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REVIEW ARTICLE

Sex Differences in Non-AIDS Comorbidities Among People With Human Immunodeficiency Virus

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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 (PWH) [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

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Table 1. Considerations by Sex of Modern Antiretroviral Therapy Use Among Women and Men With HIV by Antiretroviral Agent/Class and At-Risk Comorbid Condition

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]
TDF[a]	Among women vs men, TDF exposure was associated with femoral neck BMD loss of –0.0032 vs –0.0026 g/cm^2 and lumbar spine BMD loss of –0.0031 vs –0.0031 g/cm^2 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
TAF[b]	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/m^2, respectively) were significant for those with preswitch BMI <30 kg/m^2 (but not ≥30 kg/m^2)[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 lipoatrophy [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		
Doravirine		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]
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, .9–3.4) and 1.2 (95% CI, .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 –3.28 cm [95% CI, –5.65 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 –2.01 cm [95% CI, -4.32 to .31], $P = .0901$) [150]	7.4% 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				
Dolutegravir	Switching from TDF/FTC + NNRTI to ABC/3TC/DTG resulted in improved total hip and lumbar spine BMD among women (mean adjusted increase of 1% and 3%, respectively) [153]	Sex-adjusted DTG-associated weight gain negatively impacts lipids and fasting glucose levels [154]; among women over median of 2 years, unfavorable changes in HbA1c and systolic and diastolic BP observed [155]	Women but not men experienced significant weight gain after switch to DTG [154] from non-INSTI ART; among women over mean 2 years of follow-up, weight increased by 2.1 kg, BMI by 0.8 kg/m^2, and WC by 2.0 cm [156]	Women more likely than men to discontinue DTG due to neuropsychiatric adverse effects (HR, 2.64 [95% CI, 1.23–5.65]) [157]
Bictegravir	BIC-associated changes in BMD appear similar to DTG [158]; sex-stratified data not available	BIC appears to be lipid-neutral and even have favorable lipid effect if switched from boosted-PI regimen [159]; sex-stratified data not available	Weight gain associated with BIC exposure among treatment-naive PWH appears similar to DTG [160]; sex-stratified data not available	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
Cabotegravir	Research priority area: phase 3 clinical trial data (FLAIR, ATLAS, ATLAS-2M) not reported as sex-stratified			

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATLAS, antiretroviral therapy as long acting suppression; ATLAS-2M, antiretroviral therapy as long acting suppression every 2 months; ATV, atazanavir; BIC, bictegravir; BMI, body mass index; BMD, bone mineral density; BP, blood pressure; CI, confidence interval; CNS, central nervous system; CVD, cardiovascular disease; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; FLAIR, first long-acting injectable regimen; FTC, emtricitabine; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; LDL, low-density lipoprotein; MI, myocardial infarction; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, persons with HIV; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; WC, waist circumference.

[a]Can be used safely in patients with normal kidney function (estimated glomerular filtration rate [eGFR] ≥60 min/mL/1.73 m^2).

[b]Can be used safely in patients with moderately reduced kidney function (eGFR ≥30 min/mL/1.73 m^2) but should be avoided in those with severely reduced kidney function not on hemodialysis; drug interactions possible with rifamycins and certain anticonvulsants.

osteoporosis and fracture [21–23]. In the general population, postmenopausal women have a 3-fold increased fracture risk compared with men [24], suggesting sex differences in bone health and disease that may be exaggerated among PWH.

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/cm^2 [lumbar spine], –0.05 g/cm^2 [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 exacerbates 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).

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).

Table 2. Summary of Studies Reporting Sex Differences for Bone Disease Among People With HIV

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	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	• PWH from US enrolled in 2 ACTG studies (A5224 & A5303) • 46% White, 32% Black, 19% Hispanic • Mean age: 37 y (women), 40 y (men)	BMD at left hip & lumbar spine at baseline (ART-naive) and 48 wk post–ART initiation	• WWH vs MWH had lower adjusted baseline BMD at spine (–0.39 g/cm^2, $P < .05$) and hip (–0.05 g/cm^2, $P < .05$) • WWH vs MWH had 1.7% greater adjusted BMD decline at hip ($P < .05$) • WWH vs MWH had 0.6% greater BMD decline at hip per 100 CD4$^+$ cells/μL increase ($P < .05$)	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 = 875 (100% PWH) 659 men, 216 women	• PWH cared for at single HIV unit in Barcelona, Spain • Racial/ethnic data not available • Median age: 42 y	• Risk of progression to different BMD category after age 45 stratified by ART regimen: PI and/or TDF (primary) • Probability of progression to different BMD category over 10 y (secondary)	• WWH vs MWH had higher risk of progression from osteopenia to osteoporosis after age 45 y on a PI regimen: HR, 5.9 (95% CI, 1.2–27.6) vs 1.8 (95% CI, .9–3.4), respectively • 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, .6–2.6), respectively • Probability of progression to lower BMD over 10 y was greater among MWH vs WWH up to age 50; however, greater among WWH vs MWH after age 50	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	• ART-naive PWH and adults enrolled in TNT-HIV 003 bone substudy from Thai Red Cross AIDS Research Centre, Bangkok • Median age: 38 y	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	• PWH cared for at 35 healthcare facilities across Japan • Mean age: 41 y (women), 40 y (men)	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 vs MWH were older at time of first fracture (66 vs 43 y) • WWH vs MWH had shorter average time to first fracture post–TDF initiation (123 vs 1438 d)	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	• PWH cared for at 2 Boston hospitals • Racial/ethnic data not available • Mean age: 41 y (women), 44 y (men)	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 • MWH vs WWH had a higher osteoporotic fracture risk across most age strata (IRR range, 1.07–1.54) except for those aged 46–55 (IRR, 0.88) • MWH vs WWH had similar risk of lifetime osteoporotic fractures (IRR, 1.26 [95% CI, .90–1.75]) • MWH vs WWH had similar lifetime IR of fracture at any site (IRR, 1.00 [95% CI, .83–1.19])	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

