CONCISE COMMUNICATION

Hormone therapy and fractures in postmenopausal women

Michael T. Yin[a], Donald R. Hoover[b], Qiuhu Shi[c], Phyllis C. Tien[d,e], Mardge H. Cohen[f], Seble Kassaye[g], Deborah Gustafson[h], Adaora Adimora[i], M. Neale Weitzmann[j,k], Hector Bolivar[l], Amy Warriner[m], Sara H. Bares[n] and Anjali Sharma[o]

See related paper on page 1731

Background: Fracture rates have been reported to be higher among older women living with HIV (WLWH) than HIV− women. Hormone therapy with estrogen can reduce vasomotor symptoms (VMS) associated with menopause and prevent fractures. As data are limited on the benefits of hormone therapy use in WLWH, we examined associations of hormone therapy, use and fractures.

Methods: A prospective study of 1765 (1350 WLWH and 415 HIV−) postmenopausal Women's Interagency HIV Study (WIHS) participants was performed, including self-reported hormone therapy, use and fracture data from 2003 to 2017. Proportional hazard models determined predictors of new fractures at any site or at typical fragility fracture sites (hip, spine, wrist).

Results: At the first postmenopausal visit, the median (IQR) age of WLWH was slightly younger than HIV− women [49.8 (46.4–53) vs. 50.7 (47.5–54), $P = 0.0002$] and a smaller proportion of WLWH reported presence of VMS (17% vs. 26%, $P < 0.0001$). A greater proportion of WLWH than HIV− women reported hormone therapy use (8% vs. 4%, $P = 0.007$) at the first postmenopausal visit. In multivariate analyses, white race and smoking were significant predictors of incident fracture at any site but hormone therapy ($P = 0.69$) and HIV status ($P = 0.53$) were not.

Conclusion: Our study did not find evidence of benefit or harm with regards to fracture outcomes in postmenopausal WLWH receiving hormone therapy. Further research is needed to determine whether hormone therapy has benefits beyond treatment of VMS, such as prevention of adverse aging-associated outcomes.

AIDS 2022, **36**:1683–1688

[a]Department of Medicine, College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY, [b]Department of Statistics and Institute for Health, Healthcare Policy and Aging Research, Rutgers University, Piscataway, NJ, [c]School of Health Sciences and Practice, New York Medical College, Valhalla, NY, [d]Department of Veterans Affairs Medical Center, [e]Department of Medicine, University of California San Francisco, San Francisco, CA, [f]Department of Medicine, Stroger Hospital, Chicago, IL, [g]Georgetown School of Medicine, Washington DC, [h]State University of New York Downstate Medical Center, Brooklyn, NY, [i]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, [j]Department of Medicine, Emory University School of Medicine, Atlanta, [k]the Atlanta VA Medical Center, Decatur, GA, [l]Department of Medicine, University of Miami, Miami, FL, [m]Department of Medicine, University of Alabama, Birmingham AL, [n]Department of Medicine, University of Nebraska Medical Center, Omaha, NE, and [o]Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA.

Correspondence to Michael T. Yin, Columbia University Irving Medical Center, New York, NY 10032, USA.
E-mail: mty4@cumc.columbia.edu
Received: 25 March 2022; revised: 16 May 2022; accepted: 18 May 2022.

DOI:10.1097/QAD.0000000000003292

Keywords: fractures, HIV, menopause, vasomotor symptoms, women

Introduction

With successful antiretroviral therapy (ART), over half of women living with HIV (WLWH) in the United States are at least 50 years old; many are transitioning through menopause. Menopause is marked by declining estrogen production and often accompanied by vasomotor symptoms (VMS), such as hot flushes and night sweats [1]. Women experience frequent VMS for 7.4 years on average, with black women having the most enduring VMS of any racial/ethnic group [2]. Some studies suggest that WLWH experience menopause at earlier ages [3–6] and VMS more commonly than women without HIV [7–10]. Bone loss accelerates substantially during the first 2 years of menopause and is a major risk factor for fractures in older age [11]. Fracture rates are 30–70% higher in older adults with HIV compared with the general population [12–14], and may be related to higher levels of pro-resorptive inflammatory cytokines, negative effects of specific ART on bone cells, and a higher prevalence of traditional osteoporosis risk factors [15].

