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Clin Infect Dis. 2020 Sep 15;ciaa1396.

which has been published in final form at

<https://doi.org/10.1093/cid/ciaa1396>

Effects of HCV Eradication on Bone mineral density in HIV/HCV Coinfected Patients

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Key points

Eradication of HCV following anti-HCV therapy was not associated with significant changes in bone mineral density or biomarkers of bone remodeling in HIV/HCV-coinfected persons.

Abstract

Background: Little is known about the effects of eradication of HCV on bone mineral density (BMD) and biomarkers of bone remodeling in HIV/HCV coinfecting patients.

Methods: We prospectively assessed standardized BMD (sBMD) at the lumbar spine and femoral neck, World Health Organization (WHO) BMD categories at both sites, and plasma concentrations of soluble receptor activator of nuclear factor- κ B ligand (sRANKL), and osteoprotegerin (OPG) at baseline (the date of initiation of anti-HCV therapy) and at 96 weeks.

Results: A total of 238 patients were included, median age 49.5 years, 76.5% males, 48.3% with cirrhosis, 98.3% on antiretroviral therapy, median CD4+ cell count 527 cells/mm³, 86.6% with HIV-1 RNA < 50 copies/mL. The prevalence of osteoporosis at baseline at the lumbar spine (LS) and femoral neck (FN) was 17.6% and 7.2%, respectively. Anti-HCV therapy comprised pegylated interferon and ribavirin (PegIFN-RBV) plus one direct-acting antiviral in 53.4%, PegIFN-RBV in 34.5%, and sofosbuvir/RBV in 12.2%. A total of 145 (60.9%) patients achieved sustained viral response (SVR). No significant effect of SVR was observed on sBMD for the interaction between time and SVR either in the LS (P=0.801) or the FN (P=0.911). Likewise, no significant effect of SVR was observed in plasma levels of sRANKL (P=0.205), OPG (P=0.249), and sRANKL/OPG ratio (P=0.123) for the interaction between time and SVR. No significant correlation was found between fibrosis by transient elastography, and LS and FN sBMD, at baseline, and week 96

Conclusions: SVR was not associated with significant changes in BMD nor biomarkers of bone remodeling in HIV/HCV-coinfected persons.

Key Words

HIV; Hepatitis C; Antiviral Agents; Coinfection; Osteoporosis; Bone; Biomarkers.

Accepted Manuscript

Introduction

Osteoporosis and bone fractures are common among patients with liver cirrhosis [1, 2], particularly among those of advanced age, smokers, postmenopausal women, individuals with alcoholism, malnourished individuals, and in liver disease of cholestatic etiology [3].

Nevertheless, viral hepatitis has been associated with reduced bone mineral density (BMD), and several factors have been hypothesized to contribute to it. On the one hand, elevated serum levels of inflammatory cytokines could inhibit bone formation and increase bone resorption. On the other hand, progressive hepatitis-induced liver dysfunction may be associated with reduced hepatic hydroxylation of vitamin D, hypogonadism, and impaired hepatic production of insulin-like growth factor-1 and osteoprotegerin, both of which promote bone formation. The association between non-cirrhotic chronic Hepatitis C virus (HCV) infection and osteoporosis is, however, controversial [4].

The prevalence of osteoporosis in Human Immunodeficiency Virus (HIV)-infected persons is approximately 15%, which is more than three times greater than reported in HIV uninfected controls [5]. HCV infection has been associated with an increased risk of osteoporosis and bone fractures in HIV-infected persons [6]. However, the mechanism is not well understood and may involve the severity of the liver disease, a reduction BMD, microstructural abnormalities associated with HCV infection, and increased levels of inflammatory markers [7-10].

Nevertheless, unmeasured confounders, including behavioral and nutritional factors, have not been completely ruled out.

Little is known about the effects of sustained viral response (SVR) on BMD in patients with HCV infection [11-13], and to the best of our knowledge, the subject has not been assessed in patients coinfecting with HIV/HCV. Our study's main objective was to assess the effects of eradication of HCV on BMD and biomarkers of bone remodeling in HIV/HCV-coinfecting individuals. Knowing the effects of therapeutic HCV eradication on BMD may contribute to understanding better the etiopathogenesis of bone loss among HIV/HCV-infected individuals.

Besides, this research question is clinically relevant in the current era of direct-acting anti-HCV agents (DAAs) is which sustained viral response (SVR) can be achieved in most HIV/HCV-infected individuals, even in those with advanced liver disease [14].

Methods

Design and Patient Selection

Ours was a multicenter prospective study of HIV/HCV-coinfected patients initiating anti-HCV therapy between Feb 2012 and Feb 2016 in 14 centers distributed across 5 regions in Spain: Madrid (N=7), Valencia (N=3) Catalonia (N=2), Basque Country (N=1), and Andalusia (N=1). The cohort included both naïve and anti-HCV therapy experienced HIV/HCV-coinfected patients with compensated liver disease, who initiated treatment against HCV. Infectious-diseases physicians decided to administer anti-HCV therapy and regimen selection at each institution according to contemporary guidelines. The ethics committees of Hospital General Universitario Gregorio Marañón and Hospital Universitario La Paz approved the study. This work was conducted following the Declaration of Helsinki. All patients provided written, informed consent for the study. All the centers were monitored (following the last patient's first visit, interim monitoring, and following the last patient's last visit) to verify that all the information in the case report form was consistent with the patient's clinical history.