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	Study Population (Location, Race/Ethnicity, Age)	Outcomes Measured	Key Findings	Limitations
Hypertension					
Frazier et al, 2019 [46]	Cross-sectional N = 7436 (100% PWH)5584 men, 1852 women	• Older PWH receiving HIV care across the US who enrolled in the Medical Monitoring Project (national HIV surveillance program) • 40% Black, 39% White, 17% Hispanic • Age range: ≥50 y	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 (41% vs 36%, $P < .05$) but not significantly among those aged ≥65 y (58% vs 50%, $P = .06$) • WWH in both age strata had a higher adjusted prevalence of elevated cholesterol than MWH ($P < .05$) • WWH in both age strata had a higher adjusted prevalence of elevated LDL than MWH ($P < .05$)	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.
Kent et al, 2017 [48]	Cross-sectional N = 49 (100% PWH)36 men, 13 women	• PWH receiving care at the UAB 1917 HIV Clinic • 51% White, 49% Black • Mean age: 44 y	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, $P = .12$); however, differences by sex were attenuated in adjusted analyses • 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 • The prevalence of awake hypertension for MWH vs WWH was 47% vs 15% ($P = .05$)	Small sample size. Only adjusted for age, race, and education. Did not include persons without HIV for comparison. Did not capture menopause status.
Reinsch et al, 2008 [49]	Cross-sectional N = 802 (100% PWH) 669 men, 133 women	• PWH enrolled in HIV-HEART study cohort across central Europe • 89% White • Mean age: 44 y	Prevalence of PAH and sPAP with and without symptoms (sPAP assessed by Doppler echocardiography)	• sPAP did not significantly differ among MWH vs WWH (44.7 vs 45.3 mm Hg, $P = .9$) • Ratio of WWH to MWH with symptomatic elevated sPAP was 1.4:1 ($P < .05$) • Ratio of MWH to WWH with asymptomatic elevated sPAP was 4.6:1 ($P < .05$)	Did not include persons without HIV for comparison Did not capture menopause status.
Atherosclerotic plaque					
Fitch et al, 2013 [50]	Cross-sectional N = 233 (70% PWH) 143 men, 90 women	• Women recruited from HIV clinics, community health centers, or areas surrounding Boston, MA • Women: 64% White, 36% non-White • Mean age: 47 y • Male data from separate but similar study • Men: 62% White, 21% Black, 11% Hispanic • Mean age: 46 y	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 (vs 33%, $P < .05$) • Sex significantly modified the effect of HIV status on plaque ($P < .05$), such that WWH had the greatest proportion of noncalcified plaque compared with all other HIV sex strata • WWH had higher levels of immune activation markers (soluble CD163 and soluble CD14) than MWH ($P < .05$)	Small sample size
Foldyna et al, 2018 [47]	Cross-sectional N = 145 (100% PWH) 97 men, 48 women	• WWH living in Boston, MA • Male data from separate but similar study in Boston, MA • 62% White, 56% Black, 12% Hispanic • Mean age: 48 y	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 (35% vs 62%, $P < .05$) as well as prevalent obstructive plaque (0% 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, $P < .05$) • 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])	Small sample size. Did not include persons without HIV for comparison. Did not capture menopause status.

Table 3. Continued

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	Study Population (Location, Race/Ethnicity, Age)	Outcomes Measured	Key Findings	Limitations
Hanna et al, 2018 [52]	Nested cohort N = 3026 (67% PWH) 1304 men, 1722 women	• Adults enrolled in WIHS and MACS • 46% Black, 34% White, 20% Hispanic • Median age: 40 y (women), 50 y (men)	Effect of carotid plaque presence and arterial stiffness on all-cause mortality by sex and HIV status	• 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 ($P = .008$) and dHIV serostatus ($P < .001$) • 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, .93–2.91]) vs WWH (aHR, 1.15 [95% CI, .78–1.71]). $P = .048$ 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, .61–1.89]); among PWH, this association was attenuated (among WWH: aHR, 1.47 [95% CI, .94–2.28]; among MWH: aHR, 0.99 [95% CI, .56–1.93])	Did not capture menopause status
Myocardial infarction					
Triant et al, 2007 [40]	Longitudinal cohort N = 1 048 440 (0.37% PWH) 429 868 men, 618 568 women	• 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)	AMI rates per 1000 PY across 6 age strata stratified by sex and HIV status	• Men had a higher AMI rate than women overall (RR, 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])	Models reported did not adjust for smoking. Did not capture menopause status.
Durand et al, 2011 [53]	Longitudinal cohort N = 34 734 (20% PWH) 27 086 men, 7648 women	• 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	Hazard ratio for AMI per 1000 PY	• 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 ($P = .17$)	Women were underrepresented. Models did not adjust for smoking, or HIV characteristics. Did not capture menopause status.
Fris-Moller et al, 2007 [43]	Longitudinal cohort N = 23 437 (100% PWH) 17 788 men, 5649 women	• 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	Incident MI rate	• MWH vs WWH had a higher MI rate in unadjusted analysis (RR, 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 (RR, 1.13 vs 1.36, $P = .40$)	Did not include persons without HIV for comparison. Did not capture menopause status.
Heart failure					
Butt et al, 2011 [54]	Longitudinal cohort N = 8486 (28% PWH) 8486 men, 0 women	• Adults enrolled in VACS Virtual Cohort and Large Health Study of Veteran Enrollees • 39% White, 40% Black, 10% Hispanic • Mean age: 48 y	Incidence rate and HR for HF diagnosis per 1000 PY stratified by HIV status	• Rate of HF incidence was 7.12 per 1000 PY (95% CI, 6.90–7.34) among MWH and 4.82 per 1000 PY (95% CI, 4.72–4.91) among men without HIV • 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	Women were not included. Models did not adjust for smoking or HIV characteristics.