Hormone therapy, given as estrogen-only therapy after hysterectomy or as estrogen with progestogen for women with an intact uterus, is considered the most effective treatment of VMS [16–18] and also prevents menopausal bone loss and decreases long-term risk of fracture [19–21]. However, menopausal hormone therapy is uncommon in the general population and among WLWH [22,23] because of lingering concerns about cardiovascular and breast cancer risk raised by the Women's Health Initiative studies [24–26]. We previously found that fracture rates were higher in WLWH than HIV-seronegative women of similar age in the Women's Interagency HIV Study (WIHS) [27]. In order to explore potential benefits of hormone therapy for WLWH, this analysis evaluates whether hormone therapy exposure reduces rate of fracture.

Methods

Study design

This was an observational study of time to fracture. The WIHS enrolled a prospective cohort of women in 1994–1995 from six sites nationally, and with additional enrollment in 2001–2002 and 2011–2012 including WLWH and HIV-seronegative women at increased risk of acquiring HIV [28,29]. Participants attended semiannual visits, which included an interviewer-administered questionnaire, physical examination, and collection of laboratory specimens.

Study outcomes

Starting in 2003 (visit 17), all WIHS participants were asked whether they ever had a fracture of the hip, wrist, spine or other body site. Fracture type (s) was determined and classified as fragility (resulting from fall from standing height or less) and nonfragility.

Inclusions and exclusions

In all subsequent semi-annual study visits, participants were asked if they had new fractures (since the previous visit) with type of fracture similarly determined. We restricted analysis to participants that answered fracture questions at least once, met criteria for postmenopausal status and additionally excluded participants with a history of fracture prior to the first postmenopausal visit. Postmenopausal status was determined by participant report of hysterectomy or amenorrhea for 12 months (i.e. lack of menses in the prior 6 months at two consecutive semiannual visits) [19]. The first postmenopausal visit was the earliest post hysterectomy visit or otherwise of the first of two consecutive visits that determined postmenopausal status.

Study population

In total, 1765 participants (1350 WLWH) with at least one semi-annual study visit after the first postmenopausal visit, were included in the analysis. This analysis uses data from 2003 (visit 18) through 2017 (visit 47), including all fractures at any body site [27,30,31].

Other covariates

Demographics, HIV treatment history, and known predictors of fracture [27,30,31] were quantified, including: age; self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, other/hispanic); BMI in kg/m^2; current cigarette smoking; heavy alcohol (>12 drinks per week); injection drug use (IDU), opiates or cocaine use; calcium supplementation; glucocorticoid use (ever); history of diabetes; estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) calculation; and active hepatitis C virus (HCV) status by the presence of detectable plasma HCV RNA level at or prior to the index visit. Frequency of vasomotor symptoms (hot flashes, night sweats, cold sweats) during the previous 2 weeks were recorded as not at all, 1–5, 6–8, 9–13 days, or daily in WIHS semi-annual visits [32]. Significant hormone therapy exposure was defined by use on at least two consecutive study visits.

Statistical analysis

Means, medians, standard deviations, interquartile ranges, and proportions summarized study variables, depending upon whether they were continuous or categorical. This

includes serial cross-sectional use of hormone therapy. *P* values for comparisons of groups are from rank tests for continuous and exact tests for categorical variables. Proportional hazards models determined predictors of new fracture incidence by time since first postmenopausal visit. In these models, hormone therapy use was time updated; all other covariates were time invariant and assessed at the first postmenopausal visit. For each participant, the end of follow-up was either the visit with first fracture event, or the last visit prior to visit 48 if no fracture was reported. Only the first new fracture was included in the analysis. Bivariate analyses comparing each predictor to the outcome were considered for WLWH and women without HIV together. All variables were entered into multivariate proportional hazards models.

