Minimal change in bone density and no association with HIV factors over 12 months in HIV-infected men

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Introduction

- HIV infection is postulated to be associated with an increased risk of reduced bone mass and osteoporosis.
- In combination antiretroviral therapy (cART)-naïve patients, studies have shown loss of bone mineral density (BMD) associated with initiating cART, which stabilised after the first couple of years.
- In cART-experienced patients, results relating to change in BMD over time have been inconclusive, with some studies showing no significant change in BMD over time in HIV-positive men, whilst others have shown an increase in BMD, mainly at the lumbar spine.

Aims

- To describe changes in absolute BMD from baseline to follow-up at 12 months in men with chronic HIV infection.
- To identify factors associated with loss of BMD over 12 months in these men, including traditional osteoporosis risk factors and HIV-related factors.

Methods

- Chronically-infected HIV-positive men attending the HIV outpatient clinic at Brighton, UK were randomly selected to participate in a longitudinal study investigating BMD and osteoporosis.
- The following data were collected at baseline and at 12 months:
  - Demographic and HIV-related details, including cART history, were obtained from the HIV clinic database, and risk factors for low BMD were evaluated using data from self-reported questionnaires.
  - Additional information relating to HIV, bone and renal parameters were obtained from fasted blood and urine samples.
  - Absolute BMD (g/cm^2) at the lumbar spine (LS) and the non-dominant total hip (TH) and the non-dominant femoral neck (FN) was measured using the GE Healthcare Lunar iDXA bone densitometer.
- Osteopenia was defined as T-score <-1 and >-2.5, and osteoporosis as T-score ≤-2.5 in men ≥50 years and Z-score ≤-2 in men <50 years.
- As the precision of BMD measurements by dual energy x-ray absorptiometry (DXA) varies by 1 – 2% at the lumbar spine and by up to 2.5% at the femoral neck[1], assessing a decrease in BMD greater than the smallest detectable difference (SDD), which is the smallest change that exceeded the variability associated with measuring BMD at two different time points, can be used[2].
- The SDD cut-offs for a single DXA machine of a decrease in BMD of ≥0.034, 0.027 and 0.036 g/cm^2 at the lumbar spine, total hip and femoral neck, respectively, were used[3].
- To investigate the factors associated with absolute BMD at baseline, linear regression was performed, and all factors significant at the 10% level in univariable analysis were tested in a multivariable model, with statistical significance denoted by p-value ≤0.05.
- Change in absolute BMD and percentage BMD at 12 months was assessed using paired t-tests.
- Men with more than the SDD decrease in BMD of 0.034, 0.027 and 0.036 g/cm^2 at the LS, the non-dominant TH and the non-dominant FN, respectively, at 12 months were identified.
- To investigate factors associated with a greater than SDD decrease in BMD, logistic regression was performed with factors adjusted for baseline BMD only due to small numbers of events at each site.

Results

- The baseline characteristics of the 422 HIV-infected men are shown in Table 1.
- Baseline prevalence of osteopenia was 43%, 40% and 51%, and osteoporosis was 11%, 5% and 3% at the LS, the non-dominant TH and the non-dominant FN, respectively.
- Table 2 shows the factors significantly associated with baseline BMD at the LS, the non-dominant TH and the non-dominant FN.
  - At all 3 sites, higher body mass index (BMI, overweight: BMI 25 – 30 kg/m^2 and obese: BMI > 30 kg/m^2) was associated with higher BMD and current smoking was associated with lower BMD.
  - No HIV-related factors (including duration of HIV infection, nadir or current CD4 count, clinical stage of HIV infection, HIV RNA viral load or current cART use) were associated with BMD at baseline.
  - Other factors associated with higher BMD were non-white ethnicity at the non-dominant TH and non-dominant FN, and doing some regular exercise at the LS.
  - Other factors associated with lower BMD were older age at the non-dominant FN and bisphosphonate use at the non-dominant TH.
- Of the 338 men that returned for a second visit at 12 months, there were 334, 328 and 330 paired BMD results at the LS, the non-dominant TH and the non-dominant FN, respectively.
- The mean absolute BMD at baseline and at 12 months is shown in Table 3 and the change in BMD at 12 months is shown in Figure 1.
  - Over 12 months, there was a significant increase in mean absolute BMD at the LS (p=0.01) and a significant decrease at the non-dominant FN (p=0.02), but no significant difference at the non-dominant TH (p=0.48).
- There was a greater than SDD decrease in BMD at 12 months in 44 (13%), 25 (8%) and 31 (9%) at the LS, the non-dominant TH and the non-dominant FN, respectively.
- Table 4 shows the factors significantly associated with a greater than SDD decrease in BMD at the non-dominant TH and the non-dominant FN at 12 months (no factors were associated with a greater than SDD decrease at the LS):
  - At the non-dominant TH, having hepatitis C co-infection and using antacids were associated with an increased likelihood of a greater than SDD decrease, whilst being overweight (BMI 25 - 30 kg/m^2) and having symptomatic HIV infection were associated with a reduced risk of a greater than SDD decrease.
  - At the non-dominant FN, longer duration of HIV infection and higher current CD4 count were associated with a reduced risk of a greater than SDD decrease.
  - At both the non-dominant TH and FN, older age, having an undetectable HIV RNA viral load (<40 copies/ml), current protease inhibitor (PI) use or current concomitant tenofovir (TDF) and PI use were associated with a reduced risk of a greater than SDD decrease.