Table 3. Continued

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	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 (IRR, 2.3 [95% CI, 1.2–4.5]) • In adjusted analysis, WWH vs women without HIV had a higher incidence of total cardiovascular events (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.
Cerebrovascular events					
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, .95–1.47]) (aHR, 1.05 [95% CI, .84–1.32]) • Among persons without HIV, women vs men had lower risk of ischemic stroke (HR, 0.54 [95% CI, .46–.65]); however, risk was not significantly different by sex among PWH (HR, 0.97 [95% CI, .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 (RR, 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.
Mortality					
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

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 (range, +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, .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/m^2 vs 1.39 kg/m^2 ($P < .001$) [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 lipohypertrophy [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) No. of Men and Women	Study Population (Location, Race/Ethnicity, Age)	Outcomes Measured	Key Findings	Limitations
Diabetes and insulin resistance					
Butt et al, 2009 [62]	Case-control N = 6567 (51% PWH) 6226 men, 342 women	• 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, .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 [63]	Longitudinal cohort N = 6513 (27 798 PY) (100% PWH) 4494 men, 2019 women	• 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 [65]	Cross-sectional N = 70 (100% PWH) 40 men, 30 women	• 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/m^2, $P < .05$ 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/m^2, $P < .05$ for sex*FMI interaction) in multivariate model	Did not include persons without HIV for comparison. Did not capture menopause status.
Arama et al, 2013 [66]	Cross-sectional N = 89 (100% PWH) 51 men, 38 women	• 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. • MWH vs WWH had greater IR prevalence (72.5% vs 57.6%) • Among MWH, 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 [67]	Cross-sectional N = 419 (100% PWH) 331 men, 88 women	• 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	• WWH vs MWH 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 MWH had greater fasting insulin ($\beta = .1$, $P < .05$) and IR ($\beta = .103$, $P < .05$) in multivariate analysis	Did not include persons without HIV for comparison. Did not capture menopause status.

Table 4. Continued

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	Study Population (Location, Race/Ethnicity, Age)	Outcomes Measured	Key Findings	Limitations
Fat quantity and distribution					
Bares et al, 2018 [73]	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	Association between sex and changes in BMI at 96 wk post–ART initiation	• WWH vs MWH had greater absolute BMI increase (+1.91 vs +1.39 kg/m^2 [95% CI, .29–.75], $P < .05$) and relative BMI increase (+7.65% vs +5.92%) over 96 wk post–ART initiation in multivariate analyses • WWH had mean BMI increase of 0.59 kg/m^2 more than MWH over 96 wk post–ART initiation ($P < .05$) in multivariate analyses	Did not include persons without HIV for comparison. Did not capture menopause status.
Hadigan et al, 2001 [74]	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, $P > .05$) • WWH had a greater waist-to-hip ratio compared with HIV-negative women (+0.14, $P < .05$) • MWH had a greater waist-to-hip ratio compared with HIV-negative men (+0.04, $P < .05$)	Sex difference analyses were not adjusted.
Joy et al, 2008 [75]	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 • In normal and overweight categories, MWH had less SAT compared with HIV-negative men ($P < .05$), whereas WWH had similar amount of SAT compared with HIV-negative women ($P > .05$) • In the obese category, WWH had greater SAT than women without HIV (+72.3 cm^2, $P < .05$); however, there was no significant difference in SAT by HIV serostatus for men ($P = .87$)	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 [80]	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 $r = 0.096$, $P < .05$) • Among all participants (men and women), HIV status did not significantly modify the effect of BMI on hs-CRP or of BMI on IL-6	Control group was very small. Did not capture menopause status.

Table 4. Continued

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	Study Population (Location, Race/Ethnicity, Age)	Outcomes Measured	Key Findings	Limitations
Galli et al, 2003 [81]	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 [82]	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 [83]	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, .20–.75], $P < .05$)	Did not control for BMI
Liver Disease					
Kardashian et al, 2017 [86]	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, HIV, 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

Table 4. Continued

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	Study Population (Location, Race/Ethnicity, Age)	Outcomes Measured	Key Findings	Limitations
Guaraldi et al, 2008 [87]	Cross-sectional N = 225 (100% PWH) 163 men, 62 women	• PWH cared for at the metabolic clinic of University of Modena and Reggio Emilia School of Medicine in Italy • Race/ethnicity data not reported • Mean age: 48 y	Prevalence and predictors on NAFLD among PWH and NAFLD diagnosed by CT (liver-to-spleen attenuation ratio <1.1)	• Prevalence of NAFLD was greater among MWH than WWH (44% vs 19%, $P < .05$) • PWH with NAFLD were 3.2 times more likely to be male than female in univariate analysis (95% CI, 1.59–6.49) and 2.5 times more likely to be male than female in multivariate analysis (95% CI, 1.07–5.81)	PWH had high prevalence of metabolic abnormalities and findings may not be generalizable to all PWH. Did not include persons without HIV for comparison.

Abbreviations: ACTG, AIDS Clinical Trial Group; aOR, adjusted odds ratio; ART, antiretroviral therapy; ATA, adipose tissue alteration; BMI, body mass index; BOBCAT, boosting health by changing activity ; CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; CPCRA, Community Program for Clinical Research on AIDS; CT, computed tomography; FMI, fat mass index; FRAM, Study of Fat Redistribution and Metabolic Change in HIV Infection; HCV, hepatitis C virus; hs-CRP, high-sensitivity C-reactive protein; IL6, interleukin 6; IR, insulin resistance; IRR, incidence rate ratio; LFF, liver fat fraction; MWH, men with HIV; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PWH, persons with HIV; PY, person-years; QUICKI, Quantitative Insulin Sensitivity Check Index; *r*, correlation coefficient; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes mellitus; TN, Tennessee; VACS, Veterans Aging Cohort Study; VAMC, Veterans Affairs Medical Center; VAT, visceral adipose tissue; WWH, women with HIV.