Results

Participant characteristics at postmenopausal visit

WLWH were younger than women without HIV (median age of 49.8 vs. 50.7, $P = 0.0002$) at the first postmenopausal visit (Table 1). WLWH were less likely to be non-Hispanic black (68% vs. 75%, $P = 0.001$) and have BMI greater than 30 kg/m^2 than women without HIV (39% vs. 58%, $P < 0.0001$). WLWH were less likely to have diabetes mellitus (20% vs. 27%, $P = 0.004$) but more likely to have detectable HCV RNA (30% vs. 22%, $P = 0.003$) and eGFR less than 60 ml/min (11% vs. 6%, $P = 0.002$). WLWH were also less likely to report current smoking, heavy alcohol consumption, cocaine use than women without HIV, but more likely to report calcium supplementation (Table 1). Among WLWH at the index visit, median CD4$^+$ T-cell count was 490 (288, 714 cells/μl), 82% reported ART use (including 41% on protease inhibitor and 38% on tenofovir disoproxil fumarate-containing regimens), and 65% had an HIV RNA less than 200 copies/ml on ART. WLWH who reported hormone therapy use at any time during the study period ($n = 230$) were younger, more likely to be white, to be a nonsmoker, and take calcium supplementation than WLWH who did not use hormone therapy ($n = 1123$) but did not differ in other respects at the first postmenopausal visit (Table S1, http://links.lww.com/QAD/C545).

Vasomotor symptoms and hormone therapy use

At the index visit, fewer postmenopausal WLWH than women without HIV reported having VMS at least one

Table 1. Characteristics at fist postmenopausal visit (index visit) and incident fracture after index visit.

Variable	Women living with HIV ($N = 1353$)	Women without HIV ($N = 412$)	*P* value
Age at index [years, median (IQR)]	49.8 (46.4–53.0)	50.7 (47.5–54.0)	0.0002
Age >60 years	34 (3%)	13 (3%)	0.48
Race/ethnicity			0.001
White	232 (17%)	40 (10%)	
Black	925 (68%)	311 (75%)	
Hispanic/other	196 (14%)	61 (15%)	
WIHS site			0.63
Bronx/Manhattan	243 (18%)	84 (20%)	
Brooklyn	174 (13%)	55 (13%)	
Washington DC	162 (12%)	49 (12%)	
Los Angeles	131 (10%)	29 (7%)	
San Francisco	194 (14%)	55 (13%)	
Chicago	160 (12%)	45 (11%)	
Southern	289 (21%)	95 (23%)	
Weight [kg, median (IQR)]	73.0 (61.7–88.0)	82.6 (68.0–96.6)	<0.0001
BMI at least 30 kg/m^2	532 (39%)	239 (58%)	<0.0001
Smoking	653 (48%)	233 (57%)	0.003
Alcohol use	88 (7%)	63 (15%)	<0.0001
Injection drug use	29 (2%)	14 (3%)	0.15
Opiate use	132 (10%)	43 (10%)	0.69
Cocaine use	18 (1%)	12 (3%)	0.03
Diabetes mellitus	274 (20%)	110 (27%)	0.005
HCV status (RNA+)	402 (30%)	92 (22%)	0.003
eGFR less than 60 ml/min (by MDRD)	145 (11%)	23 (6%)	0.002
Glucocorticoid use (ever)	449 (33%)	118 (29%)	0.08
Calcium supplementation	114 (8%)	17 (4%)	0.004
Vasomotor symptoms more than one time per day	224 (17%)	108 (26%)	<0.0001
Hormone therapy	114 (8%)	17 (4%)	0.007
Incident fractures after index			
Fracture at any site[a]	234 (17%)	62 (15%)	0.29
Hip fractures	13 (1%)	1 (0%)	0.15
Spine fractures	9 (1%)	4 (1%)	0.53
Wrist fractures	27 (2%)	6 (1%)	0.48

IQR, interquartile range; MDRD, Modification of Diet in Renal Disease.
[a]In addition to typical fragility fracture sites (hip, spine, wrist), fractures occurred in ankles, clavicles, elbows, feet, hands, knees, legs, pelvis, ribs, shoulders/arms, and unidentified sites.

