

Lifetime and recent alcohol use and bone mineral density in adults with HIV infection and substance dependence

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Abstract

Low bone mineral density (BMD) is common in people living with HIV infection (PLWH), increasing fracture risk. Alcohol use is also common in PLWH and is a modifiable risk factor for both HIV disease progression and low BMD. In PLWH, alcohol's effect on BMD is not well understood.

We studied adult PLWH with substance dependence. We measured lifetime alcohol use (kg) and recent (i.e., past 30-day) alcohol use (categorized as: abstinent, low risk, or high risk). In adjusted multivariable regression analyses, we tested associations between lifetime and recent alcohol use and (i) mean BMD (g/cm²) at the femoral neck, total hip, and lumbar spine and (ii) low BMD diagnosis (i.e., osteopenia or osteoporosis). We also examined associations between 2 measures of past alcohol use (i.e., total consumption [kg] and drinking intensity [kg/year]) and BMD outcome measures during 3 periods of the HIV care continuum: (i) period before first positive HIV test, (ii) period from first positive HIV test to antiretroviral therapy (ART) initiation, and (iii) period following ART initiation.

We found no significant associations between lifetime alcohol use and mean femoral neck (β -0.000, P = .62), total hip (β -0.000, P = .83) or lumbar spine (β 0.001, P = .65) BMD (g/cm²), or low BMD diagnosis (adjusted odds ratio [aOR] = 0.98, 95% Confidence Interval [CI]: 0.95–1.01). There was no significant correlation between past 30-day alcohol use and mean BMD (g/cm²). Past 30-day alcohol use was associated with low BMD diagnosis (P = .04); compared to abstainers, the aOR for high risk alcohol use was 1.94 (95% CI: 0.91–4.12), the aOR for low risk alcohol use was 4.32 (95% CI: 1.30–14.33). Drinking intensity (kg/year) between first positive HIV test and ART initiation was associated with lower mean BMD (g/cm²) at the femoral neck (β -0.006, P = .04) and total hip (β -0.007, P = .02) and increased odds of low BMD (aOR = 1.18, 95% CI = 1.03–1.36).

In this sample of PLWH, we detected no association between lifetime alcohol use and BMD. However, recent drinking was associated with low BMD diagnosis, as was drinking intensity between first positive HIV test and ART initiation. Longitudinal studies should confirm these associations.

Abbreviations: 25(OH)D = 25-hydroxy-vitamin D, aOR = adjusted odds ratio, ART = antiretroviral therapy, BMD = bone mineral density, BMI = body mass index, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition, DXA = dual energy x-ray absorptiometry, FN = femoral neck, GE = General Electric, LS = lumbar spine, NHANES III = Third National Health and Nutrition Examination Survey, PLWH = people living with HIV, SD = standard deviation, TH = total hip, TLFB = Timeline Followback, US = United States, WHO = World Health Organization.

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Authorship contributions: ASV and RS conceived the study question. ASV wrote the first draft of the manuscript. MRW and GJP conducted statistical analyses and TCH supported interpretation of results. Both AYW and MS provided HIV clinical expertise and facilitated clinic access. MFH provided expertise on measurement and interpretation of bone mineral density. SMM assisted with oversight of data collection. RS was the Principal Investigator of the Boston ARCH Cohort study and JHS was the Principal Investigator of the URBAN ARCH Consortium. All authors met criteria for authorship and read and approved the final draft of the manuscript.

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1. Introduction

Low bone mineral density (BMD) is common in people living with HIV infection (PLWH); osteoporosis is 3 times more common in PLWH than in uninfected populations.^[1] Low BMD is a risk factor for fracture in PLWH.^[2] Fractures are more common among PLWH than among uninfected controls^[3–6] and the general, age-matched US population.^[7,8] Fracture, a serious cause of morbidity and mortality, is expected to become a significant cause of impairment in aging PLWH. The etiology of low BMD in PLWH is multifactorial, ranging from HIV infection itself, to treatments for HIV infection, to co-existing risks and exposures.^[9]

In the absence of antiretroviral therapy (ART), HIV infection is independently associated with a loss of BMD likely due to immune activation, viral, and inflammatory effects that disrupt bone remodeling.^[10–13] *In vitro* and *in vivo* studies have demonstrated the direct effects of HIV on bone formation by suppressing osteoblast activity,^[14] and on bone resorption by stimulating osteoclast activity,^[15] resulting in an uncoupling and subsequent loss of bone mass.