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,

Table 5. Summary of Studies Reporting Sex Differences for Neurocognitive Impairment Among People With HIV

Author, Year [Ref]	Study Design Study Size (% PWH) No. of Men and Women	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 (72% 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.

Notes

Author contributions. R. A. P. developed searches; reviewed literature; selected articles for inclusion; organized data; and synthesized background knowledge and study findings in writing, tables, and figures. L. F. C. applied clinical and research expertise in sex differences in HIV and non-AIDS comorbidities to synthesize the literature and guide development of tables and figures by providing continual feedback. L. F. C. also performed iterative edits of the manuscript. C. D. L. conceived of the idea, helped define the scope and approach to reviewing sex differences, guided structure of the manuscript, provided feedback and edits throughout the writing process, and performed iterative edits of the manuscript.

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References

1. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet **2008**; 372:293–9.
2. Brooks JT, Buchacz K, Gebo KA, Mermin J. HIV infection and older Americans: the public health perspective. Am J Public Health **2012**; 102:1516–26.
3. High KP, Brennan-Ing M, Clifford DB, et al; OAR Working Group on HIV and Aging. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. J Acquir Immune Defic Syndr **2012**; 60(Suppl 1):S1–18.
4. Hasse B, Ledergerber B, Egger M, et al. Aging and non-HIV associated co-morbidity in HIV+ persons: the SHCS [Abstract 792]. In: 18th Conference on Retroviruses and Opportunistic Infections, 27 February–3 March **2011**.
5. Onen NF, Overton ET, Seyfried W, et al. Aging and HIV infection: a comparison between older HIV-infected persons and the general population. HIV Clin Trials **2010**; 11:100–9.
6. Joint United Nations Programme on HIV/AIDS. Fact sheet—World AIDS Day 2020. Geneva, Switzerland: UNAIDS; **2020**.
7. Clayton JA, Collins FS. NIH to balance sex in cell and animal studies. Nature **2014**; 509:282–3.
8. Curno MJ, Rossi S, Hodges-Mameletzis I, et al. A systematic review of the inclusion (or exclusion) of women in HIV research: from clinical studies of antiretrovirals and vaccines to cure strategies. J Acquir Immune Defic Syndr **2016**; 71:181–8.
9. Palella FJ, Hart R, Armon C, et al; HIV Outpatient Study (HOPS). Non-AIDS comorbidity burden differs by sex, race, and insurance type in aging adults in HIV care. AIDS **2019**; 33:2327–35.
10. Collins LF, Sheth AN, Mehta CC, et al. The prevalence and burden of non-AIDS comorbidities among women living with or at risk for human immunodeficiency virus infection in the United States. Clin Infect Dis **2021**; 72:1301–11.
11. Meier A, Chang JJ, Chan ES, et al. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. Nat Med **2009**; 15:955–9.
12. Fan MD, Maslow B-S, Santoro N, Schoenbaum E. HIV and the menopause. Menopause Int **2008**; 14:163–8.
13. Ferreira CE, Pinto Neto AM, Conde DM. Menopause symptoms in women infected with HIV: prevalence and associated factors. Gynecol Endocrinol **2007**; 23:198–205.
14. Clark RA, Cohn SE, Jarek C. Perimenopausal symptomatology among HIV-infected women at least 40 years of age. J Acquir Immune Defic Syndr Human Retrovirology **2000**; 23:99–100.
15. Imai K, Sutton MY, Mdodo R, Del Rio C. HIV and menopause: a systematic review of the effects of HIV infection on age at menopause and the effects of menopause on response to antiretroviral therapy. Obstet Gynecol Int **2013**; 2013:340309.
16. Sandelowski M, Lambe C, Barroso J. Stigma in HIV-positive women. J Nurs Scholarsh **2004**; 36:122–8.
17. Sohler NL, Xuan L, Cunningham CO. Gender disparities in HIV health care utilization among the severely disadvantaged: can we determine the reasons? AIDS Patient Care STDS **2009**; 23:775–83.
18. Collins LF, Armstrong WS. What it means to age with HIV infection: years gained are not comorbidity free. JAMA Netw Open **2020**; 3:e208023.
19. Scully EP. Sex differences in HIV infection. Curr HIV/AIDS Rep **2018**; 15:136–46.
20. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS **2006**; 20:2165–74.
21. Bhatta DN, Subedi A, Sharma N. Tobacco smoking and alcohol drinking among HIV infected people using antiretroviral therapy. Tob Induc Dis **2018**; 16:16.
22. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis **2010**; 51:937–46.
23. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis **2011**; 53:1120–6.
24. Kudlacek S, Schneider B, Resch H, et al. Gender differences in fracture risk and bone mineral density. Maturitas **2000**; 36:173–80.
25. Kalayjian RC, Albert JM, Cremers S, et al; ACTG A5224s, A5303 Teams. Women have enhanced bone loss associated with phosphaturia and $CD4^+$ cell restoration during initial antiretroviral therapy. AIDS **2018**; 32:2517–24.
26. Titanji K, Vunnava A, Sheth AN, et al. Dysregulated B cell expression of RANKL and OPG correlates with loss of bone mineral density in HIV infection. PLoS Pathog **2014**; 10:e1004497.
27. Ofotokun I, Titanji K, Vunnava A, et al. Antiretroviral therapy induces a rapid increase in bone resorption that is positively associated with the magnitude of immune reconstitution in HIV infection. AIDS **2016**; 30:405–14.
28. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. AIDS **2000**; 14:F63–7.

