Women are grossly underrepresented in human immunodeficiency virus (HIV) clinical and translational research. This is concerning given that people with HIV (PWH) are living longer, and thus accumulating aging-related non-AIDS comorbidities (NACMs); emerging evidence suggests that women are at higher risk of NACM development and progression compared with men. It is widely recognized that women vs men have greater immune activation in response to many viruses, including HIV-1; this likely influences sex-differential NACM development related to differences in HIV-associated chronic inflammation. Furthermore, many sociobehavioral factors that contribute to aging-related NACMs are known to differ by sex. The objectives of this review were to (1) synthesize sex-stratified data on 4 NACMs among PWH: bone disease, cardiovascular disease, metabolic dysfunction, and neurocognitive impairment; (2) evaluate the characteristics of key studies assessing sex differences in NACMs; and (3) introduce potential biological and psychosocial mechanisms contributing to emerging trends in sex-differential NACM risk and outcomes among PWH.

**Keywords.** HIV; HIV and aging; non-AIDS comorbidities; sex differences; women with HIV.

Antiretroviral therapy (ART) has extended the life expectancy of people with human immunodeficiency virus (HIV) [1], such that in the United States (US), >50% of PWH are ≥50 years old [2]. Increasingly, morbidity and mortality among PWH is due to aging-related non-AIDS comorbidities (NACMs), which occur at higher prevalence and earlier onset when compared with human immunodeficiency virus (HIV)–seronegative individuals [2–5].

More than half of HIV infections globally occur among women [6]; however, women remain underrepresented in HIV research and clinical trials [7, 8]. This is concerning as PWH age, given that emerging sex-stratified data suggest a higher burden of NACMs occurring among women with HIV (WWH) vs men with HIV (MWH) [9, 10]. Women have greater immune activation than men in response to HIV-1 infection, possibly mediating observed sex differences in the development of inflammation-associated NACMs [11]; this effect may be compounded by the menopausal transition [12–14], potentially occurring prematurely in HIV [15]. Finally, WWH, compared with MWH, may be at greater risk of sociobehavioral and structural factors (eg, interpersonal violence, economic instability) leading to isolation, healthcare underutilization, and poor health outcomes [16, 17].

Care of PWH increasingly requires dedicated attention to comorbidity screening, prevention, and management; however, best practices on providing NACM care to women and men remain unknown [2, 3, 18]. To optimize care delivery and outcomes, it is critical to understand sex differences among aging PWH in NACM risk, pattern, and progression so that sex-tailored chronic disease care strategies, including NACM identification and risk mitigation tools, can be developed and implemented [19].

The objectives of this review were to (1) synthesize sex-stratified (primary) or sex-specific HIV-attributable risk (secondary) data on 4 NACMs among PWH: bone disease, cardiovascular disease, metabolic dysfunction, and neurocognitive impairment; (2) evaluate key studies assessing sex differences in NACMs; and (3) introduce potential biological and psychosocial mechanisms contributing to emerging trends in sex-differential NACM risk and outcomes among PWH.

**HIV-ASSOCIATED NON-AIDS COMORBIDITIES**

**Bone Disease**

PWH have an increased lifetime fracture risk compared with HIV-seronegative peers. In a recent meta-analysis, PWH had a 6.4-fold greater odds of bone mineral density (BMD) loss compared with HIV-negative persons, and ART-exposed PWH had a 2.5-fold greater odds compared with ART-naive PWH [20]. BMD loss among PWH is multifactorial, attributable to HIV-1 infection, ART-associated immune reconstitution, ART toxicity (Table 1), and a high prevalence of substance use, coalescing to accelerate...
| ART Agent or Class | Bone Disease | Cardiovascular Risk | Metabolic Dysfunction | Neuropsychiatric Effects |
|-------------------|--------------|---------------------|-----------------------|-------------------------|
| **Nucleoside reverse transcriptase inhibitors** |   |   |   |   |
| Abacavir | Switching from TDF to ABC led to improved femoral neck BMD at 48 wk, though no significant difference compared with those maintained on TDF and data not sex-stratified [129] | Association of ABC with MI remains unclear and controversial [130], though sex not associated with increased MI risk [131]; among women, ABC use was associated with higher triglycerides vs no use [132] | ABC use has not been associated with significant metabolic effects among PWH | Neuropsychiatric sequelae of ABC use are limited to case reports of mania occurring among men, though headache and mood alterations may be earlier indicators [133] |
| TDFa | Among women vs men, TDF exposure was associated with femoral neck BMD loss of –0.0032 vs –0.0026 g/cm² and lumbar spine BMD loss of –0.0031 vs –0.0031 g/cm² over median 4.6 y [134] | TDF has been noted to have a favorable effect on lipids [135]; among women, self-reported use of TDF was associated with lower triglyceride values (129 vs 147 mg/dL, P = .009 for users vs nonusers) [132] | Women vs men gained 3.2 vs 3.0 kg 48 weeks after DTG-based ART initiation plus TDF [136] | There are limited data on the neuropsychiatric effects of tenofovir drugs, and overall TDF and TAF are considered well-tolerated in terms of possible CNS effects |
| TAFa | Switching from TDF- to TAF-based ART improved bone outcomes among virologically suppressed PWH, but data not sex-stratified [137]; providers may consider weighing the overall risk of accelerated BMD loss among women vs greater TAF-associated weight gain for women | Levels of triglycerides and HDL and LDL cholesterol were higher among patients receiving TAF than TDF; however, the total cholesterol-to-LDL ratio did not differ [138]; sex-stratified data not available | Women vs men gained 6.4 vs 4.7 kg 48 weeks after DTG-based ART initiation plus TAF [136]; among women switching to TAF (without INSTI), the observed increase in weight and BMI (+0.4 kg and +0.2 kg/m², respectively) were significant for those with preswitch BMI <30 kg/m² (but not ≥30 kg/m²) [139] |   |
| **Nonnucleoside reverse transcriptase inhibitors** |   |   |   |   |
| Efavirenz | There are limited data on the effects of NNRTI agents on BMD, and overall NNRTI-related bone effects are considered minimal | EFV use has been associated with better HDL cholesterol and less deleterious triglyceride responses among women than men [132] | Women are more likely than men to experience lipohypertrophy, and in particular truncal obesity, associated with NNRTI/EFV use, whereas men vs women are more likely to experience lipatrophy [140]; body fat distribution changes appear similar for those on EFV- vs RPV-based ART [141] | CNS symptoms are more commonly observed with EFV than RPV [142]; higher incidence of abnormal dreams/nightmares among men vs women, but no sex differences in headache, somnolence, insomnia [143] |
| Rilpivirine | RPV has been shown to have less effect on lipids than EFV [144]; switching from PI/ritonavir to RPV was associated with improved lipid profiles and 10-year Framingham score [145]; sex-stratified data not available | More favorable lipid effects among those on DOR vs EFV; sex differences not apparent [146] | Mean 96-wk weight gain higher among women vs men (3.2 vs 2.2 kg); sex not associated with ≥10% weight gain or BMI class increase in multivariate analyses [147] | Fewer neuropsychiatric effects experienced on DOR than EFV; sex differences not apparent [146] |
| Doravirine | Mean 96-wk weight gain higher among women vs men (3.2 vs 2.2 kg); sex not associated with ≥10% weight gain or BMI class increase in multivariate analyses [147] |   |   |   |
| **Protease inhibitors** |   |   |   |   |
| Atazanavir (boosted) | Among women, osteoporosis risk was increased for use of PI + no TDF (HR, 5.9 [95% CI, 1.2–27.6]) and for PI + TDF (HR, 6.9 [95% CI, 1.4–34.4]) compared with no PI + no TDF; however, the corresponding values among men were 1.8 [95% CI, 0.3–10.2] and 1.2 [95% CI, 0.6–2.6], respectively [30] | ATV appears protective against ischemic CVD; sex not associated with ATV-associated effect [148, 149] | The treatment difference for change in WC for ATV/ritonavir vs RAL was greater for women than for men (differential mean change of –3.2 cm [95% CI, –6.5 to .92], P = .0065) [150] | Little evidence of specific CNS toxicity associated with PI use, although there may be a risk of peripheral neuropathy with ATV [151]; sex-stratified data not available |
| Darunavir (boosted) | 9.6% of men compared with 3.7% of women experienced grade 2–4 adverse lipid effects after DRV/cobicistat initiation [152] | The treatment difference for change in WC for DRV/ritonavir vs RAL was greater for women than for men (differential mean change of –2.0 cm [95% CI, –4.32 to .31], P = .0901) [150] | 74% of women compared with 3.1% of men experienced grade 2–4 adverse CNS effects after DRV/cobicistat initiation [152] |   |
| Table 1. Continued |
|------------------|
| **ART Agent or Class** | **Bone Disease** | **Cardiovascular Risk** | **Metabolic Dysfunction** | **Neuropsychiatric Effects** |
| Integrase strand transfer inhibitors | Women more likely than men to discontinue DTG | Women but not men experienced significant weight gain after switch to DTG [154] | Women but not men experienced significant weight gain after switch to DTG [154]; among women over mean 2 years of follow-up, weight increased by 2.1 kg, BMI by 0.8 kg/m², and WC by 2.0 cm [158] | Head-to-head trial of ABC/3TC/DTG vs TAF/FTC/BIC showed a similar distribution of CNS and psychiatric adverse events [159]; sex-stratified data not available |
| Bictegravir | BIC-associated changes in BMD showed favorable lipid effect if switched from boosted-PI | BIC appears to be lipid-neutral and even have favorable lipid effect if switched from boosted-PI | BIC-associated changes in BMD showed favorable lipid effect if switched from boosted-PI | BIC-associated changes in BMD showed favorable lipid effect if switched from boosted-PI |
| | BIC-associated changes in BMD showed favorable lipid effect if switched from boosted-PI | BIC-associated changes in BMD showed favorable lipid effect if switched from boosted-PI | BIC-associated changes in BMD showed favorable lipid effect if switched from boosted-PI | BIC-associated changes in BMD showed favorable lipid effect if switched from boosted-PI |

