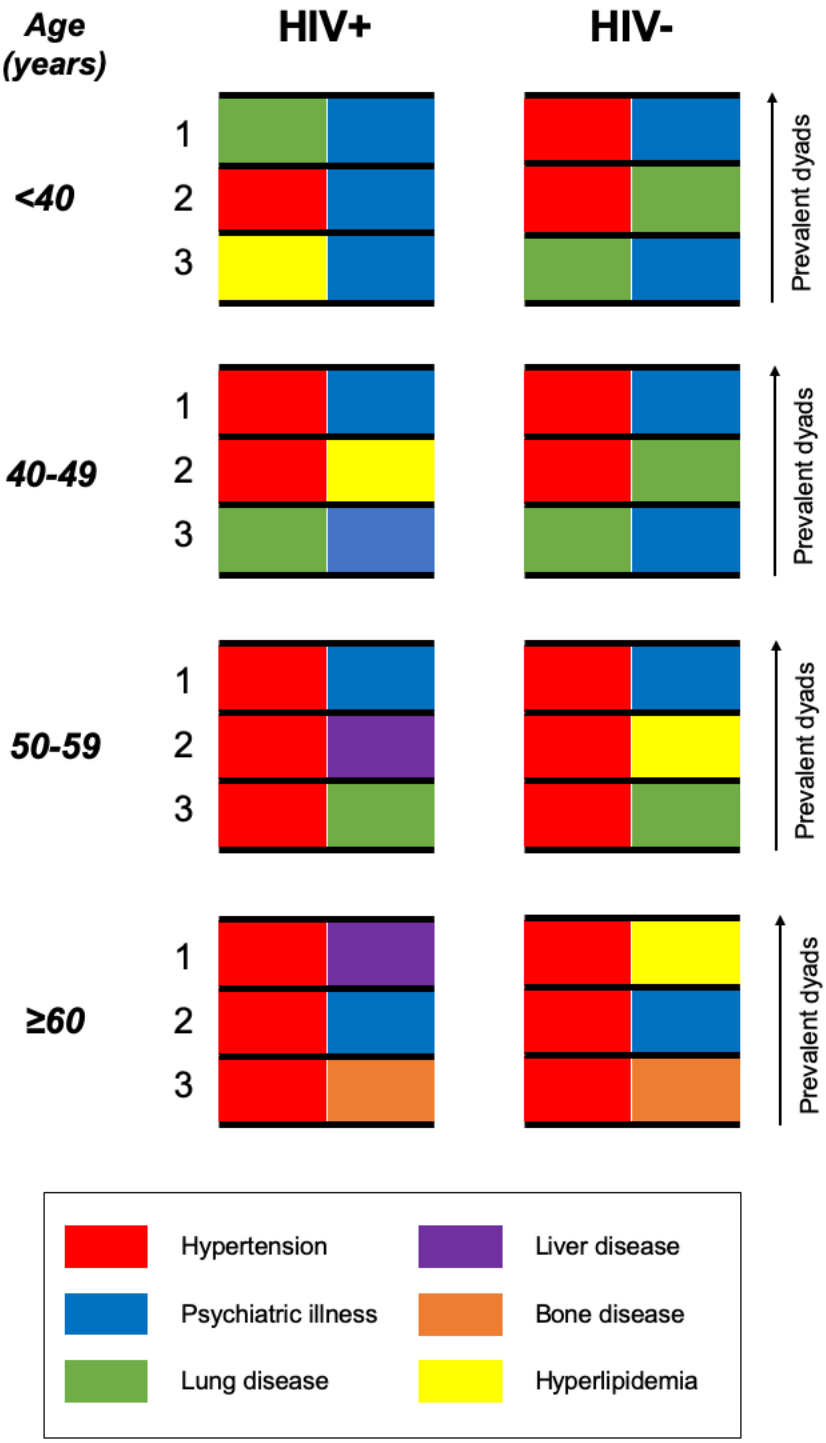


Figure 3. The three most common co-occurring non-AIDS comorbidity dyads in women living with or at-risk for HIV infection, stratified by HIV serostatus and age group and ranked as most prevalent (1), second most prevalent (2) and third (3) by each HIV*age stratum. The dyad of hypertension-psychiatric illness is represented in each stratification of HIV serostatus and age.