Investigation

Baseline was the date of anti-HCV treatment initiation. Patients with an undetectable serum HCV-RNA level 12 weeks after discontinuation of anti-HCV therapy were classified as having SVR. Clinical and laboratory variables were collected at baseline, every four weeks during anti-HCV treatment, and every 12 weeks after discontinuation of therapy, until 96 weeks after the initiation of treatment. All the information was recorded at each institution using a shared database via an online form, which satisfied local requirements of data confidentiality.

Baseline variables included demographics, height and weight, and systolic and diastolic blood pressure. It also included clinical information related to HIV, HCV-related liver disease, other comorbid conditions, prior anti-HCV therapy, whether or not patients were receiving cART or other medications (including opioid substitution therapy), smoking history, ongoing alcohol intake more than 50 g/day. Laboratory tests included complete blood counts, coagulation tests, a comprehensive serum biochemistry profile (including serum lipids, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, creatinine, 25 OH vitamin D, thyroxine [T4], thyrotropin [TSH], and parathyroid hormone [PTH]), HIV-1-RNA, and HCV-RNA quantification, HCV genotype, hepatitis B surface antigen (HBsAg), and determination of CD4 + and CD8 + T lymphocytes.

Assessment of liver fibrosis

Liver fibrosis at baseline was assessed using transient elastography (FibroScan; Echosens, Paris, France) performed by trained operators. Results were expressed in kilopascals (kPa) with a range of 2.5–75 kPa. We considered 10 acquisitions with a success rate of at least 60% and an interquartile range less than 30% of the median value as representative measurements of liver stiffness. Fasting was not routinely required before the examination. Cirrhosis was defined as a liver stiffness value ≥ 12.5 kPa [15] or by liver biopsy.

Assessment of bone mineral density

BMD was assessed using dual-energy X-ray absorptiometry (DXA) at the lumbar spine and femoral neck. In accordance with the World Health Organization (WHO) definitions, osteoporosis was defined as a T score of -2.5 standard deviation (SD) or lower and osteopenia as a T score between -1 and -2.5 SD [16]. Normal status was defined as a T score above -1 SD. As different densitometers were used (Hologic® [n=8], Lunar® [n=3], and Norland® [n=2]), standardized BMD (sBMD) was also calculated based on published equations [17, 18].

Biomarkers of bone remodeling

Plasma samples were taken at baseline and 96 weeks after the initiation of therapy and stored frozen in the **HIV BioBank of Hospital General Universitario Gregorio Marañón** (<http://hivhgmbiobank.com>). **Two** biomarkers of bone formation and resorption were determined in these samples: soluble receptor activator of nuclear factor- κ B ligand (sRANKL) and osteoprotegerin (OPG) [19]. These biomarkers are implicated in the pathogenesis of low bone density in HIV-infected patients [20, 21], and different studies have found an association between imbalances of these biomarkers and BMD loss in ART-treated HIV-infected individuals [22, 23]. Both biomarkers were measured by ProcartaPlex™ multiplex immunoassay (Bender MedSystems GmbH, Vienna, Austria) using a Luminex 200™ analyzer (Luminex Corporation, Austin, TX, United States) and according to the manufacturer's specifications [24]. After all clinical tests were completed, the sRANKL/OPG ratio was calculated.

Statistics

For the descriptive study, values were expressed as absolute number and percentage, and median and interquartile range (IQR). Differences between groups were analyzed using the chi-square test, t-test, or Mann-Whitney test, as appropriate. Normality was analyzed using the Kolmogorov–Smirnov test. Pearson correlation and Spearman's rho were used to assessing the correlations between sBMD and liver stiffness. Univariable and multivariable logistic regression analyses were used to identify variables associated with osteoporosis at the lumbar spine and the femoral neck at baseline. Variables analyzed included age, sex, body mass index (BMI), current smoking, alcohol intake > 50 g/day, methadone use, history of injection drug use (IDU), Centers for Disease Control and Prevention (CDC) clinical category, tenofovir disoproxil fumarate (TDF) use, HIV-RNA, CD4+ cell count, nadir CD4+ cell count, CD4+/CD8+ ratio, HIV-RNA, HCV genotype, HCV-RNA, liver stiffness, 25 OH vitamin D, T4, TSH, and PTH. Variables included in the multivariable analysis included age, sex, and those with a P-value <0.1 in

univariable analysis. Linear mixed models for longitudinal data were used in analyses to account for repeated measures of sBMD, with SVR and time and their interaction taken as fixed effects, and the patient as a random effect. Least-square means and their 95% confidence intervals (CI) are reported for these models. Besides, to study changes between baseline and week 96 WHO BMD categories, tests for repeated measures were used (paired t-test and Wilcoxon test). IBM SPSS Statistics for Windows, Version 21.0, was used for all calculations. All statistical tests were performed two-sided, and a P-value of <0.05 was considered statistically significant.