In individuals taking ART, BMD decreases by an estimated 2%–6% within the first 2 years following initiation, regardless of medication regimen.^[16–24] Specific ART regimens (i.e., tenofovir,^[25] and to a lesser degree, protease inhibitors^[26]) have been associated with accelerated decline in BMD. Immune reconstitution, or the repopulation of T-cells, which immediately follows initiation of ART, can prompt production of inflammatory cytokines and may partly explain the mechanism of BMD decline common to all ART regimens.^[27,28]

Traditional risk factors and secondary causes for low BMD and osteoporosis (e.g., low body mass index, weight loss, smoking, hepatitis C coinfection, secondary hyperparathyroidism, and chronic kidney disease) are highly prevalent and strongly associated with low BMD in PLWH.^[29,30] Other risk factors for decreased BMD prevalent in PLWH include: vitamin D deficiency,^[31,32] physical inactivity,^[33] alcohol use,^[23] opioid use,^[6,34–36] and cocaine use.^[5]

Alcohol use, commonly identified as a risk factor for low BMD in the general population, is prevalent in PLWH.^[37–42] Alcohol has a toxic effect on bone, due to decreased bone formation,^[43–47] likely exacerbated by hormonal, inflammatory, and dietary factors associated with alcohol use.^[48] “Moderate” alcohol consumption has been associated with increased BMD,^[49–51] though a 2008 review concluded that the variability in measures used to assess alcohol use across studies made it impossible to determine the presence or magnitude of a dose–response relationship.^[52] Studies of alcohol and BMD have used little or no detailed validated measurement of recent or lifetime alcohol use; effects of prolonged alcohol exposure on BMD remain largely unknown.

The population of PLWH is aging and many individuals have been exposed to multiple risk factors for low BMD—such as alcohol and ART—for decades. Lifetime drinking trajectories of PLWH are heterogeneous and alcohol use changes following entry into the HIV care continuum (i.e., HIV diagnosis).^[53] Yet the cumulative effects of recent and lifelong exposure to alcohol on BMD in PLWH are unknown. Further, BMD may be more susceptible to the effects of alcohol in PLWH during certain periods due to factors previously described, representing potential targets for interventions. Accordingly, this study assessed the association between total lifetime and recent alcohol consumption and BMD. Additionally, we conducted an

exploratory analysis to examine associations between past alcohol use during 3 periods of the HIV care continuum and BMD (Fig. 1): (i) period prior to first positive HIV test, (ii) period from first positive HIV test to ART initiation, and (iii) period following initiation of ART.

2. Methods

2.1. Participants

Research participants were in the Boston ARCH Cohort, a study to examine the effect of alcohol on bone health in PLWH with substance dependence. Participants were recruited between December 2012 and November 2014 from an urban academic hospital-based HIV primary care clinic and a community health center-based HIV primary care clinic serving homeless men and women. Inclusion criteria were: (1) documentation of HIV infection in any medical record, determined by confirmatory HIV testing algorithm approved by the Massachusetts Department of Public Health at time of screening, or HIV viral load >10,000 copies/mL; (2) past 12-month *Diagnostic and Statistical Manual of Mental Disorders* 4th edition (*DSM-IV*) drug or alcohol dependence assessed by Mini International Neuropsychiatric Interview (M.I.N.I. 6.0) or ever injection drug use; (3) ability to speak English; (4) ≥18 years old; (5) willingness to provide contact information ≥1 person. Exclusion criteria were: (1) pregnancy (assessed by urine test); (2) plans to leave the Boston area in the next year; (3) cognitive impairment resulting in inability to provide informed consent. Additional inclusion criteria specific to the current study included: (1) completion of the Lifetime Drinking History and (2) BMD measured at ≥1 bone sites at study entry.

Participants provided written informed consent and received compensation for completing study assessments. The Boston University Medical Campus Institutional Review Board approved the study, including follow-up of incarcerated participants, and we obtained a Certificate of Confidentiality from the National Institute on Alcohol Abuse and Alcoholism.

2.2. Primary outcome variables

The primary outcome variables were BMD measured by dual energy x-ray absorptiometry (DXA) in grams per square centimeter (g/cm^2) at the femoral neck (FN), total hip (TH), and lumbar spine (LS) (L₁–L₄). All measurements were performed by bone densitometry technologists certified by the International Society for Clinical Densitometry. Due to machine availability, baseline measurements were completed on 3 densitometers: (1) Hologic QDR 4500 Discovery W (software version 12.6.1) (Waltham, MA); (2) Hologic QDR 4500 Discovery W (software version 13.4.2) (Waltham, MA) (a replacement for the first densitometer); and (3) General Electric (GE) Lunar iDXA (GE Healthcare, Madison, WI). The 2 Hologic DXAs were cross-calibrated using a standard phantom. All BMD measurements taken from the GE Lunar iDXA were converted to Hologic-equivalent values by applying industry-accepted conversion formulas.^[54]

2.3. Secondary outcome variable

The secondary outcome variable was low BMD diagnosis (dichotomous) defined by T-score indicative of osteopenia or osteoporosis at ≥1 bone site (i.e., TH, FN, or LS) versus normal

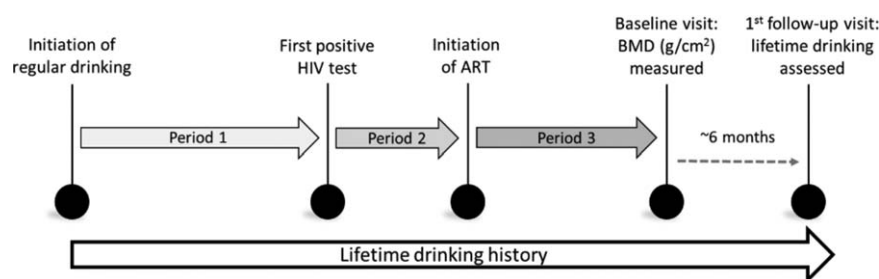


Figure 1. Periods of the HIV care continuum and timeline of primary measurements.