**Cardiovascular Disease**

Cardiovascular disease (CVD) is the leading cause of non-AIDS mortality among PWH [37–39]. Compared with persons without HIV, PWH experience a 2-fold higher risk of cardiovascular-related morbidity and mortality [40] and a 4.5 times higher risk of sudden cardiac death [41]. Differences in CVD outcomes are likely driven by HIV-related immune activation [42], ART-associated dyslipidemia [43], and an overrepresentation of traditional risk factors [44] among PWH. While female sex has been considered protective against CVD in the general population, recent data comparing PWH vs HIV-negative counterparts revealed that CVD mortality was higher among women (rate ratio [RR], 2.24 [95% confidence interval (CI), 2.07–2.43]) than men (RR, 1.23 [95% CI, 1.16–1.30]) [45] (Table 3).

**BMD Loss**

BMD loss pre–ART initiation is greater among WWH than MWH. In adjusted models, WWH vs MWH had lower BMD pre-ART (−0.39 g/cm² [lumbar spine], −0.05 g/cm² [hip]) [25]. ART initiation accelerates HIV-associated bone resorption [26, 27], with the greatest effect during the first 2 years of ART [28, 29], and the effect of ART exposure on BMD loss appears greater for women than men. Among PWH aged ≥45 years, the risk of developing osteoporosis on a protease inhibitor (PI)–containing regimen (vs no PI) was increased 5.9-fold among WWH but only 1.8-fold among MWH. Regimens containing both a PI and tenofovir disoproxil fumarate (TDF) (vs neither) increased osteoporosis risk 7-fold among WWH, but there was no increased risk among MWH [30]. Similarly, after 48 weeks of TDF, WWH had a 1.7% greater decline in hip BMD than MWH [25]. In a 5-year study, ART-treated WWH vs MWH were 3 times more likely to experience ≥5% BMD loss at the lumbar spine [31] (Table 2).

**Fracture**

ART-exposed WWH vs MWH are at significantly greater risk of osteoporotic fracture [32]. Among ART-naive PWH initiating TDF, WWH had a 3 times greater fracture rate than MWH, and first osteoporotic fracture occurred sooner among women than men (123 vs 1438 days, respectively) [32]. Another study including adult PWH showed that while MWH had a 1.5 times higher incident fracture rate compared with WWH from ages 36 to 46 years, the difference by sex diminished in older age groups [33]. The menopausal transition likely exacerabtes HIV-associated BMD loss, given an accelerated fracture risk among postmenopausal WWH compared with postmenopausal women without HIV or with MWH [34–36] (Table 2).
Table 2. Summary of Studies Reporting Sex Differences for Bone Disease Among People With HIV

| Author, Year, Ref. | Study Design | Study Population (Location, Race/Ethnicity, Age) | Outcomes Measured | Key Findings | Limitations |
|--------------------|--------------|--------------------------------------------------|-------------------|--------------|-------------|
| **Bone mineral density** | | | | | |
| Kalayjian et al, 2018 [25] | Longitudinal | N = 499 (100% PWH) 438 men, 61 women | BMD at left hip & lumbar spine at baseline (ART-naive) and 4 wk post-ART initiation | WWH vs MWH had lower adjusted baseline BMD at spine (–0.39 g/cm², P < .05) and hip (–0.05 g/cm², P < .05). | WWH were underrepresented, older, and more often Black compared with MWH. Did not control for substance use or capture menopause status. Did not include persons without HIV for comparison. |
| Negredo et al, 2018 [30] | Longitudinal | N = 675 (100% PWH) 659 men, 216 women | Risk of progression to different BMD category after age 45 stratified by ART regimen: PI and/or TDF (primary) | WWH vs MWH had higher risk of progression from osteopenia to osteoporosis after age 45 on combined PI + TDF regimen: HR, 6.9 (95% CI, 1.4–34.4) vs 1.2 (95% CI, 0.6–2.6), respectively. | WWH were underrepresented. Did not control for BMD loss risk factors including menopause status. Did not report statistical significance of sex differences. Did not include persons without HIV for comparison. |
| Han et al, 2020 [31] | Prospective longitudinal cohort | N = 172 (62% PWH) 88 men, 84 women | BMD loss (≥5%) at total hip, lumbar spine, and femoral neck at baseline, 1, 2, and 5 y post-ART initiation | WWH vs MWH had higher adjusted odds of BMD loss at lumbar spine over 5 y (aOR, 3.0 [95% CI, 1.0–8.8], P = .05) but not at total hip (P = .2) or femoral neck (P = .8). | High rates of loss to follow-up among PWH. Did not capture menopause status. |
| **Fracture** | | | | | |
| Komatsu et al, 2018 [32] | Longitudinal | N = 3251 (100% PWH) 3040 men, 211 women | Cumulative risk of osteoporosis-related fracture after initiating TDF-containing regimen | WWH vs MWH had higher fracture rate (42.2 vs 13.5 per 10000 PY) | WWH were underrepresented. Few total fractures reported over follow-up period. Did not report statistical significance of sex differences. Did not control for many fracture risk factors including menopause status. Did not include persons without HIV for comparison. |
| Gedmintas et al, 2014 [33] | Longitudinal | N = 3161 (100% PWH) 2292 men, 869 women | Incident fracture rate at osteoporotic sites and nonosteoporotic sites overall and across 5 age strata | No significant sex differences in fracture rates within any age stratum. | Not powered to detect sex differences between age strata. Did not control for many fracture risk factors including menopause status. Did not include persons without HIV for comparison. |