Results

Overall, 238 patients were included in the study, 145 of which (60.9%) achieved SVR; the full characteristics of these patients, categorized by whether or not achieved SVR, are shown in **Table 1**. In brief, 76.5% were male, the median age was 49.5 years, 27.3% had had prior AIDS-defining conditions, 98.3% were on cART, the median baseline CD4 cell count was 527 cells/mm³, 86.6% had an undetectable HIV viral load, 62.6% were infected with HCV genotype 1, the median HCV-RNA load was 6.4 log₁₀ IU/mL, and 3.4% were HBsAg positive. Liver cirrhosis was detected in 48.3% of patients, and 11.3% had received prior anti-HCV therapy. Alcohol intake > 50 g/d was reported by 2.1% patients, 68.1% were current smokers, 13.0% had arterial hypertension, and 8.4% had diabetes mellitus. Anti-HCV regimens included pegylated interferon (Peg-IFN) plus ribavirin (RBV) 34.5%, Peg-IFN plus RBV plus a first-generation anti-HCV protease inhibitor (PI) 47.5%, Peg-IFN plus RBV plus daclatasvir 5.9%, and sofosbuvir plus RBV 12.2%. HCV-RNA and the type of anti-HCV therapy were the only baseline variables in which significant differences were found between responders and non-responders. The overall prevalence of osteoporosis at the lumbar spine and femoral neck in HIV/HCV-coinfected patients was 17.6% and 7.2%, respectively, without significant differences between responders and non-responders (**Table 1**). Logistic regression analyses of variables associated with osteoporosis at the lumbar spine and the femoral neck at baseline are shown in **Table 2**.

Lower BMI was the only variable independently associated with osteoporosis at the lumbar spine (adjusted odds ratio ([aOR] 0.853; 95% confidence interval [CI] 0.735 – 0.991, P=0.037). BMI was also associated with osteoporosis at the femoral neck in the univariable analysis but not in multivariable analysis.

No significant correlation was found between liver fibrosis, assessed by transient elastography, and lumbar spine and femoral neck sBMD, at baseline, and week 96 **Figure 1**.

Changes in sBMD in the lumbar spine and femoral neck from baseline to 96 weeks in responders and non-responders are shown in **Figure 2**. No significant effect of SVR was observed on sBMD for the interaction between time and SVR in the lumbar spine (P=0.801) or the femoral neck (P=0.911). The median (95% CI) change from baseline to week 96 in sBMD at the lumbar spine was -0.007 (-0.033 – 0.032) g/cm² in responders and -0.006 (-0.028 – 0.027) g/cm² in non-responders. Likewise, the change in sBMD at the femoral neck was -0.023 (-0.065 – 0.012) g/cm² in responders and -0.024 (-0.052 – 0.019) g/cm² in non-responders. Two sensitivity analyses were carried out, the first without the eight patients that were coinfecting with HBV, and the second without the four patients not on ART; the results of these sensitivity analyses did not change the results found in the primary analysis (data not shown).

No significant changes in BMD WHO categories from baseline to 96 weeks were found in the lumbar spine and femoral neck either in responders or non-responders (**Figure 4**).

Changes in plasma levels of sRANKL, OPG, and sRANKL/OPG ratio from baseline to 96 weeks in responders are shown in **Figure 4**. No significant effect of SVR was observed in plasma levels of sRANKL (P=0.205), OPG (P=0.249), and sRANKL/OPG ratio (P=0.123) for the interaction between time and SVR.

Discussion

In this prospective study, with 238 HIV/HCV-coinfecting patients half of which had liver cirrhosis and approximately one-third of which achieved SVR following anti-HCV therapy, we

did not observe an association between HCV eradication and significant changes in sBMD, BMD WHO categories, and plasma levels of biomarkers of bone remodeling. To the best of our knowledge, ours is the largest prospective study analyzing the effects of HCV eradication after anti-HCV therapy in patients with chronic HCV infection, and the first analyzing this issue among HIV/HCV-coinfected patients.

We found that among the study population, the prevalence of osteoporosis at the lumbar spine and femoral neck was 17.6% and 7.2% respectively, differences that can be explained because lumbar spine consists of trabecular bone, which is more metabolically active with a higher rate of turnover and may be affected earlier and more severely in comparison with the cortical bone of the femoral neck [25]. Lower BMI was the only baseline variable associated with osteoporosis. It must be considered, however, that we could not assess appropriately advanced age and female sex, as patients in our cohort were within a narrow age range in their forties and fifties, and more than three quarters were males. We did not find a correlation between liver fibrosis, assessed by transient elastography and sBMD at baseline and week 96 after initiation of anti-HCV therapy, something consistent with what has been found in previously published studies with a limited number of patients [11-13].