Supplemental Table 1. Definitions of Non-AIDS Comorbidities (NACM) in Women living with or at-risk for HIV Infection

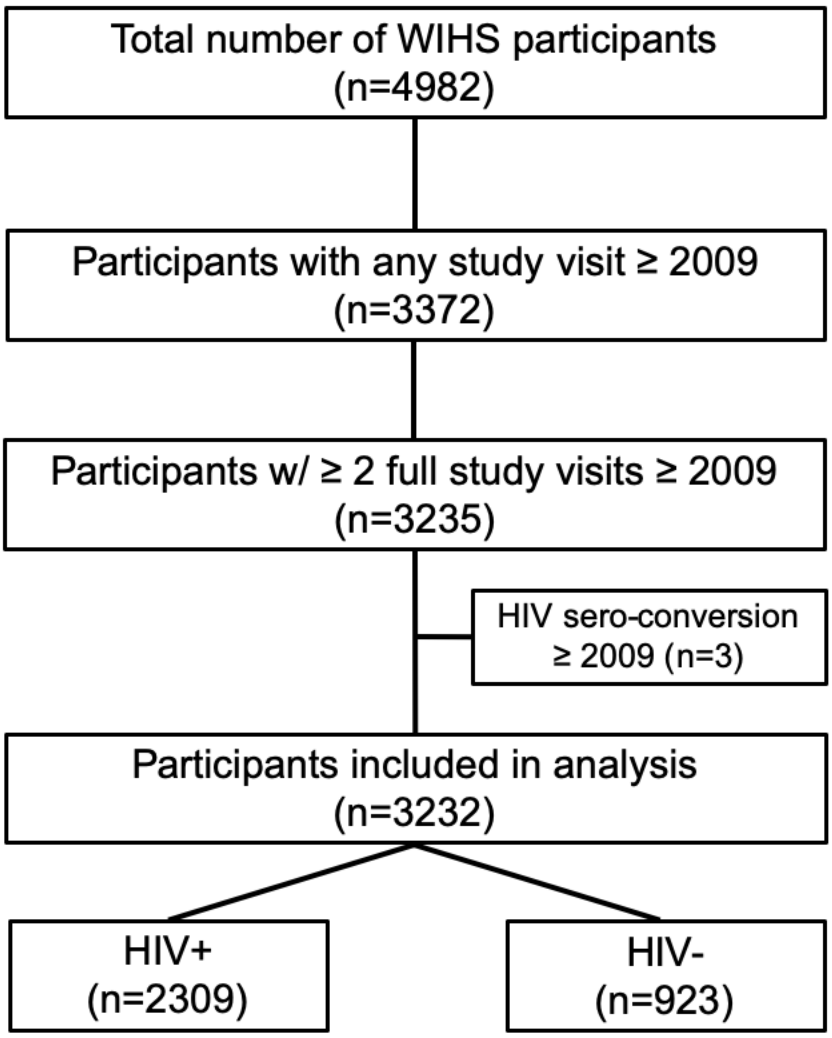
NACM	Definition	Source	Comments
Bone disease	Low bone density, osteopenia, osteoporosis, fracture *Or* receipt of osteoporosis medication	Self-report	Included if any one of listed diagnoses was reported
Cancer, non-AIDS	Breast, lung, colon, uterine, cervical, ovarian, liver, Hodgkin's lymphoma	Self-report	Excluded skin cancer, Kaposi's sarcoma, Non-Hodgkin's lymphoma, central nervous system lymphoma, "metastatic cancer," "other cancers"
Cardiovascular disease	Myocardial infarction or heart attack, revascularization or angioplasty, transient ischemic attack/stroke, angina or hospitalization for heart condition	Self-report	Included if any one of listed diagnoses was reported
Chronic kidney disease	eGFR <60 mL/min/1.73 m^2 (determined by the CKD-epi formula)	Laboratory	Required laboratory abnormality on two consecutive study visits
Psychiatric illness	Depression, anxiety, psychiatric problem, or hospitalization for psychiatric illness *And* receipt of anti-depressant/-psychotic medication *Or CES-D* ≥16 on two consecutive study visits	Self-report or clinic measurement	N/A
Diabetes mellitus, type 2	Receipt of anti-diabetic medication *Or* FBG ≥126 mg/dL on two study visits *Or* HgbA1c ≥6.5% and FBG above threshold at one study visit	Self-report or laboratory	N/A
Dyslipidemia	Receipt of lipid-lowering medication *Or* LDL ≥130 mg/dL *And* HDL <40 mg/dL	Self-report or laboratory	N/A
Hypertension	Receipt of anti-hypertensive medication *Or* elevated blood pressure on any two study visits (systolic ≥140 and/or diastolic ≥90)	Self-report or clinic measurement	N/A
Liver disease	Chronic hepatitis B or C viral infection *Or* APRI score >0.7 *Or* FIB-4 score >3.25	Laboratory	N/A
Lung disease	Asthma, chronic obstructive pulmonary disease, or hospitalization for a lung problem other than pneumonia	Self-report	Included if any one of listed diagnoses was reported