Table 2. Factors associated with incident fracture in proportional hazards models

Variable	Univariate	*P* value	Multivariate	*P* value
Hormone therapy: yes vs. no	1.21 (0.78, 1.87)	0.39	0.98 (0.62, 1.53)	0.91
HIV status	1.20 (0.90, 1.58)	0.21	1.12 (0.83, 1.50)	0.46
Age per-5 at baseline	0.97 (0.88, 1.07)	0.57	0.94 (0.85, 1.03)	0.19
Race: white vs. black	1.87 (1.43, 2.46)	<0.0001	1.87 (1.40, 2.50)	<0.0001
Race: other vs. black	0.80 (0.56, 1.14)	0.22	0.90 (0.62, 1.30)	0.57
BMI (kg/m^2)	1.00 (0.98, 1.01)	0.54	1.00 (0.98, 1.02)	0.98
Smoking: current vs. never	1.47 (1.05, 2.05)	0.03	1.42 (0.99, 2.05)	0.06
Smoking: former vs. never	1.75 (1.23, 2.49)	0.002	1.80 (1.25, 2.59)	0.0021
Alcohol (>12 drinks/week)	1.27 (0.83, 1.93)	0.27	1.19 (0.76, 1.84)	0.45
HCV status	1.18 (0.92, 1.50)	0.19	1.06 (0.82, 1.38)	0.64
Cocaine: former vs. never	1.71 (0.76, 3.85)	0.20	1.57 (0.67, 3.69)	0.30
Cocaine: current vs. never	1.01 (0.76, 1.32)	0.96	0.93 (0.69, 1.25)	0.63

HCV, hepatitis C virus.

time per day for the 2 weeks prior to their last visit (17% vs. 26%, $P < 0.0001$). At the index visit, 8% of postmenopausal WLWH and 4% of women without HIV reported hormone therapy use ($P = 0.007$). Among those who used hormone therapy, the following indications were reported: menopausal symptoms or VMS (50%), post-hysterectomy (19%), osteoporosis prevention or treatment (7%), cardiovascular and neuropsychiatric reasons (1%), and other/nonidentified (22%). Over the 14-year observation period, the proportion of postmenopausal women reporting hormone therapy steadily decreased. In 2003, 19% and 15% ($P = 0.37$) of postmenopausal with and without HIV, respectively, reported hormone therapy use at their first semi-annual study visit. By 2017, the final year for this analysis, only 3% of postmenopausal with and without HIV-reported hormone therapy at their first semi-annual visit.

Associations with incident fracture

During the period of observation, incident fractures at any body site occurred in 17% and 15% of women with and without HIV, respectively ($P = 0.09$). Similarly, the incidence rate for fracture was 3.26 vs. 2.73 per 100 person-years for women with and without HIV, respectively ($P = 0.22$). Fragility fractures at the hip, spine, or wrist were uncommon and did not differ between women with and without HIV (Table 1). In bivariate analyses, race (white vs. black) and smoking (ever) were statistically associated with higher incident fracture ($P \leq 0.05$), whereas HIV status and hormone therapy use were not (Table 2). In multivariate analyses, the above associations of white race and smoking with incident fracture remained statistically significant.

Discussion

In this cohort of postmenopausal women, WLWH were less likely to report VMS and more likely to report hormone therapy use than women without HIV at the time of their first postmenopausal visit. We found an association of established predictors of fracture, white race and smoking, with incident fractures but did not find an association of hormone therapy use with decreased incident fracture as hypothesized.

In contrast to previous fracture analyses in this cohort [27], we did not find a statistically significant difference between fracture incidence by HIV status. This could be explained by the smaller sample size and shorter follow-up. By restricting the analyses to postmenopausal women, the current sample size was smaller ($n = 1765$) than prior ($n = 2375$), and the median follow-up duration was reduced from 10 to 4 years; however, fracture incidence rate was higher among postmenopausal WLWH in this analysis (3.26 per 100 person-years) than in WLWH over age 40 years in the prior analysis (2.19 per 100 person-years) [27]. In contrast to other studies [7–10], we found that VMS was less frequently reported in WLWH but our analysis was limited to data from the first postmenopausal visit and the questionnaire utilized. A comprehensive comparison of VMS patterns and severity between WLWH and women without HIV are beyond the scope of this analysis.