The effects of SVR on BMD have been previously assessed in small studies, including HCV-monoinfected patients. In a prospective study with 36 treatment naïve non-cirrhotic patients with chronic hepatitis C with SVR following Peg-IFN plus RBV, BMD values at the lumbar spine and the femoral neck at 24 and 48 weeks of antiviral therapy and 48 weeks after the end of treatment were significantly higher in comparison with baseline values [11]. A limitation of this study is the non-availability of comparable data on the patients who did not achieve SVR. In a prospective study with 46 non-cirrhotic children with chronic hepatitis C treated with Peg-IFN plus RBV, 23 of which achieved SVR, follow-up DXA scans results 24 weeks after the end of treatment showed statistically significant improvement in BMD from baseline; however, an effect of SVR on BMD could not be evaluated [12]. In a study with 30 non-cirrhotic patients with chronic hepatitis C treated with Peg-IFN plus RBV, 19 of which achieved SVR, BMD increased

significantly by the end of 48-week therapy in comparison with baseline but decreased by the end 24-week follow-up period without significant differences between patients with SVR and patients with viral relapse [13]. The authors also found a decrease in osteocalcin and C-terminal propeptide of type I collagen during Peg-IFN plus RBV therapy supporting the findings of the DXA measurements.

Our study is limited because we used different densitometers to assess BMD, something that we tried to correct calculating sBMD according to published equations. Another limitation is the lack of central reading of DXA scans. It also needs to be mentioned that almost 90% of our patients received Peg-IFN and 100% RBV, both of which modulate bone metabolism, with IFN inhibiting excessive osteoclastogenesis resulting in reduced bone resorption [26, 27], and RBV, exhibiting oppositional effects [28, 29]. Other limitations include the lack of an HCV-monoinfected group and the lack of an age, sex-, and race matched control group. However, the study has the strengths of the prospective design, the large sample size, the assessment of both sBMD and biomarkers of bone remodeling at baseline and 96 weeks after treatment initiation, and the fact that responders and non-responders were well matched in many relevant characteristics limiting the possibility of confounding.

In conclusion, in this prospective cohort of HIV/HCV-coinfected patients, half of which had compensated cirrhosis, no significant correlation was found between liver-stiffness and BMD at baseline and week 96 after initiation of anti-HCV therapy. Besides, in the medium term, eradication of HCV following anti-HCV therapy was not associated with significant changes in sBMD, BMD WHO categories, and plasma levels of biomarkers of bone remodeling. Our findings do not support a causal association between HCV infection and reduced BMD in HIV/HCV-coinfected persons with compensated liver disease. They suggest that lifestyle and other factors may have a more significant impact on BMD than the severity of liver fibrosis in this population group.

Acknowledgements

We are indebted to all the patients who participated in this research.

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Funding

This study was supported by Instituto de Salud Carlos III (ISCIII), grant numbers PI11/01556, PI14/01094, PI14/01581, and PI14CIII/00011, and by Ministerio de Sanidad, Servicios Sociales e Igualdad, grant number EC11-241. The study was also funded by the RD16/0025/0017, RD16/0025/0018 and RD16CIII/0002/0002 projects as part of the Plan Nacional R + D + I and cofunded by ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER).

Conflict of Interest

JB reports grants from MSD, Gilead, and Viiv Healthcare; and personal fees from MSD, Gilead, Viiv Healthcare, and Janssen, outside the submitted work. MJG reports personal fees from Gilead, MSD, Janssen, and Viiv Healthcare. JMG reports personal fees from Gilead and Viiv Healthcare, outside the submitted work. EM reports grants from Gilead, MSD, and Viiv, and personal fees from Gilead, Janssen, MSD, and Viiv, outside the submitted work. JG reports grants and personal fees from Gilead, MSD, Janssen, and Viiv Healthcare; and non-financial support from Gilead, outside the submitted work. All other authors declare that they have no conflicts of interest.

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Figure Legends

Figure 1.

Pearson and Spearman correlations between lumbar spine and femoral neck bone mineral density and liver fibrosis assessed by transient elastography at baseline (A) and at 96 weeks (B). **Abbreviations:** sBMD, standardized bone mineral density

Figure 2.

Estimated means (95% confidence interval) of bone mineral density in the lumbar spine and femoral neck at baseline and 96 weeks in responders and non-responders to anti-HCV therapy. **Abbreviations:** sBMD, standardized bone mineral density; SVR, sustained viral response.

Figure 3.

Changes in bone mineral density, World Health Organization (WHO) categories from baseline to 96 weeks at the lumbar spine for responders (A) and non-responders (B); and at the femoral neck in responders (C) and non-responders (D). **Abbreviations:** sBMD, standardized bone mineral density; SVR, sustained viral response.

Figure 4. Estimated means (95% confidence interval) of plasma biomarkers concentrations at baseline and 96 weeks in responders and non-responders to anti-HCV therapy: sRANKL (A), OPG (B), and sRANKL/OPG ratio (C). **Abbreviations:** SVR, sustained viral response; sRANKL, soluble receptor activator of nuclear factor- κ B ligand; OPG, osteoprotegerin.