Abbreviations: ACTG, AIDS Clinical Trial Group; aOR, adjusted odds ratio; ART, antiretroviral therapy; BMD, bone mineral density; CI, confidence interval; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio; MWH, men with HIV; PI, protease inhibitor; PWH, persons with HIV; PY, person-years; TDF, tenofovir disoproxil fumarate; WWH, women with HIV.
Table 3. Summary of Studies Reporting Sex Differences for Cardiovascular Disease Among People With HIV

| Study Design | Study Population (Location, Race/Ethnicity, Age) | Outcomes Measured | Key Findings | Limitations |
|--------------|-------------------------------------------------|-------------------|--------------|-------------|
| Frazier et al, 2019 [46] | Older PWH receiving HIV care across the US who enrolled in the Medical Monitoring Project (national HIV surveillance program) | Prevalence of HTN, total cholesterol, LDL, stratified by age (50-64 vs ≥65 y) and sex | • WWH vs MWH had higher adjusted prevalence of HTN among those aged 50-64 y (141% vs 36%, P < .05) but not significantly among those aged ≥65 y (88% vs 50%, P = .06) | WWH were underrepresented. WWH were less likely to be virally suppressed than MWH. Did not include persons without HIV for comparison. Did not capture menopause status. |
| N = 7436 (100% PWH) | 5584 men, 1852 women | | • WWH in both age strata had a higher adjusted prevalence of elevated cholesterol than MWH (P < .05) | |
| Kent et al, 2017 [48] | PWH receiving care at the UAB 1917 HIV Clinic | Sex differences in clinic and ambulatory BP values, and prevalence of ambulatory BP monitoring phenotypes stratified by race and sex | • MWH vs WWH had significantly higher awake SBP (127 vs 120 mm Hg, P < .05) but not sleep SBP (112 vs 107 mm Hg, P = .12); how-ever, differences by sex were attenuated in adjusted analyses | Small sample size. Only adjusted for age, race, and education. Did not include persons without HIV for comparison. Did not capture menopause status. |
| N = 49 (100% PWH) | 36 men, 13 women | | • MWH vs WWH had higher awake DBP (84 vs 77 mm Hg, P < .05) and sleep DBP (69 vs 65 mm Hg, P = .28); sex differences remained significant in adjusted analyses | |
| Reinsch et al, 2008 [49] | PWH enrolled in HIV-HEART study cohort across central Europe | Prevalence of PAH and sPAP with and without symptoms (sPAP assessed by Doppler echocardiography) | • The prevalence of awake hypertension for MWH vs WWH was 47% vs 15% (P < .05) | Did not include persons without HIV for comparison. Did not capture menopause status. |
| N = 802 (100% PWH) | 669 men, 133 women | | | |
| Fitch et al, 2013 [50] | Women recruited from HIV clinics, community health centers, or areas surrounding Boston, MA | Group differences in absolute and percentage of calcified and noncalcified coronary artery plaque | • WWH had a higher proportion of coronary segments with noncalcified plaque vs MWH (75% vs 50%, P < .05) and vs men without HIV (73%, P < .05) | Small sample size |
| N = 233 (70% PWH) | 143 men, 90 women | | • WWH had higher prevalence than MWH of any subclinical coronary atherosclerotic plaque (95% vs 62%, P < .05) as well as prevalence of obstructive plaque (6% vs 5%, P < .05), positively remodeled plaque (25% vs 51%, P < .05), and number of vascular segments with plaque (1.3 vs 2.1, P < .05) and positively remodeled plaque segments (0.5 vs 1.2, P < .05) | |
| Foldyna et al, 2018 [47] | WWH living in Boston, MA | Prevalence of subclinical coronary atherosclerotic plaque characteristics: any plaque, plaque type (calcified, noncalcified, plaque with high-risk morphology features (positive remodeling, low attenuation), and obstructive plaque | • WWH had lower prevalence than MWH of any subclinical coronary atherosclerotic plaque (55% vs 62%, P < .05) as well as prevalent obstructive plaque (6% vs 5%, P < .05), positively remodeled plaque (25% vs 51%, P < .05), and number of vascular segments with plaque (1.3 vs 2.1, P < .05) and positively remodeled plaque segments (0.5 vs 1.2, P < .05) | Small sample size. Did not include persons without HIV for comparison. Did not capture menopause status. |
| N = 145 (100% PWH) | 97 men, 48 women | | • No sex differences noted in prevalence or number of noncalcified plaque nor of low attenuation plaque | |
| | | | • MWH vs WWH had greater adjusted odds of any coronary artery plaque (aOR, 3.8 [95% CI, 1.4–11.4]) and positively remodeled plaque (aOR, 3.7 [95% CI, 1.4–10.9]) | |

Summary of studies reporting sex differences for cardiovascular disease among people with HIV.
### Study Population (Location, Race/Ethnicity, Age)
- Adults enrolled in WIHS and MACS
- 46% Black, 34% White, 20% Hispanic
- Median age: 40 y (women), 50 y (men)

### Outcomes Measured
- Effect of carotid plaque presence and arterial stiffness on all-cause mortality by sex and HIV status

### Key Findings
- Among all participants, the presence of carotid artery plaque (vs no plaque) increased the risk of all-cause mortality (aHR, 1.44 [95% CI, 1.10–1.88]) and was significantly modified by sex ($p = 0.008$) and dHIV serostatus ($p < 0.001$)
- Plaque was associated with all-cause mortality among men (aHR, 2.19 [95% CI, 1.41–3.43]) but not among women
- Among PWH, the risk of all-cause mortality associated with plaque vs no plaque was greater among MWH (aHR, 1.65 [95% CI, 0.93–2.91]) vs WWH (aHR, 1.15 [95% CI, 0.79–1.71]). $p = 0.048$ for sex difference
- Among all participants, arterial stiffness was significantly associated with all-cause mortality among women (aHR, 1.71 [95% CI, 1.11–2.61]) but not among men (aHR, 1.08 [95% CI, 0.61–1.89]); among PWH, this association was attenuated (among WWH: aHR, 1.47 [95% CI, 0.94–2.28]; among MWH: aHR, 0.99 [95% CI, 0.56–1.93]).

### Limitations
- Did not capture menopause status.

### Study Design
- Nested cohort
- N = 3026 (67% PWH)
- 1304 men, 1722 women

### Study Population (Location, Race/Ethnicity, Age)
- Adults enrolled in WIHS and MACS
- 46% Black, 34% White, 20% Hispanic
- Median age: 40 y (women), 50 y (men)

### Outcomes Measured
- AMI rates per 1000 PY across 6 age strata stratified by sex and HIV status

### Key Findings
- Men had a higher AMI rate than women overall (IRR, 1.72 [95% CI, 1.68–1.77])
- WWH had higher AMI rates than MWH across most age strata
- In unadjusted analyses, WWH vs women without HIV had a higher AMI rate (12.71 vs 4.88); however, no significant difference was observed among men by HIV status (10.48 vs 11.44)
- In adjusted analyses, PWH vs persons without HIV had a higher AMI rate among women (aRR, 2.98 [95% CI, 2.33–3.75]) and among men (aRR, 1.40 [95% CI, 1.16–1.67]).

### Limitations
- Models reported did not adjust for smoking. Did not capture menopause status.

### Study Design
- Longitudinal cohort
- N = 1048440 (0.37% PWH)
- 429868 men, 618568 women

### Study Population (Location, Race/Ethnicity, Age)
- Adults cared for at 2 academic centers in Boston, MA (RPDR)
- 66% White, 7% Hispanic, 7% Black, 0.6% Asian
- Median age: 39 y (persons without HIV), 38 y (PWH)

### Outcomes Measured
- Hazard ratio for AMI per 1000 PY

### Key Findings
- HIV was associated with increased risk of AMI among women (aHR, 3.77 [95% CI, 1.79–7.96]) and among men (aHR, 2.04 [95% CI, 1.62–2.57]). However, sex did not significantly modify the effect of HIV on AMI risk ($p = 0.17$).

### Limitations
- Women were underrepresented. Models did not adjust for smoking, or HIV characteristics. Did not capture menopause status.

### Study Design
- Longitudinal cohort
- N = 34734 (20% PWH)
- 27086 men, 7648 women

### Study Population (Location, Race/Ethnicity, Age)
- Publicly insured adults in Québec, Canada. Data collected from Québec Health Insurance Board & Med-Echo database
- No race/ethnicity data available
- Mean age: 40 y

### Outcomes Measured
- Incidence rate and HR for HF diagnosis per 1000 PY stratified by HIV status

### Key Findings
- MWH vs men without HIV had higher rate of incident HF (aHR, 1.81 [95% CI, 1.39–2.36])
- MWH vs men without HIV had higher rate of incident HF (aHR, 1.96 [95% CI, 1.29–2.98]) in analyses excluding veterans with history of alcohol dependence.