Concerns related to adverse cardiovascular outcomes highlighted by the Women's Health Initiative (WHI) studies in 2002 [25,26,33] led to declining hormone therapy use among women in the United States. However, subsequent analyses of the WHI found that risk of cardiovascular events depended on the timing of hormone exposure: no excess risk was observed in women under 60 years of age who were less than 10 years postmenopause [34,35]. Among women without HIV, mortality rates were actually lower in younger postmenopausal women on hormone therapy vs. hormone therapy nonusers. As a result, the North American Menopause Society (NAMS), the Endocrine Society, and the International Menopause Society have determined that benefits of hormone therapy may outweigh risks for certain populations of women, depending on age, onset of menopause, duration of hormone therapy, and comorbid conditions [16–18]. Despite these published guidelines and the availability of

safer transdermal formulations of estrogen, hormone therapy use remains low among perimenopausal and postmenopausal women under age 60 years.

Our data are consistent with a 2018 report from the Metro Vancouver Study that found only 5.5% of menopausal WLWH reported being on hormone therapy [22]. WLWH are more likely to have early menopause or primary ovarian insufficiency than women without HIV [3,4], which are both indications for hormone therapy according to the NAMS. Hormonal changes that begin during menopause not only result in increased risk fracture but also cardiovascular disease and neurocognitive disorders, comorbidities that disproportionately affect WLWH [12–14,36,37]. Hormone therapy may have benefits beyond treatment of VMS in reducing risk for several aging-related comorbidities relevant to HIV but data are lacking.

The low overall utilization of hormone therapy, which declined over successive years limited our ability to draw conclusions about its effect on fractures. Our study assessment of hormone therapy was also limited and did not allow differentiation of estrogen formulation, dose or route of administration. In addition, we lacked specificity on use of nonhormonal treatments for osteoporosis including bisphosphonates, teriparatide, and denosumab.

In conclusion, the potential benefits of hormone therapy for reducing fractures in postmenopausal WLWH remain unclear. Unfortunately, even well characterized longitudinal cohorts, such as the WIHS are limited by low overall hormone therapy utilization, potential indication bias of hormone therapy,, and low event rates for clinically defined complications, such as fracture, as well as cardiovascular events and malignancies. Defining a role for hormone therapy beyond treatment of menopausal symptoms in WLWH will therefore require a larger cohort study or randomized clinical trial with use of clinical surrogates.

Acknowledgements

The authors gratefully acknowledge the contributions of the study participants and dedication of the staff at the MWCCS sites. This research was also supported by R01-AI095089 and K24- AI155230 (M.T.Y.) and K23-AR06199301 (A.S.).

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS), now the MACS-WIHS Combined Cohort Study. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH).

MWCCS (Principal Investigators): Atlanta CRS (Ighovwerha Ofotokun, Anandi Sheth, and Gina Wingood), U01-HL146241; Baltimore CRS (Todd Brown and Joseph Margolick), U01-HL146201; Bronx CRS (Kathryn Anastos and Anjali Sharma), U01-HL146204; Brooklyn CRS (Deborah Gustafson and Tracey Wilson), U01-HL146202; Data Analysis and Coordination Center (Gypsyamber D'Souza, Stephen Gange and Elizabeth Golub), U01-HL146193; Chicago-Cook County CRS (Mardge Cohen and Audrey French), U01-HL146245; Chicago-Northwestern CRS (Steven Wolinsky), U01-HL146240; Northern California CRS (Bradley Aouizerat, Jennifer Price, and Phyllis Tien), U01-HL146242; Los Angeles CRS (Roger Detels and Matthew Mimiaga), U01-HL146333; Metropolitan Washington CRS (Seble Kassaye and Daniel Merenstein), U01-HL146205; Miami CRS (Maria Alcaide, Margaret Fischl, and Deborah Jones), U01-HL146203; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo), U01-HL146208; UAB-MS CRS (Mirjam-Colette Kempf, Jodie Dionne-Odom, and Deborah Konkle-Parker), U01-HL146192; UNC CRS (Adaora Adimora and Michelle Floris-Moore), U01-HL146194. The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), with additional co-funding from the *Eunice Kennedy Shriver* National Institute Of Child Health & Human Development (NICHD), National Institute On Aging (NIA), National Institute Of Dental & Craniofacial Research (NIDCR), National Institute Of Allergy And Infectious Diseases (NIAID), National Institute Of Neurological Disorders And Stroke (NINDS), National Institute Of Mental Health (NIMH), National Institute On Drug Abuse (NIDA), National Institute Of Nursing Research (NINR), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute on Minority Health and Health Disparities (NIMHD), and in coordination and alignment with the research priorities of the National Institutes of Health, Office of AIDS Research (OAR). MWCCS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR003098 (JHU ICTR), UL1-TR001881 (UCLA CTSI), P30-AI-050409 (Atlanta CFAR), P30-AI-073961 (Miami CFAR), P30-AI-050410 (UNC CFAR), P30-AI-027767 (UAB CFAR), and P30-MH-116867 (Miami CHARM).