29. Thomas J, Doherty SM. HIV infection—a risk factor for osteoporosis. J Acquir Immune Defic Syndr **2003**; 33:281–91.
30. Negredo E, Langohr K, Bonjoch A, et al. High risk and probability of progression to osteoporosis at 10 years in HIV-infected individuals: the role of PIs. J Antimicrob Chemother **2018**; 73:2452–9.
31. Han WM, Wattanachanya L, Apornpong T, et al; TNT 003.1 Study Team. Bone mineral density changes among people living with HIV who have started with TDF-containing regimen: a five-year prospective study. PLoS One **2020**; 15:e0230368.
32. Komatsu A, Ikeda A, Kikuchi A, et al. Osteoporosis-related fractures in HIV-infected patients receiving long-term tenofovir disoproxil fumarate: an observational cohort study. Drug Saf **2018**; 41:843–8.
33. Gedmintas L, Wright EA, Losina E, et al. Comparative risk of fracture in men and women with HIV. J Clin Endocrinol Metab **2014**; 99:486–90.
34. Yin M, Dobkin J, Brudney K, et al. Bone mass and mineral metabolism in HIV^+ postmenopausal women. Osteoporos Int **2005**; 16:1345–52.
35. Cortés YI, Yin MT, Reame NK. Bone density and fractures in HIV-infected postmenopausal women: a systematic review. J Assoc Nurses AIDS Care **2015**; 26:387–98.
36. Yin MT, Shi Q, Hoover DR, et al. Fracture incidence in HIV-infected women: results from the Women's Interagency HIV Study. AIDS **2010**; 24:2679–86.
37. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis **2010**; 50:1387–96.
38. Trickey A, May MT, Vehreschild J, et al; Antiretroviral Therapy Cohort Collaboration (ART-CC). Cause-specific mortality in HIV-positive patients who survived ten years after starting antiretroviral therapy. PLoS One **2016**; 11:e0160460.
39. Feinstein MJ, Bahiru E, Achenbach C, et al. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. Am J Cardiol **2016**; 117:214–20.
40. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab **2007**; 92:2506–12.
41. Tseng ZH, Secemsky EA, Dowdy D, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. J Am Coll Cardiol **2012**; 59:1891–6.
42. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA **2012**; 308:379–86.
43. Friis-Møller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med **2007**; 356:1723–35.
44. Triant VA, Grinspoon SK. Epidemiology of ischemic heart disease in HIV. Curr Opin HIV AIDS **2017**; 12:540–7.
45. Hanna DB, Ramaswamy C, Kaplan RC, et al. Sex- and poverty-specific patterns in cardiovascular disease mortality associated with human immunodeficiency virus, New York City, 2007-2017. Clin Infect Dis **2020**; 71:491–8.
46. Frazier EL, Sutton MY, Tie Y, et al. Differences by sex in cardiovascular comorbid conditions among older adults (aged 50-64 or ≥65 years) receiving care for human immunodeficiency virus. Clin Infect Dis **2019**; 69:2091–100.
47. Foldyna B, Fourman LT, Lu MT, et al. Sex differences in subclinical coronary atherosclerotic plaque among individuals with HIV on antiretroviral therapy. J Acquir Immune Defic Syndr **2018**; 78:421–8.
48. Kent ST, Schwartz JE, Shimbo D, et al. Race and sex differences in ambulatory blood pressure measures among HIV+ adults. J Am Soc Hypertens **2017**; 11:420–7.e3.
49. Reinsch N, Buhr C, Krings P, et al; Competence Network of Heart Failure. Effect of gender and highly active antiretroviral therapy on HIV-related pulmonary arterial hypertension: results of the HIV-HEART Study. HIV Med **2008**; 9:550–6.
50. Fitch KV, Srinivasa S, Abbara S, et al. Noncalcified coronary atherosclerotic plaque and immune activation in HIV-infected women. J Infect Dis **2013**; 208:1737–46.
51. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation **2003**; 108:1664–72.
52. Hanna DB, Moon JY, Haberlen SA, et al. Carotid artery atherosclerosis is associated with mortality in HIV-positive women and men. AIDS **2018**; 32:2393–403.
53. Durand M, Sheehy O, Baril J-G, et al. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's Public Health Insurance Database. JAIDS **2011**; 57:245–53.
54. Adeel A. Butt M, Chung-Chou C, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. Arch Intern Med **2011**; 171:737–43.
55. Janjua SA, Triant VA, Addison D, et al. HIV infection and heart failure outcomes in women. J Am Coll Cardiol **2017**; 69:107–8.
56. Womack JA, Chang CC, So-Armah KA, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc **2014**; 3:e001035.
57. Chow FC, Regan S, Feske S, et al. Comparison of ischemic stroke incidence in HIV-infected and non–HIV-infected patients in a US health care system. J Acquir Immune Defic Syndr **2012**; 60:351–8.
58. Chow FC, Wilson MR, Wu K, et al. Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials Cohort. AIDS **2018**; 32:1125–35.
59. Wilson PW, D'Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation **2005**; 112:3066–72.
60. Bonfanti P, Giannattasio C, Ricci E, et al. HIV and metabolic syndrome a comparison with the general population. J Acquir Immune Defic Syndr **2007**; 45:426–31.
61. Grundy SM, Hansen B, Smith SC Jr, et al; American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation **2004**; 109:551–6.
62. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al; Veterans Aging Cohort Study. HIV infection and the risk of diabetes mellitus. AIDS **2009**; 23:1227–34.
63. Ledergerber B, Furrer H, Rickenbach M, et al; Swiss HIV Cohort Study. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. Clin Infect Dis **2007**; 45:111–9.
64. Worm SW, Friis-Møller N, Bruyand M, et al; D:A:D Study Group. High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome. AIDS **2010**; 24:427–35.
65. Koethe JR, Jenkins CA, Petucci C, et al. Superior glucose tolerance and metabolomic profiles, independent of adiposity, in HIV-infected women compared with men on antiretroviral therapy. Medicine (Baltimore) **2016**; 95:e3634.
66. Arama V, Tiliscan C, Streinu-Cercel A, et al; SLD-ART Study Group. Insulin resistance and adipokines serum levels in a Caucasian cohort of HIV-positive patients undergoing antiretroviral therapy: a cross sectional study. BMC Endocr Disord **2013**; 13:4.
67. El-Sadr WM, Mullin CM, Carr A, et al. Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naive cohort. HIV Med **2005**; 6:114–21.
68. Cicero AF, Magni P, Moré M, et al. Adipokines and sexual hormones associated with the components of the metabolic syndrome in pharmacologically untreated subjects: data from the Brisighella Heart Study. Int J Endocrinol **2011**; 2011:724816.
69. Damouche A, Lazure T, Avettand-Fènoël V, et al. Adipose tissue is a neglected viral reservoir and an inflammatory site during chronic HIV and SIV infection. PLoS Pathog **2015**; 11:e1005153.
70. Robles DT, Habashy J. Lipodystrophy in HIV. Medscape **2016**. https://emedicine.medscape.com/article/1082199-overview. Accessed 5 November 2021.
71. Hadigan C, Liebau J, Andersen R, et al. Magnetic resonance spectroscopy of hepatic lipid content and associated risk factors in HIV infection. J Acquir Immune Defic Syndr **2007**; 46:312–7.
72. Torriani M, Hadigan C, Jensen ME, Grinspoon S. Psoas muscle attenuation measurement with computed tomography indicates intramuscular fat accumulation in patients with the HIV-lipodystrophy syndrome. J Appl Physiol **2003**; 95:1005–10.
73. Bares SH, Smeaton LM, Xu A, et al. HIV-infected women gain more weight than HIV-infected men following the initiation of antiretroviral therapy. J Womens Health (Larchmt) **2018**; 27:1162–9.
74. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. HIV/AIDS **2001**; 32:130–9.
75. Joy T, Keogh HM, Hadigan C, et al. Relation of body composition to body mass index in HIV-infected patients with metabolic abnormalities. J Acquir Immune Defic Syndr **2008**; 47:174–84.
76. Haase J, Weyer U, Immig K, et al. Local proliferation of macrophages in adipose tissue during obesity-induced inflammation. Diabetologia **2014**; 57:562–71.
77. Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med **2011**; 17:179–88.
78. Longenecker CT, Jiang Y, Yun CH, et al. Perivascular fat, inflammation, and cardiovascular risk in HIV-infected patients on antiretroviral therapy. Int J Cardiol **2013**; 168:4039–45.
79. Longenecker CT, Margevicius S, Liu Y, et al. Effect of pericardial fat volume and density on markers of insulin resistance and inflammation in patients with human immunodeficiency virus infection. Am J Cardiol **2017**; 120:1427–33.
80. Chen M, Hung CL, Yun CH, et al. Sex differences in the association of fat and inflammation among people with treated HIV infection. Pathog Immun **2019**; 4:163–79.
81. Galli M, Veglia F, Santambrogio S, et al. Gender differences in antiretroviral drug–related adipose tissue alterations. J Acquir Immune Defic Syndr **2003**; 34:58–61.