### Limitations
- Women were not included. Models did not adjust for smoking or HIV characteristics.

### Study Design
- Longitudinal cohort
- N = 23437 (100% PWH)
- 17788 men, 5649 women

### Study Population (Location, Race/Ethnicity, Age)
- PWH enrolled in the D:A:D Study (11 cohorts across 21 countries in Europe, US, Australia)
- 78% White, 17% Black, 3% Hispanic, 2% Asian
- Median age: 39 y

### Outcomes Measured
- Incident MI rate

### Key Findings
- MWH vs WWH had a higher MI rate in unadjusted analysis (IRR, 3.27 [95% CI, 2.26–4.73]), demographically adjusted analysis (aRR, 1.91 [95% CI, 1.28–2.86]), and after further adjustment for cardiovascular risk factors (aRR, 2.13 [95% CI, 1.29–3.52])
- ART-attributable MI risk was similar between MWH and WWH (IRR, 1.13 vs 1.36, $p = .40$)

### Limitations
- Did not include persons without HIV for comparison. Did not capture menopause status.
### Table 3. Continued

| Author, Year [Ref] | Study Design | Study Size (% PWH) | Study Population (Location, Race/Ethnicity, Age) | Outcomes Measured | Key Findings | Limitations |
|-------------------|--------------|--------------------|-------------------------------------------------|-------------------|--------------|-------------|
| Janjua et al, 2017 [55] | Longitudinal cohort | N = 15,169 (9% PWH) 0 men, 15,169 women | Adults cared for at 2 academic centers in Boston, MA (RPDR) Race/ethnicity data not available Mean age: 59 y | Incident rate for HF hospitalization after HF diagnosis per 1000 PY | • Incidence of HF diagnosis was 0.27% per year among WWH and 0.07% per year among women without HIV  
• WWH vs women without HIV had a higher incidence of HF hospitalization (20 vs 8 per 1000 PY, P < .05)  
• In adjusted analyses, WWH vs women without HIV had a higher risk of incident HF hospitalization after HF diagnosis (aHR, 2.58 [95% CI, 1.55–4.29]) | Men were not included. Models did not adjust for smoking or HIV characteristics. Did not capture menopause status. |
| Womack et al, 2014 [56] | Longitudinal cohort | N = 2187 (32% PWH) 0 men, 2187 women | Women enrolled in the VACS-Virtual Cohort 60% Black, 30% White Mean age: 44 y | Incidence rate of various cardiovascular events (AMI, unstable angina, ischemic stroke, and HF) stratified by HIV status | • WWH vs women without HIV had a higher crude incidence of HF (IRR, 2.5 [95% CI, 1.5–4.5]), incidence of cardiovascular events excluding HF (aHR, 2.8 [95% CI, 1.7–4.6]) | Men were not included. HF analysis did not adjust for CVD risk factors or HIV characteristics. Did not capture menopause status. |
| Chow et al, 2012 [57] | Longitudinal cohort | N = 36,731 (12% PWH) 24,177 men, 12,554 women | Adults cared for at 2 academic centers in Boston, MA (RPDR) 52% White, 22% Black, 17% Hispanic Mean age: 41 y | Incidence rate and HR for ischemic stroke per 1000 PY stratified by sex and HIV status | • WWH vs women without HIV had higher risk of ischemic stroke (HR, 2.16 [95% CI, 1.53–3.04]; aHR, 1.76 [95% CI, 1.24–2.52])  
• MWH vs men without HIV had higher risk of ischemic stroke (HR, 1.18 [95% CI, 0.95–1.47]); (aHR, 1.05 [95% CI, 0.84–1.32])  
• Among persons without HIV, women vs men had lower risk of ischemic stroke (HR, 0.54 [95% CI, 0.46–0.65]; however, risk was not significantly different by sex among PWH (HR, 0.97 [95% CI, 0.50–1.89]) | Models did not adjust for HIV characteristics. Did not capture menopause status. |
| Chow et al, 2018 [58] | Longitudinal cohort | N = 6933 (100% PWH) 5563 men, 1370 women | ART-naive PWH enrolled in multiple ACTG trials 40% White, 37% Black, 21% Hispanic Median age: 37 y | Incidence rate of first ever ischemic stroke or TIA per 1000 PY after ART initiation stratified by sex and age | • Overall, WWH vs MWH had higher risk of incident TIA/stroke (2.88 vs 1.40 per 1000 PY; aHR, 1.96 [95% CI, 1.04–3.67])  
• WWH vs MWH had higher risk of TIA/stroke at age 40 (IRR, 3.17 [95% CI, 1.45–6.93]) and at age 50 (RR, 1.94 [95% CI, 1.03–3.66]); however, this sex-differential risk attenuated among PWH ≥50 y | Did not include persons without HIV for comparison. Did not capture menopause status. |
| Hanna et al, 2020 [45] | Longitudinal cohort | N = 147,915 (100% PWH) 108,083 men, 39,832 women | PWH in New York City HIV Surveillance and Vital Statistics Registries 44% Black, 33% Hispanic Median age: 45 y | CVD mortality per 1000 PY over 11 y of follow-up stratified by sex and neighborhood poverty level | • In unadjusted analyses, women had a higher CVD mortality risk associated with HIV status (RR, 2.24 [95% CI, 2.07–2.43]) than men (RR, 1.23 [95% CI, 1.16–1.30])  
• In adjusted analyses, women had a higher CVD mortality risk associated with HIV status (aRR, 1.73 [95% CI, 1.62–1.85]) than men (aRR, 1.20 [95% CI, 1.15–1.26]) overall and within poverty strata  
• Sex significantly modified the effect of HIV on CVD mortality (P < .05 for HIV×sex interaction) within all poverty strata | Analyses did not control for lifestyle factors. Did not capture menopause status. |

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**Abbreviations:** ACTG, AIDS Clinical Trial Group; aHR, adjusted hazard ratio; AMI, acute myocardial infarction; aOR, adjusted odds ratio; aRR, adjusted rate ratio; ART, antiretroviral therapy; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs Study; DBP, diastolic blood pressure; HF, heart failure; HR, hazard ratio; HTN, hypertension; IRR, incidence rate ratio; LDL, low-density lipoprotein; MA, Massachusetts; MACS, Multicenter AIDS Cohort Study; MI, myocardial infarction; MWH, men with HIV; PAH, pulmonary arterial hypertension; PWH, persons with HIV; PY, person-years; RPDR, Research Patient Data Registry; RR, rate ratio; SBP, systolic blood pressure; sPAP, systolic pulmonary arterial pressure; TIA, transient ischemic attack; UAB, University of Alabama at Birmingham; US, United States; VACS, Veterans Aging Cohort Study; WIHS, Women’s Interagency Health Study; WWH, women with HIV.
Hypertension
In a retrospective analysis, prevalent hypertension was higher among WWH than MWH <65 years old (41% vs 36%, \(P = .002\)) and this trend by sex persisted among those ≥65 years old (58% vs 50%, respectively, \(P = .06\)) [46].

Contrarily, a study of PWH with traditional CVD risk factors reported that MWH had higher prevalent hypertension than WWH (27% vs 13%, \(P = .04\)) [47]. In adjusted models, MWH vs WWH had significantly elevated awake systolic and sleep systolic blood pressures (+5.4 to +7.6 mm Hg); however, the prevalence of awake, sleep, and masked hypertension were not significantly different by sex [48].

In the Cardiovascular Diseases in HIV-Infected Subjects (HIV-HEART) cohort study, systolic pulmonary arterial pressure (sPAP) and symptoms of pulmonary arterial hypertension (PAH) were assessed. Among cases of manifest PAH, defined as having dyspnea symptoms and sPAP >35 mm Hg, WWH had a 40% higher PAH risk than MWH [49]. However, among asymptomatic PWH with elevated sPAP, MWH had a 360% higher PAH risk than WWH (Table 3).