Abbreviations: APRI = AST to Platelet Ratio Index; CES-D = Center for Epidemiologic Studies-Depression Scale; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated Glomerular Filtration Rate; FBG = Fasting Blood Glucose; FIB-4 = Fibrosis-4; HDL = High-Density Lipoprotein; HgbA1c = Hemoglobin A1c; LDL = Low-Density Lipoprotein

Supplemental Table 2. Most Common Co-occurring Non-AIDS Comorbidity Dyads in Women living with or at-risk for HIV Infection

Category	*n*	**Top 5 comorbidity dyads**	**Frequency**
All women, *all ages*	*3232*	1. HTN-Psych 2. HTN-Dyslipidemia 3. HTN-Lung 4. HTN-Liver 5. HTN-Bone	40.1% 31.5% 31.3% 29.4% 28.8%
HIV+ women, *all ages*	*2309*	1. HTN-Psych 2. HTN-Liver 3. HTN-Dyslipidemia 4. HTN-Lung 5. HTN-Bone	41.5% 33.2% 32.2% 31.2% 30.5%
HIV- women, *all ages*	*923*	1. HTN-Psych 2. HTN-Lung 3. HTN-Dyslipidemia 4. Psych-Lung 5. HTN-Bone	36.4% 31.6% 29.8% 26.0% 24.4%
All women, *<40 y*	*520*	1. Psych-Lung 2. HTN-Psych 3. HTN-Lung 4. Psych-Dyslipidemia 5. Psych-Liver	14.8% 14.4% 11.9% 8.8% 8.1%
All women, *40-49 y*	*996*	1. HTN-Psych 2. HTN-Lung 3. Psych-Lung 4. HTN-Dyslipidemia 5. Psych-Liver	32.7% 23.3% 22.9% 22.8% 19.3%
All women, *50-59 y*	*1241*	1. HTN-Psych 2. HTN-Lung 3. HTN-Dyslipidemia 4. HTN-Liver 5. HTN-Bone	49.1% 39.9% 38.2% 36.2% 36.1%
All women, *≥60 y*	*475*	1. HTN-Psych 2. HTN-Bone 3. HTN-Dyslipidemia 4. HTN-Liver 5. HTN-Lung	60.0% 58.9% 58.3% 58.3% 46.9%
HIV+ women, *<40 y*	*315*	1. Psych-Lung 2. HTN-Psych 3. Psych-Dyslipidemia 4. HTN-Lung 5. Psych-Liver	15.2% 13.0% 9.8% 9.8% 9.8%

HIV+ women, *40-49 y*	*711*	1. HTN-Psych 2. HTN-Dyslipidemia 3. Psych-Lung 4. HTN-Lung 5. Psych-Liver	35.3% 24.9% 23.8% 23.6% 21.9%
HIV+ women, *50-59 y*	*936*	1. HTN-Psych 2. HTN-Liver 3. HTN-Lung 4. HTN-Bone 5. HTN-Dyslipidemia	48.3% 39.6% 38.2% 36.8% 36.0%
HIV+ women, ≥*60 y*	*347*	1. HTN-Liver 2. HTN-Psych 3. HTN-Bone 4. HTN-Dyslipidemia 5. Psych-Liver	63.7% 62.0% 61.1% 59.1% 49.3%
HIV- women, <*40 y*	*205*	1. HTN-Psych 2. HTN-Lung 3. Psych-Lung 4. HTN-Dyslipidemia 5. Lung-Dyslipidemia	16.6% 15.1% 14.1% 7.8% 7.3%
HIV- women, *40-49 y*	*285*	1. HTN-Psych 2. HTN-Lung 3. Psych-Lung 4. HTN-Dyslipidemia 5. Psych-Bone	26.3% 22.5% 20.7% 17.5% 14.4%
HIV- women, *50-59 y*	*305*	1. HTN-Psych 2. HTN-Dyslipidemia 3. HTN-Lung 4. Psych-Lung 5. Psych-Dyslipidemia	51.5% 44.9% 44.9% 35.7% 35.4%
HIV- women, ≥*60 y*	*128*	1. HTN-Dyslipidemia 2. HTN-Psych 3. HTN-Bone 4. HTN-Lung 5. HTN-Liver	56.3% 54.7% 53.1% 46.9% 43.8%



Supplemental Figure. Flow diagram of participants in the Women's Interagency HIV Study (WIHS) eligible for this analysis.