Roles of authors: M.T.Y., A.S., D.R.H., Q.S. contributed to design, analysis and drafted the manuscript. P.C.T., M. H.C., S.K., D.G., A.A., M.N.W., H.B., A.W., S.H.B. revised the manuscript. All authors provided final approval.

Conflicts of interest

There are no conflicts of interest.

References

1. Prior JC. **Perimenopause: the complex endocrinology of the menopausal transition.** *Endocr Rev* 1998; **19**:397–428.
2. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, *et al*., Study of Women's Health Across the Nation. **Duration of menopausal vasomotor symptoms over the menopause transition.** *JAMA Intern Med* 2015; **175**:531–539.
3. Boonyanurak P, Bunupuradah T, Wilawan K, Lueanyod A, Thongpaeng P, Chatvong D, *et al*. **Age at menopause and menopause-related symptoms in human immunodeficiency virus-infected Thai women.** *Menopause* 2012; **19**:820–824.
4. de Pommerol M, Hessamfar M, Lawson-Ayayi S, Neau D, Geffard S, Farbos S, *et al*. **Menopause and HIV infection: age at onset and associated factors, ANRS CO3 Aquitaine cohort.** *Int J STD AIDS* 2011; **22**:67–72.
5. 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.
6. Van Ommen CE, King EM, Murray MCM. **Age at menopause in women living with HIV: a systematic review.** *Menopause* 2021; **28**:1428–1436.
7. Looby SE. **Symptoms of menopause or symptoms of HIV? Untangling the knot.** *Menopause* 2018; **25**:728–730.
8. Schnall R, Jia H, Olender S, Gradilla M, Reame N. **In people living with HIV (PLWH), menopause (natural or surgical) contributes to the greater symptom burden in women: results from an online US survey.** *Menopause* 2018; **25**:744–752.
9. Agaba PA, Meloni ST, Sule HM, Ocheke AN, Agaba EI, Idoko JA, *et al*. **Prevalence and predictors of severe menopause symptoms among HIV-positive and -negative Nigerian women.** *Int J STD AIDS* 2017; **28**:1325–1334.
10. Looby SE, Psaros C, Raggio G, Rivard C, Smeaton L, Shifren J, *et al*. **Association between HIV status and psychological symptoms in perimenopausal women.** *Menopause* 2018; **25**:648–656.
11. Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, *et al*. **Bone mineral density changes during the menopause transition in a multiethnic cohort of women.** *J Clin Endocrinol Metab* 2008; **93**:861–868.
12. Triant VA, Brown TT, Lee H, Grinspoon SK. **Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system.** *J Clin Endocrinol Metab* 2008; **93**:3499–3504.
13. Womack JA, Goulet JL, Gibert C, Brandt C, Chang CC, Gulanski B, *et al*., Veterans Aging Cohort Study Project Team. **Increased risk of fragility fractures among HIV infected compared to uninfected male veterans.** *PloS one* 2011; **6**:e17217.
14. Young B, Dao CN, Buchacz K, Baker R, Brooks JT, HIV Outpatient Study (HOPS) Investigators. **Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 2000–2006.** *Clin Infect Dis* 2011; **52**:1061–1068.
15. Shiau S, Arpadi SM, Yin MT. **Bone update: is it still an issue without tenofovir disoproxil fumarate?** *Curr HIV/AIDS Rep* 2020; **17**:1–5.
16. Baber RJ, Panay N, Fenton A, IMS Writing Group. **2016 IMS Recommendations on women's midlife health and menopause hormone therapy.** *Climacteric* 2016; **19**:109–150.
17. Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, *et al*. **Treatment of symptoms of the menopause: an endocrine society clinical practice guideline.** *J Clin Endocrinol Metab* 2015; **100**:3975–4011.
18. The North American Menopause Society. **The 2017 hormone therapy position statement of The North American Menopause Society.** *Menopause* 2017; **24**:728–753.