Table 1. Baseline characteristics of the study population

Characteristic	No SVR (n=93)	SVR (n=145)	P	TOTAL (n=238)
Male sex, No. (%)	66 (70.9)	116 (80.0)	0.109	182 (76.5)
Age, years, median (IQR) (baseline)	49.1 (46.6 - 52.6)	49.7 (46.3 - 53.2)	0.629	49.5 (46.4 - 53)
BMI, median (IQR)	24.1 (22.1 - 26.1)	24.4 (21.5 - 27.3)	0.460	24.2 (21.8 - 26.6)
Prior injection drug use, No. (%)	73 (78.5)	107 (73.8)	0.410	180 (75.6)
Methadone therapy, No. (%)	13 (14.0)	16 (11.0)	0.707	29 (12.2)
CDC disease category C, No. (%)	31 (33.3)	34 (23.4)	0.229	65 (27.3)
CD4 ⁺ , nadir, cells/mm ³ , median (IQR)	160 (69 - 253)	162 (84 - 246)	0.901	160 (72 - 250)
cART during anti-HCV treatment, No. (%) ^a	92 (98.9)	142 (97.9)	0.708	234 (98.3)
Antiretroviral drugs, No. (%)			0.561	
Tenofovir disoproxil fumarate	56 (60.9)	86 (60.6)		142 (60.7)
Emtricitabine	53 (57.6)	83 (58.5)		136 (58.1)
Lamivudine	14 (15.2)	35 (24.6)		49 (20.9)

Abacavir	13 (14.1)	32 (22.5)		45 (19.2)
Raltegravir	35 (38.0)	54 (38.0)		89 (38.0)
Darunavir/ritonavir	21 (22.8)	22 (15.5)		43 (18.4)
Atazanavir/ritonavir	14 (15.2)	24 (16.9)		38 (16.2)
Lopinavir/ritonavir	4 (4.3)	5 (3.5)		9 (3.8)
Fosamprenavir/ritonavir	3 (3.3)	1 (0.7)		4 (1.7)
Etravirine	18 (19.6)	23 (16.2)		41 (17.5)
Efavirenz	15 (16.3)	19 (13.4)		34 (14.5)
Rilpivirine	3 (3.3)	6 (4.2)		9 (3.8)
Nevirapine	2 (2.2)	5 (3.5)		7 (3.0)
Maraviroc	0 (0)	2 (1.4)		2 (0.9)
CD4 ⁺ , baseline, cells/mm ³ , median (IQR)	550 (372 - 822)	518 (385 - 772)	0.556	527 (380 - 803)
Undetectable HIV RNA load at baseline, No. (%)	77 (82.8)	129 (89)	0.230	206 (86.6)
Prior anti-HCV therapy, No. (%)	9 (9.7)	18 (12.4)	0.516	27 (11.3)
HCV genotype, No. (%)			0.334	
1	55 (59.1)	94 (64.9)		149 (62.6)
2	3 (3.2)	2 (1.4)		5 (2.1)
3	19 (20.4)	24 (16.6)		43 (18.1)
4	10 (10.8)	10 (6.9)		20 (8.4)
Other/mixed	6 (6.5)	14 (9.7)		20 (8.4)

Unknown	0 (0)	1 (0.7)		1 (0.4)
HCV-RNA, Log ₁₀ IU/mL, median (IQR)	6.5 (6.1 - 6.9)	6.3 (5.8 - 6.6)	0.001	6.4 (5.9 - 6.7)
HBsAg positivity, No. (%)	3 (3.2)	5 (3.4)	0.655	8 (3.4)
Serum albumin, g/dL, median (IQR)	4.2 (3.95 - 4.5)	4.3 (4.1 - 4.6)	0.030	4.3 (4.0 - 4.6)
Liver cirrhosis, No. (%) (METAVIR 4 or TE>12,5)	41 (44.1)	74 (51)	0.295	115 (48.3)
Current alcohol intake > 50 g/d, No. (%)	1 (1.1)	4 (2.8)	0.560	5 (2.1)
Diabetes mellitus, No. (%) ^b	9 (9.7)	11 (7.6)	0.570	20 (8.4)
Current smoking, No. (%)	65 (69.9)	97 (66.9)	0.910	162 (68.1)
Arterial hypertension, No. (%) ^b	14 (15.1)	17 (11.7)	0.456	31 (13)
Anti-HCV therapy, No. (%)			0.003	
Peg-IFN + RBV	29 (31.2)	53 (36.6)		82 (34.5)
Peg-IFN + RBV + HCV protease inhibitor	36 (38.7)	77 (53.1)		113 (47.5)
Peg-IFN + RBV + Daclatasvir	6 (6.5)	8 (5.5)		14 (5.9)
Sofosbuvir + RBV	22 (23.7)	7 (4.8)		29 (12.2)
WHO diagnostic classification at the lumbar spine*– No./with data (%)			0.825	
Osteoporosis	13/82 (15.9)	24/128 (18.8)		37/210 (17.6)
Osteopenia	32/82 (39.0)	42/128 (32.8)		74/210 (35.2)
Normal	37/82 (45.1)	62/128 (48.4)		99/210 (47.1)
WHO diagnostic classification at femoral neck#– No./with data (%)			0.260	
Osteoporosis	7/81 (8.6)	8/127 (6.3)		15/208 (7.2)

Osteopenia	44/81 (54.3)	54/127 (42.5)	98/208 (47.1)
Normal	30/81 (37.0)	65/127 (51.2)	95/208 (45.7)

^aThree patients were not receiving ART because they were elite controllers of HIV (i.e., HIV-infected patients with spontaneous control of HIV replication at undetectable levels). One patient was not receiving ART because he was a long-term non-progressors with a CD4+ cell count of 633 cells/mm³ and an HIV-RNA load of 299 copies/mL.