Table 1: Patient characteristics at recruitment

	Total (N=422)
Age, years, mean (SD)	47 (9.8)
Ethnicity, n (%) White Black Other	 398 (94.3) 15 (3.6) 9 (2.1)
HIV transmission risk, n (%) MSM Heterosexual sex IVDU/blood products	 392 (92.9) 26 (6.2) 4 (0.9)
Hepatitis B co-infection, n (%)	17 (4.0)
Hepatitis C co-infection, n (%)	59 (14.0)
Duration of HIV infection, years, median (IQR)	9.6 (5.0, 15.5)
Clinical stage of HIV infection, n (%) Asymptomatic Symptomatic AIDS	 193 (45.7) 115 (27.3) 114 (27.0)
CD4, cells/μL, median (IQR) Nadir At recruitment	 191 (100, 277) 547 (411, 696)
HIV RNA viral load < 40, copies/mL, n (%)	365 (86.5)
cART status, n (%) Naïve Previous Current	 34 (8.1) 7 (1.7) 381 (90.3)

cART: combination antiretroviral therapy; IVDU: intravenous drug user; MSM: men who have sex with men

Table 2: Factors associated with BMD at baseline in multivariable linear regression at a) LS; b) non-dominant TH; and c) non-dominant FN

Factor	LS		Non-dominant TH		Non-dominant FN	
	B* (95% CI)	P	B* (95% CI)	P	B* (95% CI)	P
Age (per 10 year increase)	-	-	-	-	-0.02 (-0.03, -0.003)	0.02
Non-white vs. white ethnicity	-	-	0.07 (0.02, 0.12)	0.01	0.07 (0.01, 0.12)	0.02
BMI < 25 vs. 25 – 30 kg/m^2	0.08 (0.05, 0.11)	<0.0001	0.09 (0.06, 0.11)	<0.0001	0.08 (0.06, 0.11)	<0.0001
BMI < 25 vs. > 30 kg/m^2	0.10 (0.05, 0.14)	<0.0001	0.13 (0.09, 0.17)	<0.0001	0.10 (0.06, 0.14)	<0.0001
Current vs. never smoking	-0.05 (-0.08, -0.01)	0.008	-0.03 (-0.06, -0.004)	0.03	-0.04 (-0.07, -0.01)	0.01
Exercise in some weeks vs. no exercise	0.08 (0.01, 0.15)	0.02	-	-	-	-
Bisphosphonate use vs. none	-	-	-0.08 (-0.14, -0.01)	0.02	-	-

*B is the mean difference in absolute BMD
BMI: body mass index; cART: combination antiretroviral therapy; FN: femoral neck; LS: lumbar spine; PI: protease inhibitor; TDF: tenofovir; TH: total hip
Factors inserted into model: age, ethnicity, HIV transmission risk, current hepatitis B co-infection, current hepatitis C co-infection, smoking, alcohol, recreational drug use, exercise, BMI, liver disease, hypogonadism, diabetes, renal disease, rheumatoid arthritis, antidepressants, antacids, oral steroids, calcium supplementation, vitamin D supplementation, bisphosphonates, testosterone, duration of HIV infection, CD4 count (nadir and current), clinical stage of HIV infection, HIV RNA viral load, current cART (none, cART including TDF, cART including PI, cART including TDF and PI, other), cumulative cART exposure

Table 3: Absolute BMD at baseline and at 12 months

Site	N	Absolute BMD, g/cm^2, mean (SD), at baseline	Absolute BMD, g/cm^2, mean (SD), at 12 months	Change in absolute BMD, g/cm^2, mean (SD)	P
LS	334	1.137 (0.16)	1.143 (0.16)	0.006 (0.03)	0.01
Non-dominant TH	328	0.998 (0.14)	0.999 (0.14)	0.001 (0.02)	0.48
Non-dominant FN	330	0.947 (0.14)	0.943 (0.13)	-0.004 (0.03)	0.02