Atherosclerosis
Fitch et al evaluated atherosclerotic coronary artery plaque quantity and features in relation to immune activation patterns among asymptomatic PWH [50]. After adjusting for traditional CVD risk factors, total plaque was comparable between MWH and WWH. However, the proportion of noncalcified plaque was significantly greater among WWH compared with HIV-seronegative women and with MWH. Noncalcified plaque was associated with greater immune activation despite similar HIV-1 viremia among WWH and MWH, which may contribute to sex-differential myocardial infarction (MI) risk given the characteristic instability of noncalcified plaque [51]. In a follow-up study of ART-treated PWH without known CVD, WWH vs MWH had significantly decreased prevalence of the majority of coronary atherosclerotic plaque morphologies (ie, subclinical, obstructive, and positively remodeled plaques); however, noncalcified plaque prevalence was comparable between sexes [47]. Among PWH who had coronary plaque, the proportion and number of noncalcified segments were significantly greater in WWH than MWH [47].

Among Multicenter AIDS Cohort Study/Women’s Interagency HIV Study participants, the presence of carotid artery plaque (vs no plaque) increased the risk of all-cause mortality (adjusted hazard ratio [aHR], 1.44 [95% CI, 1.10–1.88]), and MWH had a higher plaque-associated risk compared with WWH (aHR, 1.65 vs 1.15; \(P = .048\)) [52] (Table 3).

Myocardial Infarction
In a study leveraging registry data that adjusted for dyslipidemia, diabetes, and hypertension, the HIV-attributable risk of MI was 2-fold greater among women than men [40]. A nested case-control study similarly found that MI risk was higher among WWH vs women without HIV (aHR, 3.77 [95% CI, 1.79–7.96]) than among MWH vs men without HIV (aHR, 2.04 [95% CI, 1.62–2.57]) [53]. In contrast, a 2-fold greater MI risk was observed among MWH compared with WWH in a larger prospective Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study [43] (Table 3). Greater diversity in the D:A:D population and adjusting for smoking could explain the discrepancy in these findings.

Heart Failure
Although sex-stratified data on heart failure outcomes among PWH are lacking, sex-specific studies suggest a higher relative contribution of HIV to heart failure risk among women than men. A study including Veterans found that MWH had a 1.8-fold greater risk of incident heart failure compared with HIV-seronegative men; this differential risk by HIV serostatus was even greater among men without CVD risk factors [54]. In comparable studies of women balanced on traditional CVD risk factors, the unadjusted incidence of heart failure was nearly 4 times greater among WWH vs women without HIV [55] and 2.5 times greater when excluding women with baseline CVD [56] (Table 3).

Cerebrovascular Events
A single-center study of PWH and matched HIV-negative controls found higher ischemic stroke risk among women vs men overall [57]. In adjusted analyses, HIV was significantly associated with increased ischemic stroke risk among women (aHR, 1.76 [95% CI, 1.24–2.52]) but not men (aHR, 1.05 [95% CI, 0.84–1.32]), a finding driven by disproportionate risk among young WWH. Similarly, in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) cohort, WWH vs MWH had a higher adjusted risk of incident stroke or transient ischemic stroke, and the greatest difference by sex in risk was among younger PWH: WWH vs MWH had a 3-fold increased risk at age 40 and 2-fold at age 50, and this trend diminished as age increased [58] (Table 3).

METABOLIC DYSFUNCTION
Principal components of metabolic syndrome, including impaired glucose tolerance, dyslipidemia, hypertension, and central adiposity, are precursors to CVD and type 2 diabetes (T2D) and common among aging populations [59]. PWH are at increased risk of metabolic syndrome pathologies due to HIV-associated chronic inflammation and immune activation, ART use (Table 1), and associated pathologies including adipose tissue disorders and insulin resistance [60, 61].

Insulin Resistance and T2D
Several studies have reported a 1.5- to 2-fold increased risk of T2D among MWH compared with WWH [62–64], a sex trend consistent with that of the general population [59],
which may be compounded by HIV [63, 65, 66]. A study of ART-treated PWH without T2D found that WWH vs MWH had significantly better glucose tolerance despite older age and longer ART duration [65]. After adjusting for age, race, adiposity, and ART duration, WWH had significantly higher insulin sensitivity, lower insulin release, and lower levels of T2D-associated metabolites than MWH. In contrast, a study of ART-naive PWH found significantly increased fasting insulin levels and insulin resistance among WWH compared with MWH [67].

In a cohort of 89 ART-treated nondiabetic PWH, the crude prevalence of insulin resistance among MWH vs WWH was 73% vs 58%, respectively [66]. The authors evaluated patterns of adipokines involved in glucose homeostasis, and known to vary by sex, and found that insulin resistance was associated with lower serum adiponectin and higher triglycerides among MWH, and with hyperleptinemia among WWH [66, 68] (Table 4).

**Lipodystrophy**

PWH may experience lipodystrophy, or adipose tissue disturbances characterized by changes in fat quantity, quality, and/or distribution. A confluence of factors promoting metabolic dysfunction likely contribute to HIV-associated lipodystrophy development—that is, obesity risk factors, ART-associated effects on glucose and lipid metabolism, and chronic immune activation and inflammation related to HIV-1 infection [69]. Among PWH, lipodystrophy involves increased ectopic fat accumulation in visceral, dorsocervical, intramuscular, and hepatic tissue, and accompanying loss of subcutaneous adipose tissue in the face, arms, buttocks, and legs [70–72].

**Fat Quantity**

A pooled analysis of 3 clinical trials demonstrated that WWH had significantly greater body mass index (BMI) increases 96 weeks post–ART initiation compared with MWH. Adjusting for age, race/ethnicity, baseline CD4+ count, and HIV-1 viral load, WWH vs MWH had an average BMI increase of 1.91 kg/m² vs 1.39 kg/m² (P < .001) [73]. Waist-to-hip ratio was similar among MWH and WWH with lipodystrophy, but differed among WWH vs HIV-negative women (0.96 vs 0.82, P < .0001) and among MWH vs HIV-negative men (0.98 vs 0.94, P < .0001) [74]. Compared with respective HIV-negative peers, MWH and WWH had lower total extremity fat (~1.1 kg and ~0.85 kg, respectively); MWH and WWH both had increased visceral adipose tissue, though only MWH and not WWH had decreased subcutaneous adipose tissue, relative to men and women without HIV [75] (Table 4).

**Fat Quality**

Women vs men may be at heightened risk of inflammatory consequences associated with metabolically unhealthy fat including HIV-related adipocyte hypertrophy [76, 77] and ectopic fat accumulation [78, 79]. A cross-sectional study of PWH and age-/sex-matched HIV-negative persons found that HIV did not significantly modify the association of chronic inflammatory markers and ectopic adipose tissue; however, there was a statistically significant sex difference in correlations between interleukin 6 (IL-6) and BMI [80] (Table 4).

**Fat Distribution**

In a cross-sectional analysis of ART-treated PWH, the adjusted risk of adipose tissue alterations in any body region was significantly higher among WWH vs MWH. While the commonest lipodystrophy pattern among men was pure lipoatrophy, women more frequently experienced combined lipoatrophy and lipo hypertrophy [81]. In the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM), MWH vs HIV-negative men had a higher prevalence of peripheral lipoatrophy (38% vs 5%, P < .001) and lower prevalence of central lipohypertrophy (40% vs 56%, P = .001); and WWH vs HIV-negative women had a higher prevalence of peripheral lipoatrophy (28% vs 4%, P < .001) but no significant difference in central lipohypertrophy [82]. PWH had less subcutaneous adipose tissue compared with HIV-negative persons regardless of sex; however, visceral adipose tissue amount was higher for WWH but not MWH vs HIV-negative controls [83] (Table 4).

**Hepatic Steatosis**

Hepatic steatosis risk among PWH is higher than the general population given an overrepresentation of contributing factors (eg, metabolic pathologies, chronic inflammation, ART exposure), which is further compounded by an increased prevalence of chronic viral hepatitis [84].

Estrogen is considered hepatoprotective, playing an important role in determining susceptibility to nonalcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and liver disease progression, especially in the context of hepatitis C virus [84, 85]. Data from the general population indicate that hypoestrogenism, as occurs with the menopausal transition, is associated with accelerated liver pathology, including incident hepatic fibrosis and NAFLD, among perimenopausal and postmenopausal women [85]. Among WWH, the hepatoprotective effect of estrogen appears lowered with menopause onset, which may occur earlier than among HIV-negative peers [85, 86].