82. Bacchetti P, Gripshover B, Grunfeld C, et al. Fat distribution in men with HIV infection. J Acquir Immune Defic Syndr **2005;** 40:121–31.
83. Tien PC. Fat distribution in women with HIV infection. J Acquir Immune Defic Syndr **2006**; 42:562–71.
84. Soti S, Corey KE, Lake JE, Erlandson KM. NAFLD and HIV: do sex, race, and ethnicity explain HIV-related risk? Curr HIV/AIDS Rep **2018**; 15:212–22.
85. Brady CW. Liver disease in menopause. World J Gastroenterol **2015**; 21:7613–20.
86. Kardashian A, Ma Y, Scherzer R, et al. Sex differences in the association of HIV infection with hepatic steatosis. AIDS **2017**; 31:365–73.
87. Guaraldi G, Squillace N, Stentarelli C, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis **2008**; 47:250–7.
88. Bertrand L, Velichkovska M, Toborek M. Cerebral vascular toxicity of antiretroviral therapy. J Neuroimmune Pharmacol **2021**; 16:74–89.
89. Heaton RK, Clifford DB, Franklin DR Jr, et al; CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology **2010**; 75:2087–96.
90. Heaton RK, Franklin DR Jr, Deutsch R, et al; CHARTER Group. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. Clin Infect Dis **2015**; 60:473–80.
91. Albert SM, Marder K, Doonief G, et al. Neuropsychologic impairment in early HIV infection. A risk factor for work disability. Arch Neurol **1995**; 52:525–30.
92. Tozzi V, Balestra P, Serraino D, et al. Neurocognitive impairment and survival in a cohort of HIV-infected patients treated with HAART. AIDS Res Hum Retroviruses **2005**; 21:706–13.
93. Tozzi V, Balestra P, Galgani S, et al. Neurocognitive performance and quality of life in patients with HIV infection. AIDS Res Hum Retroviruses **2003**; 19:643–52.
94. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol **2014**; 10:634–42.
95. Kompella S, Al-Khateeb T, Riaz OA, et al. HIV-associated neurocognitive disorder (HAND): relative risk factors. Curr Top Behav Neurosci **2020**; 50:401–26.
96. Rubin LH, Neigh GN, Sundermann EE, et al. Sex differences in neurocognitive function in adults with HIV: patterns, predictors, and mechanisms. Curr Psychiatry Rep **2019**; 21:94.
97. Burlacu R, Umlauf A, Luca A, et al. Sex based differences in neurocognitive functioning in HIV infected young adults. AIDS **2018**; 32:139–48.
98. Sundermann EE, Heaton RK, Pasipanodya E, et al; HNRP Group. Sex differences in HIV-associated cognitive impairment. AIDS **2018**; 32:2719–26.
99. Maki PM, Rubin LH, Springer G, et al. Differences in cognitive function between women and men with HIV. J Acquir Immune Defic Syndr **2018**; 79:101–7.
100. Royal W 3rd, Cherner M, Burdo TH, et al. Associations between cognition, gender and monocyte activation among HIV infected individuals in Nigeria. PLoS One **2016**; 11:e0147182.
101. Carey CL, Woods SP, Gonzalez R, et al; HNRC Group. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol **2004**; 26:307–19.
102. Kabuba N, Menon JA, Franklin DR Jr, et al. HIV- and AIDS-associated neurocognitive functioning in Zambia—a perspective based on differences between the genders. Neuropsychiatr Dis Treat **2016**; 12:2021–8.
103. Collins LF, Sheth AN, Mehta CC, et al. Incident non-AIDS comorbidity burden among women with or at risk for human immunodeficiency virus in the United States. Clin Infect Dis **2021**; 73:e2059–69.
104. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. Immunity **2013**; 39:633–45.
105. Hunt PW. HIV and inflammation: mechanisms and consequences. Curr HIV/AIDS Rep **2012**; 9:139–47.
106. Zanni MV, Awadalla M, Toribio M, et al. Immune correlates of diffuse myocardial fibrosis and diastolic dysfunction among aging women with human immunodeficiency virus. J Infect Dis **2020**; 221:1315–20.
107. Appay V, Almeida JR, Sauce D, et al. Accelerated immune senescence and HIV-1 infection. Exp Gerontol **2007**; 42:432–7.
108. Ziegler S, Altfeld M. Sex differences in HIV-1-mediated immunopathology. Curr Opin HIV AIDS **2016**; 11:209–15.
109. Mathad JS, Gupte N, Balagopal A, et al; New Work Concept Sheet 319 and AIDS Clinical Trials Group A5175 (PEARLS) Study Teams. Sex-related differences in inflammatory and immune activation markers before and after combined antiretroviral therapy initiation. J Acquir Immune Defic Syndr **2016**; 73:123–9.
110. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med **2006**; 12:1365–71.
111. Kim YS, Unno T, Kim BY, Park MS. Sex differences in gut microbiota. World J Mens Health **2020**; 38:48–60.
112. Rizzetto L, Fava F, Tuohy KM, Selmi C. Connecting the immune system, systemic chronic inflammation and the gut microbiome: the role of sex. J Autoimmun **2018**; 92:12–34.