^bDiabetes and hypertension were defined as diagnoses included in the medical record

^cBaseline BMD at the lumbar spine was determined in 210 patients.

^dBaseline BMD at the femoral neck was determined in 208 patients

Abbreviations: SVR, sustained viral response; IQR, interquartile range, BMI, body mass index; CDC, Centers for Disease Control and Prevention; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; HCV, hepatitis C virus; RNA, ribonucleic acid; HBsAg, hepatitis B surface antigen; TE, transient elastography; Peg-IFN, pegylated interferon alpha; RBV, ribavirin; WHO, world health organization.

Table 2. Logistic regression analysis of variables associated with osteoporosis at the lumbar spine and the femoral neck at baseline

Variable	Lumbar Spine						Femoral Neck					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
	OR	95%CI	P	aOR	95%CI	P	OR	95%CI	P	aOR	95%CI	P
Age	1.029	0.95 - 1.114	0.485	1.037	0.933 - 1.152	0.505	1.063	0.99 - 1.142	0.091	1.100	0.984 - 1.231	0.095
Male sex	1.199	0.509 - 2.826	0.678	1.400	0.559 - 3.503	0.472	0.608	0.197 - 1.877	0.387	0.404	0.089 - 1.825	0.239
BMI	0.853	0.751 - 0.969	0.015	0.853	0.735 - 0.991	0.037	0.833	0.712 - 0.975	0.023	0.830	0.678 - 1.017	0.072
History of IDU	0.893	0.399 - 1.998	0.783				0.910	0.276 - 3.001	0.877			
CD4+/CD8+	1.116	0.913 - 1.365	0.285				0.159	0.022 - 1.164	0.070	0.100	0.010 - 1.038	0.054
Methadone	2.707	1.059 - 6.922	0.038	2.246	0.858 - 5.877	0.099	NA	NA	NA			
TDF use	0.684	0.334 - 1.397	0.297				0.568	0.197 - 1.636	0.295	1.444	0.392 - 5.328	0.581
Current smoking	2.181	0.901 - 5.282	0.084	1.796	0.647 - 4.980	0.261	1.815	0.492 - 6.696	0.371			
Alcohol intake > 50 g/day	0.556	0.257 - 1.203	0.136				1.028	0.342 - 3.085	0.961			
Clinical category C (CDC)	0.926	0.415 - 2.069	0.852				1.255	0.408 - 3.855	0.692			
Nadir CD4+ cell count	0.999	0.996 - 1.002	0.471				0.998	0.994 - 1.002	0.275			
CD4+ cell count	0.999	0.998 - 1.000	0.197				0.999	0.996 - 1.001	0.360			
HIV-RNA BLQ	1.254	0.47 - 3.343	0.651				0.982	0.209 - 4.622	0.982			
HCV genotype 3	0.853	0.328 - 2.221	0.744				1.701	0.509 - 5.678	0.388			
Log10 HCV-RNA	1.572	0.895 - 2.761	0.115				0.740	0.386 - 1.417	0.363			
Liver stiffness	5.502	0.468 - 64.65	0.175				1.000	0.347 - 2.883	1.000			

Vitamin D	0.976	0.946 - 1.007	0.133				0.985	0.949 - 1.023	0.436			
T4	1.025	0.887 - 1.183	0.739				0.926	0.738 - 1.162	0.508			
TSH	0.961	0.863 - 1.07	0.467				0.753	0.462 - 1.228	0.256			
PTH	1.006	0.996 - 1.015	0.249				1.005	0.996 - 1.015	0.273			

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; IDU, injection drug use; TDF, tenofovir disoproxil fumarate; CDC, Centers for Diseases Control and Prevention; BLQ, below the limit of quantification; T4, thyroxine; TSH, thyrotropin; PTH, parathyroid hormone