Among Italian PWH without chronic viral hepatitis or excessive alcohol use, NAFLD risk was associated with male sex, nucleoside reverse transcriptase inhibitor exposure, increased waist circumference, increased visceral adipose tissue, and elevated aspartate aminotransferase/alanine aminotransferase ratio. MWH had a greater odds of NAFLD compared with WWH (adjusted odds ratio, 2.49 [95% CI, 1.07–5.81]) [87]. In a cross-sectional
Table 4. Summary of Studies Reporting Sex Differences for Metabolic Dysfunction Among People With HIV

| Author, Year [Ref] | Study Design        | Study Size (% PWH) | Study Population (Location, Race/Ethnicity, Age)                                                                 | Outcomes Measured                                                                                                                                  | Key Findings                                                                                                                                                                                                 | Limitations                                                                                                                                                                                                 |
|-------------------|---------------------|--------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Butt et al, 2009  | Case-control        | N = 6567 (51% PWH) | • Veterans enrolled in VACS across 8 major US cities • 64% Black, 22% White, 10% Hispanic • Mean age: 50 y                                                  | Odds of prevalent diabetes mellitus (T2D) stratified by HIV status                                                                                     | • Among PWH, adjusted odds of prevalent T2D was higher for men than women (aOR, 2.51 [95% CI, 0.96–6.52]) • Among people without HIV, adjusted odds of prevalent T2D was higher for men than women (aOR, 1.65 [95% CI, 1.09–2.49]) | Veterans with HIV may not be representative of general population with HIV. Women were severely underrepresented. Did not capture menopause status. |
| Ledergerber et al, 2007 | Longitudinal cohort | N = 6513 (27,798 PY) (100% PWH) | • PWH enrolled in Swiss HIV Cohort Study • 84% White, 11% Black • Median age: 38 y                                                                 | Incidence rate of diabetes per 1000 PY stratified by HIV status                                                                                       | • In univariable models, incidence of T2D was 5.12 among MWH (95% CI, 4.20–6.24) and 2.89 among WWH (95% CI, 1.95–4.28) • MWH vs WWH had higher incidence of T2D in univariate (IRR, 1.77 [95% CI, 1.14–2.75]) and multivariate (IRR, 2.5 [95% CI, 1.5–4.2]) models | Did not include persons without HIV for comparison. Did not capture menopause status. |
| Koethe et al, 2016 | Cross-sectional     | N = 70 (100% PWH)  | • PWH cared for at Vanderbilt Comprehensive Care Clinic in Nashville, TN • 46% White, 54% non-White • Median age: 44 y (men), 46 y (women)                      | Effect modification of FMI on relationship between sex and glucose tolerance and other plasma metabolites                                               | • WWH vs MWH had significantly higher insulin sensitivity and less reduction in insulin sensitivity per unit of FMI (–0.017 vs –0.055 kg/m², P < .05 for sex × FMI interaction) in multivariate model • WWH vs MWH had significantly lower insulin release and lower rise in insulin levels per FMI unit (0.009 vs 0.038 kg/m², P < .05 for sex × FMI interaction) in multivariate model | Did not include persons without HIV for comparison. Did not capture menopause status. |
| Arama et al, 2013  | Cross-sectional     | N = 89 (100% PWH)  | • Young nondiabetic PWH cared for at National Institute of Infectious Diseases in Bucharest, Romania • 100% White • Median age: 32 y (men), 21 y (women)           | Association between metabolic parameters (adiponectin, leptin, triglycerides) and QUICKI values determined by sex-specific regression analysis with corresponding correlation coefficients | • Relationship between IR and certain adipokines differed by sex. • MVH vs WWH had greater IR prevalence (72.5% vs 57.6%) • Among MVH, those with IR had lower serum adiponectin (8.3 vs 14.1 μg/mL, P < .05) and higher serum triglycerides (217 vs 117.5 mg/dL, P < .05) compared to those without IR • Among WWH, those with IR had higher serum leptin (5.3 vs 2.8 ng/mL, P < .05) compared with those without IR | Study population was small. Cohort included younger participants thus not those with active aging. Did not capture menopause status. |
| El-Sadr et al, 2005 | Cross-sectional     | N = 419 (100% PWH) | • ART-naive PWH enrolled in CPCRA 058 & CPCRA 061 substudies from 49 clinics throughout US. • 60% Black, 30% White, 10% Latinx • Mean age: 38 y                      | Association between demographic and HIV disease characteristics on serum lipids and glucose homeostasis                                             | • MVH vs MVH had greater mean fasting insulin levels (12.1 vs 8.9 microunits/mL, P < .05) and mean IR score (2.6 vs 2.0, P < .05) • WWH vs MVH had greater fasting insulin (β = .1, P < .05) and IR (β = .103, P < .05) in multivariate analysis | Did not include persons without HIV for comparison. Did not capture menopause status. |
| Study Design       | Study Size (% PWH) | Study Population (Location, Race/Ethnicity, Age)                                                                                                                                                                                                 | Outcomes Measured                                                                                      | Key Findings                                                                                                                                                                                                 | Limitations                                                                                                                                 |
|--------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Fatty quantity and distribution |                    |                                                                                                                                                                                                                                                  | Association between sex and changes in BMI at 96 wk post-ART initiation                                                                                   | WWH vs MWH had greater absolute BMI increase (+1.91 kg/m² vs +1.39 kg/m², 95% CI: -2.89 to -0.85, P < .05) and relative BMI increase (+0.75% vs +0.52%) over 96 wk post-ART initiation in multivariate analyses | Did not include persons without HIV for comparison. Did not capture menopause status.                                                           |
| Bares et al, 2018  | Longitudinal N = 3801 (100% PWH) 3041 men, 760 women | • ART-naive PWH enrolled in 3 ACTG ART initiation trials in the US • 38% White, 37% Black, 22% Hispanic • Mean age: 38 y                                                                                                                            |                                                                                                      | WWH had mean BMI increase of 0.59 kg/m² more than MWH over 96 wk post-ART initiation (P < .05) in multivariate analyses                                                                                       |                                                                                                                                             |
| Hadigan et al, 2001 | Case-control N = 404 (25% PWH) 268 men, 136 women | • PWH from Boston area and persons without HIV from Framingham Offspring Study • PWH: 77% White, 11% Black, 11% Hispanic • Mean age: 41 y                                                                                                      | Group differences in anthropometric measurements and metabolic parameters stratified by sex and HIV status | Differences in the waist-to-hip ratio for women vs men were observed in control population (0.82 vs 0.94, P < .05) but not among PWH with lipodystrophy (0.96 vs 0.98, P > .05) | Sex difference analyses were not adjusted.                                                                                                  |
| Joy et al, 2008    | Cross-sectional N = 413 (74% PWH) 236 men, 177 women | • PWH enrolled in metabolic studies at Massachusetts General Hospital and persons without HIV recruited from Boston community • 55% White, 30% Black, 12% Hispanic • Mean age: 42 y                                                                 | Group differences in regional fat distribution (SAT, VAT, and total extremity fat) stratified by sex and BMI category | MWH had 1.1 kg less extremity fat than HIV-negative men; and WWH had 0.85 kg less extremity fat than HIV-negative women                                                                                     | PWH had a high prevalence of metabolic abnormalities (eg, lipodystrophy); therefore findings may not be generalizable to all PWH. Did not capture menopause status. |
| Chen et al, 2019   | Cross-sectional N = 125 (84% PWH) 79 men, 46 women | • PWH enrolled in BOBCAT study, a diet and behavior change intervention, in Cleveland, Ohio • 89% Black • Mean age: 52 y                                                                                                                              | Effect modification of sex on relationship between BMI and inflammation markers (IL-6, hs-CRP) stratified by sex and HIV status | In adjusted models (not stratified by HIV), women vs men had a stronger correlation between BMI and hs-CRP (r = 0.584 vs r = 0.189, P = .06), and between BMI and IL-6 (r = 0.560 vs r = 0.096, P < .05) | Control group was very small. Did not capture menopause status.                                                                          |
| Author(s) | Study Design | Study Size (% PWH) | Study Population (Location, Race/Ethnicity, Age) | Outcomes Measured | Key Findings | Limitations |
|-----------|--------------|--------------------|-------------------------------------------------|-----------------|--------------|-------------|
| Galli et al, 2003 | Cross-sectional | N = 2258 (100% PWH) 1585 men, 673 women | - PWH enrolled in Lipodystrophy Italian Multicentre Study across 5 cities - Race/ethnicity data not available - Median age: 37 y (men), 35 y (women) | Odds of ATAs since ART initiation in specific regions and patterns (Marrakesh categories) stratified by sex | - MWH vs WWH had lower adjusted odds of ATA in any given region (all P < .05) - MWH vs WWH had lower adjusted odds of pure lipohypertrophy (aOR, 0.58, P < .05) and combined lipodystrophy (aOR, 0.28, P < .05) - The adjusted odds of pure lipoatrophy was not significantly different from MWH vs WWH (aOR, 0.89, P = .52) | ATAs were self-reported, which could introduce bias. Did not include persons without HIV for comparison. Did not capture menopause status. |
| Bacchetti et al, 2005 | Cross-sectional | N = 577 (74% PWH) 577 men, 0 women | - MWH enrolled in the FRAM study and controls recruited from the CARDIA study - 56% White, 35% Black, 9% Hispanic - Mean age: 40 y | Group differences in adipose tissue volumes at peripheral (cheeks, face, arms, buttocks, leg) and central sites (neck, chest, upper back, waist, abdominal fat); associations between peripheral and central fat distribution stratified by presence of lipoatrophy | - Peripheral lipoatrophy was more frequent among MWH vs HIV-negative men (39% vs 5%, P < .05) - Central lipohypertrophy was less frequent among MWH vs HIV-negative men (40% vs 56%, P < .05) - Among MWH, presence of central lipohypertrophy did not increase the odds of peripheral lipoatrophy (OR, 0.71 [95% CI, .47–1.06], P = .10) | Did not control for BMI. Did not include women but has a complementary study (described below). |
| Tien et al, 2006 | Cross-sectional | N = 325 (56% PWH) 0 men, 325 women | - WWH enrolled in the FRAM study and controls recruited from the CARDIA study - 39% White, 54% Black, 6% Hispanic - Median age: 39 y (WWH), 42 y (controls) | Group differences in adipose tissue volumes at peripheral (cheeks, face, arms, buttocks, leg) and central sites (neck, chest, upper back, waist, abdominal fat); associations between peripheral and central fat distribution stratified by presence of lipoatrophy | - Peripheral lipoatrophy was more frequent among WWH vs HIV-negative women (28% vs 4%, P < .05) - Central lipohypertrophy prevalence was similar among WWH and HIV-negative women (62% vs 63%, P > .05) - Among WWH, those with central lipohypertrophy were less likely to have peripheral lipoatrophy than those without central lipohypertrophy (OR, 0.39 [95% CI, 0.20–0.75], P < .05) | Did not control for BMI |
| Liver Disease | Cross-sectional | N = 229 (53% PWH) 142 men, 87 women | - Women enrolled in WIHS from San Francisco and men enrolled in the Study of Visceral Adiposity, HIBV, and HCV at the San Francisco VAMC - 47% White, 45% Black - Mean age: 50 y | Association of HIV and sex with LFF and steatosis (LFF >5%) | - In unadjusted analysis, MWH had 81% greater LFF than WWH (95% CI, 32%–148%, P < .05); however, findings attenuated after adjustment (LFF 25% [95% CI, 9%–73%]) - HIV was associated with 82% lower adjusted odds of steatosis among women (P < .05), but no significant difference in the odds of steatosis among men (P = .633) - In demographic-adjusted models, sex modified the effect of HIV on LFF (P < .05), however, this interaction attenuated in the fully adjusted model (P = .10) | Small study population |
study of adults without chronic viral hepatitis, hepatic steatosis was more prevalent among MWH vs WWH (41% vs 17%). However, in multivariable analysis, HIV did not significantly modify the effect of sex on hepatic steatosis [86] (Table 4).