113. Vancamelbeke M, Vermeire S. The intestinal barrier: a fundamental role in health and disease. Expert Rev Gastroenterol Hepatol **2017**; 11:821–34.
114. Raghavan A, Rimmelin DE, Fitch KV, Zanni MV. Sex differences in select non-communicable HIV-associated comorbidities: exploring the role of systemic immune activation/inflammation. Curr HIV/AIDS Rep **2017**; 14:220–8.
115. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol **2016**; 16:626–38.
116. Das B, Dobrowolski C, Luttge B, et al. Estrogen receptor-1 is a key regulator of HIV-1 latency that imparts gender-specific restrictions on the latent reservoir. Proc Natl Acad Sci U S A **2018**; 115:E7795–804.
117. Szotek EL, Narasipura SD, Al-Harthi L. 17β-Estradiol inhibits HIV-1 by inducing a complex formation between β-catenin and estrogen receptor α on the HIV promoter to suppress HIV transcription. Virology **2013**; 443:375–83.
118. Greenblatt RM, Ameli N, Grant RM, et al. Impact of the ovulatory cycle on virologic and immunologic markers in HIV-infected women. J Infect Dis **2000**; 181:82–90.
119. Giglio T, Imro MA, Filaci G, et al. Immune cell circulating subsets are affected by gonadal function. Life Sciences **1994**; 54:1305–12.
120. Feeney ER, Mallon PW. Insulin resistance in treated HIV infection. Best Pract Res Clin Endocrinol Metab **2011**; 25:443–58.
121. Centers for Disease Control and Prevention. Social determinants of health and selected HIV care outcomes among adults with diagnosed HIV infection in 32 states and the district of Columbia. HIV Surveillance Report Suppl **2014**; 21:7.
122. Clum G, Chung SE, Ellen JM; Adolescent Medicine Trials Network for HIV/AIDS Interventions. Mediators of HIV-related stigma and risk behavior in HIV infected young women. AIDS Care **2009**; 21:1455–62.
123. Althoff KN, Gebo KA, Moore RD, et al; North American AIDS Cohort Collaboration on Research and Design. Contributions of traditional and HIV-related risk factors on non-AIDS-defining cancer, myocardial infarction, and end-stage liver and renal diseases in adults with HIV in the USA and Canada: a collaboration of cohort studies. Lancet HIV **2019**; 6:e93–104.
124. Heise L, Greene ME, Opper N, et al; Gender Equality, Norms, and Health Steering Committee. Gender inequality and restrictive gender norms: framing the challenges to health. Lancet **2019**; 393:2440–54.
125. Leddy AM, Zakaras JM, Shieh J, et al. Intersections of food insecurity, violence, poor mental health and substance use among US women living with and at risk for HIV: evidence of a syndemic in need of attention. PLoS One **2021**; 16:e0252338.
126. Kharsany AB, Karim QA. HIV infection and AIDS in sub-Saharan Africa: current status, challenges and opportunities. Open AIDS J **2016**; 10:34–48.
127. Joint United Nations Programme on HIV/AIDS. The Gap Report. Geneva, Switzerland: UNAIDS; **2014**.
128. Cohen MH, Hotton AL, Hershow RC, et al. Gender-related risk factors improve mortality predictive ability of VACS Index among HIV-infected women. J Acquir Immune Defic Syndr **2015**; 70:538–44.
129. Negredo E, Domingo P, Pérez-Álvarez N, et al. Improvement in bone mineral density after switching from tenofovir to abacavir in HIV-1-infected patients with low bone mineral density: two-centre randomized pilot study (OsteoTDF study). J Antimicrob Chemother **2014**; 69:3368–71.
130. Nan C, Shaefer M, Urbaityte R, et al. Abacavir use and risk for myocardial infarction and cardiovascular events: pooled analysis of data from clinical trials. Open Forum Infect Dis **2018**; 5:ofy086.
131. Elion RA, Althoff KN, Zhang J, et al; North American AIDS Cohort Collaboration on Research and Design of IeDEA. Recent abacavir use increases risk of type 1 and type 2 myocardial infarctions among adults with HIV. J Acquir Immune Defic Syndr **2018**; 78:62–72.
132. Anastos KL, Qiuhu S, Tien PC, et al. Association of serum lipid levels with HIV serostatus, specific antiretroviral agents, and treatment regimens. J Acquir Immune Defic Syndr **2007**; 45:34–42.
133. Brouilette MJ, Routy JP. Abacavir sulfate and mania in HIV. Am J Psychiatry **2007**; 164:979–80.
134. Erlandson KM, Lake JE, Sim M, et al. Bone mineral density declines twice as quickly among HIV-infected women compared with men. J Acquir Immune Defic Syndr **2018**; 77:288–94.
135. Gallant JE. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA **2004**; 292:191–201.
136. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med **2019**; 381:803–15.
137. Tao X, Lu Y, Zhou Y, et al. Virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens: a meta-analysis of randomized controlled trials. Int J Infect Dis **2019**; 87:43–53.
138. Venter WD. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV **2020**; 7:e666–76.