BMD at all sites. T-scores, expressed in standard deviations (SDs), compare the site-specific BMD value with the mean peak BMD value of a young healthy reference population of the same sex and race/ethnicity. FN and TH T-scores were calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference database; LS T-scores were calculated from the manufacturer-supplied U.S. Hologic QDR reference database. Consistent with World Health Organization (WHO) Guidelines, normal BMD was defined as a T-score between 1 and -1 .^[55] Osteopenia was defined as a T-score < -1.0 and ≥ -2.5 and osteoporosis was defined as a T-score < -2.5 .

2.4. Main independent variable

The main independent variable was total lifetime alcohol use summarized in 100 kilogram (kg) units, assessed by the Lifetime Drinking History and administered as a supplement to the first follow-up assessment after study entry (for most, within 6 months).^[56] The Lifetime Drinking History is a structured interview that provides detailed data on patterns of alcohol use throughout an individual's lifetime.^[57] Chronologically, the interviewer collected information beginning with onset of regular drinking (i.e., ≥ 1 drink per month) about quantity, frequency and variability of alcohol consumption, and life events that marked a change in alcohol use—recording each phase of alcohol use (or abstinence) in the participant's lifetime. The reliability and validity of the Lifetime Drinking History has been well established.^[58] Further, lifetime alcohol exposure derived from the Lifetime Drinking History has been found to be associated with adverse health outcomes, such as alcoholic liver disease, which may not be easily predicted by episodic risky drinking.^[59]

2.5. Additional independent variables: recent and past alcohol use

In face-to-face interviews at study entry, we assessed past 30-day drinking by Timeline Followback (TLFB, a validated calendar method for measuring past month daily alcohol use).^[60] The past 30-day alcohol use was categorized into 3 groups using a standard “high risk” threshold associated with alcohol use disorder, injury, or other alcohol-related health problems:^[61] (i) no alcohol, (ii) low risk use, or (iii) high risk use. High risk alcohol use was defined as >14 standard drinks (standard drink = 14g ethanol) per week on average for males (>7 for females) or ≥ 1 heavy drinking day (>4 drinks in a day for males, >3 for females).

From the Lifetime Drinking History, we calculated: (1) total alcohol consumption (kgs) and (2) drinking intensity (10 kg/year) for each of the 3 periods displayed in Fig. 1. When age of first positive HIV test or initiation of ART fell in the middle of a phase

on the Lifetime Drinking History, total alcohol consumption for the phase was applied proportionally to each period. If a participant reported that first positive HIV test and initiation of ART occurred in the same year, both total alcohol consumption and drinking intensity for Period 2 were coded as “0.”

2.6. Covariates

We assessed the following by in-person interview at study entry: age, biological sex, race/ethnicity, smoking,^[62] weight-bearing physical activity, lowered sexual drive, menopausal status, and average daily calcium intake (mg).^[63] Years of regular cocaine and heroin use were assessed using the Addiction Severity Index.^[64] We also assessed ever exposure to illicit or prescribed opioids, ever exposure to tenofovir, and duration of HIV infection.

At study entry, each participant's medical record was reviewed and the most recent CD4 cell count (cells/mm³) and HIV viral load (copies/mL) values were recorded. If not available within 3 months of study entry, we tested them. Blood was tested for total 25-hydroxy-vitamin D (25(OH)D) by liquid chromatography-tandem mass spectrometry.^[65] Height and weight were used to calculate body mass index (BMI). DXA manufacturer, and software version were also included as covariates.

2.7. Statistical analysis

All analyses were conducted using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC). Influential outliers were identified using Cook's Distance and Studentized Residuals. Covariates were chosen for inclusion in models based on factors known to affect BMD. We checked for possible co-linearity of all independent variables and covariates. For pairs of variables with a Spearman's rho >0.43 or -0.43 , only 1 variable was included in each regression model. Years of HIV infection and years of ART were highly correlated ($r=0.69$), as were years of regular heroin use and ever injection drug use ($r=0.66$); years of HIV infection and years of regular heroin use were selected for inclusion in regression models. Adjusted odds ratios (aOR), mean adjusted changes (betas, as appropriate) and 95% confidence intervals (CI) are reported for each model. All analyses were conducted using 2-sided tests and a significance level of 0.05.

Primary analyses evaluated the associations between total lifetime alcohol use, recent alcohol use, and each outcome variable: FN, TH, and LS BMD (g/cm²), and low BMD diagnosis. Separate adjusted multivariable regression models were fit to evaluate the association between total lifetime alcohol use (100kg units) and each outcome variable, adjusting for all aforementioned covariates. Models were repeated using FN, TH, and LS T-scores as outcome variables (see Supplementary Content Table 6, [3](http://</p>
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links.lww.com/MD/B676 for results of regression models). Due to use of multiple DXA machines, we performed a sensitivity analysis; each regression model was stratified by type of DXA machine and software version used. Results of the sensitivity analyses were similar to those of the primary analyses and are not shown.