Figure 1

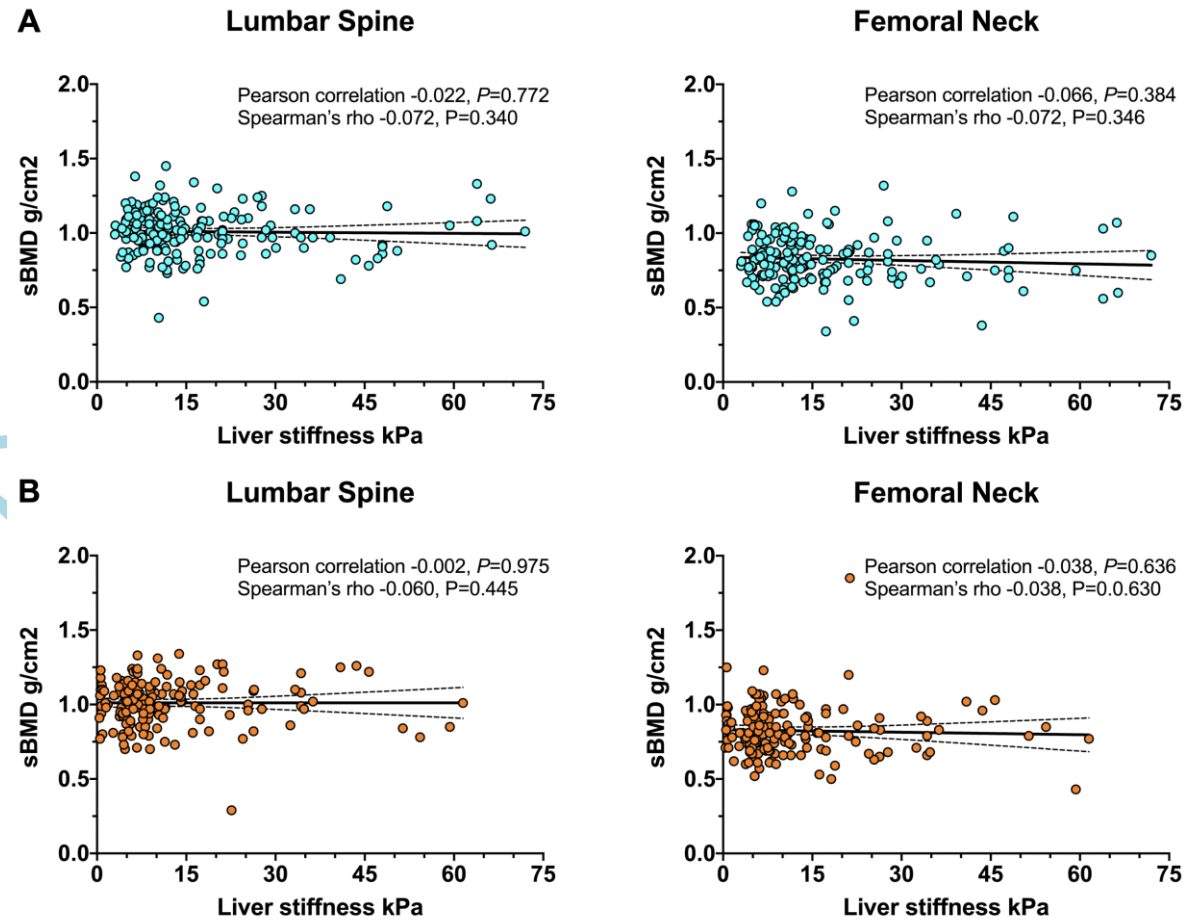


Figure 2

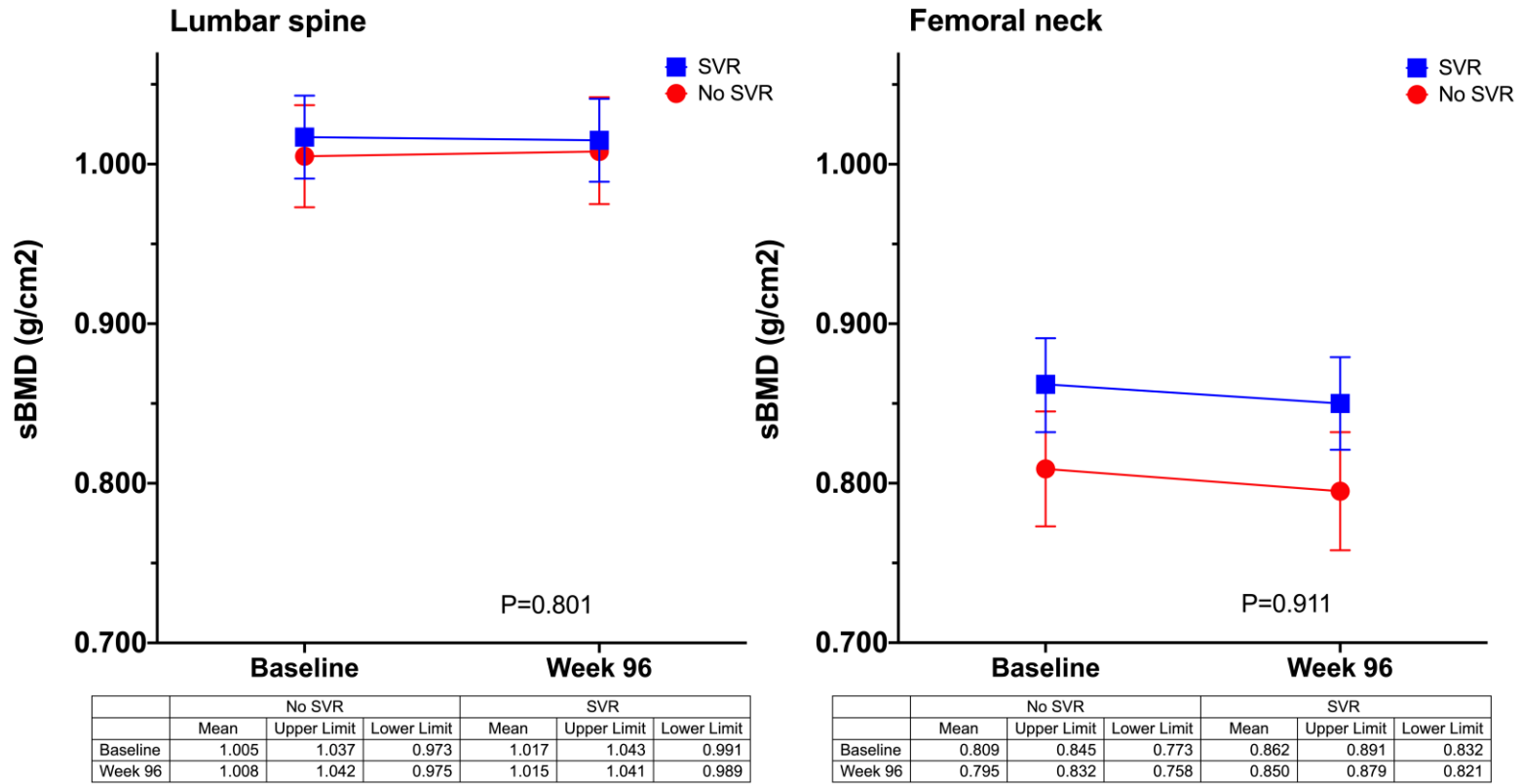