139. Lahiri CD, Xu Y, Wang K, et al. Weight and body mass index change after switching to integrase inhibitors or tenofovir alafenamide among women living with HIV. AIDS Res Hum Retroviruses **2021**; 37:461–7.
140. Clark R. Sex differences in antiretroviral therapy-associated intolerance and adverse events. Drug Saf **2005**; 28:1075–83.
141. Tebas P, Sension M, Arribas J, et al; ECHO and THRIVE Study Groups. Lipid levels and changes in body fat distribution in treatment-naive, HIV-1-infected adults treated with rilpivirine or efavirenz for 96 weeks in the ECHO and THRIVE trials. Clin Infect Dis **2014**; 59:425–34.
142. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. AIDS **2014**; 28:989–97.
143. Hodder S, Arasteh K, De Wet J, et al. Effect of gender and race on the week 48 findings in treatment-naïve, HIV-1-infected patients enrolled in the randomized, phase III trials ECHO and THRIVE. HIV Med **2012**; 13:406–15.
144. Molina JM, Cahn P, Grinsztejn B, et al; ECHO Study Group. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet **2011**; 378:238–46.
145. Palella FJ Jr, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS **2014**; 28:335–44.
146. Thompson M, Orkin C, Molina JM, et al. Once-daily doravirine for initial treatment of adults living with human immunodeficiency virus-1: an integrated safety analysis. Clin Infect Dis **2020**; 70:1336–43.
147. Orkin C, Elion R, Thompson M, et al. Changes in weight and BMI with first-line doravirine-based therapy. AIDS **2021**; 35:91–9.
148. Li M, Chan WW, Zucker SD. Association between atazanavir-induced hyperbilirubinemia and cardiovascular disease in patients infected with HIV. J Am Heart Assoc **2020**; 9:e016310.
149. Crane HM, Nance RM, Heckbert SR, et al. Association between bilirubin, atazanavir, and cardiovascular disease events among people living with HIV across the United States. J Acquir Immune Defic Syndr **2019**; 81:e141–7.
150. Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in waist circumference in HIV-infected individuals initiating a raltegravir or protease inhibitor regimen: effects of sex and race. Open Forum Infect Dis **2018**; 5:ofy201.
151. Treisman GJ, Soudry O. Neuropsychiatric effects of HIV antiviral medications. Drug Saf **2016**; 39:945–57.
152. Pérez Elías MJ, Alejos B, Vivancos MJ, et al; CODAR Study Group. Outcomes by sex following treatment initiation with darunavir/cobicistat in a large Spanish cohort of the CODAR study (GeSIDA 9316). J Antimicrob Chemother **2019**; 74:3044–8.
153. Ibrahim F, Samarawickrama A, Hamzah L, et al; BESTT Trial Team. Bone mineral density, kidney function, weight gain and insulin resistance in women who switch from TDF/FTC/NNRTI to ABC/3TC/DTG. HIV Med **2021**; 22:83–91.
154. Lake JE, Wu K, Bares SH, et al. Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy. Clin Infect Dis **2020**; 71:e471–7.
155. Summers NA, Lahiri CD, Angert CD, et al. Metabolic changes associated with the use of integrase strand transfer inhibitors among virally controlled women. J Acquir Immune Defic Syndr **2020**; 85:355–62.
156. Kerchberger AM, Sheth AN, Angert CD, et al. Weight gain associated with integrase stand transfer inhibitor use in women. Clin Infect Dis **2020**; 71:593–600.
157. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med **2017**; 18:56–63.
158. Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV **2019**; 6:e355–63.
159. Stellbrink HJ, Lazzarin A, Woolley I, Llibre JM. The potential role of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) single-tablet regimen in the expanding spectrum of fixed-dose combination therapy for HIV. HIV Med **2020**; 21(Suppl 1):3–16.
160. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis **2020**; 71:1379–89.