Exploratory models were fit to assess whether total alcohol consumption (kg) during 3 periods of the HIV care continuum (Fig. 1) was associated with TH, FN, and LS BMD (g/cm^2), and low BMD diagnosis. To assess for an independent association with each time period, multivariable regression models were fit to include Period 1, 2, and 3, recent alcohol consumption, and all covariates, in the same model. A second set of multivariable regression models were fit to assess associations between drinking intensity (10 kg/year) during Period 1, 2, and 3 and all 4 outcome variables, also including recent alcohol consumption and all covariates.

The sample size of 250 was chosen based on power calculations for the primary study of the Boston ARCH Cohort which sought to assess the association between change in alcohol use and change in BMD.

3. Results

3.1. Study participants

Of 1460 times patients were approached, 673 completed screening; 299 did not meet eligibility criteria; the most common reason was that the patient did not have past 12-month alcohol or drug dependence or had never injected drugs (82%). Of the 374 patients who met all eligibility criteria, 250 (67%) enrolled in the Boston ARCH Cohort. Of the 250 Boston ARCH participants, 246 (98%) completed the Lifetime Drinking History. All 246 participants received a DXA scan at ≥ 1 bone site at study entry.

3.1.1. Demographic and clinical characteristics. Approximately 37% of the 246 study participants were female; 52% of female study participants were postmenopausal, defined as an absence of menstruation for a period of one year or greater. The mean age of study participants was 48.6 years old; the mean number of years since first positive HIV test was 16.4 years. The majority of the sample had achieved viral suppression: 71.1% had an HIV viral load <200 copies/mL. The study sample was comprised largely of ethnic minorities: 50.8% identified as black and 24.4% identified as Hispanic. Over half the study sample had a BMI in the overweight (33.3%) or obese (24.8%) range; 37.8% of participants had a normal BMI and only 10 (4.1%) had a BMI classified as underweight. Additional demographic and clinical characteristics are detailed in Table 1.

3.1.2. Substance use characteristics. Two-thirds (67%) of the study sample reported recent alcohol use (i.e., 1 or more standard drink [14 g pure ethanol] in the 30 days prior to assessment). Of those who drank recently, 126 (51.2%) of the entire study sample exceeded the “high risk” drinking threshold. Total lifetime alcohol consumption ranged from 0 to 6610 kg; mean cumulative lifetime alcohol consumption was 710 kg. Over half the study participants had ever injected drugs (57.3%), 85.4% had ever been exposed to an opioid (licit or illicit) and almost all participants (94%) had ever used cocaine.

The median length of Phase 1 (i.e., time from initiation of drinking to first positive HIV test) was 15.6 years. During Phase 1 total mean alcohol consumption was 395.5 kg; mean drinking intensity was 22.6 kg/year. The median length of Phase 2 (i.e., time from first positive HIV test to initiation of ART) was 1.1 years. During Phase 2 total mean alcohol consumption was 96.6 kg; mean drinking

Table 1

Demographic and clinical characteristics (n=246).

Variable	
Age, years, median (IQR)	50 (43–56)
Biological sex, no. (%)	
Female	90 (36.6)
Male	156 (63.4)
Race/ethnicity, no. (%) [*]	
Black	125 (50.8)
White	61 (24.8)
Hispanic	60 (24.4)
BMI, median (IQR)	26.0 (22.8–30.0)
Postmenopausal, no. (%) [†]	
Yes	47 (19.1)
No	199 (80.9)
CD4 cell count, cells/mm ³ , no. (%)	
≥ 500	138 (56.1)
200– <500	82 (33.3)
<200	26 (10.6)
HIV viral load <200 copies/mL, no. (%)	
<200	175 (71.1)
≥ 200	71 (28.9)
Ever taken tenofovir, n=244, no. (%)	
Yes	212 (86.9)
No	32 (13.1)
Years since first positive HIV test, median (IQR)	16.4 (9.8–23.6)
Years since initiation of ART, median (IQR)	13 (5–18)
Total daily calcium intake, mgs, n=245, median (IQR) [‡]	1,310.1 (785.7–1967.7)
Past year loss of sex drive, no. (%)	
Yes	142 (57.7)
No	104 (42.3)
Weekly weight bearing physical activity category, no. (%)	
Minimal	64 (26.0)
Low	55 (22.4)
Adequate	92 (37.4)
High	35 (14.2)
Total 25-hydroxyvitamin D, ng/mL, median (IQR)	25.6 (16.7–35.8)

ART = antiretroviral therapy, BMI = body mass index, IQR = interquartile range, SD = standard deviation.

^{*} Race/ethnicity as recorded in DXA machine at time of scan.

[†] Males coded as “no.”

[‡] Assessed by NIH Short Calcium Questionnaire.

intensity was 19.5 kg/year. The median length of Phase 3 (i.e., time from initiation of ART test to time of first follow-up assessment) was 11.1 years. During Phase 3 total mean alcohol consumption was 208.8 kg; mean drinking intensity was 17.8 kg/year. Additional substance use characteristics are described in Table 2.