19. Torgerson DJ, Bell-Syer SE. **Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials.** *BMC Musculoskelet Disord* 2001; **2**:7.
20. Torgerson DJ, Bell-Syer SE. **Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials.** *JAMA* 2001; **285**:2891–2897.
21. Banks E, Beral V, Reeves G, Balkwill A, Barnes I, Million Women Study Collaborators. **Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women.** *JAMA* 2004; **291**:2212–2220.
22. Duff PK, Money DM, Ogilvie GS, Ranville F, Kestler M, Braschel MC, *et al*., SHAWNA Project. **Severe menopausal symptoms associated with reduced adherence to antiretroviral therapy among perimenopausal and menopausal women living with HIV in Metro Vancouver.** *Menopause* 2018; **25**:531–537.
23. King EM, Prior JC, Pick N, van Schalkwyk J, Kestler M, Tkachuk S, *et al*. **Menopausal hormone therapy for women living with HIV.** *The lancet HIV* 2021; **8**:e591–e598.
24. Lobo RA. **Hormone-replacement therapy: current thinking.** *Nat Rev Endocrinol* 2017; **13**:220–231.
25. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*., Writing Group for the Women's Health Initiative Investigators. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.** *JAMA* 2002; **288**:321–333.
26. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, *et al*., Women's Health Initiative Steering Committee. **Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial.** *Jama* 2004; **291**:1701–1712.
27. Sharma A, Shi Q, Hoover DR, Anastos K, Tien PC, Young MA, *et al*. **Increased Fracture Incidence in Middle-Aged HIV-Infected and HIV-Uninfected Women: Updated Results From the Women's Interagency HIV Study.** *J Acquir Immune Defic Syndr* 2015; **70**:54–61.
28. Adimora AA, Ramirez C, Benning L, Greenblatt RM, Kempf MC, Tien PC, *et al*. **Cohort profile: the Women's Interagency HIV Study (WIHS).** *Int J Epidemiol* 2018; **47**:393–394i.
29. D'Souza G, Bhondoekhan F, Benning L, Margolick JB, Adedimeji AA, Adimora AA, *et al*. **Characteristics of the MACS/WIHS Combined Cohort Study: opportunities for research on aging with HIV in the Longest US Observational Study of HIV.** *Am J Epidemiol* 2021; **190**:1457–1475.
30. Sharma A, Shi Q, Hoover DR, Tien PC, Plankey MW, Cohen MH, *et al*. **Frailty predicts fractures among women with and at-risk for HIV.** *AIDS* 2019; **33**:455–463.
31. Yin MT, Shi Q, Hoover DR, Anastos K, Sharma A, Young M, *et al*. **Fracture incidence in HIV-infected women: results from the Women's Interagency HIV Study.** *AIDS* 2010; **24**:2679–2686.
32. Rubin LH, Sundermann EE, Cook JA, Martin EM, Golub ET, Weber KM, *et al*. **Investigation of menopausal stage and symptoms on cognition in human immunodeficiency virus-infected women.** *Menopause* 2014; **21**:997–1006.
33. Howard BV, Rossouw JE. **Estrogens and cardiovascular disease risk revisited: the Women's Health Initiative.** *Curr Opin Lipidol* 2013; **24**:493–499.
34. Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, *et al*., Women's Health Initiative Investigators. **Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative.** *Arch Intern Med* 2006; **166**:357–365.
35. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, *et al*. **Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause.** *JAMA* 2007; **297**:1465–1477.
36. 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**:2506–2512.
37. Womack JA, Chang CC, So-Armah KA, Alcorn C, Baker JV, Brown ST, *et al*. **HIV infection and cardiovascular disease in women.** *J Am Heart Assoc* 2014; **3**:e001035.