**NEUROCOGNITIVE IMPAIRMENT**

Despite ART [88], nearly half of PWH suffer from HIV-associated neurocognitive disorder (HAND) [89, 90]. Furthermore, as PWH age, the population at risk of HAND is growing, leading to neurocognitive disease burden with devastating impact on work capabilities [91], daily life activities [92, 93], and survival [92].

Six key domains of neurocognitive function include perceptual-motor function; language; executive function; learning and memory; complex attention; and social cognition [94]. Importantly, well-established risk factors for HAND (eg, coinfections, metabolic disease, psychiatric disorders, substance use, socioeconomics, education, literacy) significantly differ by sex [95].

**Global Neurocognitive Impairment**

In a systematic review, WWH vs MWH had significantly greater global neurocognitive impairment (NCI), attributable to differences in memory, information processing, and motor function [96]. However, individual studies evaluating sex differences in overall NCI, measured by the global deficit score (an average of adjusted T-scores from each domain-specific test) [97–101], are conflicting (Table 5). This is likely due to many studies being underpowered to assess sex differences and inconsistently adjusting for sex-differential NCI-relevant covariates [90].

**Learning and Memory**

Sex-stratified analyses suggest that WWH experience greater impairment in the learning and memory domains than MWH [100, 102]; additionally, WWH but not MWH performed significantly worse than respective HIV-seronegative counterparts [100], even after adjusting for substance use, psychiatric disorders, and education level.

**Information Processing Speed**

In several studies, WWH scored significantly lower than MWH on information processing speed. In a cross-sectional study of Nigerian adults, WWH vs MWH were more impaired on verbal fluency and information processing, and among WWH, NCI severity was associated with higher HIV-1 viremia and activated circulating monocyte levels [100]. Studies that adjusted for HIV indices similarly noted that MWH vs WWH had less impairment in information processing [99, 102].