3.1.3. Bone characteristics. At baseline, 66.5% of participants met clinical criteria for low BMD diagnosis (≥ 1 T-score < -1); 20.3% met criteria for osteoporosis (≥ 1 T-score ≤ -2.5). T-score values for TH ranged from 0.51 to 1.36; mean TH T-score was 0.94. T-scores for the FN ranged from -3.5 to 2.2; mean FN T-score was -1.04 . T-scores for the TS ranged from 0.67 to 2.0; mean TS T-score was 1.02. See Table 3 for additional bone characteristics and outcome variables.

3.2. Multivariable models of alcohol consumption and BMD

3.2.1. Lifetime alcohol use. In adjusted multivariable regression models, total lifetime alcohol consumption (kg) was not associated with FN, TH, or LS BMD (g/cm^2), or low BMD

Table 2**Substance use characteristics (n=246).**

Variable	
Current smoker, n=245, no. (%) [*]	
Yes	193 (78.8)
No	52 (21.2)
Past 30-day risky alcohol use, no. (%) [†]	
No alcohol use	81 (32.9)
Low risk use	39 (15.9)
High risk use	126 (51.2)
Ever opioid exposure, no. (%) [‡]	
Yes	210 (85.4)
No	36 (14.6)
Ever injection drug use, no. (%)	
Yes	141 (57.3)
No	105 (42.7)
Years of regular cocaine use, median (IQR) [§]	7.0 (0.0–15.0)
Years of regular heroin use, median (IQR)	(0.0–12.0)
Length of Period 1 [¶] , years, n=240, median (IQR) [#]	15.6 (9.1–24.1)
Length of Period 2 ^{**} , years, n=244, median (IQR) ^{††}	1.1 (1.1–6.1)
Length of Period 3 ^{**‡} , years, n=244, median (IQR) ^{††}	11.1 (3.1–18.1)
<i>Main independent variable</i>	
Total lifetime alcohol consumption, 100 kg, mean (SD, median, IQR)	7.1 (10.5, 3.08, .84–8.12)
<i>Additional exploratory independent variables</i>	
Period 1 [¶] : total alcohol consumption, kg, n=245, mean (SD, median, IQR)	395.5 (616.6, 154.02, 42.3–522.1)
Period 2 ^{**} : total alcohol consumption, kg, n=244, mean (SD, median, IQR)	96.6 (321.3, 2.7, 0–58.7)
Period 3 ^{**‡} : total alcohol consumption, kg, n=244, mean (SD, median, IQR)	208.8 (562.7, 22.2, 0–142.4)
Period 1 [¶] : drinking intensity, kg/year, n=245, mean (SD, median, IQR)	22.6 (32.4, 10.1, 3.2–27.4)
Period 2 ^{**} : drinking intensity, kg/year, n=244, mean (SD, median, IQR)	19.5 (43.2, 1.0, 0–12.6)
Period 3 ^{**‡} : drinking intensity, kg/year, n=244, mean (SD, median, IQR)	17.8 (42.7, 2.4, 0–17.8)

ART=antiretroviral therapy, ASI=addiction severity index, IQR=interquartile range, LDH=lifetime drinking history, SD=standard deviation.

^{*} CDC definition: ≥ 100 cigarettes in lifetime and now smoking "every day" or "some days."

[†] National Institute on Alcohol and Alcohol Abuse standard threshold for risky drinking: > 14 standard drinks per week on average for males (> 7 for females) or ≥ 1 heavy drinking day (> 4 drinks in a day for males, > 3 for females) in the past 30 days; assessed by 30-day timeline follow-back method.

[‡] Includes both prescription and illicit opioids.

[§] Regular cocaine use: ≥ 3 x/week on average or 2 day binges/week, assessed by ASI.

^{||} Regular heroin use: ≥ 3 x/week on average, assessed by ASI.

[¶] Period from beginning of regular drinking to first positive HIV test.

[#] 5 participants reported no lifetime regular drinking during and were therefore excluded from Period 1.

^{**} Period from first positive HIV test to initiation of ART.

^{††} 2 participants were excluded from Period 2 and Period 3: 1 participant was missing a date of first positive HIV test and date of ART initiation; the other participant was missing date of ART initiation.

^{**‡} Period from initiation of ART to time of assessment.

diagnosis (i.e., osteopenia or osteoporosis defined by T-score) (Table 4).

3.2.2. Recent alcohol use. Compared with those reporting no alcohol use in the past 30 days, participants reporting high risk drinking (aOR = 1.94, 95% CI: 0.91–4.12) and low risk drinking (aOR = 4.32, 95% CI: 1.30–14.33) had greater odds of low BMD diagnosis. The past 30-day use was not significantly associated with FN, TH or LS BMD (g/cm²). (See Supplementary Content Table 7, <http://links.lww.com/MD/B676> for full results of multivariable regression models, including all covariates.)