Figure 3

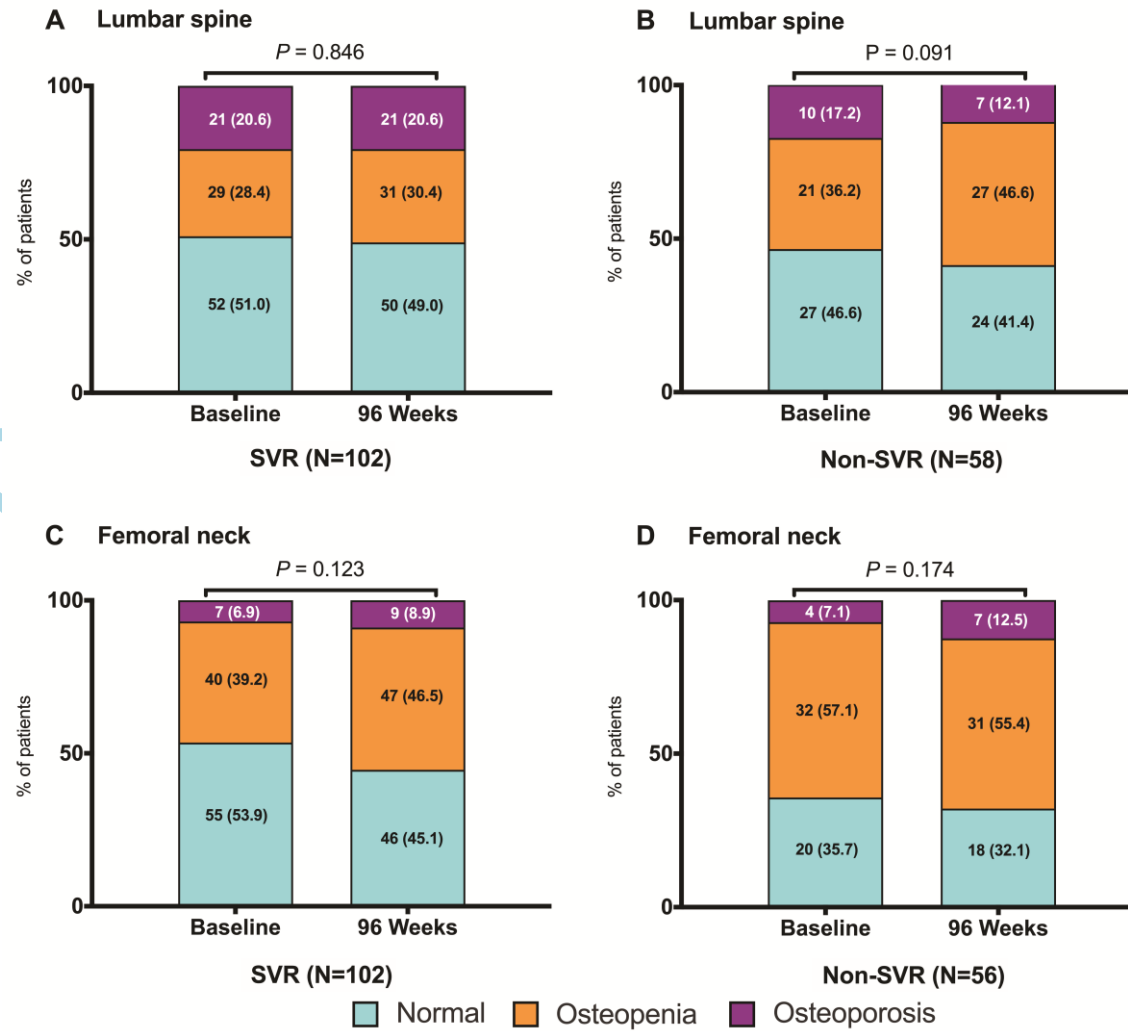


Figure 4