BMD: bone mineral density; FN: femoral neck; LS: lumbar spine; TH: total hip

Figure 1: Changes in BMD from baseline to 12 months at a) LS; b) non-dominant TH; and c) non-dominant FN

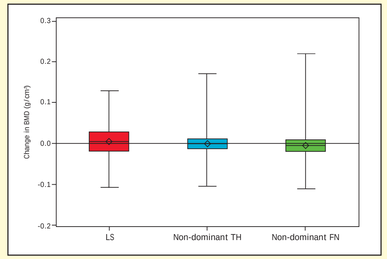

Table 4: Factors associated with a greater than SDD decrease in BMD at 12 months, after adjustment for baseline BMD, at a) non-dominant TH; and b) non-dominant FN

Factor	Non-dominant TH		Non-dominant FN	
	OR* (95% CI)	P	OR* (95% CI)	P
Age (per 10 year increase)	0.50 (0.31, 0.79)	0.003	0.60 (0.40, 0.91)	0.02
BMI < 25 vs. 25 – 30 kg/m^2	0.14 (0.03, 0.63)	0.01	-	-
Hepatitis C co-infection vs. no co-infection	2.87 (1.12, 7.37)	0.03	-	-
Antacid use vs. none	2.50 (0.98, 6.37)	0.05	-	-
Duration of HIV infection, years	-	-	0.93 (0.88, 0.99)	0.03
Clinical stage of HIV infection	0.28 (0.08, 0.97	0.04	-	-
Current CD4 count, cells/μL	-	-	0.90 (0.83, 0.99)	0.03
HIV RNA viral load < 40 copies/ml	0.22 (0.09, 0.53)	0.001	0.37 (0.15, 0.89)	0.03
Current PI use vs. none	0.10 (0.01, 0.86)	0.04	0.09 (0.01, 0.84)	0.04
Current TDF and PI use vs. none	0.27 (0.07, 1.01)	0.05	0.27 (0.07, 1.02)	0.05

* Odds ratios adjusted for baseline BMD
BMI: body mass index; cART: combination antiretroviral therapy; FN: femoral neck; PI: protease inhibitor; SDD: smallest detectable difference; TDF: tenofovir; TH: total hip
Factors inserted into model: age, ethnicity, current hepatitis B co-infection, current hepatitis C co-infection, smoking, alcohol, recreational drug use, exercise, BMI, liver disease, hypogonadism, diabetes, renal disease, rheumatoid arthritis, antidepressants, antacids, oral steroids, calcium supplementation, vitamin D supplementation, bisphosphonates, duration of HIV infection, CD4 count (nadir and current), clinical stage of HIV infection, HIV RNA viral load, current cART (none, cART including TDF, cART including PI, cART including TDF and PI, other)

Discussion

- Although the prevalence of osteopenia and osteoporosis at the LS, the non-dominant TH and the non-dominant FN was relatively high, the change in BMD was small at all three sites, with only a minority experiencing a significant decrease over 12 months.
- This may reflect the relative wellness of this cohort where the majority of men had well-controlled HIV infection, but may also reflect the relatively short follow-up period.
- At baseline, only traditional risk factors for osteoporosis (e.g. age, ethnicity, smoking) were associated with a decrease in BMD, suggesting that traditional factors may be of more importance than HIV-related factors in men with well-controlled HIV infection.
- An increase in BMD at the LS at 12 months was in keeping with other studies, and most likely reflects age-associated degenerative spondylotic changes.
- At 12 months, better controlled HIV infection appeared to be associated with a reduced risk of a decrease in BMD at the non-dominant FN and the non-dominant TH, suggesting that good immune function may play a role in preventing loss of BMD.
- There did not appear to be an association between cART use and a decrease in BMD, especially with drugs such as TDF and boosted PIs which have previously been implicated in the reduction of BMD.
- The limitations of this study were the relatively short period of follow-up and the inability to perform a multivariable analysis relating to change in BMD at 12 months due to small numbers of events at each site.

Conclusions

- In this mainly white, MSM, cART-experienced cohort of HIV-positive men, only a minority had a significant decrease in BMD over 12 months.
- HIV-related factors (including longer duration of HIV infection, symptomatic HIV infection, an undetectable HIV RNA viral load, current PI use or current concomitant TDF and PI use) appeared to be protective against a reduction in BMD at the hip, although no association was found at the LS.
- Our data suggest that good control of HIV infection may be helpful in preventing loss of BMD in HIV-infected men.

References

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