3.3. Multivariable models of drinking intensity across the HIV care continuum and BMD

3.3.1. Lifetime alcohol use. In adjusted multivariable regression models that included drinking intensity (increments of 10 kg/year) for Periods 1, 2, and 3 in the same model, drinking intensity during Period 1 (i.e., initiation of drinking to first positive HIV test) was associated with decreased odds of low BMD diagnosis and was not associated with FN, TH, or LS BMD (g/cm²) (Table 5). Drinking intensity during Period 2 (i.e., first positive HIV test to initiation of ART) was associated with higher

odds of low BMD diagnosis and lower FN, TH, and LS BMD (g/cm²). Drinking intensity during Period 3 (i.e., initiation of ART to time of assessment) was associated with lower odds of low BMD diagnosis and higher FN, TH, and LS BMD (g/cm²).

3.3.2. Recent alcohol use. Compared with participants reporting no alcohol use in the past 30 days, participants who reported high risk drinking (aOR = 2.22, 95% CI: 1.01–4.88) and low risk drinking (aOR = 4.34, 95% CI: 1.26–14.91) had greater odds of low BMD diagnosis. (See Supplementary Content Table 8, <http://links.lww.com/MD/B676> for full results of multivariable regression models, including total alcohol consumption [kgs] for each period of the HIV care continuum and all covariates. See Supplementary Content Table 9, <http://links.lww.com/MD/B676> for full results of multivariable regression models, including alcohol intensity [10 kg/year] for each period of the HIV care continuum and all covariates.)

4. Discussion

The main objective of this study was to assess the association between alcohol use—particularly lifetime use—and BMD in

Table 3**Bone characteristics (n = 246).**

Variable	
Osteoporosis at baseline (determined by T-score), n = 242, no. (%)	
Yes	49 (20.3)
No	193 (79.7)
T-scores, SDs, median (IQR)	
FN, n = 242	-1.0 (-1.7--0.4)
TH, n = 242	-0.8 (-1.4--0.2)
LS, n = 243	-1.1 (-2.1--0.1)
Machine and software version used for DXA scan, no. (%)	
Hologic QDR 4500 Discovery W (software version 12.6.1)	150 (61.0)
Hologic QDR 4500 Discovery W (software version 13.4.2)	77 (31.3)
GE Lunar iDXA	19 (7.7)
Outcome variables	
BMD, g/cm ² , mean (SD, median, IQR)*	
FN, n = 242	0.83 (0.14, 0.82, 0.73–0.91)
TH, n = 242	0.94 (0.14, 0.93, 0.84–1.03)
LS, n = 243	1.02 (.17, 1.00, .90–1.12)
Low bone density at baseline, n = 242, no. (%)	
Normal BMD	81 (33.5)
Low bone density (osteopenia or osteoporosis)	161 (66.5)

BMD = bone mineral density, DXA = dual-energy x-ray absorptiometry, FN = femoral neck, GE = General Electric, IQR = interquartile range, LS = lumbar spine, SD = standard deviation, TH = total hip.

* Due to the presence of metal, 2 participants did not receive a DXA scan of the LS at baseline; a third participant was also unable to contribute a LS measurement due to a missing L1 value. Additionally, 4 participants did not receive a DXA scan of the hip due to a bilateral total hip replacement.

PLWH. Unexpectedly, we did not detect an association between total *lifetime* alcohol consumption and BMD (g/cm²) or low BMD diagnosis (i.e., osteopenia or osteoporosis). The prevalence of low BMD and osteoporosis in our cohort of older, well

suppressed PLWH, who also had substance dependence, was high and similar to that reported in other studies.^[1,66,67] The prevalence of secondary causes of low BMD (e.g., smoking, opioid use) was also high. It is possible that an effect of alcohol use was not detectable in the context of these numerous competing risks. In multivariable models we did detect an association with recent alcohol use and odds of low BMD diagnosis; the association between low BMD diagnosis and *past 30-day low risk* alcohol use was clearly associated with increased odds of low BMD diagnosis. The association between low BMD diagnosis and *past 30-day high risk* alcohol use was less clear; the aOR was elevated in both sets of multivariable models but only significant in the model that included all 3 periods of the HIV care continuum. The fact that we detected an association with recent alcohol use and low BMD diagnosis, but not BMD (g/cm²) at any bone site, was surprising, though this may be attributable to a threshold effect.

We also conducted exploratory analyses to generate hypotheses about the effect of alcohol consumption and drinking intensity on BMD during phases of the HIV care continuum. Median drinking intensity in our cohort decreased after first positive HIV test and increased after initiation of ART, though not to pre-HIV levels. Jacobs et al. similarly found that in a cohort of HIV-infected veterans, almost half reported a reduction in drinking post-HIV infection; drinking post-initiation of ART was not assessed.^[53]

We identified a small but statistically significant relationship between greater drinking intensity during each period and odds of low BMD diagnosis. The most consistent effect was following first positive HIV test to initiation of ART during which greater drinking intensity was associated with lower BMD (g/cm²) at all 3 sites and low BMD diagnosis. Unexpectedly, greater drinking intensity post-ART was associated with higher BMD. We do not have an explanation for this latter finding, nor do we believe that the results should be taken as definitive. The most appropriate conclusion to draw is that alcohol use may have different effects on BMD during different periods of the HIV care continuum, possibly based on how it interacts with HIV and its treatment.