**Motor Function**

Motor mean T-scores among PWH were significantly different by sex only after adjusting for current and nadir CD4+ count,
| Author, Year [Ref] | Study Design | Study Size (% PWH) | Study Population (Location, Race/Ethnicity, Age) | Outcomes Measured | Key Findings | Limitations |
|-------------------|--------------|--------------------|------------------------------------------------|-------------------|--------------|-------------|
| Burlacu et al., 2018 [97] | Cross-sectional | N = 322 (78% PWH) 162 men, 160 women | Children with perinatally acquired HIV in Bucharest, Romania; Race/ethnicity data not available; Mean age: 23 y | Global neurocognition and domain scores (verbal fluency, working memory, processing speed, learning and memory, executive function, and motor function) | WWH scored lower than MWH in working memory domain (P < .05); WWH scored lower than women without HIV in motor domain (P < .05); HIV significantly modified the effect of sex in the motor domain (P < .05) | WWH had less advanced HIV disease than MWH. Did not capture menopause status. |
| Sundermann et al, 2018 [98] | Cross-sectional | N = 2063 (66% PWH) 1645 men, 418 women | Adults enrolled in UCSD HIV Neuro-behavioral Research Program; 25% Black, 56% White, 14% Hispanic, 2% Asian; Mean age: 42 y | Global neurocognitive deficit and domain deficit scores (verbal fluency, working memory, processing speed, verbal and visual learning and delayed recall, executive function, and motor function) | Compared with women and men without HIV, the odds of NCI was higher among WWH (OR, 2.90 [95% CI, 1.93–4.35]) and MWH (OR, 1.95 [95% CI, 1.54–2.47]), respectively; Odds of NCI associated with HIV were attenuated after adjusting for reading level among women (aOR, 2.33 [95% CI, 1.52–3.57], P < .05) but not men | Women were underrepresented. Did not capture menopause status. |
| Maki et al, 2018 [99] | Longitudinal cohort | N = 1420 (60% PWH) 710 men, 710 women | Adults enrolled in the MACS/WIHS Combined Cohort Study; 67% African American, 11% White, 20% Hispanic; Mean age: 41 y | Performance on 5 neurocognitive tests (TMTA, TMTB, SDMT, Stroop, and GP) | WWH scored significantly worse than MWH on TMTA, TMTB, SDMT, GP dominant, and GP nondominant; WWH vs MWH had higher odds of scoring in the impaired range on TMTA (OR, 2.54, P < .05) and GP nondominant (OR, 5.12, P < .05); these differences persisted after adjusting for HIV-related characteristics | Did not compare verbal learning and memory domains. Did not control for mental health factors other than depression. Did not capture menopause status. |
| Royal et al, 2016 [100] | Cross-sectional | N = 207 (60% PWH) 77 men, 130 women | PWH cared for at 2 HIV centers in Abuja, Nigeria (National Hospital and the University of Abuja Teaching Hospital); Race/ethnicity data not available; Mean age: 30 y (people without HIV), 34 y (PWH) | Global neurocognitive deficit and domain deficit scores (verbal fluency and category fluency, working memory, processing speed, learning and memory, executive function, and motor function) | WWH compared with women without HIV had greater impairment in processing speed (28% vs 5%, P < .05); WWH vs MWH had greater impairment in learning (27% vs 7%, P < .05) and memory (26% vs 9%, P < .05) domains; Sex significantly modified the effect of HIV on performance in processing speed, learning, and memory domains | Small sample sizes. Unbalanced HIV status and sex groups. Did not capture menopause status. |
| Kabuba et al, 2016 [102] | Cross-sectional | N = 266 (100% PWH) 107 men, 159 women | PWH cared for at 6 urban clinics in Lusaka, Zambia; Mean age: 41 y | Global neurocognitive deficit and domain deficit scores (verbal fluency, working memory, processing speed, learning, delayed recall, executive function, and motor function) | No significant differences between MWH and WWH in any demographic-adjusted domain score or global score; After adjusting for HIV characteristics, WWH performed worse than MWH in the delayed recall domain (mean T-score: 43.68 vs 47.99, P < .05) | Did not include persons without HIV for comparison (although normative data from 324 persons without HIV for comparison). Did not capture menopause status. |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; GP, grooved pegboard; MACS/WIHS, Multicenter AIDS Cohort Study/Women’s Interagency HIV Study; MWH, men with HIV; NCI, neurocognitive impairment; OR, odds ratio; PWH, people with HIV; SDMT, Symbol Digit Modalities Test; TMTA, Trail Making Test A; TMTB, Trail Making Test B; UCSD, University of California, San Diego; WWH, women with HIV.
with WWH performing worse than MWH [102]. Additional studies provide evidence that motor impairment was associated with HIV among women but not among men [97, 99], and that sex differences in motor function are most notable after covariate adjustment.

**MECHANISMS AND DRIVERS OF HIV-ASSOCIATED INFLAMMATION**

Higher prevalence and earlier onset of NACMs among PWH vs HIV-seronegative peers, exacerbated among women in these emergent analyses, is likely due to the complex interplay of HIV-associated chronic immune activation and inflammation, sex hormone effects, ART toxicity, and structural factors [3]. Evidence suggests that these sex-differential contributors may act synergistically to confer a greater risk of premature multimorbidity among WWH compared with MWH [2, 103].

**Chronic Immune Activation and Inflammation**

Inflammatory biomarkers (ie, high-sensitivity C-reactive protein, IL-6, D-dimer, soluble CD14, key chemokines) have been associated with NACM events and mortality among PWH, suggesting an important role of systemic inflammation on the causative pathway to aging-related comorbidity development [104–106]. Direct and indirect inflammatory effects of HIV-1 exhaust the replicative capacity of immune cells [107], leading to the term “inflammaging,” given that patterns of specific T-cell subset deficiencies mirror those of the natural aging process. Increased expression of certain X-encoded genes may play a role in the more robust immune responses initiated by viral infections observed among women compared with men [108]. ART-naive WWH have lower viral loads during early stages of HIV infection and greater CD8+ T-cell activation and interferon-γ and tumor necrosis factor–α expression at a given viral load as HIV progresses compared to MWH [19, 108, 109]. This likely contributes to sex-differential chronic disease outcomes [11].

Another possible mechanism driving sex differences in NACMs is microbial gut translocation facilitated by increased gut permeability precipitated by HIV-associated inflammation [105, 110]. The gut microbiome composition is highly sensitive to sex hormone profiles and fluctuations, which modulate gut permeability and immune homeostasis [111, 112], key players associated with development of a broad range of diseases [113].

**Sex Hormone Effects**

Estrogen and androgens modulate various key immunological pathways, with estrogens predominantly activating immune components and androgens generally suppressing them [114, 115]. In the context of HIV, estrogen has been shown to have an inhibitory effect on HIV transcription [116, 117]. Estrogen also modulates the expression of genes involved in cytotoxic T-cell pathways and enhances TLR7-dependent production of IFN-α [108]. One study demonstrated that fluctuations in HIV-1 viral load coincided with women’s menstrual cycles. No such fluctuations were observed among postmenopausal WWH [118]. Postmenopausal women’s response to ART may be hindered by exaggerated estrogen deficiency affecting CD4+ cell recovery [15], further compounded by aging-related and HIV-specific immunosenescence [119].

**ART Toxicity**

Sex-differential risk associated with specific ART agents that may affect NACM development is beyond the scope of this review, especially considering that agents have distinct mechanisms affecting hormonal and metabolic pathways within and between drug classes [120]. Table 1 summarizes available data on key sex differences in the effects of modern ART on mediating comorbidity-associated risks.

**Structural Factors**

Compared with their HIV-seronegative peers, sociobehavioral factors portending worsened health outcomes are more common among PWH [3, 121, 122]. Importantly, many such factors affect women more than men (eg, trauma, social isolation, HIV stigmatization), including social determinants of health such as education, income, and affordable healthcare access. Emerging literature suggests that traditional risk factors such as smoking, substance use, race, BMI, and social determinants of health may impact aging-related comorbidity development more so than HIV-related indices such as CD4+ count or HIV-1 viremia [10, 43, 123]. Physiological effects of substance use may also differ by sex [124, 125]. Finally, structural inequities including sex- and gender-biased research compound sociobehavioral vulnerabilities and biologic differences, thereby exacerbating worsened health outcomes experienced by women [124].

**LIMITATIONS AND FUTURE DIRECTIONS**

This review is primarily limited by the gross underrepresentation of women enrolled into clinical trials and cohort studies, inadequate power of many studies to detect sex differences, and lack of sex-stratified analyses and/or consideration of sex-specific sociobiologic comorbidity risk factors that have persisted despite the Revitalization Act, which established guidelines for inclusion of women in clinical trials [8]. As such, discordance of results between studies are difficult to interpret. Furthermore, among studies reporting sex-stratified data, nearly all were conducted in high-income countries where a minority of WWH reside [126, 127].

Development of sex-specific approaches for the screening, prevention, and management of NACMs among PWH requires future studies being specifically designed and powered to assess...
sex differences. This is critical as WWH may bear a greater and premature burden of multimorbidity associated with chronic inflammatory diseases compared with MWH.

Future studies should prioritize elucidation of NACM pathogenesis, including investigating unifying mechanistic drivers such as inflammation and microbiome alterations, and how these may differ for women vs men. To assess the relationship between inflammation and NACMs among PWH, sex-specific tool development and validation involving measurement of inflammation biomarker levels could be considered, such as the inflammation index metrics incorporated into the Veterans Aging Cohort Study Index [128]. Perimenopausal hormone changes are a potentially significant contributor to HIV-associated inflammatory comorbidity outcomes, and consensus biological definitions of pre-, peri-, and postmenopause are needed, along with an associated metric for assessing this transition, among WWH specifically [116]. Furthermore, data elements reflecting social determinants of health should be accurately and consistently captured to evaluate how these factors influence NACM development, including differences by sex. More balanced representation across sex, race/ethnicity, and social determinants of health among participants recruited for HIV clinical research would allow for more robust analyses on key variables affecting NACM occurrence and inform the development of sex-tailored strategies for comorbidity risk mitigation among PWH [116]. While sex-specific tools are being developed, identifying and intervening on modifiable risk factors should be prioritized.

Finally, it is critical to assess how HIV-related multimorbidity affects one’s functional status, quality of life, and mortality by sex, as the impact of NACM burden is likely different for women than for men.

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Notes

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