Table 4**Adjusted multivariable regression models assessing associations between total lifetime alcohol use (100 kg) and femoral neck, total hip, and lumbar spine bone mineral density (g/cm²) and low bone density^{*,†,‡}.**

Main Independent Variable	Femoral neck BMD, g/cm ² , n = 235		Total hip BMD, g/cm ² , n = 235		Lumbar Spine BMD (g/cm ²) n = 236		Low bone density n = 237	
	Adjusted beta (95% CI)	P value	Adjusted beta (95% CI)	P value	Adjusted Beta (95% CI)	P Value	aOR (95% CI)	P value
Total lifetime alcohol use (100kg)	-0.000 (-0.002–0.001)	.62	-0.000 (-0.002–0.002)	.83	0.001 (-0.002–0.003)	.65	0.98 (0.95–1.01)	.16
Past 30-day risky alcohol use		.73		.86		.45		.04
Abstinent [ref]	–		–		–		–	
Low risk use	-0.019 (-0.071–0.034)		-0.010 (-0.062–0.043)		-0.015 (-0.078–0.048)		4.32 (1.30–14.33)	
High risk use	-0.012 (-0.052–0.027)		-0.011 (-0.050–0.029)		-0.030 (-0.077–0.017)		1.94 (0.91–4.12)	

aOR = adjusted odds ratio, BMD = bone mineral density, CI = confidence interval; ref = reference group.

* Covariates included in all models, included: age, sex, race, BMI, current smoking status, menopause, ever opioid exposure, CD4 cell count, HIV Viral Load ≥200 copies/mL, total 25(OH)D, ever tenofovir use, daily calcium intake, past-year loss of sex drive, years of HIV infection, weight-bearing physical activity, years of regular cocaine use, years of regular heroin use, DXA machine/software version (see Supplemental Content Table 7, <http://links.lww.com/MD/B676>).

† Lifetime alcohol consumption was not significantly associated with baseline FN, TH or LS T-score; statistical significance and direction of associations between all covariates and each T-score were similar to associations with BMD, with the exception of sex which was significantly associated with FN T-score (Adjusted β = 0.50 SDs; P = .01) (see Supplemental Content Table 6, <http://links.lww.com/MD/B676>).

‡ 1 participant with an extreme FN BMD value and extreme total lifetime alcohol consumption was excluded from all regression models for which FN or TH BMD were the primary outcome. Another participant with an extreme LS value was excluded from all regression models for which LS BMD was the primary outcome. 1 participant was unable to contribute BMD measurements for any site due to a positioning error that occurred during both DXA scans.

Table 5

Adjusted multivariable regression models assessing associations between drinking intensity (10 kg/year) during 3 periods of HIV care continuum and femoral neck, total hip and lumbar spine bone mineral density (g/cm²) and low bone density^{*,†}.

Independent variable	Femoral neck BMD, g/cm ² , n = 235		Total hip BMD, g/cm ² , n = 235		Total spine BMD (g/cm ²) n = 236		Low bone density n = 237	
	Adjusted beta (95% CI)	P value	Adjusted beta (95% CI)	P value	Adjusted beta (95% CI)	P value	aOR (95% CI)	P value
Period 1 drinking intensity, 10 kg/year	0.004 (−0.003–0.011)	.29	0.004 (−0.003–0.011)	.27	0.002 (−0.006–0.009)	.67	0.87 (0.76–0.99)	.04
Period 2 drinking intensity, 10 kg/year	−0.006 (−0.012–0.001)	.02	−0.007 (−0.012–−0.001)	.02	−0.006 (−0.013–0.000)	.05	1.18 (1.03– 1.36)	.02
Period 3 drinking intensity, 10 kg/year	0.005 (0.0003–0.010)	.04	0.006 (0.001–0.011)	.02	0.009 (0.001–0.013)	.02	0.85 (0.75–0.96)	.01
Past 30-day risky alcohol use [‡]		.71		.74		.39		.03
Abstinent [ref]	–		–		–		–	
Low risk use	−0.012 (−0.064–0.040)		−0.002 (−0.054–0.050)		−0.012 (−0.074–0.050)		4.34 (1.26–14.91)	
High risk use	−0.016 (−0.055–0.023)		−0.014 (−0.053–0.025)		−0.032 (−0.079–0.015)		2.22 (1.01– 4.88)	

aOR = adjusted odds ratio, BMD = bone mineral density, CI = confidence interval, ref = reference group.

* Covariates included in all models: age, sex, race, BMI, current smoking status, menopause, ever opioid exposure, CD4 cell count, HIV viral load ≥ 200 copies/mL, total 25(OH) D, ever tenofovir use, daily calcium intake, past-year loss of sex drive, years of HIV infection, weight-bearing physical activity, years of regular cocaine use, years of regular heroin use, DXA machine/software version (see Supplemental content Table 9, <http://links.lww.com/MD/B676>).

† Total alcohol consumption (100 kg) during Period 1 (i.e., initiation of drinking to first positive HIV test), Period 2 (i.e., first positive HIV test to initiation of ART) and Period 3 (initiation of ART to time of assessment) were not significantly associated with TH, FN or LS BMD (g/cm²) or low baseline BMD in adjusted multivariable regression models that included all 3 periods (see Supplemental Content Table 8, <http://links.lww.com/MD/B676>). Again, compared with participants reporting no alcohol use in the past 30 days at baseline, participants whose alcohol use exceeded the risky drinking threshold (AOR = 4.32, 95% CI: 1.30–14.33) and those who reported alcohol use but did not exceed the risky drinking threshold (AOR = 1.94, 95% CI: 0.91–4.12) had greater odds of low baseline BMD. No significant association was detected between FN, TH, or LS BMD (g/cm²) and past 30-day alcohol use in this set of models.

We expected to find that alcohol use would be associated with BMD. We expected long-term exposure to be important for BMD, and shorter term exposure to have little effect. We expected that alcohol would have different effects based on its use before and after HIV diagnosis and ART initiation. Overall we found little effect of alcohol on BMD except a possible detrimental effect of recent use, and possible effects of use between HIV testing and ART initiation. These findings should be placed in the context of prior literature.

Titanji et al found markers of bone resorption were elevated and not matched by increases in bone formation in PLWH, and that the latter were significantly associated with any past 30-day alcohol use.^[68] Animal studies have demonstrated that alcohol consumption suppresses bone formation with no effect or an increased effect on bone resorption.^[44] High rates of alcohol consumption have been associated with increased risk of fracture in PLWH; the role of BMD is not clear and could be related to injury risk. In a large 10-year cohort study of PLWH, the incidence of fracture was 2.9 times greater among those reporting heavy drinking.^[69] Yet, studies have not consistently identified an association between alcohol consumption and BMD in people with^[16,17,29,32,34,35,67,70–73] and without HIV infection,^[44,52,74,75] possibly because most studies do not include measures of lifetime alcohol use, and many do not include valid detailed measures of recent use.

BMD does decline following initiation of ART and it occurs rapidly^[23,76,77]; increased markers of bone resorption have been detected as early as 2 weeks after initiation of ART.^[27] Longitudinal studies have found that this BMD decrease post-ART is not permanent, and that BMD stabilizes or increases after about a year of ART.^[24,29,78–80] In studies of HIV-uninfected adults, the deleterious effects of alcohol on bone also occur rapidly; it is unclear if the alcohol-induced changes to bone metabolism are permanent.^[48] In PLWH, any possible differential effects of alcohol on bone pre- and post-ART are not well understood.

Our findings should be considered in the context of study limitations. Although the Lifetime Drinking History is a validated instrument,^[56,58] it relies on self-report and may be subject to recall and social desirability bias. The dates assigned to events (e.

g., ART initiation) may also be subject to recall bias, which could result in imprecise measures of alcohol use across the HIV care continuum. We do not, however, have reason to believe that there are biases that would affect the association between alcohol use and BMD. Quantity measures (e.g., lifetime alcohol consumption) do not account for drinking patterns and therefore we cannot discern differences between individuals who may have consumed large quantities of alcohol in a short time period from those who consumed the same amount over a longer time period. However, in this cohort, total lifetime alcohol consumption and years of very heavy drinking were highly correlated, making the distinction between total consumption and drinking pattern less relevant.^[81]

Study participants had current substance dependence or ever injection drug use at time of enrolment; therefore, our findings may not be generalizable to other PLWH. In fact, the real-world context of multiple competing risks in our cohort may partially explain our findings. We used 3 different DXA machines to measure BMD, which could introduce measurement error as measurements can vary between manufacturers by as much as 11%.^[82] We did however use an industry-accepted conversion formula to account for between-machine differences, performed a sensitivity analysis stratifying results by DXA machine, and controlled for DXA machine and software version in all regression models.

The study has a number of strengths. We enrolled a sample of PLWH at high risk for low BMD, and assessed alcohol use using validated tools, identified numerous potential confounders, and measured BMD in a standardized fashion. To evaluate cumulative effects, we obtained detailed information on past and recent alcohol use from 98% of participants, most reporting decades of alcohol exposure. We examined associations in a number of different ways to look for consistent findings. Although the sample size was modest, the primary null findings for the association between lifetime alcohol use and bone density are robust with effect sizes of 0 and confidence intervals of ~ 0.004 g/cm², consistent across several analyses.

In conclusion, we did not detect an association between lifetime alcohol consumption and bone mineral density (BMD). We did

however detect an association between recent alcohol use and osteopenia or osteoporosis, and between intensity of use during several periods of the HIV care continuum, most consistently an association between use following first positive HIV test—but before beginning antiretroviral therapy—and lower BMD. As the population of PLWH ages, the prevalence of age-related complications and comorbidities, such as osteoporosis, are also increasing; the need to identify and better understand modifiable risk factors is clear. Prospective studies in PLWH should assess how alcohol use affects BMD, osteoporosis, and fractures over time.

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